Bournemouth University

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Exploring Gastro-oesophageal Reflux in Infants and Children

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DECLARATION

I declare that I conducted the work represented in this thesis entitled *Gastro-oesophageal reflux in Infants and Children* and composed it myself. The work that is presented is, to the best of my knowledge, original, except as acknowledged in the script. As a thesis written for PhD by publication, there are contributions made by others as outlined in detail below. This thesis has not been submitted previously, either as a whole or in part, for a degree at this or any other university.

Mark Tighe

Dr Mark P Tighe

25/7/2024

Acknowledgements:

I'd like to thank my wife (Jules) and my family, as without their support, none of this would have been possible, and Dr Edwin van Teijlingen, my supervisor at Bournemouth University for his kind guidance and support, as well as my colleagues at University Hospitals Southampton (Prof Beattie and Dr Afzal) for their support, and the great library teams at University Hospitals Dorset and Bournemouth University.

Abstract

Background: Gastro-oesophageal reflux in babies, young children and teenagers is a frequent cause of symptoms, parental concern and paediatric referrals. Sequelae can include failure to thrive, haematemesis, and recurrent aspiration. Current conservative management includes reassurance, feeding assessment and parental education, whilst more interventionist options include medications and surgery. Prior to 2008, clinical practice was often individualised, with a paucity of evidence for treatments in infants and children (or treatment decisions were extrapolated from evidence in adults), and no robust synthesis of the evidence was available to provide evidence-based guidance so clinicians could understand best how to treat their patients.

Aims and Objectives: This PhD research aimed to identify the current issues in infants and children with either gastro-oesophageal reflux (GOR) or gastro-oesophageal reflux disease (GORD) and investigate the evidence-base for current management strategies. I highlight the current gaps, and aim to improve current management of GORD, including expanding the evidence-base.
To understand the current evidence-base, I initially undertook a systematic review of all original trials of pharmacological treatments for GOR/GORD (Article I). I evaluated the role of pH studies as a key objective outcome for infants and children with GORD (Article II). This technique has now evolved to include impedance, and based on this evidence, I set up a pH/impedance monitoring service in Poole for paediatric patients. I then appraised the evidence-base using Cochrane methodology given the improved robustness of evidence given by well-designed randomised controlled trials (Article III). As part of this research series, I was then invited to be one of the two general paediatric expert advisors in developing National Institute of Health and Care Excellence (NICE) guidelines (NG1) and supportive information including patient information, an audit tool and costing template, including developing the ten important clinical questions, leading this through stakeholder feedback, robustly interpreting the evidence base to make national guidance and research recommendations (Article IV). I pilot-tested the audit tool locally to ensure that the paediatric department at Poole hospital appropriately recognises 'Red Flag' symptoms for gastro-oesophageal reflux (Article V) and helped develop NICE Quality Standards: a series of evidence-based statements against which clinicians caring for children with reflux could audit their practice. I then led the updating of the Cochrane evidence-base between 2016-2022 using new methodology, having independently extracted the data (Article VI).
The NICE reflux guidance (NG1) research recommendations and Articles III and VI recommendations included better assessments and treatment for GORD in children with neurodisability, such as cerebral palsy. I then undertook a service evaluation of children with neurodisability to understand

how many of them had received treatment for GORD (Article VII), and learned there was a lack of an appropriate symptom tool to evaluate symptoms of GORD in children with neurodisability, given their affected gastrointestinal motility, alternative feeding strategies (e.g. tube feeding), multiple interacting medications, and issues with communication. I have developed a symptom tool based on modification of the PGSQ (Paediatric Gastro-oesophageal Reflux Symptom Questionnaire) and have tested this in the patient population (Article VIII).

Methods: This mixed-methods thesis incorporates secondary data in the form of literature reviews through Oxford Centre for Evidence-Based Research (CEBM), then the Cochrane reviews following standard methodologies (including Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach and primary data collection.

Summary of Results: The studies in this thesis added to the body of knowledge through providing unique evidence for the following:

- There is now a detailed evaluation of the existing literature using Cochrane and NICE methodology to help clinicians best decide how to treat children with GORD.
- The appropriate utility of investigations such as pH/impedance monitoring (effective in linking symptoms with episodes of GOR), endoscopy and barium swallows (do not use to assess GORD) is characterised.
- H2 antagonists and proton pump inhibitors are effective treatments for reflux oesophagitis in children (in terms of symptom relief, improvements of pH/impedance metrics, and oesophageal healing on endoscopy.
- There is evidence of an absence of effect for Domperidone, which has associated risks in adults in terms of QT prolongation, and the prescribing of domperidone has been restricted to specialist use only.
- The NICE audit tool is effective at assessing services' ability to identify children with other causes for symptoms of GORD.
- Children with neurodisability and GORD have a tailored symptom tool for evaluation of their reflux symptoms

Conclusion: The evidence-base contained in this thesis provides a robust foundation for caring for infants and children with GORD and identifies the issues with the current evidence-base for assessing and treating children with neurodisability; who often have more severe GORD, combined with an inability to adequately communicate the degree of discomfort, and are more at risk of

severe complications (vomiting blood/oesophagitis/aspiration pneumonia). This thesis makes further suggestions for future studies, having developed a symptom severity assessment tool in children with neurodisability.

Contents

Appendix 1: **List of Abbreviations:**

ALTE Acute Life-Threatening Event
BMI Body Mass Index
CEBM Centre for Evidence-Based Medicine
CI Confidence Interval
CMPA Cow's Milk Protein Allergy
EMA European Medicines Agency
GI Gastrointestinal
GOR/GER Gastro-oesophageal reflux
GORD/GERD Gastro-oesophageal reflux disease
GP General Practitioner
GRADE Grading of Recommendations, Assessment, Development and Evaluation
H2RA Histamine 2 receptor antagonist
I-GERQ Infant Gastro-oesophageal Reflux Questionnaire
LR+/LR− Positive likelihood ratio/negative likelihood ratio
LRTI Lower respiratory tract infection
MD Mean difference
MHRA Medicines Health Regulatory Authority
NASPGHAN-ESPGHAN North American Society of Paediatric Gastroenterology, Hepatology and Nutrition- European Society of Paediatric Gastroenterology, Hepatology and Nutrition
NCC National Collaborating Centre
NHS National Health Service
NICU Neonatal Intensive Care Unit
NICE National Institute of Health and Care Excellence
NIHR National Institute for Health and Care Research
OA Oesophageal atresia
OR Odds ratio
P-GSQ Paediatric Gastro-oesophageal Reflux Symptom Questionnaire
PEDS-QL Pediatric Quality of Life Questionnaire
pH potential of hydrogen (measure of hydrogen ion concentration in a water-based substance)
PPI Proton Pump Inhibitor
PPV Positive Predictive Value
QALY Quality Adjusted Life Year
PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO International Prospective Register of Systematic Review
PWR Paediatric written request
RCT Randomised Controlled Trial
SD Standard Deviation
SMD Standardised Mean Difference
SIDS Sudden Infant Death Syndrome
UHD University Hospitals Dorset
USA United States of America
WESPGHAN Wessex Society of Paediatric Gastroenterology, Hepatology and Nutrition

List of tables:

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List of publications:

Tighe MP, Afzal NA, Bevan A, Beattie RM. Current pharmacological management of gastro-oesophageal reflux in children. *Pediatric Drugs*. 2009 Jun;11(3):185-202.

Tighe MP, Cullen M, Beattie RM. How to use: a pH study. *Archives of Disease in Childhood-Education and Practice*. 2009 Feb 1;94(1):18-23.

Tighe M, Afzal NA, Bevan A, Hayen A, Munro A, Beattie RM. Pharmacological treatment of children with gastro-oesophageal reflux. *Cochrane Database of Systematic Reviews* 2014, Issue 11. Art. No: CD008550.

NICE guideline: Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people: 14 Jan 2015: www.nice.org.uk/guidance/ng1 (including audit tool)

NICE quality standards: Gastro-oesophageal reflux in children and young people: www.nice.org.uk/guidance/qs112: 28 Jan 2016

Greig, RJE, Tighe MP. "G188 (P) Gastro-oesophageal reflux disease in children: 'Red flags' clinical audit." *Archives of Disease in Childhood* 2017 102 (Suppl 1): A75-A76.

Tighe MP, Andrews E, Liddicoat I, Afzal NA, Hayen A, Beattie RM. Pharmacological treatment of gastro-oesophageal reflux in children. Cochrane Database of Systematic Reviews 2023, Issue 8. Art. No.: CD008550. DOI: 10.1002/14651858.CD008550.pub3.

Britton F, Keast J, Tighe MP: G196 (P) A service evaluation of the pharmacological management of gastro-oesophageal reflux disease (GORD) in children with cerebral palsy (CP), and their communicative ability *Archives of Disease in Childhood* 2017: 102 (Suppl 1): A75-76

Mills S, Tuffrey C, Tbaily L, Tighe MP Modification of the Paediatric Gastro-oesophageal Reflux Disease Symptom and Quality of Life Questionnaire (PGSQ) for children with cerebral palsy: a preliminary study BMJ Paediatrics Open 2024;8:e002256. doi: 10.1136/bmjpo-2023-002256.

Initially published as a poster, and presented at BSPGHAN (2022) Mills S, Tuffrey C, Tbaily L, Tighe MP. G23 Gastro-oesophageal reflux and neuro-disability in CHILDren:(GRaNDCHILD): modification of the P-GSQ for use in children with neuro-disability. *Frontline Gastroenterology* 2022;13(Suppl 1):A1–A57

All the publications are published under licenses allowing re-publication within a doctoral thesis.

Other relevant publications:

Tighe MP, Beattie RM. Managing gastro-oesophageal reflux in infancy (editorial). *Archives of Disease in Childhood* 2010:95: 243-244.

I wrote and edited this review, which helped integrate an RCT assessing a 40° bed for infants with reflux (the Multicare-AR bed) into the existing evidence-base and provided readers with a practical understanding of the likely improvement of GOR symptoms in infants with gastrointestinal maturation and weaning.

Tighe MP, Martin J, Afzal NA. Guideline debrief: GORD in children. Pulse Learning. 2014 http://pulse-learning.co.uk/clinical-modules/gastroenterology/guideline-debrief-gord#

I wrote this module as a learning summary to disseminate awareness of the knowledge base above and help colleagues in primary care understand and manage infants and children with GOR/GORD.

M Tighe, N Afzal, A Bevan, A Hayen, A Munro, M Beattie: G61 Pharmacological treatment for gastro-oesophageal reflux in children: *Archives of Disease in Childhood* Apr 2014, 99 (Suppl 1) A26-A27

This poster summarised the output from article III and was commended as an oral presentation at RCPCH conference 2014.

Chapter 1: Introduction

Gastro-oesophageal reflux can significantly affect a high proportion of infants and young children, causing pain or discomfort, affecting sleep, and is a common problem presenting to clinicians by families seeking symptom relief. Older children with symptoms, and children with other underlying conditions, can continue to have problems persisting through adulthood and are at risk of long-term morbidity and poorer quality of life.

To ensure clarity of the phenomena under study, two clinical definitions are central to this thesis:

- Gastro-oesophageal reflux (GOR) is a common phenomenon, characterised by the effortless regurgitation of gastric contents into the oesophagus (Tighe 2010), and is diagnosed if it occurs frequently or persistently without an underlying cause.
- Gastro-oesophageal reflux disease (GORD) is the term applied when gastro-oesophageal reflux is associated with sequelae or faltering growth (Faubion 1998). Following NICE guidelines and NASPGHAN 2018, significant distress was added as one of the key discriminating features.

The main aims of treatment are to alleviate symptoms, promote normal growth and prevent complications. Conservative treatment options include improving parental understanding, positioning of infants upright after feeds, managing feeding technique and using a prethickened formula.

Medical treatments include:

1) Altering the viscosity of the feeds with alginates (not suitable for prethickened formulae).
2) Altering the gastric pH with antacids, H2-receptor antagonists (ranitidine/famotidine) and Proton Pump Inhibitors (PPIs: omeprazole/lansoprazole).
3) Altering the motility of the gut with prokinetics, such as erythromycin and domperidone (and metoclopramide).

Surgical treatments include fundoplication and options are further discussed below.

Introduction to the patient group:

When considering the patient group, it is important to consider infants and young children under 18 months of age, and then older children as separate groups. Physiological or functional GOR in infants is very common, either in a primary-care or secondary-care setting. Up to 50% of infants less than three months old regurgitate at least one feed daily (Nelson 1997). It tends to improve with age. Most reflux occurs in otherwise healthy, well-grown infants. Nevertheless, it carries a significant

symptom burden and can cause considerable anxiety. Martin (2002) found that less than five percent of children with vomiting or regurgitation in infancy continued to have symptoms after the age of two years, as originally noted by Carre (1959). This is due to a combination of factors including growth in length of the oesophagus, a more upright posture, increased tone of the lower oesophageal sphincter, and a more solid diet. Shepherd et al (1987) assessed 126 children with GORD diagnosed in infancy in a paediatric gastroenterology clinic and showed that 55% were symptom-free by 10 months and 81% by 18 months of age.

For children older than 18 months of age, remaining symptomatic into adulthood is more likely, and the presentation can be a spectrum of symptoms similar to adults, with symptoms such as recurrent epigastric pain and heartburn being expressed. These older children may be more likely to respond to some medications.

Overall, the frequency of families seeking help for reflux-related symptoms is increasing, due to the distress of the baby and impact on family functioning. USA-based administrative claims database estimated an incidence of diagnosis of GORD of 12.3% in infants in 2005 (rising sharply from 3.4% in 2000), and about 1% in older children and adolescents (Nelson 2009). In 2008, a study of French children attending primary care practitioners (GPs) and paediatricians estimated a GORD prevalence of 12.6% for infants, 4.1% for children aged 2–11 years, and 7.6% for adolescents aged 12–17 years (Martigne 2012). Part of the focus of this work is to differentiate between most infants (in whom treatment may be less effective but normally progress to symptom resolution), from older children in whom GORD is likely to persist for many years, but treatment is likely to be more effective.

Why is this work important?

Prior to undertaking this work, many children often had empirical treatment as there was a shortage of evidence, and assessing symptoms is practically difficult. Some of these medications had significant side-effects, and the withdrawal of cisapride due to cardiac arrhythmias brought the treatment of GOR in children into sharp focus for clinicians. GOR still presents a significant burden in NHS primary and secondary care. On an individual patient level: gastro-oesophageal reflux disease (GORD) often presents with vomiting, associated with irritability, excessive crying, disturbed sleep, or respiratory problems. The assessment of severity of GOR based on reported symptoms can be difficult. Episodes of regurgitation are often used by parents as a marker of severity, as is length of crying.

However, how much regurgitation is normal? In one questionnaire-based study of healthy infants seen at routine office visits, daily regurgitation was seen in 67% of four-month-old infants, reducing to 21% at seven months and 5% at 10–12 months of age (Nelson 1997). Even in infants with

more than four episodes of regurgitation a day (considered to be the most affected subgroup), the pattern of resolution was similar with and without treatment. For an older child, similar to adults, transient episodes of GOR are common, but the oesophagus should be exposed to acid (pH<4) less than 4% in 24hr.

Also, how much crying is normal in infants? Studies of healthy infants assessing average daily duration showed a peak in the second month of life at 2–2.5 h/day, decreasing thereafter to a mean of one hour/day in infants at 4–12 months of age (St James-Roberts 1991, Tremblay 2006). However, 29% of infants less than three months of age appeared to form a subgroup that cried for over 3 h per day. Nevertheless, when this cohort was 3–12 months old, less than 10% of infants cried for more than three hours per day (St James-Roberts 1991). Night-time waking may however be more marked in infants with GOR: in one study 3–12-month-old infants with acid reflux confirmed on 24 hr oesophageal pH study, were compared to a 'normal' infant population and 50% (vs 13%; p<0.0001) were found to wake more than three times a night (Ghaem 1993). Contextualising the normal range of crying with other symptoms (night-time waking or regurgitation) is useful for clinicians quantifying for families the likelihood of clinical improvement with any treatment for GOR or GORD.

A diagnosis of GOR following evaluation is usually based on the infant's symptom profile and its impact, with further investigation reserved for infants with symptoms in whom the diagnosis is not clear or for children with suspected GORD in whom investigations may impact on treatment. It is however important to be aware of the wide differential diagnosis of regurgitation/vomiting in infancy, and prior to undertaking work in this area, many infants may have had other causes for vomiting misdiagnosed as reflux or had treatment 'for presumed GOR' to try to mitigate normal crying.

The diagnosis of GOR should be distinguished from GOR disease (GORD) which has recently been defined by international consensus as 'GOR associated with troublesome symptoms or complications', although this definition is complicated by unreliable and inconsistent reporting of 'troublesome' symptoms in infants, and hence the distinction between the diagnosis of GOR and GOR disease can be quite difficult (Sherman 2009).

Gastrointestinal complications of GORD include oesophagitis, haematemesis, oesophageal stricture formation, and Barrett's oesophagitis. Severe oesophagitis at presentation has been identified as a risk factor for persistent GORD (Hyams 1998) and oesophageal strictures from GORD in childhood have been reported (Salvatore 2006). Long-term GORD can predispose to metaplastic changes in the oesophagus and then oesophageal cancer. Extra-intestinal manifestations of GORD include chronic otitis media, sinusitis, anaemia, apnoea and chronic respiratory disease (NICE 2015, NASPGHAN-ESPGHAN 2018).

The presence of complications is more helpful in making the distinction between GOR and GORD and includes faltering growth, food refusal, and oesophagitis with pain and haematemesis. GORD is much more common in infants and children with coexisting problems, such as asthma, cerebral palsy, epilepsy and congenital heart disease, and may be part of a complex interaction of pathologies as a primary or secondary phenomenon. Prior to undertaking this work, there was no research in high-risk subgroups such as children with neurodisability, which can be a significant burden in OPD clinic or inpatient settings, and a significant contributor to the volume of children referred for fundoplication (a surgical operation to reduce oesophageal exposure to acid by augmenting the lower oesophageal sphincter).

Patients with additional risk factors for severe GORD include neurological impairment (e.g. cerebral palsy), repaired oesophageal atresia (OA) or congenital diaphragmatic hernia and chronic respiratory disease. In many of these children, the GORD is a manifestation of an underlying whole gut motility disorder. Children with severe GORD and impaired swallow can aspirate, causing pneumonia and early mortality.

Introduction to setting, and management options:

Most paediatric patients are managed as outpatients in primary, secondary and tertiary care. Children may occasionally have a day-case investigative procedure such as pH/impedance monitoring or upper gastrointestinal endoscopy or are admitted to hospital with sequelae of GORD, such as failure to gain weight in infants, haematemesis or food bolus obstruction in otherwise well children, or pneumonias secondary to aspiration in children with cerebral palsy.

The practical management of diagnosed GOR is an important issue for paediatricians, primary care physicians and allied healthcare professionals. There is little evidence to support the pharmacological management of diagnosed GOR as a first-line strategy. The principle of 'primum non nocere' (first, do no harm) should apply in the management of parental expectations regarding the natural history of diagnosed GOR, and conservative measures should be tried before H2 antagonists, proton pump inhibitors or prokinetic agents are introduced.

Positioning of infants has been evaluated both in terms of angle of inclination and body position (prone/supine/on side). Prone positioning, particularly at 30°, has previously been shown to improve regurgitation and acid reflux (Meyers 1982, Vandenplas 1985). However, prone positioning is currently not recommended due to the increased risk of sudden infant death syndrome (SIDS) compared to the supine position (Mitchell 1997). Similarly, the side sleeping position (right or left lateral) has also been found to have an increased risk of SIDS compared to the supine. Supine positioning has previously been attempted at 10°, and at 30° by Meyers 1982 and Bagucka 1999, with no symptomatic improvement.

A Cochrane review (Craig 2004) of simple strategies for the management of GOR assessed 20 trials (n=771 children with GOR). Five assessed positioning, and eight assessed thickened feeds. All children within the selected studies were developmentally normal. Of the five positioning studies, all utilised oesophageal pH monitoring as their outcome measure. The authors noted that comparisons were limited, and summary conclusions were often based on two or three studies. Two studies assessed children in seats at 60°, one study compared the prone horizontal position to prone at 30° elevation, one study utilised the 10° elevation and one study utilised different positions (prone, supine, right and left lateral) over 48 h, when positioned at 30° elevation and horizontally. No clear pattern emerged from these trials to inform advice on positioning, with the Cochrane review concluding that elevating the head of the bed for treating reflux in the supine position was not justifiable based on oesophageal pH data. However, Cochrane criteria exclude non-RCT based trials and did not assess the impact of positioning on symptoms.

The Cochrane review also assessed the effect of thickened feeds and demonstrated a reduction in regurgitation severity score (standardised mean difference (SMD) −0.94; 95% CI −1.35 to −0.52) and regurgitation frequency (SMD −0.91; 95% CI −1.22 to −0.61). However, on oesophageal pH study the reflux index was not reduced (weighted mean difference (WMD) 0.48%; 95% CI −3.27 to 4.23).

Other clinically effective simple strategies for diagnosed GOR include reducing feed volumes if greater than 150 ml/kg/day, and a two-week trial of a hydrolysed formula if there is a family history or features suggestive of cow's milk protein allergy (Nielsen 2004). Orenstein and McGowan (2008) demonstrated a 78% improvement in the I-GER-Q score of 50 infants with GOR when a nurse provided information on feeding modifications, positioning and tobacco smoke avoidance ($p<0.0001$) over a two-week period. Of these 50 infants, 59% improved their I-GER-Q score by five points and 24% to within the normal range. Parents were advised to position their infants prone, except in situations where current health promotion advice applies, such as when using a car seat for travelling or placing the infant to sleep. Feeding modifications included feeding at 120 ml/kg/day, a trial of a thickened hydrolysed formula in formula-fed infants, and for breast-feeding infants, a trial of a diet free of cow's milk and soya was advised for their mothers.

In summary, diagnosed GOR is common. Practical management includes positioning, avoidance of overfeeding, and consideration of thickening feeds. A period of cow's milk exclusion can be considered if the symptom burden is high. These strategies should be evaluated before investigation or empirical pharmacological therapies are considered. The benign prognosis needs to be emphasised.

In terms of medical management of infants and children with GORD (Tighe 2010): the evidence for treatments can be considered according to age, with infants much more likely to grow out of their diagnosed GOR, and so treating symptoms whilst allowing for physiological improvement in gut motility and improving parental/carer understanding is key. In children older than 1 year, where reflux-related symptoms are more likely to improve with treatment, but untreated symptoms are more likely to give long-term sequelae, there is a greater quality evidence of efficacy of treatment. According to the proposed mechanism of action, reducing regurgitation through thickening feeds e.g. with alginates can reduce the degree of regurgitation but may not improve pain/distress. Proton pump inhibitors and H2 antagonists can reduce oesophageal acid and improve oesophageal healing, so aiming to reduce distress, but may not alter the degree of regurgitation. Prokinetics aim to empty the stomach quicker: reducing reflux as more of the stomach contents enter the small bowel. No cost-effectiveness analyses have been undertaken regarding the relative costs of treatment in children, and this work below outlines in detail the relative efficacy based on the available evidence based on Oxford CEBM and Cochrane methodology, embedded within NICE guidance. Overall, the detailed evaluation of the literature revealed a low certainty of evidence, with some evidence for PPIs especially in children over one year of age. There was no evidence of efficacy for prokinetics, and no evidence available for children with neurodisability.

For children needing fundoplication, NICE identified no cost-effectiveness data in children, but in adults, the average discounted lifetime cost per patient of surgery was £5026, made up of the initial cost of the cost of surgery (£2132), repair of surgery (£746), return to medical management (£1360) and other health care (£788), and provides an incremental cost effectiveness ratio of £2648 (€3110; US$4385) per quality adjusted life year (which is likely to be lower in children due to their increased life-span.

Introduction to author: As a paediatric consultant with a special interest in paediatric gastroenterology, I have over 20 years' experience of caring for children with GORD as well as having undertaken detailed work in this area to improve understanding and treatment, both through developing guidelines and expanding the literature base. Currently GORD is a very common condition causing distress to babies, children and families affecting 50% of all babies and 1% of children. I've experienced the practical implications of paediatric care with a lack of knowledge and individual care with rapidly escalating empirical treatments and referral of refractory children for consideration of fundoplication. Since the publication of the Cochrane reviews and NICE guidance the number of prescriptions for domperidone and erythromycin has fallen significantly, except in the neurodisability population (Wood 2016), the number of barium swallows requested for reflux has reduced (Hart 2007,2010), as well as the number of reflux-related admissions.

Children with neurodisability remain a vulnerable subset and I care for children with neurodisability, such as cerebral palsy and Rett syndrome, who have had multiple admissions with life-threatening reflux-related complications such as haematemesis and aspiration pneumonia as well as daily pain and distress affecting both their and their families' quality of life. If we are to design better treatment protocols for these children, robust outcome measures are needed that reflect the range of difficulties in children with neurodisabilities, and demonstrate improved accuracy of assessment. I'm proud of this body of work, undertaken over 15 years, which demonstrates a field of endeavour to improve the life of children with reflux across a range of metrics through robust literature appraisal, wide dissemination through NICE and Cochrane, establishment of an audit gold standard, and further focus to address a particular highly-vulnerable group under-represented by research. This body of work is arranged in order of dates of publication, showing the development of the knowledge-base in addressing different dimensions of this difficult clinical presentation. Where citations or downloads are mentioned, they are correct as of 15th September 2023.

Figure 1.1 Cohesion of articles

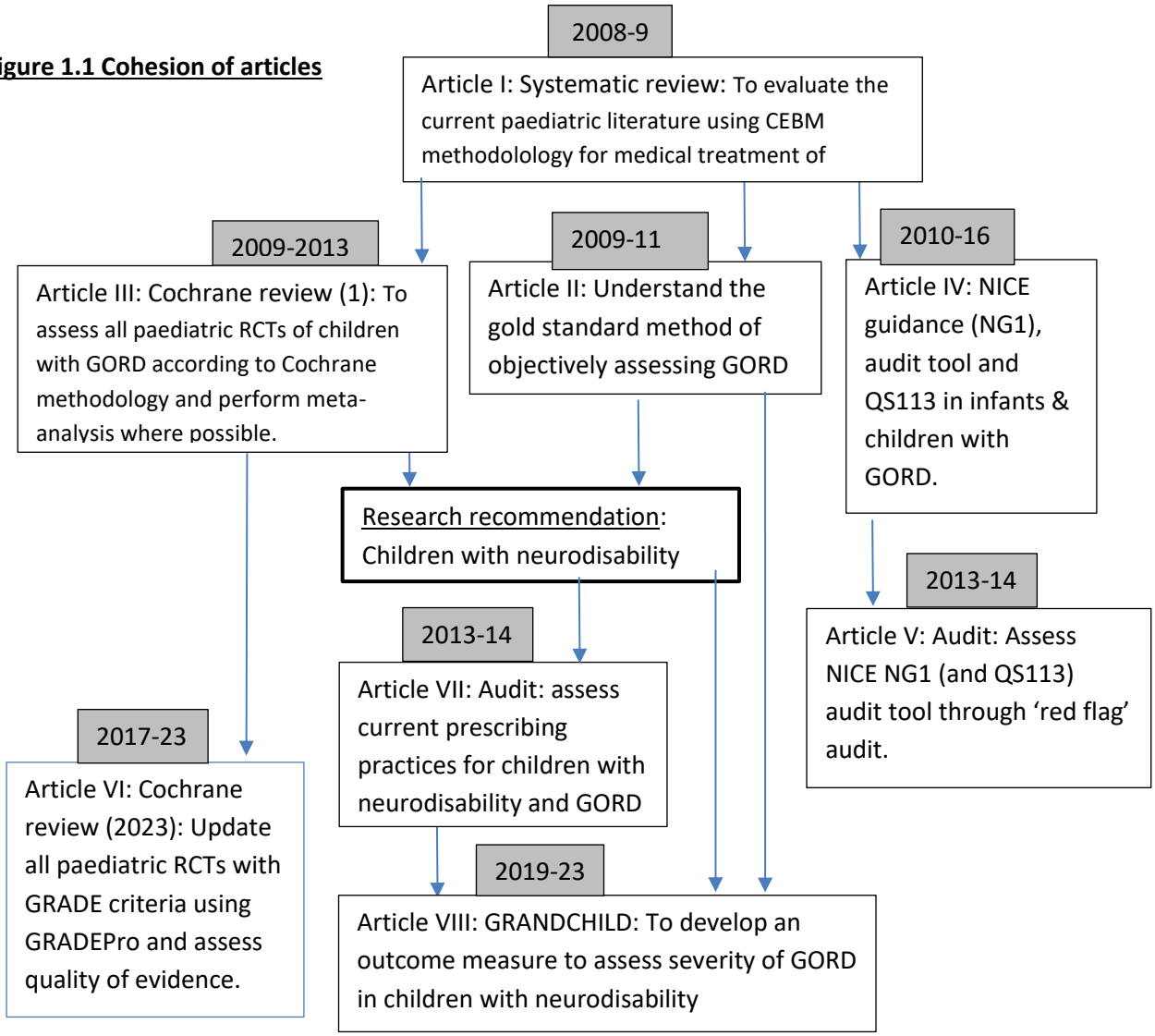
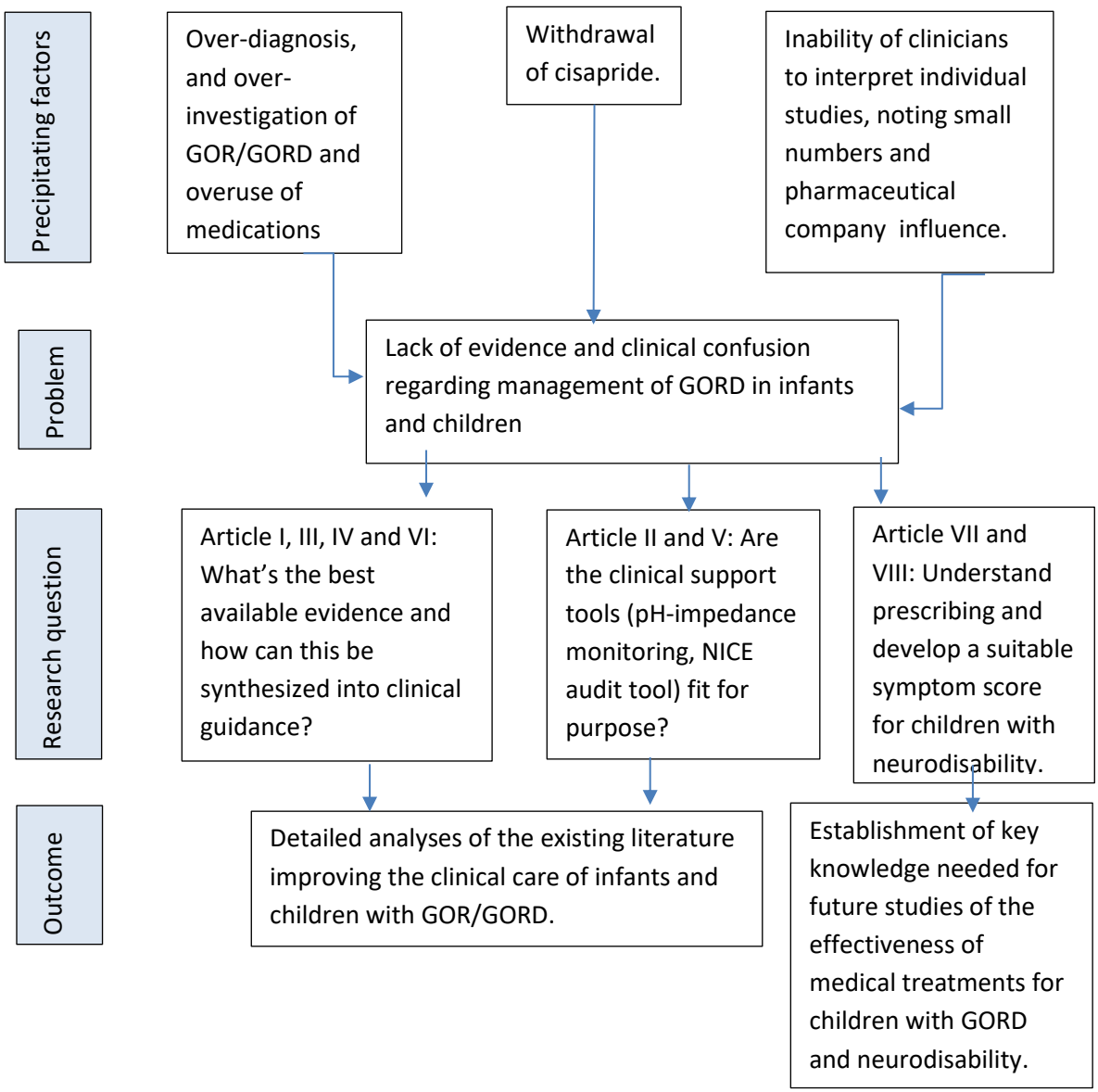


Figure 1.2: Timeline of publications:

Study	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
I																
II																
III																
IV																
V																
VI																
VII																
VIII																

Figure 1.3: Schematic summary of thesis:



Chapter 2: Methodology and Methods:

Philosophy of thesis: In this thesis, I take a positivist conceptual framework and use a deductive approach using a mixed-methods methodology to identify and analyse the mainly quantitative data, with some qualitative data. The positivist framework is based on observable clinical phenomena (symptoms and investigation results) allowing the generation of objective quantitative data, and parental/clinician opinions form the basis of the qualitative data. The data arises from secondary analysis of clinical trials (Articles I, II, III, IV) and primary data collection (V, VI, VII, and VIII), with Articles I-VIII providing quantitative data and Articles VII and VIII providing additional qualitative data. Central to this corpus of knowledge is evaluating the quality of evidence of studies assessing children with functional GOR and GORD, which underpins the recommendations for care. This allowed identification of the areas of agreement, and areas of further work needed. Whilst this thesis is primarily based on a medical model of care, there are aspects of the thesis that draws on a psychosocial focus of individual behaviours and perceptions (such as the understanding of the normal range of crying infants and parental/carer views) underpinned by data analysis. Figure 1.2 outlines the timelines of the included papers; while Articles I and II are more than 10years from publication, they are included, as Article I contains a breadth of articles not included in Articles III and VI, including cohort and case-control studies that would be excluded by Cochrane and NICE methods, and so adds an additional dimension to the evidence considered elsewhere, and Article II reviews in detail this key investigation of acid reflux, highlighting the strengths and drawbacks and allowing clinicians and parents to better understand how this quantifiable outcome links to symptoms and symptom scores.

Article I outlines the Levels of Evidence adopted by the Oxford Centre for Evidence-based Medicine. This review critically appraised the paediatric evidence base for the medical treatment of GOR Grades of recommendation are included based on the level of evidence (Figure 1).

Figure 2.1: Levels of Evidence Grades of Recommendation

Level	Therapy		**Grade**	
1a	Systematic Review (SR) (homogeneity of RCTs)		**A**	consistent level 1 studies
1b	Individual RCT (with narrow Confidence Interval)		**B**	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
2a	SR (with homogeneity) of cohort studies		**C**	level 4 studies ***or*** extrapolations from level 2 or 3 studies
2b	Individual cohort study (+ low quality RCT;		**D**	level 5 evidence ***or*** troublingly inconsistent or

	e.g., <80% follow-up)			inconclusive studies of any level
3a	SR (with homogeneity) of case-control studies			
3b	Individual Case-Control Study			
4	Case-series (and poor quality cohort and case-control studies)			
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"			(Phillips 2001)[i]

I designed the search strategy in Article I and agreed it in advance with the other authors, and searched PubMed, Adis, Medline, Embase and then handsearched reviews from the past 5 years for the key words “gastro-oesophageal (or gastroesophageal), reflux, oesophagitis, and child$ (or infant) and drug$ or therapy” for articles up to 2009. I included articles in English with an abstract. Reviews were excluded but hand searched. Abstracts only were excluded. All authors then reviewed the output (74 papers) collectively face to face and excluded full papers if the treatment group was adult (>16 years old), if the treatment was either conservative (e.g. dietary) or surgical, or gastro-oesophageal reflux was not the main focus of the article. Studies on cisapride were excluded as cisapride has now been withdrawn due to a MHRA alert related to arrhythmias. The remaining papers were graded according to the CEBM criteria above. Any disagreement was resolved with discussion with the other pair. The overall impression was how small the evidence-base was, and the risk of significant bias, which was captured within the systematic review. Whilst the risk of bias was articulated, only some articles could be downgraded if serious bias was identified using the CEBM methodology. Figure Two shows the PRISMA diagram outcome of the search, excluded papers by reason for exclusion and number of papers selected for review.

The studies were assessed for all reported outcomes that are meaningful to clinicians making decisions about treating gastro-oesophageal reflux. This included impact of clinical symptoms, pH study profile and oesophageal appearance at endoscopy. The available evidence for each treatment was appraised, and treatment-specific clinical bottom-lines generated, with relevant readable conclusions for the clinician. I identified the key role of pH-impedance monitoring in providing objective evidence of acid reflux, and the absence of a synthesized guide for clinicians for infants and children and sought to address this in Article II. I also noted the importance of RCTs in decision-making, and considered a Cochrane review would help to focus the evidence-base using RCTs in article III.

For Article II: How to use a pH-probe: I undertook a literature review using Embase and Medline searching for the terms “gastro-oesophageal (or gastroesophageal), reflux, oesophagitis, and (child$ or infant) and investigation$ or pH or pH/impedance” up to 2010. I also developed, and agreed with the other co-authors, key clinical questions to address and key clinical bottom-lines for each section so the reading clinician was able to take the distilled evidence to make informed judgements.

For Article III: All randomised controlled trials (RCTs) were considered and evaluated, and the search strategy was undertaken by Cochrane Gut and is published within the article (please refer to the article due to length) as well as the PRISMA diagram. The methods section within the article is detailed and extensive and I’ve used this section to highlight the changes as the article was developed. The initial review protocol was submitted in 2008 and based on peer review, which was supportive, Cochrane advised the group to not assess thickeners or cisapride (alginates were included as available on prescription and some have antacid properties), but to include open label / randomized trials that included objective assessments of pre- and post-intervention criteria. All children (birth to 16 years) were included. I analysed data on all children younger than 16 years of age with 'GOR associated with troublesome symptoms or complications.' Subgroup analysis was undertaken in two groups: infants younger than 12 months of age, and children between 12 months and 16 years of age. Studies assessing pharmacological treatments for children with GORD with co-existent conditions such as tracheo-oesophageal fistula (TEF) or asthma that predispose to GORD were excluded to avoid heterogeneity between participants.

Types of interventions: All currently available medical treatments for gastro-oesophageal reflux in children were included in this review, with all randomised controlled trials considered— including those that compare the medication in question versus placebo or versus other medications. Metoclopramide and thickened feeds had already been assessed in 2007, as discussed above (Craig 2007), and were excluded.

Types of outcome measures: All reported outcomes likely to be meaningful to clinicians (such as general practitioners and paediatricians) were included. Primary outcome included clinical symptoms and adverse events. Secondary outcomes included investigations (including 24-Hour pH probe and/or impedance studies, and endoscopy with histology). Outcome measures on investigation included reflux index on pH/impedance probe (percentage of time with oesophageal pH < 4) and number of reflux episodes, and macroscopic appearance of oesophagus and histological evidence of GORD through endoscopy. In cases of uncertainty, corresponding authors were

contacted for clarification. Search methods for identification and selection of studies, and data collection, extraction and analysis are included in the methods section of the article.

This methodology was agreed with Cochrane Gut and was subject to significant change in article VI.

For Article IV: **NICE guidance**: The Guideline development (GD) methodology outlined here is adapted from the GD Process – Information for National Collaborating Centres and GD Groups (available at www.nice.org.uk) and commissioned by NICE.

Developing review questions and protocols and identifying evidence: The GD group including myself formulated review questions based on the given scope (limited to 9-10) and prepared a protocol for each review question (see Appendix E). These became the basis for systematic reviews of relevant evidence. Published evidence was identified by applying systematic search strategies to databases: Medline (1948 onwards), Embase (1980 onwards) and 4 Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects and the Health Technology Assessment [HTA] database) with an inclusion of economic studies using the above databases and the NHS Economic Evaluation Database (NHS EED). 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 and I was able to integrate the studies identified by the Cochrane review I was leading in parallel. This process was completed by April 2014.

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 study design, limitations in the design or execution of the study (including concealment of allocation, blinding, loss to follow up), inconsistency of effects across studies, indirectness of the available evidence to the specific review question, imprecision (the confidence in the estimate of effect) which can affect the rating of quality of evidence and was useful for Article VI. For continuous variables, the guideline development (GD) group predefined minimally important differences (the smallest difference between treatments that healthcare professionals or patients think is clinically beneficial). For each review question the highest available level of evidence was sought; 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. Using the GRADE approach, a body of evidence based entirely on such studies has an initial quality rating of high, which may be

downgraded 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 as 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, and pooled effect sizes presented as pooled risk ratios (RRs), pooled odds ratios (ORs) or weighted mean differences. By default, meta-analyses were conducted by fitting fixed effects models, but where statistically significant heterogeneity was identified, random effects models were used to investigate the impact of the heterogeneity. Where quantitative meta-analysis could not be undertaken (for example because of heterogeneity in the included studies) the range of effect sizes reported in the included studies was presented.

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

Outcome measures: For this guideline, the review questions were judged on a number of outcomes. The justification was based on their relevance and consensus among members of the GD group and 7 or 8 outcomes for each review question were selected when assessing the effectiveness of a particular treatment. The health economic input to the guideline informed the GD group of new economic issues relating to reflux in children and young people, and to consider whether the recommendations continued to represent a cost-effective use of healthcare resources (ideally in terms of quality adjusted life years [QALYs]), harms and costs of different care options. A number of clinical questions were prioritised where it was thought that economic considerations would be particularly important in formulating recommendations (• antacids/alginates • H2-receptor antagonists • proton pump inhibitors • prokinetic agents • enteral tube feeding • fundoplication surgery).

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 GD group to agree short clinical and, where appropriate, cost effectiveness

evidence statements which were presented alongside the evidence profiles. Statements summarising our 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 GD group also identified areas where evidence to answer its review questions was lacking and used this information to formulate recommendations for future research. 9 'key priorities for implementation' (key recommendations) were identified and 3 high priority research recommendations.

For Article V: Following developing the NICE audit tool, I undertook this study of East Dorset patients with the aim of evaluating the NICE audit tool in a moderate-sized district general hospital (DGH). I wanted to improve the robustness of assessment of vomiting children, which may have causes other than reflux. I registered our audit with our audit department and designed the search strategy using ICD-10 coding. From the hospital patient identification numbers, with a trainee, I selected a random sample of 30 paediatric inpatients aged <1 year with a new diagnosis of GORD (April 2015 to April 2016) presenting to a moderate sized DGH (6000 paediatric admissions per annum). The paper and computer notes were reviewed by myself and the trainee, and data was inputted into the NICE audit tool. This was the first published audit using the NICE audit tool for GORD, and first assessment of how a moderate-sized DGH assesses for red-flags in GORD.

For Article VI: Having undertaken the review in Article III, this re-review was separated by 6 years from the previous Cochrane review and was significantly different, with different software platforms, use of GRADE criteria to assess and adjust the quality of evidence and adherence to MECIR recommendations. As with Article III, the methods section within the article is detailed and extensive and I've used this section to highlight the differences with the previous review, which included:

- Data collection and analysis: Review Manager 5.4 and RevMan Web were used for data collection and analysis, updated from RevMan 5.1.
- Selection of studies: Reprints of articles were added to the reference list of included studies but not separately considered if they contained no new data. In the previous review articles reprints were discounted. Studies that are only in abstract form or were only identified in the ISRCTN register were entered into characteristics of studies awaiting classification.

- Participants were slightly altered compared to the previous review as the definition of GORD changed in 2018 to 'GOR associated with bothersome symptoms or complications' (NASPGHAN-ESPGHAN guidelines 2018).

- Outcomes: The outcome of 'pH/impedance studies' to 'pH/impedance indices' to account for the range of pH/impedance measurements described in the available literature were redesignated.

- Data extraction and management: I guided two other authors in independently extracting study data using a new robust data extraction form and checked and entered the data into RevMan 5.4/RevMan Web. I also led the two other authors in analysing the data, evaluating for bias and highlighting any discrepancies. Midway through the re-review: the introduction of MECIR recommendations led to a significant updating during the submission process. In the previous review I and one other author extracted and entered study data onto RevMan 5.1. Cochrane recommended not to reference every single rejected article, rather focusing on the important rejected articles.

- Measures of treatment effect: I extracted continuous data (e.g. reflux index) for summary data: with means and standard deviations to derive a standardised mean difference (SMD) with a 95% confidence interval using a fixed-effect model. The latest NASPGHAN/ESPGHAN (2018) guidelines do not define normal values for pH- and pH-impedance studies and the values of reflux index mentioned in the previous review (>10% in infants and >4% in children >12 months) have been modified here with a judgement regarding improvement/ non-improvement. Dichotomous data: such as improvement/non-improvement in endoscopic appearance produced outcome data that is presented as a risk ratio, and from which 'numbers needed to treat for an additional beneficial outcome' data were derived. In the previous review, reported data rather than independently extracting summary data was used.

- Unit of analysis issues: Issues related to multiple observations for the same outcome (e.g. repeated pH/impedance measurements) were considered; and the Cochrane Gut group offered to assist if clarification was required. If multi-arm studies are included, multiple intervention groups would be analysed in an appropriate way to prevent arbitrary omission of relevant groups or double counting of participants. In the previous review: there was some overlap in reported data e.g. according to age criteria: corrected in this review.

- Dealing with missing data: I contacted trial authors or sponsors of studies published from 2014 to 2021 to provide missing data, or clarification, where there was uncertainty about the specifics of a trial that are pertinent to analysis, could not be resolved. In the previous review: contacting authors was limited to studies less than 10 years old.

- Data synthesis: Combining studies meaningfully was not possible, due to heterogeneity of studies in terms of outcomes, comparisons, and populations. Continuous measurements would have been assessed using weighted mean differences to pool results from studies where a common measurement scale was used, and where different measurement scales have been employed, to pool standardised mean differences. Instead, difference in means and 95% confidence intervals were presented for individual agents and summary effects presented in order: Population > Comparison > Outcome following updated guidance in the current Cochrane review, and provided guidance based on individual treatments (rather than classes of treatments) to give better focus for decision-makers, and given the individual study differences and heterogeneity in study design. This differs significantly from the previous review.

- Sensitivity analysis: Where meta-analysis was required, a plan to undertake a sensitivity analysis using RevMan Web was included, to ascertain whether any decisions regarding thresholds influence result reporting (e.g. choosing age thresholds at 12 months influencing meta-analysis robustness) and integrate the findings into the results and conclusions. This was not considered in the previous review. However, a meta-analysis was not possible, and sensitivity analysis not required.

- Summary of findings and assessment of the certainty of the evidence: I led another author in using the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence for each outcome, and to draw conclusions about the certainty of evidence within the text of the review independently and disagreements reconciled by discussion, with all authors involved if a disagreement could not be reconciled. All authors then reviewed the GRADE considerations in assessing the certainty of evidence and integrated this into the SoF tables. The summary of findings tables distinguish results by age (infants and children aged 1-16 years), then comparison, and the evidence is presented by outcome measures (symptoms, adverse events, pH/impedance indices and endoscopic findings) (MECIR PR40) with clear rationales given where evidence was down or upgraded according to GRADE criteria including if the risk of bias was so great the evidence needed downgrading by two steps.

- Literature search in this update: In this updated version, I searched for WHO ITCPR and clinicaltrials.gov as suggested by MECIR, and also revisited the search strategies and added some new terms to reflect the current practice of treatment in the updated search.

Article VII: Having established the importance of further evidence in children with neurodisability (e.g. cerebral palsy) through NICE guidance and audit (articles IV, V) and the Cochrane reviews

(Articles III and VI), I wanted to plan an RCT to assess the best medications for children with GORD and needed more information regarding our study cohort (medication prevalence and communicative ability). This audit identified a cohort of children with cerebral palsy in East Dorset through use of coding data for all admissions over an 11-year period, and the data was cross-checked with clinicians caring for these children as they all need regular medical follow-up. Our coding department identified all children in East Dorset (~85,000 children) with an ICD-10 diagnosis of CP (G80) and GORD (K21), admitted between 01/01/05 and 31/12/15. 54 children with CP and GORD were identified; their hospital records were reviewed and collected data using a proforma on the anti-reflux medication prescribed, the length of time on each medication and their communicative ability, and the data was anonymised. The progress of these patients was captured; eight of 54 had died, mainly due to respiratory and gastrointestinal complications. It was important to capture how long these patients remained on medications for, and the range of communicative abilities, that then fed through into future study design.

Article VIII: An RCT was considered to assess the efficacy of treatments for children with neurodisability and GORD. I also led a NIHR Research for Patient Benefit bid to fund this RCT. I had outlined using an outcome questionnaire (P-GSQ) to assess improvements in symptoms, following patient and public involvement in study design. Unfortunately, we were unsuccessful, and feedback raised the issue of not having a validated outcome questionnaire in this subpopulation given their communicative ability and symptom profile was so different. As part of the patient-public involvement, we had offered parents (of children with neurodisability) example questionnaires such as the P-GSQ, PEDS-QL, KIDSCREEN and the I-GERQ, and families felt the design and shorter nature of the P-GSQ was more suited, given how time-pressured they were in looking after their children. However, families felt that the nature of the P-GSQ questions needed more adaptation, given the significant disabilities their children faced. I therefore wanted to modify the P-GSQ for use in this subgroup. Following stakeholder feedback (involved parents at a local special school) and contacting the owners of the intellectual property for the P-GSQ (Takeda), I achieved NIHR portfolio adoption for this validation study and a £5000 grant from BSPGHAN to support this work. All children with cerebral palsy (GMFCS level III-V) with symptoms of GORD or on treatment for presumed GORD and aged between 2-16 years were included. Exclusion criteria included children whose parent(s)/guardian(s) were not able to support their participation in the study in the opinion of the investigator (e.g. language/communication issues, health, burden). Symptom assessments through questionnaires are validated and currently our most frequently used research tool in assessing improvement in normally developing children. The Paediatric Gastro-oesophageal Reflux Symptom

Questionnaire (P-GSQ) takes on average 7 minutes to complete in typically developing children and is specific to either infants (not assessed in this trial), children or young people. The questions are very similar between the age groups, with the phrasing only taking account of the age differences. Given the communication issues identified in article VIII, the proxy version of the P-GSQ for parents was most likely to be used, and preferred by parents and carers, and was selected for modification. Permission was sought from Takeda (developers of PGSQ) to modify the existing questionnaire. Those who were eligible for recruitment were given the opportunity to participate either by phone, in clinic or by letter. Structured interviews were carried out by members of the research team trained in cognitive interview methods. Prior to the questionnaire, a standardised script was read to the participants detailing the purpose of the study to ensure that all parents/caregivers received the same information. Interviews were recorded and transcribed using Microsoft Teams or WinScribe. Participants were asked to consider the following for each question: understanding, retrieval of information, judgement, response, and construct. A copy of the questions asked during the interviews can be found in Figure 7.1. Development and modification of the questionnaire progressed using the 'talk-aloud' technique described by Willis et al. (14). This involved the participants talking through their thoughts as they read the questions which allowed us to assess their interpretation of the existing symptom questionnaire. For each individual question, it was ascertained whether they reflected important and different dimensions of the condition in our patient group. Questions were altered based on parent/carer response. Reasons for modifications included: questions repeatedly reported as not relevant, questions that were confusing or difficult to understand and questions where none of the response choices applied to this group of children. This allowed relevant adjustments of the assessment tool to better fit this subgroup of patients considering their communication issues and associated pathologies. Modifications continued until there were no further issues identified or improvements suggested.

Chapter 3: Results

Article I: Current Pharmacological Management of gastro-oesophageal reflux in children: an evidence-based systematic review.

Tighe MP, Afzal NA, Bevan A and Beattie RM, 2009. Current Pharmacological Management of Gastro-Esophageal Reflux in Children. *Pediatric Drugs*, 11 (3), 185-202. https://doi.org/10.2165/00148581-200911030-00004

What does this paper achieve?

In 2009 I designed and ran a systematic review of the paediatric literature assessing the medical management of GORD. This included co-ordinating the literature appraisals, and grading the evidence adopted by the Oxford Centre for Evidence-based Medicine (CEBM) to form consensus guidance to improve decision-making around prescribing and flow-charts to help clinicians managing babies and children with GOR. It has been cited 62 times in other publications (as of September 2023).

How does it contribute to the evidence-base?

This provided the first summary of all available evidence, both RCT-based and non-RCT studies, and tried to draw out specific conclusions and next steps, including consensus guidance for clinicians. It articulated a stepwise approach to treatment, highlighted the importance of differentiating between infants with functional GOR, who are likely to grow out of their symptoms, and older children who are likely to have symptoms and sequelae similar to adults, but are also more likely to benefit from treatment. All the studies were graded according to CEBM methodology and provided the clinicians with an evaluation regarding the strength of evidence for each medical intervention.

What were the next steps?

There were some weaknesses in this approach, as it became evident that many of the studies had potentially significant biases related to pharmaceutical support, with significant evidence of manuscript writing, and in some cases, post-hoc outcome assessment, and Cochrane methodology (Article III) would better be able to articulate the biases and modify the strength of evidence assessment accordingly. Also, by only including RCTs, the quality of the evidence assessed, and derived conclusions was likely to be more robust. The software, RevMan 5.1, would be specifically designed for this analysis. I also needed to understand the role and evidence for the 'gold-standard' investigation (24hr pH-impedance monitoring) which is explored in Article II.

REVIEW ARTICLE

Pediatr Drugs 2009; 11 (3): 185-202
1174-5878/09/0003-0185/$49.95/0

Current Pharmacological Management of Gastro-Esophageal Reflux in Children

An Evidence-Based Systematic Review

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Contents

Abstract

Gastro-esophageal reflux (GER) is a common phenomenon, characterized by the regurgitation of the gastric contents into the esophagus. Gastro-esophageal reflux disease (GERD) is the term applied when GER is associated with sequelae or faltering growth.

The main aims of treatment are to alleviate symptoms, promote normal growth, and prevent complications. Medical treatments for children include (i) altering the viscosity of the feeds with alginates; (ii) altering the gastric pH with antacids, histamine H_2 receptor antagonists, and proton pump inhibitors; and (iii) altering the motility of the gut with prokinetics, such as metoclopramide and domperidone.

Our aim was to systematically review the evidence base for the medical treatment of gastro-oesophageal reflux in children. We searched PubMed, AdisOnline, MEDLINE, and EMBASE, and then manually searched reviews from the past 5 years using the key words 'gastro-esophageal' (or 'gastroesophageal'), 'reflux', 'esophagitis', and 'child$' (or 'infant') and 'drug$' or 'therapy'. Articles included were in English and had an abstract. We used the levels of evidence adopted by the Centre for Evidence-Based Medicine in Oxford to assess the studies for all reported outcomes that were meaningful to clinicians making decisions about treatment. This included the impact of clinical symptoms, pH study profile, and esophageal appearance at endoscopy.

Five hundred and eight articles were reviewed, of which 56 papers were original, relevant clinical trials. These were assessed further. Many of the studies considered had significant methodological flaws, although based on available evidence the following statements can be made. For infant GERD, ranitidine and omeprazole and probably lansoprazole are safe and effective medications, which promote symptomatic relief, and endoscopic and histological healing of esophagitis. Gaviscon® Infant sachets are safe and can improve symptoms of reflux. There is less evidence to support the use of domperidone or metoclopramide. More evidence is needed before other anti-reflux medications can be recommended. For older children, acid suppression is the mainstay of treatment. The largest evidence base supports the early use of H_2 receptor antagonists or proton pump inhibitors.

Gastro-esophageal reflux (GER) is characterized by the effortless regurgitation of gastric contents into the esophagus. GER classically presents with effortless vomiting, in an otherwise well child with normal growth (physiological reflux).[1] Gastro-esophageal reflux disease (GERD) is defined as GER associated with sequelae or faltering growth.[2] GERD often presents with vomiting, associated with irritability, excessive crying, disturbed sleep, or respiratory problems. Gastrointestinal complications of GERD include esophagitis, hematemesis, esophageal stricture formation, and Barrett's esophagitis. Extra-intestinal manifestations of GERD include chronic otitis media, sinusitis, anemia, apnea, and chronic respiratory disease.

Physiological or straightforward GER is very common, in both primary- and secondary-care settings. Up to 50% of infants aged <3 months[3] regurgitate at least one feed daily. GER tends to improve with age. Martin et al.[4] found that <5% of children with vomiting or regurgitation in infancy continued to have symptoms after the age of 2 years, as originally noted by Carre.[5] This is due to a combination of factors, including growth in length of the esophagus, a more upright posture, increased tone of the lower esophageal sphincter, and a more solid diet. Shepherd et al.[6] assessed 126 children with GERD diagnosed in infancy in a pediatric gastroenterology clinic, and showed that 55% were symptom-free by 10 months and 81% by 18 months of age. However, some children remain symptomatic into adulthood, and older children can present with a spectrum of symptoms similar to adults, with symptoms such as recurrent epigastric pain and heartburn. Severe esophagitis at presentation has been identified as a risk factor for persistent GERD,[7] and esophageal strictures from GERD in childhood have been reported.[8] Risk factors for severe GER include neurologic impairment (e.g. cerebral palsy), repaired esophageal atresia (OA) or congenital diaphragmatic hernia, and chronic respiratory disease. In many of these children, the GER is a manifestation of an underlying whole-gut motility disorder.

Diagnosis of GER is usually made based on the symptoms alone. Investigation is reserved for those with GERD, children for whom there is doubt about the diagnosis or the need to step up therapy, or children in whom complications have arisen. Investigations can include 24-hour esophageal pH monitoring, barium radiology to exclude anatomical problems, upper gastrointestinal endoscopy with biopsy, scintigraphy, intraluminal impedence, and manometry.

The main aims of treatment are to alleviate symptoms, promote normal growth and prevent complications. Conservative options include reassurance, positioning, and altering the feed consistency. However, the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) has recommended that thickening agents should be used with caution in healthy, thriving infants who regurgitate.[9] We have not reviewed the evidence for thickened formulas in this study. Medical treatments include altering the viscosity of the feeds, altering the gastric pH, and altering the motility of the gut. Surgical options include fundoplication, which is undertaken in patients with severe GERD resistant to medical management. This subject is reviewed elsewhere.[10,11]

This review critically appraises the pediatric evidence base for the medical treatment of GER using the 'levels of evidence' adopted by the Oxford Centre for Evidence-based Medicine.[12] Grades of recommendation are included based on the level of evidence (figure 1).

1. Methods

Two of the authors (MPT and RMB) searched PubMed, AdisOnline, MEDLINE, and EMBASE, and then manually searched reviews from the past 5 years using the key words 'gastro-esophageal' (or 'gastroesophageal'), 'reflux', 'esophagitis', and 'child$' (or 'infant') and 'drug$' or 'therapy'. Articles included were in English and had an abstract. Reviews and abstracts only were excluded. Full papers were excluded if the treatment group was adult (aged >16 years), if the treatment was either conservative or surgical, or if GER was not the main focus

Level	Therapy	Grade	
1a	SR (homogeneity of RCTs)	A	Consistent level 1 studies
1b	Individual RCT (with narrow confidence interval)	B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
2a	SR (with homogeneity) of cohort studies	C	Level 4 studies or extrapolations from level 2 or 3 studies
2b	Individual cohort study (+ low quality RCT; e.g. <80% follow-up)	D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level
3a	SR (with homogeneity) of case-control studies		
3b	Individual case-control study		
4	Case series (and poor quality cohort and case-control studies)		
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'		

Fig. 1. Levels of evidence and grades of recommendation.[12] **RCT** = randomized controlled trial; **SR** = systematic review.

of the article. We also excluded studies on cisapride as it has now been withdrawn. Figure 2 shows the outcome of the search, excluded papers by reason for exclusion, and the number of papers selected for review.

All authors reviewed, in pairs, the 56 papers selected and graded them according to the criteria in figure 1. Any disagreement was resolved with discussion with the other pair.

We assessed the studies for all reported outcomes that are meaningful to clinicians making decisions about treating GER. These outcomes included the impact of clinical symptoms, pH study profile, and esophageal appearance at endoscopy.

2. Medical Treatments

2.1 Alginates

Gaviscon® Infant (Reckitt Benckiser Healthcare [UK] Ltd, Slough, Berkshire, UK) contains sodium and magnesium alginate, and mannitol; it acts as a feed thickener and prevents reflux by increasing the viscosity of feeds. This is differentiated from other Gaviscon® preparations that can also contain sodium bicarbonate/potassium bicarbonate that, in the presence of gastric acid, forms a 'foam raft' in which carbon dioxide (produced by the breakdown of bicarbonate) is trapped. This floats on top of the gastric contents and is designed to neutralize gastric acid (providing symptomatic relief) and reduce esophageal irritation.[13]

The dosage for breast-fed babies weighing <4.5 kg is one-half of a dual sachet in 5 mL water and for infants >4.5 kg is two sachets in 5 mL water. Both are diluted to 15 mL with water, and given via syringe or spoon. The dosage for bottle-fed babies is one dose (one-half of a dual sachet) in feeds <115 mL, and two doses (one dual sachet) in feeds <240 mL. To avoid confusion in the use of Gaviscon® Infant, each half of the dual sachet should be identified as 'one dose'.[16]

Caution should be used when using alginates in children at risk of dehydration (e.g. acute vomiting or diarrhea), or children at risk of intestinal obstruction.[14] In children whose feeds are already thickened (e.g. by using Enfamil AR™ [Mead Johnson, Uxbridge, Middlesex, UK], or SMA Staydown™ [SMA Nutrition, Taplow, Berkshire, UK]), adding Gaviscon® Infant has been reported to cause intestinal obstruction.[15] Gaviscon® Infant contains 0.92 mmoL Na^+/dose;[16] this should be considered if a child's sodium intake needs to be monitored

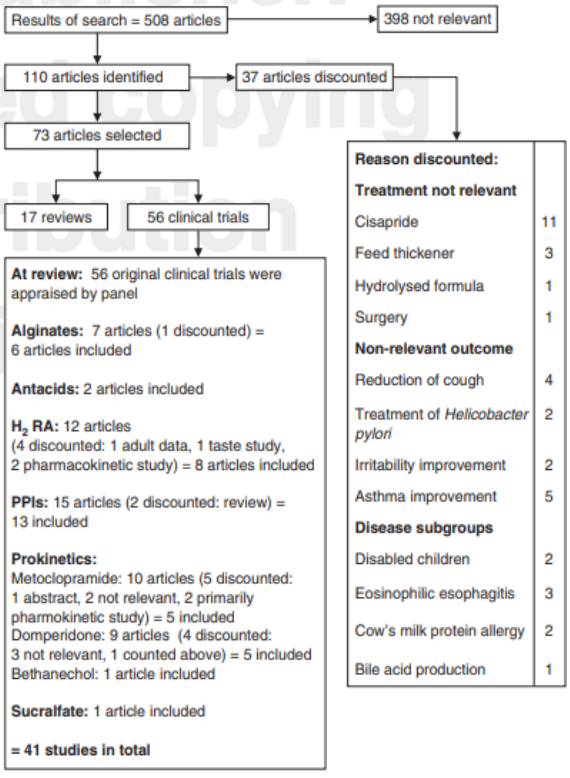

Fig. 2. Flow diagram of search strategy. **H_2RA** = histamine H_2 receptor antagonist; **PPIs** = proton pump inhibitors.

with caution (e.g. in those with renal impairment, congestive cardiac failure, preterm infants, or children with diarrhea and vomiting).[16]

Table I presents studies of alginates in children with GER or GERD. The largest randomized controlled trial (RCT) [Miller[17]] involving 90 children showed a significant reduction in the number and severity of vomiting episodes ($p=0.009$) compared with placebo, but the follow-up was short (14 days). Del Buono et al.[19] showed a significant reduction in the height of reflux compared with placebo, but no changes in other markers of GER. In the other studies where no benefit against placebo was demonstrated, Carroccio et al.[18] and Forbes et al.[21] did not include a group of patients on alginates alone, and Greally et al.[22] trialed Gaviscon® Infant against cisapride (now withdrawn). Forbes et al.[21] compared Gaviscon® Infant with metoclopramide and found that both reduced the frequency and duration of acid GER.

In conclusion, there is some evidence for the use of Gaviscon® Infant in children with GER and GERD (grade D; see figure 1).

2.2 Antacids

Magnesium hydroxide/aluminium hydroxide (MHAH) reduces gastric pH. Long-term use of aluminium-containing agents should be avoided in infants and children with renal impairment, due to the risk of accumulation and increased plasma aluminium levels.[23]

Table II presents studies of antacids in children with GER or GERD. In one RCT involving 80 children, MHAH in combination with domperidone was shown to be superior to domperidone alone, Gaviscon® Infant and placebo.[18] However, MHAH was shown to be inferior to cimetidine in another smaller RCT of 33 children.[24]

In conclusion, there is insufficient evidence to make a recommendation regarding the role of MHAH in children with GERD (grade D).

2.3 Histamine H_2 Receptor Antagonists

Histamine H_2 receptor antagonists act by reducing histamine-induced gastric acid secretion and pepsin output. They are well absorbed from the gastrointestinal tract but, due to high first-pass metabolism, bioavailability of oral doses is only 50%. Intravenous dosing provides better bioavailability (90% within 15 minutes).[16]

Ranitidine is the most commonly used H_2 receptor antagonist. It is well tolerated and has a low incidence of adverse effects (these are generally mild and include fatigue, dizziness or diarrhea).[16] Cimetidine is rarely used clinically as concerns exist about the effect on cytochrome P450 (CYP) and consequent multiple drug interactions, as well as interference with vitamin D metabolism and endocrine function.[25] Famotidine is an alternative H_2 receptor antagonist; it is not licensed for use in children in the UK but is licensed for children in the US.

Table III presents studies of H_2 receptor antagonists in children with GER or GERD. Ranitidine is an effective medical treatment of GERD. Karjoo and Kane[26] showed that 70% of 129 children with endoscopic changes consistent with peptic ulceration improved (symptoms and endoscopy) on ranitidine, although there was a tendency for a better response in those with more mild histological appearances on initial endoscopy. Eighty-seven percent of children refractory to ranitidine responded to omeprazole (20 mg/day for 8 weeks). Cucchiara et al.[27] found that if a lower dose of ranitidine failed to relieve symptoms or improve endoscopic appearances (participants were receiving ranitidine 8 mg/kg/day and cisapride 0.8 mg/kg/day for 8 weeks at recruitment), switching to a higher dose of ranitidine (20 mg/kg/day) had equal efficacy compared with omeprazole (40 mg/day/1.73 m^2). Salvatore et al.[8] showed that in a case series of 103 children whose symptoms were refractory to ranitidine and only 23% had esophagitis on endoscopy, 80% had a reflux index of <5% on pH study. The authors concluded that in most of these children the symptoms were not acid-related, and some showed signs of inadequate acid suppression.

Cimetidine also provided symptomatic and endoscopic improvements. However, some patients did require ranitidine if cimetidine failed to relieve symptoms; these patients subsequently improved.[29] There is some evidence of efficacy for the use of famotidine in GER, demonstrated in one small study, although significant adverse effects were seen.[31]

The North American Society of Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) agree that "Histamine H_2 receptor antagonists produce relief of symptoms and mucosal healing" in GER in children.[2]

In conclusion:

(1) Oral ranitidine given 2–3 times a day provides symptomatic relief and endoscopic improvement of esophagitis in children with GERD (grade B).

(2) If the initial dose of ranitidine (10 mg/kg/day) fails to relieve symptoms or endoscopic appearances in children with GERD, either higher dose ranitidine (20 mg/kg/day) or a proton-pump inhibitor (PPI) should be tried (grade B).

(3) There is evidence to support the efficacy of cimetidine at 15 mg/kg four times daily in children with GERD (grade B), but this agent has a significant adverse effect profile.

Table I. Studies of alginates in children with gastro-esophageal reflux (GER) or gastro-esophageal reflux disease (GERD)

Study	Participants	Study type[a]	Methods and comparators	Key outcomes	Comments
Miller[17]	90 children (aged 0–12 mo) recruited at 25 GP centers with recurrent GER	1b	Phase III, mc, db, r, parallel-group study. Gaviscon® Infant vs placebo	Symptoms: reduction in no. and severity of vomiting episodes ($p = 0.009$), improvement in symptoms on Gaviscon® Infant (investigators: $p = 0.008$, parents: $p = 0.002$)	Infants assessed at 7 + 14 d. Pts excluded if known esophageal/gastrointestinal disease. 11 infants withdrew due to adverse events (Gaviscon® Infant 4, placebo 7). 5 withdrew for lack of efficacy (Gaviscon® Infant 2, placebo 3). Compliance: 71% (Gaviscon® Infant), 59% (placebo)
Carroccio et al.[18]	80 children (aged 1–18 mo; median 4.5 mo) with GER but no erosions on endoscopy	2b	db RCT. MHAH + domperidone vs Gaviscon® Infant + domperidone vs domperidone vs placebo (8 wk)	Symptoms/pH probe/endoscopy: Domperidone + Gaviscon® Infant not superior to placebo for any outcome	Short-term study in young children: no child had erosions/ulcers on endoscopy prior to treatment. 80 pts divided into small groups. Pts stratified by age (<12 mo, >12 mo) and reflux index (<10%, >10%)
Del Buono et al.[19]	20 infants, (aged 34–319 d; mean 163 d), bottle fed, with GER symptoms	2b	db RCT. Gaviscon® Infant (625 mg in 225 mL milk) vs placebo (mannitol + solvito) [over 24 h]	Intraluminal impedance and pH monitoring: lower reflux height in esophagus with Gaviscon® Infant ($p < 0.001$). No difference in no. of reflux events/h/pH/reflux duration	No discussion of group demographics (age/sex) or how the infants were recruited. Symptoms/histology not recorded. Many reflux episodes diagnosed on impedance not pH probe Short-term study, small numbers
Buts et al.[20]	20 infants with symptoms of GER	2b	db RCT. Gaviscon® Infant vs placebo) for 8 d	Symptoms/pH probe: episodes of regurgitation reported by the parents decreased during Gaviscon® Infant therapy. All pH monitoring variables reduced ($p < 0.05$)	None of the children who underwent an endoscopy had evidence of esophagitis. Difference between mean ages: Gaviscon® (21 mo) vs placebo (35 mo)
Forbes et al.[21]	30 children (aged 4 mo–17 y) with GER	2b	db, RCT. Alginate + antacid vs metoclopramide 0.17 mg/kg tid (24 h period)	Symptoms/pH study: alginate + antacid, and metoclopramide reduced the frequency and duration of acid GER	No data on adverse effects. Exact preparation of alginate-antacid not discussed
Greally et al.[22]	50 infants (aged 2–18 mo)	2b	r, parallel group. Gaviscon® Infant + carobel vs cisapride	pH study/symptoms: no significant difference in no. of reflux episodes and height of reflux episodes over 24 h	All infants bottle fed and had GER proven on pH study. All were off ranitidine and none had associated organ system involvement

a Refer to figure 1 for a definition of the study type.

db = double-blind; **GP** = general practitioner; **mc** = multicenter; **MHAH** = magnesium hydroxide/aluminium hydroxide; **no.** = number; **pts** = patients; **r** = randomized; **RCT** = randomized controlled trial; **tid** = three times daily.

Table II. Studies of antacids in children with gastro-esophageal reflux (GER) or gastro-esophageal reflux disease (GERD)

Study	Participants	Study type[a]	Methods and comparators	Key outcomes	Comments
Carroccio et al.[18]	80 children (aged 1–18 mo; median 4.5 mo) with GER but no erosions on endoscopy	2b	db RCT. MHAH + domperidone vs Gaviscon® Infant + domperidone vs domperidone vs placebo	pH probe/symptoms/endoscopy: improved symptoms and reflux index (both $p < 0.0001$) in domperidone + MHAH group	Short-term study in young children: no child had erosions/ulcers on endoscopy prior to treatment (mild disease). 80 pts divided into small groups. Pts stratified by age (<12 mo, >12 mo) and reflux index (<10% and >10%)
Cucchiara et al.[24]	33 children (aged 2–42 mo)	2b	RCT, non-blinded. 12 wk MHAH (700 mmol/1.73 m^2/d) vs cimetidine 20 mg/kg/d	Symptoms/pH probe/endoscopy: improvement with cimetidine clinically ($p < 0.05$), endoscopically, and in pH studies	No adverse effects recorded. pH study and endoscopy had a blinded observer. Children not blinded

a Refer to figure 1 for a definition of the study type.

db = double-blind; **MHAH** = magnesium hydroxide/aluminium hydroxide; **pts** = patients; **RCT** = randomized controlled trial.

2.4 Proton Pump Inhibitors

PPIs increase the pH of gastric contents, decrease the total volume of secretions, and facilitate emptying.[32] This occurs by inactivation of the H^+/K^+ adenosine triphosphatase (the parietal cell membrane transporter on the basolateral membrane). The pumps are most active when 'meal stimulated' and hence the ideal time for drug administration is with the first meal of the day after an overnight fast. Omeprazole reduces both daytime and nocturnal acid secretion when given either in the morning or evening; however, morning dosing results in higher median 24-hour pH values.[33] A PPI given once daily can often result in transient acid secretion at approximately 15 hours after the dose, possibly due to an underlying circadian rhythm of synthesis and processing of pumps.[33] Nocturnal acid breakthrough (intragastric pH <4 for >60 minutes) has been observed in 50% of subjects (either healthy adults or patients with GERD), despite administration of omeprazole 20 mg twice daily or lansoprazole 30 mg twice daily.[34]

There are five PPIs approved by the US FDA: omeprazole (since 1988), lansoprazole, pantoprazole, rabeprazole, and esomeprazole (the pure *S*-isomer of omeprazole), of which only omeprazole is licensed for use in children in the UK. Lansoprazole is only recommended by the British National Formulary for children when treatment with the available formulations of omeprazole is unsuitable.[35]

Omeprazole is generally well tolerated. For children who find capsules difficult to swallow, the capsule can be opened and the granules given in a weakly acidic vehicle, such as orange juice, cranberry juice or yoghurt.[33] The granules are stable in acid but are vulnerable to degradation in a neutral or alkaline pH. If given by nasogastric tube, there is a risk of blockage, especially if the luminal diameter is small.[36] In the first few months of infancy, a relative hypochlorhydria exists due to immature parietal cells. Potentiating the hypochlorhydria in neonates further with omeprazole can result in bacterial overgrowth. Consequent increases in respiratory infections in critically ill babies have been reported; however, in infants and children who are otherwise well, no clear ill-effects have been demonstrated from this.[37] Other reported adverse effects include headaches and diarrhea[38] and there is a single case-report of omeprazole-induced hepatitis.[39] Lansoprazole has been shown to be well tolerated, with pharmacokinetic and pharmacodynamic profiles similar to those seen in adult studies; peak concentration is reached within 2 hours of ingestion. Higher peak concentrations have been seen in infants.[40]

All PPIs are metabolized by the CYP system, and may cause a minor increase in plasma levels of other drugs metabolized

Table III. Studies of histamine H_2 receptor antagonists in children with gastro-esophageal reflux (GER) or gastro-esophageal reflux disease (GERD)

Study	Participants	Study type[a]	Methods and comparators	Key outcomes	Comments
Karjoo and Kane[26]	153 children (aged 6–18 y), chronic epigastric pain	2b	Cohort study. 129 children (84%) had peptic esophagitis: given ranitidine 4 mg/kg tid. If refractory, 20 mg omeprazole daily (for 8 wk)	Symptoms/endoscopy: 129 (84%) had peptic esophagitis diagnosed on EGD. 70% responded to ranitidine. More likely to respond if more benign grading ($p < 0.05$)	Only 3 of 129 needed fundoplication. No adverse effects. Short-term follow-up. 87% of pts who did not respond to ranitidine responded to omeprazole
Cucchiara et al.[27]	32 children (aged 6 mo–13.4 y), GERD refractory to ranitidine	2b	db RCT. High-dose ranitidine (20 mg/kg/d) vs omeprazole (40 mg/d/1.73 m^2)	pH probe/endoscopy: both reduced acidity ($p < 0.05$) and esophageal exposure to acid ($p < 0.05$). Both improved symptoms ($p < 0.01$) and healed esophagitis ($p < 0.05$)	Older age of children. Subjects were children who had failed to respond to ranitidine (8 mg/kg/d) and cisapride (0.8 mg/kg/d) for 8 wk. 22% withdrawal rate
Salvatore et al.[8]	103 children on oral ranitidine with persisting symptoms (mean age 3.3 ± 1.8 mo)	4	Case series. Ranitidine (mean dose 9.4 ± 3.3 mg/kg/d) given for at least 2 wk	Symptoms/pH study (on ranitidine)/endoscopy: 80% of pts had reflux index <5% on ranitidine (more likely to be on higher dose of ranitidine [regression analysis $r = 0.21$; $p < 0.05$]). Only 23% had esophagitis on histology. Some infants with acid-related symptoms on ranitidine need better acid suppression or do not have acid-related symptoms	26% received alginates: had no effect in subgroup analysis. No comment on adverse effects. Mean treatment course prior to assessment (with pH study/endoscopy) 30 d. Symptoms and histology did not correlate with pH study or dose of ranitidine
Cucchiara et al.[28]	32 children (aged 1 mo–9.5 y), GERD and esophagiitis	2b	db RCT. Cimetidine 30–40 mg/kg/d vs placebo (12 wk)	Symptoms/pH probe/endoscopy: at 12 wk 12/17 pts with cimetidine healed (symptoms, pH probe, endoscopy $p < 0.01$). Four further pts had improved	No power calculation. All pts had received positioning advice. 4/15 placebo pts improved, 9 worsened ($p < 0.01$) and were then started on ranitidine, 8 subsequently improved
Cucchiara et al.[24]	33 children (aged 2–42 mo), GERD and esophagitis	2b	Open-label RCT. Cimetidine 20 mg/kg/d vs MHAH (700 mmol/1.73 m^2/d 12 wk)	Symptoms/pH probe/endoscopy: improvement clinically ($p < 0.05$), endoscopically and in pH studies in both groups	No adverse effects recorded. pH study and endoscopy had a blinded observer. Pts not blinded
Lambert et al.[29]	27 children, 23 enrolled (aged 3–14 y; mean 4.5 y) with GER	2b	Cohort study. Cimetidine: doses of 5, 7.5 and 10 mg/kg	Symptoms/pH probe: 75% of children given 10 mg/kg had gastric pH >4 within 2 h and lasting >2 h (better than 5 mg/kg [30%] or 7.5 mg/kg [52%])	8 poor responders given extra 15 mg/kg cimetidine (not analyzed within cohorts). 10 received ranitidine 3–6 mg/kg (also not analyzed). Multivariate analysis showed difference in duration of acid suppression between doses was not significant

Continued next page

Table III. Contd

Study	Participants	Study type[a]	Methods and comparators	Key outcomes	Comments
Argüelles-Martín[30]	75 children (aged 3 mo–13 y), esophagitis (on endoscopy). Treatment until day 56	2b	3 groups of 25: cimetidine (1) vs sucralfate suspension (2) vs sucralfate tablets (3). Doses: cimetidine: 10 mg/kg bid, sucralfate 0.5 g qid (in pts <6 y) and 1 g qid (in pts >6 y)	Symptoms/endoscopy (day 28 and 56): symptoms improved by day 56 in group 1 (79%), group 2 (92%) and group 3 (68%). Endoscopy better in group 1 (42%), group 2 (50%) and group 3 (44%). No significant difference between 3 groups	No placebo group: could this improvement be placebo effect? No adverse effects seen
Orenstein et al.[31]	35 infants (aged 1.3–10.5 mo) with GER	2b	db RCT. 4 wk. Famotidine 0.5 mg/kg vs 1 mg/kg (4wk) then 4 wk withdrawal	Symptoms. 0.5 mg/kg group: improvements in regurgitation frequency ($p = 0.04$); 1 mg/kg group: improvements in crying time and regurgitation frequency and volume ($p < 0.05$)	27 completed part I, 8 completed part II. 60% of pts had previously failed treatment with a H_2 receptor antagonist. Famotidine caused agitation in 6 pts and headache in 2 pts

a Refer to figure 1 for a definition of the study type.

bid = twice daily; **db** = double-blind; **EGD** = esophagogastroduodenoscopy; **MHAH** = magnesium hydroxide/aluminium hydroxide; **pts** = patients; **qid** = four times daily; **RCT** = randomized controlled trial; **tid** = three times daily.

by the CYP system (e.g. phenytoin, macrolides, and coumarins).[16,41] This may not be clinically significant, especially in children where, from infancy, the activity of the CYP system exceeds that of adults. PPIs are also safe in children with renal impairment.[42]

Table IV presents studies of PPIs in children with GER or GERD. Omeprazole has been shown to increase gastric pH, especially in older children, and promote mucosal healing in children with esophagitis (including those with severe esophagitis, and those refractory to ranitidine). These effects lead to improved symptom scores, and the endoscopic and histological appearance.[26,27,43-48] There are no data on the long-term safety of PPIs in children, beyond the data provided by Gunasekaran and Hassall[45] (mean follow-up 12 months – no long-term adverse effects noted). No data exist on children younger than 6 months of age. Gunasekaran and Hassall[45] also used dosages of omeprazole up to 3.3 mg/kg/day and a maximum of 60 mg, although seven patients developed a transient rise in ALT, and 50% of the study population had significant co-morbidity. Lansoprazole was also effective in promoting mucosal healing, especially at higher doses, although some patients experienced adverse effects (most commonly headache and dizziness).[50]

Pantoprazole 10 mg/day was effective in one RCT in children aged 5–11 years, but one-third of participants experienced headaches; 20 or 40 mg/day conferred no extra healing benefit.[51] Pantoprazole and esomeprazole appear to provide effective symptom relief in adolescents although adverse effects such as headaches were noted.[51-53] No comparisons with omeprazole or lansoprazole have as yet been published.

The NASPGHAN consensus statement on GER states that "Proton pump inhibitors (PPIs), the most effective acid suppressant medications, are superior to histamine H_2 receptor antagonists in relieving symptoms and healing esophagitis."[2]

In conclusion:

(1) Omeprazole is effective in children with GERD (improvement in symptoms, pH probe findings and endoscopic findings), with a good tolerability and safety profile (grade B).

(2) Omeprazole is effective in children with GERD resistant to ranitidine (grade B).

(3) Omeprazole should be a first-line treatment in severe esophagitis in children (grade B).

(4) The effect of omeprazole is dose-dependent in children (grade B).

(5) There is less data available for lansoprazole than for omeprazole, but lanosprazole appears to be effective in children (grade B).

Table IV. Studies of proton pump inhibitors in children with gastro-esophageal reflux (GER) or gastro-esophageal reflux disease (GERD)

Study	Participants	Study type[a]	Methods and comparator	Key outcomes	Comments
Cucchiara et al.[27]	32 children (aged 6 mo–13.4 y) with GERD on endoscopy	2b	db RCT. Omeprazole 40 mg/d/1.73 m^2 vs high-dose ranitidine 20 mg/kg/d (8 wk)	pH probe/endoscopy: both reduced acidity ($p < 0.05$) and esophageal exposure to acid ($p < 0.05$), improved symptoms ($p < 0.01$) and healed esophagitis ($p < 0.05$)	Older age of children. Subjects were children who had failed to respond to ranitidine and cisapride (8-wk course). 22% withdrawal rate.
Karjoo and Kane[26]	153 children (aged 6–18 y) with chronic epigastric pain	2b	Cohort study. 129 children (84%) had peptic esophagitis: given ranitidine 4 mg/kg tid. If refractory, started omeprazole 20 mg/day (>8 wk)	Symptoms/endoscopy: 30% of 129 children refractory. 87% of refractory esophagitis had symptomatic/ endoscopic improvement with omeprazole	Only 3 children of 129 needed fundoplication. No adverse effects. Short-term follow-up. No p-value given
Hassall et al.[43]	65 pts (aged 1–16 y) with erosive reflux esophagitis	2b	mc cohort study. Omeprazole 0.7–3.5 mg/kg. 3 refractory to fundoplication, 28 refractory to H_2 receptor antagonists and/or prokinetics. 24 refractory to antacids/alginates or were untreated	pH study at 2 wk, endoscopy at 3 mo, symptoms: of 57 pts, 54 healed on endoscopy (3 needed second course; 3 did not heal). Symptoms improved in 56 children. Healing dose higher for higher grade esophagitis. No adverse effects recorded	Two-thirds of pts had severe esophagitis on endoscopy. At entry 21 had neurological impairment, 7 repaired esophageal atresia. 26 had a hiatus hernia, and 8 had esophageal strictures. 8 pts left study. No details of recruitment
Martin et al.[44]	15 children (aged 1–16 y) with GER	4	Cohort study. Omeprazole 20 mg/d (<3 mo). 4 had cerebral palsy, 2 trachea-esophageal fistula, 1 Crohn, 1 Seckel dwarf	Symptoms/pH probe, follow-up 3 mo: improvement in symptoms in 11, 4 had fundoplication. No significant differences were found	All had failed treatment with cimetidine + ranitidine and antacids + cisapride. On initial pH study: 12/14 had pH <4 for >20% of time
Gunasekaran and Hassall[45]	15 children with GER refractory to H_2 receptor antagonists plus prokinetics (aged 0.8–17 y; mean 8.4 y)	4	Case series. Omeprazole (dose 20–40 mg, or 0.7–3.3 mg/kg) [mean 12.2 mo]	Symptoms: absent at 2 mo in 70%, and 100% absent at 6 mo. Endoscopy at 3 mo (6/15 healed). As 9 not improved, repeated at 6 mo, and remainder had healed. pH improved in all pts (reflux index <4% in all)	3 pts received 60 mg (1.9–2.4 mg/kg). 8 of 15 neurologically impaired. All had endoscopic diagnosis of esophagitis. pH study performed day 5: if reflux index >5%; dose increased until study normal. 7 pts had transiently raised ALT ± AST. All remained asymptomatic
Kato et al.[46]	18 patients (13 with refractory reflux esophagitis); 5 controls (aged 3–18 y)	4	Case-series. Omeprazole 0.3–0.6 mg/kg, maximum dose 40 mg/d. If unhealed at 8 wk: dose increased to 1.6 mg/kg. If unhealed at 3 mo: switched to lansoprazole 30 mg od	Endoscopy: healing rates at 2, 4, 6, and 8 wk = 46%, 85%, 92%, 92%, respectively. 3 pts needed to switch to lansoprazole at 3 mo	Esophagitis pts had failed treatment with cimetidine or famotidine or prokinetics – prokinetic not stated. 7 pts had pharmacokinetics assessed

Continued next page

Table IV. Contd

Study	Participants	Study type[a]	Methods and comparator	Key outcomes	Comments
Alliet et al.[47]	12 children (aged 2.9 ± 0.9 mo) with esophagitis and failed cimetidine, cisapride or Gaviscon® Infant	4	Case series. Omeprazole 0.5 mg/kg/d for 6 wk	Symptoms/pH probe/endoscopy (6 wk): Reduction in symptoms (83%), reduction in intragastric values; reflux index was improved from 90.4% to 21.3%. On endoscopy 75% had healed, 25% improved	No p-values. At 1 y follow-up 83% asymptomatic
De Giacomo et al.[48]	10 children (aged 25–109 mo, mean 75 mo) with severe esophagitis, failed prokinetic, H_2 antagonist or antacid therapy	4	Case series. Omeprazole 20 mg/day if weight <30 kg, 40 mg/day if weight >30 kg. Follow-up 3 mo	Symptoms/endoscopy/pH probe at 3 mo: reduction in symptoms ($p < 0.05$). Improved pH probe markers ($p < 0.05$) and endoscopic appearances ($p < 0.05$). No improvement in histology scores	4 had significant co-morbidity. 6/10 pts (60%) relapsed after treatment. 3 required fundoplication
Franco et al.[49]	35 children (aged 3–15 y) with esophagitis	2b	Case series. 12 wk course lansoprazole Group A: 12 pts (1.3–1.5 mg/kg/d) Group B: 23 pts (0.8–1.0 mg/kg/d) If treatment fails, dose increased by 50%	pH study/endoscopy/symptoms. Healing on endoscopy and symptoms: 75% of group A vs 53% group B ($\chi^2 = 3.6$: $p < 0.05$). Unchanged: 8.3% in group A (1 pt) vs 31% in group B (6 pts) $\chi^2 = 6.9$: $p < 0.01$)	Average initial reflux index in group A + B = 80%. No adverse effects reported. 12 wk follow-up. Authors recommended 1.5 mg/kg/d
Fiedorek et al.[50]	87 adolescents (aged 12–17 y) at 20 US sites with symptomatic, endoscopically proven, non-erosive GERD and erosive esophagitis	4	Open label. Cohort study. 8 wk assessment: lansoprazole 15 mg/d for non-erosive esophagitis for 8 wk or 30 mg/d for erosive esophagitis (further 4 wk if not healed)	Symptoms/endoscopy. 64 pts had non-erosive disease: 91% improved (vs 43% placebo; $p < 0.001$). 23 pts had erosive disease: 85% improved (vs 16% placebo; $p < 0.001$) by 12 wk	Good tolerability data over a short duration (12-wk follow up). 76% were >90% compliant. 20% of those with non-erosive changes had adverse effects (10% headache, 5% dizziness). Elevation in mean serum gastric levels was observed but this is of uncertain significance. Endoscopy repeated at 8 wks in those with erosive changes and at 12 wk if not healed
Tolia et al.[51]	53 children (aged 5–11 y)	2b	mc, db RCT. Pantoprazole 10, 20 and 40 mg/d. Follow up 8 wk	Symptoms, endoscopy: improvement in all symptoms (e.g. vomiting, nausea $p < 0.006$). 20 mg and 40 mg (vs 10 mg) improved symptoms ($p < 0.05$). On endoscopy, all erosive esophagitis, most non-erosive esophagitis improved (NS)	Up to one-third had symptoms of headache on all three dosages. No randomization or blinding details. Only 3 had evidence of erosions/ulcers on pre-treatment histology

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Table IV. Contd

Study	Participants	Study type[a]	Methods and comparator	Key outcomes	Comments
Tsou et al.[52]	136 adolescents (aged 12–16 y) with proven GERD	1b	mc, db RCT. 8 wk of pantoprazole (20 or 40 mg/d) [n = 68 in each group]	Symptoms: symptom scores improved in both groups (20 and 40 mg) by wk 8 ($p < 0.001$). Compliance 93% (20 mg) and 89% (40 mg)	Adverse effects: headache (n = 22 [20 mg] and 24 [40 mg]). 3 pts withdrew from 40 mg group. Minor rises in liver function tests (n = 5) and uric acid noted (n = 15)
Gold et al.[53]	148 adolescents (aged 12–17 y) with symptomatic GERD	2b	mc, db RCT. Esomeprazole 20 or 40 mg/d for 8 wk	Symptoms: symptom scores improved in both groups by the final study wk ($p < 0.0001$)	22 pts (14.9%) had adverse events: headache (8%, 12/148), abdominal pain (3%, 4/148), nausea (2%, 3/148), diarrhea (2%, 3/148)

a Refer to figure 1 for a definition of the study type.

db = double-blind; **mc** = multicenter; **NS** = not significant; **od** = once daily; **pt(s)** = patient(s); **RCT** = randomized controlled trial; **tid** = three times daily.

(6) The effect of lansoprazole is dose-dependent in children (grade B).
(7) Pantoprazole appears to be effective in children (based on limited data – grade D).
(8) Esomeprazole appears to be effective in children (based on one study – grade D).

2.5 Prokinetics

2.5.1 Metoclopramide

Metoclopramide blocks dopamine and serotonin receptors, and has α-sympathomimetic activity. Adverse effects can be seen in up to 34% of children receiving metoclopramide.[54] These include drowsiness or restlessness, and rarely extrapyramidal reactions (rigidity, trismus, and oculogyric crisis) can occur, which are more likely with higher doses.[25]

Table V presents studies of metoclopramide in children with GER or GERD. Five studies in children were appraised. One showed a clinical effect with intravenous metoclopramide, and two showed a clinical benefit from oral metoclopramide.[55,56,58] There is evidence of superiority over placebo but not over domperidone.[58] Tolia et al.[56] showed a significant benefit from metoclopramide in reducing the reflux index, and De Loore et al.[58] demonstrated a significant symptomatic benefit from metoclopramide compared with placebo (but not domperidone). Pons et al.[57] failed to find a difference in reflux index between metoclopramide and placebo. A significant adverse effect profile for metoclopramide was seen in these studies. A Cochrane review found that "metoclopramide may have some benefit in comparison to placebo in the symptomatic treatment of GER but that must be weighed against possible side effects."[60] A systematic review that included cohort, case-control and RCTs was unable to perform a meta-analysis due to the heterogeneity of the studies and small sample sizes. The available evidence was considered to be of poor quality and no conclusion was derived regarding the level of benefit or harm from routine use of metoclopramide in children.[61]

In conclusion, there is limited evidence for efficacy of metoclopramide in children with GER, and a significant potential adverse effect profile (grade B).

2.5.2 Domperidone

Domperidone is a dopamine D_2 receptor blocker that increases motility and gastric emptying and decreases postprandial reflux time. Domperidone has relatively few adverse effects; however, case reports of extrapyramidal adverse effects exist.[62,63]

Table VI presents studies of domperidone in children with GER or GERD. All the existing evidence is based on studies

Table V. Studies of metoclopramide in children with gastro-esophageal reflux (GER) or gastro-esophageal reflux disease (GERD)

Study	Participants (age)	Study type[a]	Methods and comparators	Key outcomes	Comments
Hyams et al.[55]	42 infants (0.5–13 mo mean 3.2 mo) with symptoms of GER	2b	Case control. IV metoclopramide 0.2 or 0.3 mg given as a single dose: pH probe and nurse recorded symptoms every 0.5 h, then gastric emptying study	Symptoms, pH probe, gastric emptying: metoclopramide reduced intra-esophageal pH and no. of reflux episodes ($p = 0.001$). No effect on emptying	Short-term study. 1 episode of dystonia
Tolia et al.[56]	30 infants (<1 y) with symptoms of GER and abnormal pH probe	1b	db, co, RCT. Metoclopramide 0.1 mg/kg or placebo qid, for 1 wk, crossover for 1 wk	Symptoms, pH study, scintigraphy after 4–7 d on each arm. Symptoms and scintigraphy: no difference. Reflux index better with metoclopramide ($p < 0.001$)	GER in all infants by extended pH monitoring before enrollment
Pons et al.[57]	24 infants (1–18 mo) in four centers with symptoms of GER and abnormal pH probe	2b	db, pc, dose-response trial. Metoclopramide 0.1/0.2/0.4 mg/kg vs placebo	pH study. Follow-up: 2 d. No significant difference in reflux index	All had reflux index >5% on assessment
De Loore et al.[58]	47 infants (3 wk–8 y), outpatients with symptoms of GER	2b	db, RCT. Metoclopramide 0.3 mg/kg tid vs domperidone 0.3 mg/kg tid and placebo	Symptoms: metoclopramide improved symptoms vs placebo ($p < 0.001$). Domperidone superior to metoclopramide (excellent symptom control in 10/15 pts vs 6/17 pts: NS)	Assessment of nausea in infants difficult. No differentiation for age: domperidone group (3 wk–4 y), metoclopramide (3 wk–8 y), placebo (1 mo–5 y)
Leung and Lai[59]	41 children with symptoms of GERD (21–1215 d; mean 160 d)	2b	db, RCT. 32 patients. Metoclopramide 0.125 mg/kg qid. 9 controls. Assessed at 2 and 4 wk	Symptoms: improved frequency of regurgitation ($p = 0.005$). Improved weight gain in 5 pts failing to thrive. 5 pts had adverse effects: 1 had an oculogyric crisis (after 4× prescribed dose given)	Solids started at the same time (although 1 baby 21 d of age)

a Refer to figure 1 for a definition of the study type.

co = crossover; **db** = double-blind; **IV** = intravenous; **no.** = number; **NS** = not significant; **pc** = placebo-controlled; **pts** = patients; **qid** = four times daily; **RCT** = randomized controlled trial; **tid** = three times daily.

with small patient numbers and short-term follow-up. Four of the studies showed significant improvement in symptoms compared with placebo,[18,58,64-66] with significant improvement in the number of reflux episodes (but not reflux index) compared with placebo.[18,64] Domperidone appeared to provide greater symptom relief when compared with metoclopramide, but this difference was not statistically significant (although both agents were significantly more effective than placebo).[58] The largest study (80 children but only 20 in each subgroup) showed improvement in reflux episodes ($p < 0.009$), but no overall significant difference between domperidone and placebo.[18] No study reported an episode of extrapyramidal adverse effects (total number of children 191). A systematic review of domperidone has concluded that "In view of the generally benign nature of GER and lack of evidence of efficacy, we cannot recommend that the benefits of treatment with domperidone outweigh the associated risks."[67] However, those studies demonstrating the clearest benefit included older children (up to the age of 11 years), in whom GER may not be as benign and self-limiting as in infants; further trials would strengthen the evidence-base for domperidone. The ESPGHAN working group on GER concluded that the available data for both domperidone and metoclopramide do not support their use in GERD in children.[68] Similarly, NASPGHAN concluded that the effectiveness in children of domperidone is unproven.[2]

In conclusion:

(1) There is some evidence of benefit from domperidone in GERD in children (grade D).

(2) There were no serious adverse effects noted from domperidone either at 0.3 mg/kg three times daily or 0.6 mg/kg three times daily in children (grade D).

2.5.3 Cisapride

Cisapride was previously widely marketed but was withdrawn in 2000 because of concerns about cardiac toxicity (prolonging the QT interval).[69] In view of this, we have not critically appraised the evidence, although the data on cisapride is of some interest. Cisapride is a prokinetic that stimulates motility in the lower esophagus, stomach and small intestine by increasing acetylcholine release in the myenteric plexus, controlling smooth muscle. At its peak, cisapride had been prescribed to >36 million children worldwide[70] and was recommended as "the drug of choice in chronic and persistent GERD in infants and children" by the ESPGHAN.[71] A Cochrane review found that there was no statistically significant effect of cisapride on GER[72] and, despite contrary opinions,[70] the only objective study to compare cisapride with another treatment (Gaviscon® Infant with or without Carobel® [carob seed powder], Cow & Gate, Trowbridge, Wiltshire, UK) failed to show superior efficacy.[22]

2.5.4 Erythromycin

Erythromycin is a macrolide antibiotic that increases gastrointestinal motility by acting as a motilin receptor agonist.[73] There are no published studies in children assessing the safety and efficacy of erythromycin used as a treatment of GER in children. Chicella et al.[74] reviewed nine controlled studies that used erythromycin in preterm babies establishing feeds, and concluded that it improved overall feeding and improved gastric emptying time. There are also published data to show benefit in children with gastroparesis.[75] There are concerns about an association between the use of erythromycin and an increased risk of hypertrophic pyloric stenosis in babies under 6 weeks of age (corrected gestational age).[76] There is currently not enough evidence to draw conclusions on the role of erythromycin in children with GER.

2.5.5 Bethanechol

Bethanechol is a muscarinic receptor agonist that has been shown to increase the tone of the lower esophageal sphincter. It can cause bronchospasm in patients with respiratory symptoms.[77] Table VII presents a study of bethanechol in children with GERD. This single study of bethanechol in 20 infants showed no clinical benefit, and practical difficulty in administration.[78]

In conclusion, no evidence exists to suggest efficacy of bethanechol in reducing GER in children (grade D).

2.6 Sucralfate

Sucralfate binds to inflamed upper gastrointestinal mucosa and forms a protective layer that resists further damage from gastric acid.[79] Sucralfate also encourages the production of prostaglandins and mucus that further protects mucosa whilst healing occurs. Sucralfate does not affect pH, but can slow gastric emptying.[80] Argüelles-Martin et al.[30] assessed 75 children (aged 3 mo–13 y) with esophagitis on endoscopy (2b), who were randomized to sucralfate tablets/sucralfate suspension versus cimetidine for 56 days (table III). Sucralfate improved symptoms and endoscopy appearances (non-significant difference). No adverse effects were seen.

In conclusion, further evidence is needed to assess the clinical benefit of sucralfate in GERD (grade D).

Table VI. Studies of domperidone in children with gastro-esophageal reflux (GER) or gastro-esophageal reflux disease (GERD)

Study	Participants (age)	Study type[a]	Methods and comparators	Key outcomes	Comments
Carroccio et al.[18]	80 children (1–18 mo; median 4.5 mo) with GER but no erosions on endoscopy	2b	db, RCT. MHAH+domperidone vs Gaviscon® Infant+domperidone vs domperidone vs placebo	pH probe, symptoms, endoscopy. Domperidone+MHAH group: improved symptoms and reflux index (both $p<0.0001$) but domperidone+Gaviscon® Infant and domperidone alone not superior to placebo	Short-term study in young children: no child had erosions/ulcers on endoscopy prior to treatment (mild disease). Pts stratified by age (<12 mo, >12 mo) and reflux index (<10% and >10%)
De Loore et al.[58]	47 children (3 wk–8 y), outpatients with symptoms of GER	2b	db, RCT. Domperidone 0.3 mg/kg tid vs metoclopramide 0.3 mg/kg tid vs placebo	Symptoms: domperidone better than placebo ($p<0.001$) and better than metoclopramide (excellent symptom control in 10/15 patients vs 6/17 patients; NS). Metoclopramide also improved symptoms vs placebo ($p<0.001$)	No differentiation for age: domperidone group (3 wk–4 y), metoclopramide (3 wk–8 y), placebo (1 mo–5 y). Assessment of nausea in infants difficult
Bines et al.[64]	17 children (5 mo–11 y) with symptoms of GER	2b	db, pc. Domperidone for 8 wk (0.3 mg/kg tid: 0.6 mg/kg tid if no improvement at 2 wk) vs placebo	Weight gain, symptoms, pH study, esophageal manometry, scintigraphy. At 4 wk: 11% reported improvement in symptoms on domperidone; on pH study improvement in number of reflux episodes ($p<0.01$) but not reflux index; on scintigraphy 3 of 6 pts on domperidone had improved gastric emptying (NS). At 8 wk: symptom relief in 33% of domperidone pts (0.6 mg/kg/dose) vs 11% in first 4 wk (NS)	Mild diarrhea noted as adverse effect in five pts. Three pts in the domperidone group and four in the placebo group had underlying diseases. Difference in age between groups = 2.4 y. pH probe at 4 wk 12 h duration (vs 17–24 h at initial assessment). Wk 4–8 of treatment open-label
Clara[65]	32 children (2.5 mo–10 y) with symptoms of GER	2b	db, pc. Domperidone 0.3 mg/kg for 2 wk vs placebo, domperidone 0.6 mg/kg if not better	Symptoms. Good/excellent symptom relief: 93% of domperidone group (0.6 mg/kg/dose) vs 33% in controls ($p<0.05$), less nausea/retching or regurgitation ($p<0.05$)	0.3 mg/kg failed in 50% of domperidone pts. Median age: 4 y (domperidone group) vs 6 y (control group)
Grill et al.[66]	15 infants (mean 7 mo) with symptoms of GER	2b	Cohort study. Domperidone 0.3–0.6 mg/kg tid for 6 wk	Symptoms, pH study, manometry, scintigraphy. Improved symptoms. Less reflux time and peristaltic contractions ($p<0.01$). Improvement in gastric emptying (NS). No adverse effects noted	Scintigraphy performed after IM domperidone. At end: all had pH study, on domperidone 0.6 mg/kg. The first six pts received 0.3 mg/kg then 'had option to increase to 0.6 mg/kg'. The remaining nine had 0.6 mg/kg for 6 wk

a Refer to figure 1 for a definition of the study type.

db = double-blind; **IM** = intramuscular; **MHAH** = magnesium hydroxide/aluminium hydroxide; **NS** = not significant; **pc** = placebo-controlled; **pts** = patients; **RCT** = randomized controlled trial; **tid** = three times daily.

Table VII. A study of bethanechol in children with gastro-esophageal reflux disease (GERD)

Study	Participants	Study type[a]	Methods	Key outcomes	Comments
Levi et al.[78]	20 infants and children with GERD	2b	Randomized crossover trial. 6 wk bethanechol (0.1–0.2 mg/kg qid) and antacids	pH study/symptoms. No significant difference in the degree of improvement between the two groups	Authors commented bethanechol more difficult to administer to the patients than antacids

a Refer to figure 1 for a definition of the study type.

qid = four times daily.

3. Discussion

In this article the available evidence-base for the individual medical treatments for GER in children has been evaluated and graded, according to an internationally recognized standard,[12] and recommendations made. These recommendations are based on a 'best interpretation' of the evidence base and are inevitably influenced by the clinical experience of the authors. The data does give an evidence base for some of the treatments given. However, it is clear that the evidence base is limited and heterogenous, although the condition is very common and the treatments widely prescribed. No pharmacological therapy has been studied for longer than 1 year.

3.1 Adult Data

A recent Cochrane review of the medical treatment of reflux esophagitis in adults assessed 134 trials involving 35 978 esophagitis participants. Five RCTs compared a standard dose of a PPI versus placebo (n = 965). Standard dose PPI therapy was significantly better compared with placebo in treating esophagitis (relative risk [RR] = 0.22; 95% CI 0.15, 0.31). Ten RCTs reported on the outcome for H_2 receptor antagonists versus placebo (n = 1241). These agents were also significantly better compared with placebo in improving esophagitis (RR 0.74; 95% CI = 0.66, 0.84). Three RCTs evaluated prokinetic therapy (cisapride) versus placebo in 198 participants. Prokinetics were not significantly better than placebo in healing esophagitis (RR 0.71; 95% CI 0.46, 1.10). Twenty- six RCTs reported the outcome for a PPI versus a H_2 receptor antagonist or an H_2 receptor antagonist plus a prokinetic (n = 4032). PPIs were significantly superior to histamine H_2 receptor antagonists or histamine H_2 receptor antagonists plus prokinetics in healing of esophagitis (RR 0.51; 95% CI 0.44, 0.59).[81] The Cochrane review concluded that "Prokinetic therapy has no statistically significant benefit over placebo in healing esophagitis (RR 0.71; 95% CI 0.46, 1.10)", but no RCTs assessed domperidone or metoclopramide with placebo.

3.2 Management in Children

There are multiple publications that detail practical guidelines for the management of GER and GERD, including the NASPGHAN guidelines produced by consensus.[2,25,82-86] The production of a detailed guide is beyond the scope of this review. Figures 3 and 4 give practical guidance based on a combination of the evidence base, evidence from adult studies, pediatric consensus and the practical experience of the authors.

In summary, for infant GERD:

(i) Ranitidine and omeprazole and probably lansoprazole are safe and effective medications that should provide symptomatic relief and endoscopic and histological healing of esophagitis.

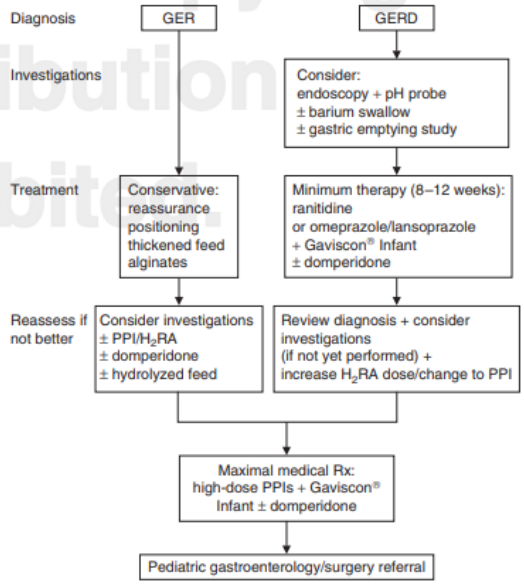

Fig. 3. Flowchart of management of gastro-esophageal reflux (GER) in infants. **GERD** = gastro-esophageal reflux disease; **H_2RA** = histamine H_2 receptor antagonist; **PPI** = proton pump inhibitor; **Rx** = treatment.

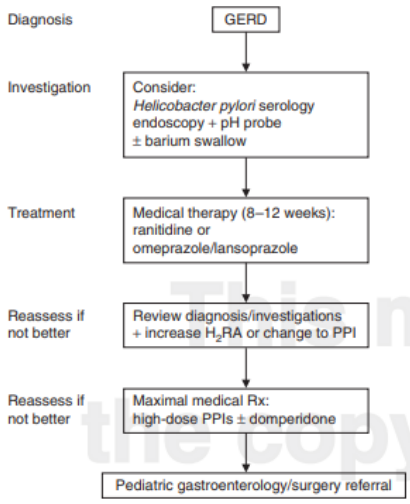

Fig. 4. Flowchart of management of gastro-esophageal reflux in older children. **GERD** = gastro-oesophageal reflux disease; **H_2RA** = histamine H_2 receptor antagonist; **PPI** = proton pump inhibitor; **Rx** = treatment.

(ii) Gaviscon® Infant (sachets) are safe and can improve symptoms of GER.
(iii) There is less evidence to support the use of domperidone, and metoclopramide has an adverse side effect profile.
(iv) More evidence is needed before other H_2 receptor antagonists/PPIs or other antireflux medications can be recommended.

In older children with GERD, acid suppression is the mainstay of treatment, and the largest evidence-base supports the initial use of H_2 receptor antagonists or PPIs.

4. Conclusion

We have appraised the existing evidence for the medical management of GER in children and thereby summarized evidence-based recommendations to enhance the current practice of treating pediatric GERD with alginates, PPIs or H_2 receptor antagonists, with or without domperidone. The drugs evaluated in this report are some of the most commonly prescribed for children and deserve a robust evidence-base, and we would call for further studies in this area. The adult evidence-base is more robust, but there are difficulties in extrapolation, particularly in younger children. This review has emphasized the need to strengthen the evidence-base for the treatment of GER/GERD with high-powered randomized, controlled pediatric studies with medium- to long-term outcome data.

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Article II: How to use: a pH study.

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What does this paper achieve?

In this study: I outlined the evidence-base for 24hr pH-impedance monitoring: the gold-standard test for acid reflux. I subsequently set up a service at Poole Hospital using the information from this article: which has assessed over 50 children and made concrete recommendations guiding treatment. This article has been downloaded over 8000 times.

The pH probe is designed to measure acidity (i.e., acid reflux) in the lower oesophagus.

The pH probe is a microelectrode passed through the nose and down the back of the throat to sit above the lower oesophageal sphincter. The probe was first used in 1969 in adults, with an acid reflux episode defined as an oesophageal pH of less than 4 for a specified minimum duration, usually 15–30 s. A set period, usually 24 hr, is recorded, with note made of the number of episodes, frequency of episodes, and the relationship of reflux to eating, position, sleeping or activity, and, especially, symptoms. The most sensitive marker of acid reflux on pH study is the reflux index. This is defined as the percentage of time that oesophageal pH is <4. This has been validated in several studies. The correct positioning of the probe should be confirmed at T9 using a chest *x* ray (CXR) or screening, due to the risk of malposition in the tracheobronchial tree or coiling in the oesophagus. More recently the addition of impedance channels to the probe helps to identify non-acid reflux and further articles identify clearly whether pH or pH/impedance monitoring is used as an objective outcome.

How does it contribute to the evidence-base?

Key clinical points include that the pH probe is a generally safe, reliable test of acid reflux in children and infants, and the more recent addition of impedance monitoring improves the utility of the test to pick up non-acid or alkaline reflux (pH/impedance monitoring) which is additionally useful in babies drinking milk. This test is a useful part of the diagnostic work up of gastro-oesophageal reflux disease, and the article highlights important considerations. Results must be interpreted in the context of clinical signs, but oesophageal pH monitoring is highly reliable for detecting acid reflux in oesophagitis. The 24-hr pH/impedance study is useful in recurrent pneumonia and children with

neurodisability but remains a poor discriminator in babies with apnoea or children with persistent cough. The period when a child's medication has been stopped for 24-hr pH/impedance monitoring can provide useful additional clinical data and providing objective evidence of resolution of acid reflux (so medication can be stopped).

There are several limitations to 24-hr pH and pH/impedance monitoring including that 24-hr pH and pH/impedance monitoring is unable to detect anatomical abnormalities (e.g. stricture, hiatus hernia or malrotation) or aspiration. The changes in environment, diet and behaviour as a result of investigation and admission to hospital may impact on results.

There is potential for technical difficulties, such as misplacement or displacement. Both 24-hr pH and pH/impedance monitoring provide no objective measures of inflammation, and so are less useful than endoscopy and biopsies for the diagnosis and grading of oesophagitis.

What were the next steps?

Having better understood the evidence-base for the gold-standard test, I was then in a better place to undertake the Cochrane review (article III) to distinguish between GOR and GORD and understand the practical limitations of the results. I set up 24hr pH testing in 2010 then switched to 24hr pH-impedance monitoring in University Hospitals Dorset in 2016, undertaking this procedure in over 100 infants and children, with meaningful results that influence parents' understanding of the severity of the condition and facilitated stopping of treatment where no longer necessary.

How to use: a pH study

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The 24 h oesophageal pH study is considered to be the gold standard for quantifying acid reflux.[1] In this review we provide an evidence-based discussion of the role of 24 h pH studies as part of the investigation of children with suspected gastro-oesophageal reflux disease (GORD), and provide a practical guide on when a pH study is indicated, how to perform pH studies and how to interpret the results.

BACKGROUND

Gastro-oesophageal reflux (GOR) is defined as the effortless regurgitation of gastric contents into the oesophagus. GORD is defined as GOR associated with sequelae (table 1) including faltering growth.[2]

Physiological reflux is common in both primary and secondary care settings, and usually improves with age.[3] Improvement is due to a combination of factors including growth in the length of the oesophagus, a more upright posture, increased tone of the lower oesophageal sphincter, and a more solid diet. In most cases, diagnosis is based on clinical assessment without the need for invasive testing. Investigation is reserved for those children in whom, for example, there is doubt about the diagnosis, or empirical therapy is considered to have failed, or for those children with extra-intestinal manifestations, such as acute life threatening events (ALTEs), apnoeas, Sandifer syndrome, asthma or faltering growth, in whom reflux is suspected to be a contributing factor.

In children with co-existing problems, such as asthma, cerebral palsy, epilepsy or congenital heart disease, GORD may be part of a complex interaction of pathologies as a primary or secondary phenomena. In such settings children may benefit from the diagnosis and treatment of GORD, and GORD may be improved by optimal treatment of the child's co-existing problems.

Children with isolated GORD can remain symptomatic into adulthood; severe oesophagitis[4] and oesophageal strictures from GORD in childhood have been reported.[5]

Table 1 Symptoms associated with gastro-oesophageal reflux disease

Intestinal manifestations	Infants: vomiting/regurgitation, irritability, back arching Older children: heartburn, dysphagia, nausea, epigastric pain
Extraintestinal manifestations	Respiratory: recurrent pneumonia, cough, sinusitis, asthma
	Neurological: apnoeas, ALTEs/SUDI, Sandifer syndrome +faltering growth, iron deficiency anaemia

ALTE, apparent life-threatening event; SUDI, sudden unexpected death in infancy.

INVESTIGATION OF REFLUX

The investigation of reflux is difficult but multiple investigative modalities are available. The clinical situation and the clinical question being asked determine the usefulness of each test, and may therefore affect the sensitivity and specificity of the test. The 24 h pH study is currently considered to be the gold standard investigation for assessing acid reflux,[1] and we will outline its role within the investigation of GORD. Upper gastrointestinal endoscopy with biopsies is the gold standard for diagnosing oesophagitis. Other investigations include a barium meal to exclude hiatus hernia or distal obstruction (eg, malrotation), scintigraphy and intraluminal impedance.

THE PHYSIOLOGICAL BASIS OF THE PH PROBE TECHNIQUE

Acid reflux into the oesophagus occurs in all infants as a physiological phenomenon and is only significant when it occurs in excess.[2] Acid reflux has been demonstrated in premature infants, who can maintain a basal gastric pH below 4 from the first day of life.[6] By 6 months of age, an infant's ability to maintain an acid intragastric pH is similar to that of an adult.[7] Transient lower oesophageal sphincter relaxation is the most common cause of reflux, the frequency and duration of which are more marked in GORD.[8] Gastric acid may also persist in the oesophagus due to impaired luminal clearance, as seen in oesophageal dysmotility.[9]

The pH probe is designed to measure acidity (ie, acid reflux) in the lower oesophagus.

The pH probe is a microelectrode passed through the nose and down the back of the throat to sit above the lower oesophageal sphincter. The probe was first used in 1969 in adults, with an acid reflux episode defined as an oesophageal pH of <4[10] for a specified minimum duration, usually 15–30 s.[6] A set period, usually 24 h, is recorded (figs 1–3), with note made of the number of episodes, frequency of episodes, and the relationship of reflux to eating, position, sleeping or activity, and, especially, symptoms. The most sensitive marker of acid reflux on pH study is the reflux index. This is defined as the percentage of time that oesophageal pH is <4. This has been validated in several studies.[2]

The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) consensus recommendation is that the upper limit of normal of the reflux index is defined as up to 12% in the first year of life and up to 6% thereafter (table 2).[2] There is considerable debate about the upper limit of normal for the reflux index in preterm and term babies.[11]

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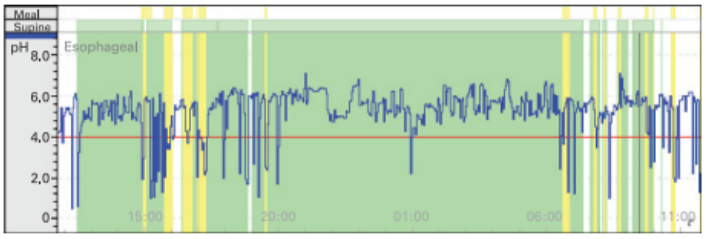

Figure 1 Example of normal 24 h pH probe; reflux index 2%.

TECHNICAL ISSUES

The patient needs to stop anti-reflux medications prior to the pH study (table 3). The child is generally monitored as an inpatient to enable supplementary observations, for example of the feeding pattern and a sleep study, and so that any technical issues that arise during the period of monitoring, such as probe displacement, can be dealt with. An ambulatory pH probe can be considered if admission to hospital is likely to significantly impact on the result.

WHERE TO SITE THE PROBE

The correct length should be estimated using the formula in table 4 and positioning should be confirmed using a chest *x* ray (CXR) or screening, due to the risk of malposition in the tracheobronchial tree or coiling in the oesophagus. The probe tip on CXR would be adequately positioned at T9. The operator should be trained in the placement of pH probes, the interpretation of CXR and the analysis of results. A pH study of <12 h duration produces less reproducible results.[12 13] A pH probe with a baseline that is rarely >4 suggests displacement into the stomach.

LIMITATIONS OF TEST

There are several limitations to pH studies, as follows:

- 1) pH studies are unable to detect anatomical abnormalities (eg, stricture, hiatus hernia or malrotation) or aspiration.
- 2) Non-acid reflux will not be detected. This should be borne in mind with non-acidic feeds such as infant formula.[14]
- 3) The changes in environment, diet and behaviour as a result of investigation and admission to hospital may impact on the result.
- 4) There is potential for technical difficulties.
- 5) pH studies provide no objective measures of inflammation, and thus are less useful than endoscopy and biopsies for the diagnosis and grading of oesophagitis.

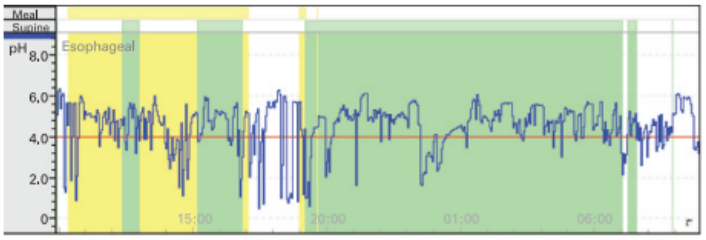

Figure 2 Example of mild acid reflux on 24 h pH probe; reflux index 8.9%.

It is crucial to have a trained operator and well-maintained equipment. The test could be misleading if, for example, the medications have inadvertently been continued, equipment is not calibrated before each test or the probe tip is misplaced or displaced.[15]

The usefulness of the test will be improved by defining a clear diagnostic question. So for a child with possible apnoeas secondary to GORD, including accurate documentation of the chronology of symptoms during the pH study is essential.

VALIDATION

Are pH studies reliable?

There is no true gold standard test for GOR, but pH studies have a sensitivity of 93–96%[1 16] in identifying acid reflux in patients diagnosed with oesophagitis on endoscopy (in both macroscopic and histological appearances). In interpreting pH studies, the most reliable marker of acid reflux is the reflux index, which has a reported sensitivity and specificity of >94%. This is significantly superior to other markers, such as the number of reflux episodes and the number of episodes of acid reflux lasting >5 min.[17 18] Normal values, used as the basis for the NASPGHAN consensus statement, were established by Vandenplas *et al*, who studied 509 healthy infants and found that the reflux index upper limit of normal (95th centile) for all infants was 12% (13% at birth, 8% at 1 year of age).[19]

Although there is a correlation between a higher reflux index and worse symptoms and endoscopy findings, there are few data to dichotomise reflux index into "mild" and "severe" (either in terms of symptom score or endoscopic appearances), so the labels of reflux index ("severe" or "mild") lie on a spectrum (figs 2 and 3).[4] There is some evidence to show that patients with a worse reflux index respond better to omeprazole compared to ranitidine.[3]

Short-term pH probes (6 h recording including up to 2 h after a meal) can be considered in selected patients. These include older children without comorbidities, for example co-existent respiratory problems. A total of 160 children (aged <12 months to 14 years) were assessed first by 6 h pH probes and then by 24 h pH probes by Barabino *et al*.[13] The authors found that the negative predictive value of the 6 h reflux index was up to 90% for selected patients, and the positive predictive value was 50–83% (lower in infants and in those with co-existing respiratory symptoms).

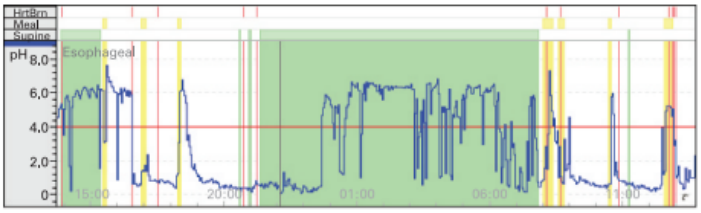

Figure 3 Example of severe acid reflux on 24 h pH probe; reflux index 48%.

Are pH studies reproducible?

In the largest study in children, Vandenplas *et al* looked at 30 children (aged 2 weeks–8 years) with a clinical diagnosis of GORD who had had two 24 h pH studies on consecutive days, using reflux index, number of reflux episodes with pH <4, longest reflux episode and the number of reflux episodes >5 min as parameters.[21] The reflux index and the number of reflux episodes >5 min were the most reproducible criteria (r = 0.97 and 0.98, respectively). They also assessed the mean difference between day 1 and day 2 readings for each parameter as a marker of reproducibility. Taking the mean difference as zero (perfectly reproducible), they expected that 95% of the differences for each parameter would fall within 2 standard deviations of the mean difference (a reproducibility coefficient adopted by the British Standards Institution).[20] Reflux index, longest reflux episode and the number of reflux episodes >5 min all satisfied this test of reproducibility. Hence the authors concluded that pH probes were reproducible.

On the other hand, Hampton *et al* looked at 13 children, 11 of whom had two 24 h pH studies on consecutive days.[22] They found that the reflux index could vary between consecutive studies; although eight children had similar reflux index results (either normal (<5%) or abnormal (>5%)) on both days, five children had one normal and one abnormal pH probe result. However, all these children had pH probes for extra-intestinal manifestations (apnoeas or respiratory symptoms) and none had undergone endoscopy. No treatments were stopped prior to the pH studies.

Wiener *et al* looked at 59 adults, with two ambulatory 24 h pH probes performed 10 days apart.[23] They assessed all pH parameters as "normal" (eg, reflux index ⩽4.4%) or "abnormal" (reflux index >4.4%) for both tests. Reflux index was the most reproducible parameter, with 93% agreement in healthy patients and patients with oesophagitis. Variability (logarithmic transformation of reflux index) between pH parameters was >90% if either very normal (reflux index <1.8%) or abnormal (>9.4%), but higher (30%) if the result was 3–4%. Murphy *et al* investigated 15 adults with GORD with two pH probes simultaneously placed 5 cm above the lower oesophageal sphincter. A number of differences were noticed between the results, and in two patients the differences were wide enough to change the clinical diagnosis.[24]

Table 2 Range of upper normal limits for age

Reflux index	Infants: 12%*
	Older: 6%*
Number of episodes of acid reflux	Infants: 72 episodes/day[18]
	1–9 years of age: 25*
Number of episodes of acid reflux lasting >5 min per day	Infants: 10 episodes/day[18]
	Children: 7*
	Adolescents/adults: 3*
Length of episode (min)	Infants: 41 min[18]
	Children: 7†

*NASPGHAN consensus[2]; †Cucchiara (n = 63).[1]
Table based on[18] Vandenplas (n = 504).

Are there alternatives to 24 h oesophageal pH studies?

Further discussion on the role of other investigations is available elsewhere[1 13 25] and pH studies should be considered as one potential modality in the diagnostic work up of GORD. Other investigations include combined intragastric and oesophageal pH monitoring, intraluminal impedance, barium swallow and scintigraphy. Combined intragastric and oesophageal pH monitoring is designed to increase the negative predictive value of a pH study by estimating the confounding impact of milk in alkalinising gastric secretions. However, no clear protocol has yet been developed in children with suspected GOR and disagreement exists as to whether a single intragastric electrode placed in the fundus or two electrodes are needed in the fundus and antrum based on evidence that the pH can be significantly different between the fundus and antrum in adult controls.[26]

Intraluminal impedance measures reflux from retrograde flow of a liquid bolus as it passes from the stomach through the oesophagus toward the oropharynx,[27] and thus is pH independent (and will detect non-acid reflux). Intraluminal impedance is increasingly being used in conjunction with pH studies.

Scintigraphy in some centres has a sensitivity of up to 59% and a specificity of up to 100% for GOR,[28] and can be used to investigate aspiration of isotope into the lungs and assess gastric emptying. A barium swallow can help to exclude surgical causes of vomiting (eg, oesophageal stricture or malrotation). The sensitivity, specificity and positive predictive value of a barium swallow for detecting GOR compared to oesophageal pH studies are 31– 86%, 21–83% and 80–82%, respectively.[2]

CLINICAL QUESTIONS

Question 1

> In children with symptoms of physiological GOR [patients], does a pH probe study [intervention] improve family satisfaction or reduce family concerns [outcome]?

A detailed history and examination is usually all that is required in this patient group to exclude

Table 3 When to stop anti-reflux medications

Medication	Pharmacokinetics	Recommended to stop
Gaviscon	Not absorbed[50] Cleared from stomach by 6 h	24 h before
Proton pump inhibitors (eg, omeprazole lansoprazole)	$t_{1/2}$: 1.2–2 h[51] Resumption of acid suppression 48 h[52]	72 h before
H2 receptor antagonists (eg, ranitidine, cimetidine)	Duration of action: 24 h. Plasma clearance in 6–8 h.	72 h before
Prokinetics		48 h before
Domperidone	Oral $t_{1/2}$: 12 h[53]	
Metoclopramide	Oral $t_{1/2}$: 4.5 h[54]	
Erythromycin	Oral $t_{1/2}$: 2 h[55 56]	

other causes. Assessment of weight gain is crucial, and a feeding history is important to exclude, for example, overfeeding. Up to 50% of infants less than 3 months old regurgitate at least one feed daily.[29] The natural history is of improvement with age; in one paediatric gastroenterology outpatient clinic, 55% of babies diagnosed with physiological GOR were symptom free by 10 months and 81% by 18 months of age.[30] A study evaluating children with GOR found no benefit in pH studies if there were no features of concern[31]; however, a pH probe may be of benefit if there is diagnostic uncertainty, or as part of the investigation of infants with a history of poor feeding or irritability. pH studies can for example be useful in demonstrating resolution of symptoms, particularly if there are continuing anxieties about feeding and it is uncertain whether reflux is a factor. The child's medications are stopped before admission. On admission the parents can be asked about symptoms off treatment, and observation of symptoms can take place over 24 h while the child is in hospital for the pH study. The pH study report and assessment of symptoms can then be used as part of the decision-making process.

Question 2

> In children with symptoms of GORD [patients], who undergo pH testing [investigation] what proportion are found to be significantly abnormal [outcome]?

An abnormal reflux index is found in 95% of paediatric patients with endoscopic oesophagitis (ulcerations or erosions) or biopsy-proven oesophagitis.[1 15]

Cucchiara looked at 24 h pH studies in 114 children (aged 1 month–12 years) and found that 45 patients had reflux without oesophagitis and 69 had reflux oesophagitis confirmed on endoscopy[1]; 63 control patients also had 24 h pH studies.

Table 4 Formula for assessing pH probe placement

Nose to diaphragm (LOS)	0.24 × patient's height (cm)+5.2	Correlation r = 0.96[57]
Mouth to diaphragm (LOS)	0.226 × patient's height (cm)+6.7	Correlation r = 0.97[58]

LOS, lower oesophageal sphincter.

Some 20–30% of all reflux patients had both a normal acid exposure time and a normal number of long lasting reflux episodes. Patients with oesophagitis had significantly more acid reflux than those with simple uncomplicated disease (except during sleep); however, increasing severity of oesophagitis was not associated with increasing acid exposure.

pH monitoring can be used to assess whether medication is still needed if symptoms have resolved and give an opportunity to assess current symptoms off treatment. The pH probe results can often be interpreted in the light of this.

Question 3

> In premature infants with apnoea [patients], does undertaking pH studies [investigation] or using anti-reflux medication [treatment] affect episodes of apnoea, cough or aspiration pneumonia [outcome]?

Apnoea secondary to reflux is more likely within 1–2 h after a feed, and may present with obstruction (persisting respiratory symptoms) rather than central apnoea (absent respiratory effort), which may reflect apnoea of prematurity.[32] Dhillon *et al* noted that 22% of all extremely low birth weight (<1 kg) infants received an empirical trial of prokinetics and/or Gaviscon for feeding intolerance and recurrent episodes of apnoea, bradycardia or desaturations,[32] indicating the frequency of the presentation. However, a causal relationship between reflux and apnoeas has not yet been demonstrated, either by assessing acid reflux using pH probes or the presence of refluxate using intraluminal impedance. Di Fiore *et al* (assessing 119 preterm babies with 6255 episodes of GOR)[33] and Barrington *et al* (45 infants with 10 apnoeas per pH probe recording) found no temporal relationship using pH probes.[34] Peter *et al* looked at 19 babies (524 reflux episodes and 2039 apnoeas) and found no temporal relationship using intraluminal impedance.[35] Varying the position of the pH probe does not alter sensitivity or specificity, for example upper oesophageal pH studies are no more sensitive than lower oesophageal pH studies for detecting upper airway complications of GOR.[36]

In some patients oesophageal pH monitoring may be within normal limits but brief episodes of GOR may result in complications such as persisting cough or aspiration pneumonia, or apnoea/ALTE.[1]

Question 4

> In children with asthma [patients], does undertaking pH studies [investigation] or using anti-reflux medication [treatment] affect respiratory symptoms [outcome]?

The relationship between poorly controlled asthma and acid reflux is complicated. Up to 60% of children with refractory asthma had abnormal oesophageal pH monitoring studies.[37–39] A

Clinical bottom line

- The pH probe is a generally safe, reliable test of acid reflux in children and infants.
- It does not detect alkaline reflux.
- It is part of the diagnostic work up of gastro-oesophageal reflux disease.
- Results must be interpreted in the context of clinical signs.
- The pH study is highly reliable for detecting acid reflux in oesophagitis.
- The pH study is useful in recurrent pneumonia but a poor discriminator in babies with apnoea or persistent cough.
- Always consider whether a pH study is the right investigation.
- The period when a child's medication has been stopped for a pH probe can provide useful clinical data.
- The pH study is useful in providing evidence of resolution of acid reflux.

Cochrane review evaluated 12 studies of which four addressed the role of acid reflux in children with asthma.[40] These studies identified some children in whom reflux was temporally associated with asthma[41 42] but no consistent effect of anti-reflux medication on asthma outcomes (eg, improved symptoms, FEV_1 or peak expiratory flow (PEF)) within these studies. Two studies showed a significant improvement in reported symptoms of wheeze. Other studies have failed to show an improvement in FEV_1, PEF or asthma symptoms with treatment of acid reflux, although in patients with asthma GORD symptoms lessened and the reflux index improved following administration of proton pump inhibitors (PPIs).[43]

The clinical bottom line is that it is not possible (with the current limited evidence) to recommend medical treatment of GOR as a means to control asthma. There may be a subgroup of responders, but they are difficult to identify.

Question 5

> In children with chronic cough [patients], does undertaking pH studies [investigation] or using anti-reflux medication [treatment] affect respiratory symptoms [outcome]?

Cough and GOR often co-exist. Three paediatric studies were assessed by a Cochrane review and none were suitable for inclusion for analysis.[44] One study (with eight patients) suggested that cough in association with known reflux persists when pH studies are normalised with high dose PPIs, and that cough can take a year to settle even after commencing a PPI.[45]

Little *et al*[46] looked at 222 children (aged 1 day–16 years) with a double probe (simultaneous oesophageal and pharyngeal pH monitoring) over 24 h. A total of 168 (76%) had abnormal findings in either one or both of the pH probes. Of those, 46% (78/168) had evidence of increased pharyngeal acid reflux with normal oesophageal acid exposure times. Patients with laryngeal or pulmonary manifestations had significantly more pharyngeal acid reflux ($p<0.001$) than patients with non-respiratory symptoms.

A validated clinical algorithm exists in adults to identify those whose cough is caused by GOR. A 24 h oesophageal pH study is one of these investigations[44] but has not been validated in children.

The clinical bottom line is that the relationship between reflux and cough is complex and further research is needed. More work is also needed to assess whether 24 h oesophageal pH studies can help to differentiate those subgroups of children with co-existent GOR and cough from those children with cough caused by GOR.

Question 6

> In children with recurrent pneumonia [patients], does undertaking pH studies [investigation] or using anti-reflux medication [treatment] affect respiratory symptoms [outcome]?

Chen *et al* performed pH studies on 23 children between 3–25 months of age, 21 of whom had an abnormal study (with 14 children having a reflux index of >10%).[47]

The clinical bottom line, as recommended in the NASPGHAN consensus statement, is that in cases of recurrent pneumonia where GORD is suspected, a 24 h oesophageal pH study may be indicated.[2]

Question 7

> In children with neurodisability and symptoms of GORD [patients], does investigation and treatment of GORD [intervention] improve quality of life, recurrent pneumonia or abdominal pain [outcome]?

Children with neurodisability often have a degree of global gut dysmotility as part of their clinical presentation and are more likely to have GOR, with delayed gastric emptying and raised intra-abdominal pressure from scoliosis, as well as increased transient relaxations of the lower oesophageal sphincter with impaired clearance of acid reflux from the oesophagus (oesophageal dysmotility). They can present with vomiting (and haematemesis) and recurrent pneumonia, or as unsettled and posturing. Schwarz *et al* assessed 79 patients with neurological impairment and feeding problems, and noted that 56% had an abnormal 24 h pH probe.[48] However, there is no formal consensus on whether pH probe is the gold standard test in this group, given the underlying dysmotility.[49] Consideration may be given to initial empirical treatment of symptoms with PPIs.

Competing interests: None.

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Article III: Cochrane review (2014): Pharmacological treatment of children with gastro-oesophageal reflux

Tighe MP, Afzal NA, Bevan A, Hayen A, Munro A, Beattie RM, 2014. Pharmacological treatment of children with gastro-oesophageal reflux. *Cochrane Database of Systematic Reviews*, (11), CD008550. https://doi.org/10.1002/14651858.CD008550.pub2

What does this paper achieve?

This review was performed using Cochrane methodology so only assessed RCTs of pharmacological treatments (not including thickened feeds or metoclopramide). I led the review, which used RevMan 5.1 and assessed the evidence-base to make robust recommendations regarding the likely treatment-effect, as well as assessing risk of bias (using RevMan). It has been well-cited (104 times) elsewhere in other related publications.

Implications for practice

The evidence base of therapies for infants is mixed. In terms of pharmacological strategies, a clear distinction was drawn between the treatment of infants with GOR and those with gastro-oesophageal reflux disease (those with sequelae of GOR, or failure to thrive). In the subgroup of infants with diagnosed GOR, the main problem appeared to be caused by the milk bolus, although acid reflux undoubtedly occurs. Underlying transient gut dysmotility, with dysfunction of the lower oesophageal sphincter, a short oesophagus, high volumes of liquid feeds and a significant proportion of time lying flat are important predisposing factors that improve with time. In such a large group, the evidence also highlighted significant discrepancies between reported symptom severity scores and endoscopic/histological findings, which are potentially affected by the numbers of children with distressing symptoms but GOR.

In terms of efficacious treatments in infants, the best evidence for treatment of diagnosed GOR appeared to relate to Gaviscon Infant®, with short-term studies with small numbers of participants. One study demonstrated lack of symptomatic benefit from PPIs in infants with diagnosed GOR. For infants with evidence of GORD on investigation (endoscopic changes or abnormal reflux index on pH or pH/impedance testing), evidence of benefit from any medical treatment is weak. Further studies would help to confirm whether PPIs or H_2 antagonists are superior in the group, and whether individual drugs offer superior efficacy. Weak evidence was found for acid suppression with PPIs/ H_2-receptor antagonists, with consequent decreased gastric enzyme activity helping healing of oesophagitis, and symptomatic improvement. The paper was

unable to comment as to whether H_2 antagonists are superior to PPIs, but no evidence supports concurrent use. No consistent evidence for prokinetics (such as domperidone) was found and one conclusion was that it is currently difficult to justify continuing prescriptions of domperidone in infants for whom no benefit from empirical use has been reported and the current MHRA (Centre of the Medicines and Healthcare Products Regulatory Agency) alert recommends restricting empirical prescriptions to two weeks and avoiding them in infants and children with co-existing cardiac disease and in those receiving treatment with CYP3A4 inhibitors (EMA 2014).

Among older children with GORD, moderate evidence of benefit from PPIs has been found, along with weak evidence of benefit from H_2 antagonists, in providing symptomatic relief and in improving endoscopic/histological appearances and pH/impedance indices. No consistent evidence has been found for prokinetics (such as domperidone) and as above, it is currently difficult to justify prescriptions for domperidone among children for whom no benefit from empirical use is apparent.

Implications for research

Undoubtedly the burden of GOR and GORD on primary and secondary care is large, and further research is essential to clarify the role of medications in treating particular aspects of GOR. This review demonstrated the benefit of the Pediatric Written Request (PWR) made by the FDA in improving our knowledge of PPIs, including an incentivising 6-month period of marketing exclusivity. This review called for this process to be extended to the remainder of the medications used to treat GOR (e.g. H_2 antagonists/Gaviscon Infant®). The review also called for comparisons that include a placebo or different drug arm, as well as/rather than comparisons between same-drug different dosing. It was evident that significant confounding interventions that would be likely to provide significant improvements as interventions in their own right (e.g. thickened or hydrolysed feeds to infants) were often given within trials to participants. Separate funding to support these calls would be a major step forward, and at least separating more clearly industry funding for the trial from manuscript preparation would reduce risk of bias. Several of the recent PPI trials carried out under the PWR have declared support in manuscript writing from pharmaceutical manufacturers, and this carries inherent risks.

The need for specific RCTs into children with underlying oesophageal dysmotility was highlighted (e.g. children with cerebral palsy), who often have difficult and protracted reflux, as most of these trials specifically excluded this subgroup. Premature babies are often also treated empirically for gastro-oesophageal reflux, for example, causing apnoea; further RCTs in this age group, using consistent outcomes, are also recommended.

How does it contribute to the evidence-base?

Using Cochrane methodology, this review provides a better perspective on the current evidence-base, allowing the strength of recommendations to be adjusted according to the risk of bias. The review highlighted the paucity of longer-term data, the evidence of absence of effect of domperidone and erythromycin, and the impact of the pharmaceutical industry on trial design and manuscript-writing.

What were the next steps?

Following this publication, and contemporaneous publication of NICE guidance (Article IV), I identified children with neurodisability (Articles VII and VIII) as being particularly vulnerable to the effects of GORD and thus a particular area needing further research. I had intended to undertake a comparative head-to-head trial of effective treatments in children with neurodisability, and in order to undertake this I needed to ascertain current prescribing practices in children with neurodisability (Article VII), and to develop a robust outcome measure. A symptom questionnaire such as I-GERQ or P-GSQ would need to be significantly altered and validated for use in any subsequent trial for this subgroup (Article VIII).

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Pharmacological treatment of children with gastro-oesophageal reflux (Review)

Tighe M, Afzal NA, Bevan A, Hayen A, Munro A, Beattie RM

Tighe M, Afzal NA, Bevan A, Hayen A, Munro A, Beattie RM.
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[Intervention Review]

Pharmacological treatment of children with gastro-oesophageal reflux

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ABSTRACT

Background

Gastro-oesophageal reflux (GOR) is a common disorder, characterised by regurgitation of gastric contents into the oesophagus. GOR is a very common presentation in infancy in both primary and secondary care settings. GOR can affect approximately 50% of infants younger than three months old. The natural history of GOR in infancy is generally that of a functional, self-limiting condition that improves with age; < 5% of children with vomiting or regurgitation continue to have symptoms after infancy. Older children and children with co-existing medical conditions can have a more protracted course. The definition of gastro-oesophageal reflux disease (GORD) and its precise distinction from GOR are debated, but consensus guidelines from the North American Society of Gastroenterology, Hepatology and Nutrition define GORD as 'troublesome symptoms or complications of GOR.'

Objectives

This Cochrane review aims to provide a robust analysis of currently available pharmacological interventions used to treat children with GOR by assessing all outcomes indicating benefit or harm.

Search methods

We sought to identify relevant published trials by searching the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 5), MEDLINE and EMBASE (1966 to 2014), the Centralised Information Service for Complementary Medicine (CISCOM), the Institute for Scientific Information (ISI) Science Citation Index (on BIDS—UK General Science Index) and the ISI Web of Science. We also searched for ongoing trials in the *meta*Register of Controlled Trials (*m*RCT).

Reference lists from trials selected by electronic searching were handsearched for relevant paediatric studies on medical treatment of children with gastro-oesophageal reflux, as were published abstracts from conference proceedings (published in *Gut* and *Gastroenterology*) and reviews published over the past five years.No language restrictions were applied.

Selection criteria

Abstracts were reviewed by two review authors, and relevant RCTs on study participants (birth to 16 years) with GOR receiving a pharmacological treatment were selected. Subgroup analysis was considered for children up to 12 months of age, and for children 12 months to 16 years of age, and for those with neurological impairment.

Data collection and analysis

Trials were critically appraised and data collected by two review authors. Risk of bias was assessed. Meta-analysis data were independently extracted by two review authors, and suitable outcome data were analysed using RevMan.

Main results

A total of 24 studies (1201 participants) contributed data to the review. The review authors had several concerns regarding the studies. Pharmaceutical company support for manuscript preparation was a common feature; also, because common endpoints were lacking, study populations were heterogenous and variations in study design were noted, individual drug meta-analysis was not possible.

Moderate-quality evidence from individual studies suggests that **proton pump inhibitors (PPIs)** can reduce GOR symptoms in children with confirmed erosive oesophagitis. It was not possible to demonstrate statistical superiority of one PPI agent over another.

Some evidence indicates that **H_2antagonists** are effective in treating children with GORD. Methodological differences precluded performance of meta-analysis on individual agents or on these agents as a class, in comparison with placebo or head-to-head versus PPIs, and additional studies are required.

RCT evidence is insufficient to permit assessment of the efficacy of **prokinetics**. Given the diversity of study designs and the heterogeneity of outcomes, it was not possible to perform a meta-analysis of the efficacy of domperidone.

In younger children, the largest RCT of 80 children (one to 18 months of age) with GOR showed no evidence of improvement in symptoms and 24-hour pH probe, but improvement in symptoms and reflux index was noted in a subgroup treated with domperidone and co-magaldrox(Maalox®). In another RCT of 17 children, after eight weeks of therapy. 33% of participants treated with domperidone noted an improvement in symptoms (P value was not significant). In neonates, the evidence is even weaker; one RCT of 26 neonates treated with domperidone over 24 hours showed that although reflux frequency was significantly increased, reflux duration was significantly improved.

Diversity of RCT evidence was found regarding efficacy of compound alginate preparations(Gaviscon Infant®) in infants, although as a result of these studies, Gaviscon Infant® was changed to become aluminium-free and has been assessed in its current form in only two studies since 1999. Given the diversity of study designs and the heterogeneity of outcomes, as well as the evolution in formulation, it was not possible to perform a meta-analysis on the efficacy of Gaviscon Infant®. Moderate evidence indicates that Gaviscon Infant® improves symptoms in infants, including those with functional reflux; the largest study of the current formulation showed improvement in symptom control but was limited by length of follow-up.

No serious side effects were reported.

No RCTs on pharmacological treatments for children with neurodisability were identified.

Authors' conclusions

Moderate evidence was found to support the use of PPIs, along with some evidence to support the use of H_2 antagonists in older children with GORD, based on improvement in symptom scores, pH indices and endoscopic/histological appearances. However, lack of independent placebo-controlled and head-to-head trials makes conclusions as to relative efficacy difficult to determine. Further RCTs are recommended. No robust RCT evidence is available to support the use of domperidone, and further studies on prokinetics are recommended, including assessments of erythromycin.

Pharmacological treatment of infants with reflux symptoms is problematic, as many infants have GOR, and little correlation has been noted between reported symptoms and endoscopic and pH findings. Better evidence has been found to support the use of PPIs in infants with GORD, but heterogeneity in outcomes and in study design impairs interpretation of placebo-controlled data regarding efficacy. Some evidence is available to support the use of Gaviscon Infant®, but further studies with longer follow-up times are recommended. Studies of omeprazole and lansoprazole in infants with functional GOR have demonstrated variable benefit, probably because of differences in inclusion criteria.

No robust RCT evidence has been found regarding treatment of preterm babies with GOR/GORD or children with neurodisabilities. Initiation of RCTs with common endpoints is recommended, given the frequency of treatment and the use of multiple antireflux agents in these children.

PLAIN LANGUAGE SUMMARY

Medicines for children with gastro-oesophageal reflux

Review question

Most babies grow out of their symptoms of reflux as they eat more solid food and spend more time upright, and as the length of the oesophagus grows, but do medicines help to make them more comfortable while this is happening? Older children can have heartburn, just like adults. Which treatment works best for them?

Background

Gastro-oesophageal reflux happens when stomach contents come back up into the food pipe (oesophagus). This can be a normal event ('functional reflux'), but in some children, and in many babies, it can happen a lot, or it can cause symptoms such as pain, weight loss or other problems (e.g. ear infection, cough, even pauses in breathing). If this happens, the condition can be labelled as gastro-oesophageal reflux disease (GORD). Sometimes the oesophagus becomes inflamed—a condition known as 'oesophagitis.'

Current medicines (e.g. Gaviscon Infant®) aim to thicken stomach contents, neutralise stomach acid (ranitidine, omeprazole, lansoprazole) or help the stomach to empty faster (domperidone). We looked at all available studies to try to find out whether any of the medicines currently used for reflux can help babies and children. We wanted to know whether these medicines make babies and children feel better, or whether test results (such as healing of the lining of the oesophagus, assessed through endoscopy (a small camera passed down the food pipe), or lowering of the amount of acidity in the oesophagus, assessed using a pH probe over 24 hours) get better when these medicines are given.

Study characteristics

We included all studies (randomised controlled trials) comparing one type of medicine against another, or against an inactive medicine (placebo). We carefully looked at study results and tried to assess those that would be important to doctors, nurses and parents. We found a lot of differences between studies, and the small numbers of children included in the studies, the short follow-up provided and differing outcomes made combining the data (meta-analysis) in a meaningful way difficult.

Key results

Overall as a result of the small numbers of children recruited to these studies, we could not be certain whether medicines improve symptoms. We found little evidence to suggest that medicines for babies younger than one year work, especially for functional reflux; mixed evidence has been found on whether Gaviscon Infant® helps, and for infants with reflux disease (changes on pH studies or on endoscopy), medicines like omeprazole and lansoprazole are likely to help. In older children, proton pump inhibitors and histamine antagonists work better to improve symptoms, endoscopy appearances and pH probe findings, but we were unable to perform a meta-analysis, or to assess further whether one medicine was superior to another.

Quality of the evidence

Overall available evidence was of moderate to low quality, depending on the medicine in question. We have made suggestions as to how future studies could be designed to provide better answers regarding which treatments are best for babies and children with reflux or reflux disease.

BACKGROUND

Description of the condition

Gastro-oesophageal reflux (GOR) is a common problem, characterised by passage of gastric contents into the oesophagus (NASPGHAN-ESPGHAN guidelines 2009). GOR is a very common presentation in both primary care and secondary care settings. GOR can affect approximately 50% of infants younger than three months of age (Nelson 1997). The natural history of GOR generally includes improvement with age, with < 5% of children with vomiting or regurgitation in infancy continuing to have symptoms after the age of 14 months (Martin 2002). This occurs because of a combination of growth in length of the oesophagus, more upright posture, increased tone of the lower oesophageal sphincter and a more solid diet.

Gastro-oesophageal reflux disease (GORD) is defined as 'GOR associated with troublesome symptoms or complications' (Sherman 2009), although the review authors caution that this definition is complicated by unreliable reporting of symptoms in children younger than eight years of age. Gastrointestinal sequelae include oesophagitis, haematemesis, oesophageal stricture formation and Barrett's oesophagitis. Extra-intestinal sequelae can include acute life-threatening events and apnoea, chronic otitis media, sinusitis, secondary anaemia and chronic respiratory disease (chronic wheezing/coughing or aspiration), as well as failure to thrive.

A recent study of 210 children with GOR in infancy diagnosed by Rome II criteria and followed up for 24 months showed that 88% were symptom-free by 12 months (Campanozzi 2009). However the presence of severe oesophagitis has been shown historically to predict the need for surgical reconstruction (Hyams 1988).

Children with certain predisposing conditions are more prone to severe GORD and include those with neurological impairment (e.g. cerebral palsy), repaired oesophageal atresia or congenital diaphragmatic hernia or chronic lung disease.

Diagnosis of functional GOR is usually made on the basis of symptoms alone, avoiding the need for expensive and possibly harmful investigations. Investigations conducted to assess the severity of GORD or in cases where GOR cannot be diagnosed on clinical grounds include 24-hour oesophageal pH monitoring, which can be combined with impedance monitoring, upper gastrointestinal endoscopy, oesophageal manometry, scintigraphy or sonography. All have been shown to correlate poorly with symptomatology and may not accurately predict the degree of improvement that can be attained with treatment (Augood 2003).

Description of the intervention

The main aims of treatment of children with GOR are to alleviate symptoms, promote normal growth and prevent complications.

Pharmacological treatments include those discussed in the following paragraphs.

Treatments that alter gastric pH

These medications improve symptoms not by reducing reflux but by reducing the acidity of refluxate, in theory reducing oesophageal irritation and providing symptomatic relief.

Proton pump inhibitors (PPIs)

PPIs such as omeprazole and lansoprazole constitute a group of drugs that irreversibly inactivate H+/K+-ATPase—the parietal cell membrane transporter. This action increases the pH of gastric contents and decreases the total volume of gastric secretion, thus facilitating emptying. Five PPIs have been approved by the US Food and Drug Administration for use in adults: omeprazole (since 1988), lansoprazole, pantoprazole, rabeprazole and esomeprazole (the pure S-isomer of omeprazole). Omeprazole is licenced in children over one year of age in the UK, and lansoprazole is recommended by the British National Formulary only for children for whom treatment with available formulations of omeprazole is unsuitable (BNF for children 2013). All are metabolised by the cytochrome P450 system within 60 minutes in adults, and all are relatively safe, with few reported side effects. PPIs are also safe in children with renal impairment, but hepatic metabolism of PPIs may be impaired. The efficacy of PPIs may be affected by immature parietal cells, which are less responsive, and by hypochlorhydria in the first 20 months. Gastric pH does provide some protection, as evidence suggests that potentiating hypochlorhydria in neonates further with omeprazole can result in bacterial overgrowth (Nelis 1994). Consequent increases in respiratory infections among critically ill patients have been identified, but in infants and children who are otherwise well, no clear ill effects have been demonstrated with this overgrowth. An MHRA (Centre of the Medicines and Healthcare Products Regulatory Agency) alert in 2012 highlights that PPIs used for longer than three months may be associated with hypomagnesaemia and increased risk of fracture in the elderly (MHRA 2012a; MHRA 2012b).

H_2-receptor antagonists (H2RAs)

Several studies have suggested that H_2 antagonists are efficacious in children. Ranitidine is well tolerated and has a low incidence of side effects (common side effects include fatigue, dizziness and diarrhoea) (Cucchiara 1993). Ranitidine is the H_2 antagonist used most commonly to reduce the acidity of gastro-oesophageal reflux. Cimetidine is rarely used clinically, as concerns surround its effects on cytochrome P450, leading to multiple drug interactions and interfering with vitamin D metabolism and endocrine function. Famotidine is a recently developed H_2 antagonist that is not commonly used in children. Tachyphylaxis from H2 antagonists has been reported (Hyman 1985).

Antacids

Magnesium hydroxide and aluminium hydroxide (MHAH)

This agent reduces gastric pH and is commercially available as Maalox®. However, aluminium should be avoided in long-term use in infants and children with chronic renal failure because of the risk of aluminium accumulation.

Treatments that alter the motility of the gut (prokinetics)

These are considered when GOR fails to improve with conservative measures. Several classes of drugs have been designed to increase gastrointestinal motility.

Domperidone is a dopamine-receptor (D-2) blocker that is associated with relatively fewer side effects, but case reports have described extrapyramidal side effects (Franckx 1984; Shafrir 1985). Domperidone acts to increase motility and gastric emptying and to decrease postprandial reflux time. Domperidone is commonly

used in clinical practise as part of empirical medical therapy for gastro-oesophageal reflux disease or for individuals with delayed gastric emptying demonstrated on a barium swallow or milk scan. Concern is now emerging (EMA 2014) regarding the risk of cardiac side effects, and current advice states that domperidone should not be used in children with co-existing cardiac disease and in those taking CYP3A4 inhibitors, and that a daily dose of 30 mg should not be exceeded in children over 12 years of age; in younger children, no more than 250 micrograms/kg three times a day should be given. Domperidone should not be used to treat children with nausea and vomiting for longer than 1 week.

Erythomycin is a macrolide antibiotic that binds to the motilin receptor to promote peristalsis and gastric emptying, to decrease postprandial reflux time. Its use as a prokinetic is as an unlicenced indication.

Metoclopramide has alpha-sympathomimetic activity and blocks dopamine and serotonin receptors. Several adverse effects have been associated with metoclopramide in 11% to 34% of children. Adverse effects can include drowsiness or restlessness and the rarer extrapyramidal reaction (neck pain, rigidity, trismus and oculogyric crisis), which may be more likely with higher doses (Cucchiara 2000). Metoclopramide has been the subject of an FDA 'black box' warning (FDA 2009), and in August 2013, the European Medicines Agency released a statement indicating that the risk of neurological adverse events (such as short-term extrapyramidal disorders and tardive dyskinesia) associated with metoclopramide outweighed the benefit, when it is taken for a prolonged time at a high dose (EMA 2013). Metoclopramide has been assessed in a separate Cochrane review (Craig 2007); therefore we do not propose to review the literature regarding metoclopramide, as metoclopramide is rarely used to treat reflux in children because of its side effect profile.

Cisapride is a gastro-oesophageal prokinetic agent that stimulates motility in the lower oesophagus, stomach and small intestine by increasing acetylcholine release in the myenteric plexus and thereby controlling smooth muscle. At its peak, cisapride had been prescribed to more than 36 million children worldwide (Vandenplas 1999) and was recommended by the European Society for Paediatric Gastroenterology and Nutrition. However concerns about the effects of cisapride in prolonging the QT interval led to its removal from general paediatric use (Com Safety Med 2000). A Cochrane review found no clear evidence that cisapride reduces symptoms of GOR (Augood 2003). However evidence of substantial publication bias favoured studies showing positive effects of cisapride. The only study known to compare cisapride with another treatment (Gaviscon® with or without Carobel) failed to show superior efficacy (Greally 1992). Given the known risks of toxicity and suspension of its manufacture, further trials of cisapride are unlikely. As Cisapride has been the subject of a separate Cochrane review and is now no longer manufactured, we did not review the literature regarding cisapride.

Treatments that alter the viscosity of gastric contents

Alginates (e.g. Gaviscon Infant®)

Compound alginate preparations (hereinafter described as Gaviscon Infant®) contain sodium and magnesium alginate and mannitol; this preparation prevents reflux by increasing the viscosity of gastric contents (BNF for children 2013) and is differentiated from other Gaviscon® preparations, which can also contain sodium bicarbonate/potassium bicarbonate that, in the presence of gastric acid, forms a gel in which carbon dioxide (derived from the breakdown of bicarbonate) is trapped. This 'foam raft' floats on top of the gastric contents and is designed to neutralise gastric acid (providing symptomatic relief), thicken the feed (to reduce reflux) and reduce oesophageal irritation (Mandel 2000).

Caution should be used when alginates that contain aluminium are used (see below) in children with vomiting or diarrhoea or at risk of intestinal obstruction (Gaviscon Product Information 2008). In children whose feeds are already thickened (e.g. Enfamil AR/SMA Staydown), co-administered Gaviscon Infant® could potentially cause intestinal obstruction (Keady 2007). Gaviscon Infant® contains 0.92 mmol Na^+/dose, which should be considered if a child's sodium intake needs to be monitored with caution (e.g. renal impairment, congestive cardiac failure, preterm delivery, diarrhoea and vomiting) (BNF for children 2013). Gaviscon Infant® was changed to become aluminium-free, with different proportions of alginate, and has been assessed in its current form in only two studies since 1999.

Antispasmodics

Baclofen is primarily an antispasmodic acting on GABA receptors and is commonly used in children with neurodisability such as cerebral palsy. It has been used to treat co-existing reflux by aiming to improve the inco-ordination of the lower oesophageal sphincter, thereby reducing transient lower oesophageal sphincter relaxations (TLESRs).

Conservative options

Such options include reassuring parents and positioning the baby to reduce gastro-oesophageal reflux, through the effects of gravity on gastric contents. Approaches include elevating the head of the cot or basket in which the baby is placed to sleep and keeping the baby in an upright sitting position after a feed.

Altering the consistency of the feed can be achieved by using feed thickeners (e.g. Carobel) and by reducing the reflux of gastric contents with increased viscosity. Some feeds are manufactured with a thickening agent added (e.g. SMA Staydown/Infamil AR). Weaning has a similar effect by increasing the viscosity of gastric contents, and gastro-oesophageal reflux is known to improve with weaning. In this review, we have considered compound alginates but not feed thickeners, as these have been covered by a previous Cochrane review (Craig 2007).

Changes in milk can also improve GOR. Some evidence suggests that using a partially hydrolysed formula (e.g. Peptijunior) or a completely hydrolysed formula (e.g. Neocate) may ameliorate gastro-oesophageal reflux resulting from food protein intolerance. Hill and Hoskings looked at "a group of infants with distressed behaviour attributed to GOR who have failed to respond to H_2-receptor antagonists, prokinetic agents and multiple formula changes. Symptoms resolved on commencement of an elemental amino acid-based formula. In two-thirds of the patients, symptoms relapsed when challenged with low-allergen soy formula or extensively hydrolysed formula" (Hill 1999).

Surgical options

Such approaches are used to limit GORD. The most common strategy consists of a Nissen fundoplication involving a 360-degree wrap (Hassall 2005). This intervention aims to combine antireflux factors: reduction of hiatal hernia, creation of a valve/high-pressure zone at the distal oesophagus, placement of the distal oesophageal segment into the abdominal cavity with exposure to intra-abdominal positive pressure, re-creation of the diaphragmatic crural mechanism and re-creation of an acute angle. However when underlying dysmotility occurs, this will persist, and retching will continue as a prominent feature.

Conservative and surgical strategies are not addressed by this Cochrane review, which seeks to assess medical treatments for which various validated studies (e.g. randomised controlled trials (RCTs)) have been carried out and more formal evidence-based statements can be made to better inform medical practitioners (general practitioners (GPs)/paediatricians). Surgery is performed for a small minority of children with gastro-oesophageal reflux, and inclusion of this treatment would divert from the main focus of this review.

Why it is important to do this review

Gastro-oesophageal reflux in children is a common condition often presenting to general practitioners (GPs) and paediatricians. No systematic review has yet assessed the medical evidence for commonly prescribed treatments. This systematic review aims to critically appraise the existing paediatric literature by assessing all relevant RCTs.

Pharmacological treatment of children with gastro-oesophageal reflux is commonly provided by medical professionals for symptomatic relief. Medical prescribing for this condition is common; this Cochrane review aimed to assess the best available evidence for these commonly used treatments and to provide evidence-based recommendations for best medical practice.

OBJECTIVES

This Cochrane review aims to provide a robust analysis of currently available pharmacological interventions used to treat children with GOR by assessing all outcomes indicating benefit or harm.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) were considered and evaluated. Exclusions of randomised studies are justified below individually.

Types of participants

All children (birth to 16 years) with 'GOR associated with troublesome symptoms or complications.' Consideration was given to participant selection and the potential for selection bias. This involved assessing the strategy of recruitment and discussion of the processes of randomisation (this should be performed independent of and remote to the investigators) and blinding (up to and after the point of treatment allocation).

We analysed data on all children younger than 16 years of age. Subgroup analysis was undertaken in two groups: infants younger than 12 months of age, and children between 12 months and 16 years of age. These subgroups have different GOR characteristics, and consensus indicates that symptoms of GORD differ with age (Sherman 2009), for example, infants with symptomatic gastro-oesophageal reflux have different symptoms when compared with older children (who generally are consuming a more solid diet and are upright). In infants, differences in the prevalence of regurgitation, food refusal and crying have been highlighted between a healthy cohort and infants with abnormal oesophageal pH studies and/or abnormal biopsy findings. Heterogeneity in the quantification of 'regurgitation' among infants has been noted. Among children over 12 months of age, the older the child, the more heartburn and waterbrash become predominant presenting symptoms, with younger children more likely to present with posseting, irritability and back arching. Some sections of the review assess treatments such as alginates, which would be used mainly in the infant population.

We also avoided studies assessing pharmacological treatments for children with GORD with co-existent conditions such as tracheo-oesophageal fistula (TEF) or asthma that predispose to GORD. These studies should be excluded from this review to avoid heterogeneity between participants.

Types of interventions

All currently available medical treatments for gastro-oesophageal reflux in children were included in this review.

We considered all randomised controlled trials—those that compare the medication in question versus placebo or versus other medications; both types of studies will be of interest. No restrictions on dose, frequency or duration were applied. We have not assessed differences between generic preparations and branded antireflux medications in this review.

We attempted comparisons of all active treatments versus placebo, with respect to treatment class (i.e. compound alginate preparations vs placebo, proton pump inhibitors (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole) vs placebo, H_2 antagonists (ranitidine, famotidine, cimetidine) vs placebo, prokinetics (domperidone, erythromycin, bethanechol) vs placebo and sucralfate vs placebo). We noted that metoclopramide and thickened feeds had already been assessed in 2007, as was discussed above (Craig 2007).

Types of outcome measures

We included all reported outcomes that were likely to be meaningful to clinicians (such as general practitioners and paediatricians) in making a medical decision about treating children with gastro-oesophageal reflux. Useful discriminators for assessing improvement include clinical symptoms and thoroughness of the investigation.

Clinical symptoms include the following.

- Number of vomiting episodes, back arching, regurgitation, failure to thrive, feeding difficulties, or abdominal pain in infants.
- Heartburn, epigastric pain or regurgitation symptoms in older children.

'Regurgitation' is defined according to the Montreal criteria as occurring when relaxation of the lower esophageal sphincter (LES) allows retrograde movement of gastric contents into the oesophagus and beyond; it can include ejection of refluxate from the mouth. Regurgitation is distinguished from vomiting physiologically by the absence of:

- a central nervous system emetic reflex;
- retrograde upper intestinal contractions;
- nausea; and
- retching.

Regurgitation is generally characterized as effortless and non-projectile, although it may be forceful in infants (Sherman 2009).

Investigative tools include the following.

- 24-Hour pH probe and/or impedance studies.
  - Reflux index on pH probe = percentage of time with oesophageal pH < 4.
  - Number of reflux episodes.
- Macroscopic appearance of oesophagus on endoscopy.

Consensus indicates that insufficient data are available for histology to be recommended as a tool to diagnose or exclude GORD in children, but that histology is useful to rule out other conditions, such as eosinophilic esophagitis, Barrett's esophagus, Crohn's disease, infection and graft-versus-host disease (Sherman 2009). However, description of histological changes was considered, and, when relevant in helping clinicians, useful findings have been described below. No studies were excluded on the basis of outcome, but studies purely assessing pharmacokinetic outcomes or taste were not included, as they did not fulfil the original protocol for inclusion; corresponding authors were contacted to ensure that no relevant participant data were not published, to exclude outcome bias. In cases of uncertainty, corresponding authors were contacted for clarification.

Primary outcomes

Primary outcomes considered included improvement in clinical symptoms. These were usually assessed through questionnaires completed by parents and child care providers and include the following: number of vomiting episodes (continuous data), episodes of back arching (continuous data), number of episodes of regurgitation (continuous), failure to thrive (binary outcome), feeding difficulties (binary outcome) and abdominal pain in infants (continuous data). In older children, the numbers of episodes of heartburn, epigastric pain or regurgitation (continuous data) were again assessed through questionnaires completed by patients, parents and healthcare professionals. These included, for example, the GOR-Q questionnaire, which was completed daily by parents and healthcare professionals and provides quantitative data through validated symptom scores. Also included are any serious reported side effects associated with individual medical treatments (these are currently classified as serious suspected adverse reactions (SSARs) or suspected unexpected serious adverse reactions (SUSARs)), as defined by the Medicines Health Regulation Authority ("All adverse events judged either by the investigator or sponsor as having a reasonable suspected causal relationship to an Investigational Medicinal Product").

Secondary outcomes

Secondary outcomes included improvement in the reflux index (continuous data) or in the number of reflux episodes on 24-hour pH probe (continuous data), results of impedance studies (continuous) and improvement of oesophagitis on endoscopy (visual appearance—binary outcome). Different grading scales are currently used to classify macroscopic appearances of the oesophagus; currently no single grading scale has been demonstrated to show superior validity to existing alternatives. The number of children within a study population who failed to improve and required fundoplication was a secondary outcome (binary outcome).

These endpoints yielded both continuous and dichotomous data. Clinical symptoms produced continuous data (e.g. number of vomiting episodes), describing outcomes in terms of mean differences and standardised mean differences. Dichotomous data such as improvement/non-improvement in endoscopic appearance produced outcomes presented as risk ratios, from which 'numbers needed to treat' data were derived.

Search methods for identification of studies

Electronic searches

We searched for relevant published trials in the following databases.

- The Cochrane Upper Gastrointestinal and Pancreatic Disease Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 5.
- MEDLINE (from 1966 to May 2014).
- EMBASE (from 1966 to May 2014).
- Centralised Information Service for Complementary Medicine (CISCOM), Institute for Scientific Information (ISI) Science Citation Index (on BIDS—UK General Science Index), ISI Web of Science.

We searched for ongoing trials in the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), which includes the UK National Health Service (NHS) National Research Register.

Search terms 1 through 29, as given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008), were used.

We interrogated PubMed, MEDLINE and EMBASE from 1966 to May 2014 (electronically) for all articles with combinations of the key words "(gastro-oesophageal or gastroesophageal or gastro-esophageal or reflux or oesophagitis NOT eosinophilic oesophagitis), and (child$ or infant) and (drug$ or therapy or treatment)".

We developed this search strategy with assistance from the Trials Search Co-ordinator of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Review Group.

Searching other resources

Reference lists from trials selected by electronic searching were scanned to identify further relevant trials. Published abstracts from conference proceedings from the United European Gastroenterology Week (published in *Gut*) and from Digestive Disease Week (published in *Gastroenterology*) were handsearched. We also handsearched reviews discovered in this search (published

over the past five years) to look for relevant paediatric studies on medical treatment of children with gastro-oesophageal reflux.

Adverse outcomes

We did not conduct a separate search for adverse events.

Language

We did not restrict our search by language and will translate papers as necessary.

Grey literature

We searched for unpublished studies by using techniques such as handsearching.

Handsearching

We searched the Specialised Register of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Review Group, which contains the results of a comprehensive programme of ongoing handsearching of gastroenterology journals and conference proceedings. We scanned the bibliographies of all individual published studies and reviews within the past five years to identify possible references to RCTs.

Data collection and analysis

We used Review Manager (RevMan 2011) to perform data analysis. We combined studies when appropriate by using a random-effects model. For continuous measurements, summarised by using means and standard deviations, we planned to use weighted mean differences to pool results from studies in which a common measurement scale had been used. When different measurement scales had been employed, standardised mean differences were pooled. For binary outcomes, we computed and summarised rate ratios. We present 95% confidence intervals for individual studies and summary effects.

When statistical analyses are not possible (or inappropriate), a descriptive summary will be provided. We looked at all studies and performed a subgroup analysis of those employing an intention-to-treat (ITT) analysis when such information was provided.

Selection of studies

Two review authors (MT and AM) checked titles and abstracts identified by the searches. If the study did not refer to a randomised controlled trial of pharmacological treatment of children or infants with gastro-oesophageal reflux, it was excluded. All review authors assessed the full-text version of each remaining study to determine whether it met the predefined selection criteria when differences of opinion occurred, and remaining differences of opinion were resolved through discussion within the review team. We list in the Characteristics of excluded studies table all studies excluded after the full text was assessed by all review authors. The only other exclusions occurred when the methodology aroused such concern that clear consensus determined that the trial should not be included.

Data extraction and management

Two review authors (MT and AM) independently extracted study data using a robust data extraction form and checked and entered the data into RevMan 2011, with AH analysing the data and highlighting discrepancies. A third review team member (NA) was available to resolve differences in opinion.

Assessment of risk of bias in included studies

We describe each study in a 'Risk of bias' table and address the following issues, which may be associated with biased estimates of treatment effect, that is, sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias (Higgins 2008). We comment specifically on:

- the method by which the randomisation sequence was generated;
- the method of allocation concealment used—considered 'adequate' if the assignment could not be foreseen;
- who was blinded and was not blinded (participants, clinicians, outcome assessors), if this is appropriate;
- how many participants in each arm were lost to follow-up, and whether reasons for losses were adequately reported; and
- whether all participants were analysed within the groups to which they were originally randomly assigned (intention-to-treat principle).

In addition, we may report on:

- baseline assessment of participants for age, sex and duration of symptoms;
- whether outcome measures were described and whether their assessment was standardised; and
- the use and appropriateness of statistical analyses when tabulated data could be extracted from the original publication.

We recorded information on all of these components in a 'Risk of bias' table. We summarise the general quality of all studies in the section, Risk of bias in included studies. Trials were insufficient for use of a funnel plot to investigate reporting (publication) bias. A sensitivity analysis would have been performed if exclusion of studies with high risk of bias was required.

Measures of treatment effect

For studies of a single pharmacological agent (e.g. omeprazole) versus placebo, if sufficient trials are available and their populations are clinically similar, meta-analyses of primary and secondary endpoints were attempted.

For meta-analyses of dichotomous outcomes (e.g. healing/not healing of oesophagitis on endoscopy), risk ratios (RRs) or odds ratios (ORs) were calculated along with 95% confidence intervals (CIs), and values were combined for meta-analysis with RevMan5 software. Data will be combined for the same duration of follow-up rounded to the nearest month.

Continuous data (e.g. symptoms scores) were combined for meta-analysis. We used means and standard deviations to derive mean differences (MDs) with 95% confidence intervals using a fixed-effect model.

Unit of analysis issues

The Cochrane Upper Gastrointestinal and Pancreatic Diseases Review Group editorial base was available for analysis issues involving included trials with multiple treatment groups and using

cluster-randomised designs. We considered cross-over trials and assessed only the first stage of therapy before cross-over, but we commented on results obtained after cross-over only if clinically relevant.

Dealing with missing data

We contacted trial authors or sponsors of studies less than 10 years old to request missing data, or clarification, when uncertainty about the specifics of a trial that are pertinent to analysis could not be resolved; we have detailed their contributions below.

Assessment of heterogeneity

Studies were screened for assessment of clinical heterogeneity, and planned subgroup analyses were considered if appropriate. We considered the forest plot and the Chi^2 test, reporting on the extent of any heterogeneity by using the I^2 statistic.

Assessment of reporting biases

We assessed for the presence of reporting bias by using a funnel plot when adequate data were available for individual pharmacological agents (Higgins 2008). If our analysis contained sufficient trials to make visual inspection of the plot meaningful (there is no standard for this, and we will seek statistical advice), and if the presence of asymmetry in the inverted funnel suggests a systematic difference between large and small trials in terms of estimates of treatment effect, we may discuss this further in the Discussion section.

Data synthesis

All individual agents were assessed separately. We considered combining data, for example, on high-dose versus low-dose proton pump inhibitors, as discussed below, to attempt to improve the population size on which conclusions were based only when similar outcomes, in a similar participant group, were assessed.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was considered for two groups. The first was based on age, that is, infants younger than one year of age and children between one and 16 years old. These subgroups have different GOR characteristics, for example, infants with symptomatic gastro-oesophageal reflux have different symptoms from those of older children (who generally are consuming a more solid diet and are maintaining an upright position). Some sections of the review assess treatments such as alginates (e.g. Gaviscon Infant®), which would be used mainly in the infant population. The other subgroup for analysis consisted of children with neurodisability, who often have considerable gut dysmotility and often require long-term antireflux therapy.

When substantial heterogeneity (I^2 > 50%) was observed between studies for the primary outcome, we explored the reasons for heterogeneity, such as severity of reflux, demographic differences (age and co-morbidity), varying outcomes and different comparison agents (same drug, different dosing). When it was inappropriate to pool the data because of clinical or statistical heterogeneity, which is highlighted below, a systematic review without meta-analysis was performed.

Sensitivity analysis

This is mentioned above with respect to potential bias and heterogeneity.

RESULTS

Description of studies

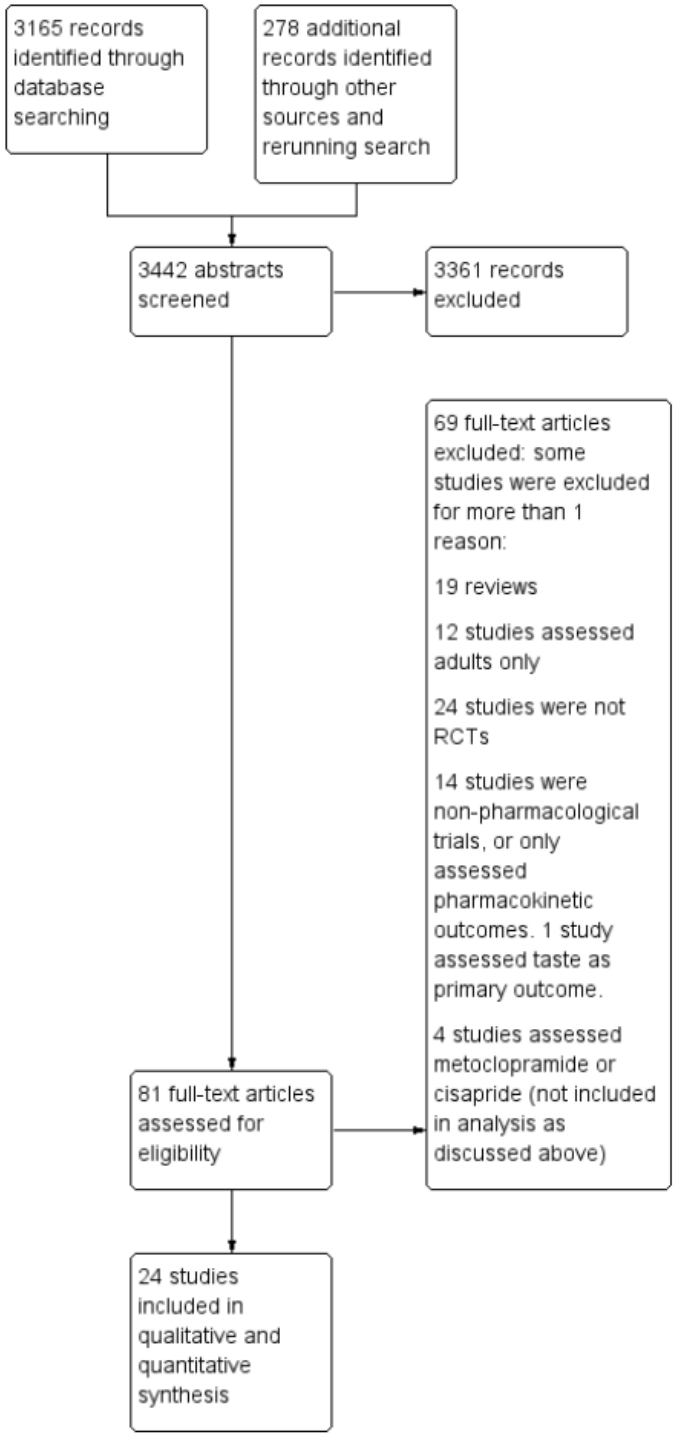
Results of the search

We searched for relevant published trials in the Specialised Register of the Cochrane Upper Gastrointestinal and Pancreatic Disease Group and the Cochrane Central Register of Controlled Trials (CENTRAL), as well as in MEDLINE via Ovid SP (January 1950 to August 2012), EMBASE via Ovid SP (January 1974 to August 2012) and the Science Citation Index via the Institute for Scientific Information (ISI) Web of Science on 1 August 2012. A total of 3165 citations were identified (MEDLINE = 483, EMBASE = 1713, CENTRAL= 396, ISI = 1505). These citations were scrutinised and abstracts evaluated. The search was rerun on 8 August 2012 for an update on new studies. A total of 278 new citations (MEDLINE = 65, EMBASE = 225, CENTRAL = 36) were identified. Of these, 81 papers were identified, including 19 reviews. These papers were evaluated and handsearched for further relevant RCTs. No studies assessed study participants with co-existing neurodisability. The search was rerun on 1 May 2014, from which five studies were identified for potential inclusion and placed in the Characteristics of studies awaiting classification.

A total of 24 original, relevant RCTs were identified that were suitable for inclusion. These are considered within their class of action.

Results of the search are shown in Figure 1.

Figure 1. Study flow diagram.



Included studies

Proton pump inhibitors

As a class, this group had the greatest number of RCTs, following a call from the Food and Drug Administration for manufacturers of PPIs for children to carry out RCTs in children, in accordance with a PWR (Paediatric Written Request) template.

Omeprazole

Moore 2003 assessed 30 irritable infants three to 12 months old (mean 5.4 months) in a four-week, randomised, double-blind, placebo-controlled cross-over trial of omeprazole. Participants had symptomatic GORD with reflux index > 5% on pH probe or histological evidence of oesophagitis on endoscopy. All had failed to improve when given previous empirical GOR treatment (cisapride 87%, H_2-receptor antagonist 73%, antacid 67%, thickening agent 20%). Infants weighing 5 to 10 kg were given 10 mg daily, and those > 10 kg were given 10 mg twice daily for two weeks versus an identical placebo. Two outcome measures were assessed, including cry/fuss time, assessed by a behaviour diary kept by parents, and a visual analogue scale score (from 0 to 10) of parental impressions of intensity of infant irritability at baseline and during treatment. Repeat pH probe was performed at cross-over.

Pfefferkorn 2006 performed a prospective, double-blind study on 18 participants, one to 13 years of age (mean 10.3 years) with symptomatic GORD with endoscopic/histological changes. Among 18 participants who received omeprazole (1.4 mg/kg once daily (maximum 60 mg)) for the first three weeks (see above for discussion of improvement on omeprazole), 16 (89%) had nocturnal acid breakthrough on pH monitoring and were randomly assigned to ranitidine 4 mg/kg or placebo, whilst continuing omeprazole. At week 17, all participants underwent repeat endoscopy and 24-hour pH monitoring. Further analysis of the additional impact of ranitidine is provided separately below. Details of symptom scoring were not given.

Cucchiara 1993 looked at 32 study participants (six months to 13.4 years of age) with symptomatic GOR whose symptoms had failed to improve with ranitidine. Participants were randomly assigned to eight weeks of standard doses of omeprazole (40 mg/d/1*73 m^2 surface area) or higher doses of ranitidine (20 mg/kg/d). Improvement was assessed by using symptoms, 24-hour pH probe data and endoscopy findings. Reflux symptoms were recorded at baseline by participants on a diary card, then weekly throughout the study. The scoring system was based on score out of 45: vomiting and/or regurgitation (0 to 9 points: 9 if vomiting > 5 days out of the week); recurrent pneumonia and/or asthma (number of episodes in six months: 6 points per episode: maximum 18 points); anorexia or early satiety (% reduction compared with daily calorie requirement: maximum 9 points if intake < 25% of expected); and pyrosis/chest pain/irritability (number of days/wk: maximum 9 points if seven days a week affected). Repeat endoscopies were performed within 48 hours of completion of the eight-week trial.

Lansoprazole

Orenstein 2008 assessed 162 infants (mean age 16 weeks; range four to 51 weeks) who were randomly assigned to lansoprazole versus placebo. Infants were included if symptomatic of GORD, that is, 'crying, fussing or irritability' within one hour after feeding (specifically, daily crying noted in diary with > 25% of feeds over four days) after one week of non-pharmacological treatment. Sixteen centres participated. Infants were excluded if PPI was taken in th previous 30 days or H_2-receptor antagonists within seven days. Both parents and assessors were blinded.

The trial occurred in three phases. In the pretreatment phase, small frequent feeds were recommended, as was reduction in smoking, hypoallergenic feeds (or, if breast-fed, mothers started dairy-free diet) and positioning advice. The treatment phase lasted four weeks, and participants were randomly assigned to lansoprazole 1:1 (0.2 to 0.3 mg/kg/d in those < 10 weeks, 1 to 1.5 mg/kg/d in those > 10 weeks) versus placebo. In the post-treatment phase, investigators can choose to put children on lansoprazole treatment. Symptom assessment was performed for 30 days following completion of the study. Parent diaries were assessed for symptom scores (using the Infant Gastroesophageal Reflux Questionnaire (I-GERQ)) and for individual symptoms. No investigation confirmed GORD, and many enrolled participants may have had functional reflux.

Borrelli 2002 performed an RCT comparing lansoprazole with alginate over eight weeks. Thirty-six participants were recruited (median age 5.6 years; range 12 months to 12 years) with diagnosis of GORD based on symptoms, 24-hour pH probe and endoscopy. Participants were randomly assigned to alginate alone (2 mL/kg/d in divided doses), lansoprazole 1.5 mg/kg twice daily before meals or lansoprazole and alginate. After baseline assessment and treatment, participants underwent 24-hour pH study at one week, symptomatic assessment at four weeks and repeat symptom assessment with final endoscopy at eight weeks. If children were noted to have severe (Hetzel-Dent grade 3 to 4) oesophagitis on endoscopy, they were not enrolled but were given a high-dose PPI.

The symptom score assessed regurgitation/vomiting, chest pain/irritability, epigastric pain/bloating and nocturnal cough/postfeeding cough (maximum 6 points for each item) at baseline and at weeks four and eight. A 24-hour pH study was performed at baseline, then at week one. Endoscopy (performed at baseline, then at week eight) was scored using Hetzel-Dent scoring (grade 0 to 4).

Gunesekaran 2003 assessed 63 adolescents (mean age 14.1 years; range 12 to 17 years) with symptomatic/endoscopic GORD, or with histological changes of oesophagitis, in a phase I multi-centre double-blind study with random assignment to two arms: lansoprazole 30 mg and 15 mg(seven days pretreatment phase, then five days of treatment). In the pretreatment phase, a physician assessment was followed by 24-hour intragastric pH probe, endoscopy and biopsy, *Helicobacter pylori* testing and a symptom diary completed for one week. After five days of treatment, participants underwent physician assessment and analysis of symptom diaries. Severity scores were graded 0 (none) to 3 (severe) for each item. Pharmacokinetics and intragastric pH monitoring are not considered here.

Esomeprazole

Omari 2007 performed a single-centre, randomised, single-blind study that compared 50 infants with symptoms of GORD (irritability/crying, vomiting, choking/gagging) and a reflux index on 24-hour pH probe suggestive of acid GOR (> 4%) who were given oral esomeprazole 0.25 mg/kg or 1 mg/kg for eight days. Symptoms were recorded on a symptom chart at baseline and at day 7, based

on the I-GERQ; severity scores were graded 0 (none) to 3 (severe) for each item. 24-Hour pH probe was performed at baseline and on day 7. Exclusions included history of upper GI surgery and congenital drug addiction. Use of any pharmacological antireflux therapy up to 24 hours before, or any PPI up to 72 hours before, the first dose of study medication was not permitted. Contemporaneous treatment with medications known to interact with esomeprazole, or to improve symptoms of reflux (e.g. H_2 antagonists), was not permitted.

Tolia 2010b assessed 109 participants across 24 sites in Europe and the USA, one to 11 years of age with GORD, confirmed on endoscopy/histology, who were randomly assigned to esomeprazole 5 mg or 10 mg daily (< 20 kg) or 10 mg or 20 mg daily (20 kg) for eight weeks. Participants with erosive oesophagitis underwent an endoscopy after eight weeks for assessment of healing of erosions. An additional 49 participants were excluded: Four had eosinophilic oesophagitis, 29 had no evidence of reflux oesophagitis on endoscopy and 16 were excluded for reasons 'not related to endoscopy.' Outcomes assessed included resolution on endoscopy and side effects. Symptoms were assessed at baseline, but no comment indicated whether symptoms were resolved. Nor was any comment made about the 51 participants with reflux oesophagitis without erosions.

A subgroup post hoc analysis of participants with GORD 12 to 36 months of age was then published in the *Journal of Pediatric Gastroenterology and Nutrition* (Tolia 2010a). As described above, participants weighing 8 kg to < 20 kg were randomly assigned 1:1 to receive esomeprazole 5 mg or 10 mg daily for eight weeks. Symptoms were measured by physicians and by parents, who telephoned daily to report symptoms of the preceding 24 hours. Symptoms were graded as none/mild/moderate/severe (PGA (Physicians Global Assessment) symptom score). Also number of vomiting episodes and use of antacids were assessed. Histological appearances were graded as healed/improved/unchanged. Funding and manuscript writing support from AstraZeneca was declared.

Pantoprazole

Tsou 2006 assessed 136 children (12 to 16 years of age) with symptoms of GORD in a multi-centre, randomised, double-blind, multi-dose, parallel-treatment group study, who were given pantoprazole 40 mg (n = 68) or pantoprazole 20 mg (n = 68) over eight weeks. Improvements were assessed using the GORD Assessment of Symptoms-Pediatric (GASP-Q) questionnaire: Outcomes were expressed as composite symptom score and individual symptom score through participant/parent records. A physician assessment was performed at baseline and at week eight (using Likert score 1 to 7).

Baker 2010 performed a randomised, double-blind study (over eight weeks) of three strengths of pantoprazole given to 60 children (one to five years of age) with symptoms of GORD and endoscopic or histological signs of GORD at recruitment. The three dose regimens included 0.3 mg/kg once daily, 0.6 mg/kg once daily and 1.2 mg/kg once daily as delayed-release granules. Symptoms were assessed using a validated GOR symptom score (Weekly GOR Symptom Frequency Scores (WGSS)) at baseline and at week eight. Individual symptoms (abdominal pain, burping, heartburn, pain after eating, difficulty swallowing) were recorded by parents daily in an eDiary, and endoscopy was performed at week eight, again only in those with erosive changes (four participants) at recruitment. No reendoscopy after treatment was performed in participants with only histological changes. No comment was made regarding blinding, and writing support was provided by Wyeth.

Kierkus 2011 performed a two-part study, the first part of which was not randomised and so will not be considered. The second part looked at 24 infants one to 11 months of age who were randomly assigned to high-dose (1.2 mg/kg)/low-dose pantoprazole (0.6 mg/kg) for six weeks. The primary outcome was provided in terms of pharmacokinetic data, but a 24-hour pH probe at baseline, then on day 5, assessed number of episodes of pH < 4, number of episodes lasting longer than five minutes or duration of episodes of pH < 4. The study and writing support were funded by Wyeth.

Tolia 2006 performed a multi-centre double-blind RCT comparing 10 mg, 20 mg and 40 mg pantoprazole over eight weeks in 53 children (five to 11 years of age) with symptomatic GORD. Symptom score was assessed using a validated questionnaire (GASP-Q) to produce a composite symptom score (CSS). Individual symptoms (number of vomiting episodes, heartburn, epigastric pain) were also assessed at week zero, then at week 1 and week 8. Endoscopy appearances were assessed and histological changes were graded using Hetzel-Dent scoring.

H2 antagonists

Ranitidine

The study of Cucchiara 1993 is discussed in the omeprazole section: Please see above.

Pfefferkorn 2006 performed a prospective, double-blind study of 18 participants, one to 13 years of age (mean 10.3 years) with symptomatic GORD with endoscopic/histological changes. Among 18 participants who received omeprazole (1.4 mg/kg once daily, maximum 60 mg) for the first three weeks (see above for discussion of improvement on omeprazole), 16 (89%) had nocturnal acid breakthrough on pH monitoring and were randomly assigned to ranitidine 4 mg/kg or placebo, whilst continuing omeprazole. At week 17, all participants underwent repeat endoscopy and 24-hour pH monitoring. Endoscopy appearances were assessed using Hetzel-Dent score (grade 0 to 4). Participants were evaluated for symptoms and adverse events during follow-up at three weeks (initiation of ranitidine/placebo), nine weeks and 17 weeks. Symptoms (heartburn, abdominal pain, vomiting, dysphagia, and "others") were recorded (none, same, better, worse) at follow-up; the scoring is discussed above.

Cimetidine

Cucchiara 1984 performed a 12-week RCT of cimetidine versus Maalox® (liquid MgOH/ALOH) on 33 infants and children two to 58 months of age (mean 10.3 months) with symptoms of GORD. A total of 33 children—20 boys and 13 girls (two to 42 months (mean nine months) of age)—with gastro-oesophageal reflux with oesophagitis were included: Diagnosis was based on a composite score of symptoms, oesophagitis on endoscopy and acid reflux on pH probe. Individual symptoms included vomiting/regurgitation (number episodes/wk), anorexia (absent to severe—0 to 4 points), pneumonia/apnoea (number of episodes in three months > 1:15 participants); anaemia (haemoglobin < 7 g/dL = nine participants). Weight-to-height ratio (centiles) < fifth: six participants.

Nizatidine

Simeone 1997 assessed 26 participants (with histological features of oesophagitis (mild to moderate); median age, 1.66 years (range, six months to eight years)) randomly assigned to double-blind treatment with nizatidine 10 mg/kg twice daily versus placebo for eight weeks. All participants received positional therapy and dietary manipulation with thickened feeds (dry rice cereal). A symptomatic score assessment was evaluated during the study, and baseline evaluation including endoscopy and 24-hour pH study was followed by a daily diary card, which was maintained by parents to record the frequency and severity of GOR symptoms during the treatment period. Severity scores were graded from 0 (none) to 3 (severe) for each item. A physical and symptomatological assessment was performed after four weeks of therapy. After eight weeks of treatment, 48 hours before cessation of therapy, clinical evaluation, laboratory tests, pH probe study and endoscopy with biopsy were again performed in all children who completed the treatment period.

Outcomes were assessed in terms of symptoms, pH scores and endoscopy/histological appearances.

Prokinetics

Domperidone

Cresi 2008 performed an RCT in which domperidone was give over 24 hours to 26 neonates (mean age (SD): control group 29.5 days (7.4) vs treatment group 24.7 days (13.7)). Participants were randomly assigned to domperidone 0.3 mg/kg or placebo at two eight-hour time periods in 24 hours, compared with the first eight hours, taken as baseline. No evidence was found of blinding of participants/parents, operator/analyser or study authors. The limited assessment of outcomes and the short study duration make drawing of wider conclusions difficult.

Carroccio 1994 performed an RCT comparing combinations of domperidone, Maalox® (magnesium hydroxide/aluminium hydroxide) and Gaviscon Infant® in 80 participants one to 18 months of age with symptoms of reflux: 50 had vomiting and slowed growth, 20 had weight loss, four had recurrent bronchopneumonia, five had prolonged crying worse after feeding and one had apnoea. Four groups were studied: Group A: domperidone (0.3 mg/kg/dose) + Gaviscon® (0.7 mL/kg/dose); Group B: domperidone (0.3 mg/kg/dose) + Maalox® (41 g/1.73 mg/d); Group C: domperidone (0.3 mg/kg/dose) only; and Group D: placebo. Outcomes were measured in terms of symptoms and 24-hour pH indices (number of episodes of pH < four, duration of episodes of pH < four and number of reflux episodes > five minutes). All children had their feeds thickened with Medigel 1%. Symptom improvement was confirmed on monthly follow-up for six months, but a detailed symptom analysis was not given. Participants who were not cured were treated with cisapride/ranitidine.

Bines 1992 performed a double-blind, placebo-controlled RCT in 17 children (five months to 11.3 years) with symptomatic GORD (confirmed on pH probe) to assess the impact of domperidone given over four weeks (double-blind), then over a further four weeks (open-label). Outcomes were assessed in terms of gastric emptying time, eight- to 12-hour oesophageal pH probe, weight gain and symptomatic change. A detailed symptom analysis was not performed.

Compound alginate preparations

Gaviscon Infant®

Del Buono 2005 assessed 20 infants (mean age 163.5 days; range 34 to 319 days) who were exclusively bottle-fed, with symptoms clinically suggestive of GOR. In this double-blind RCT, 24-hour studies of impedance and dual-channel pH monitoring were performed, during which six random administrations (3 + 3) of Gaviscon Infant® (625 mg in 225 mL milk) or placebo (mannitol and Solvito N, 625 mg in 225 mL milk) was given in a double-blind fashion. The observer interpreting the data was also blinded. Median number of reflux events/h, acid reflux events/h, minimum distal or proximal pH, total acid clearance time per hour (time with pH below pH 4) and total reflux duration per hour were assessed. This was a short-term study, and no long-term follow-up was performed.

Miller 1999 recruited 90 children (birth to 12 months) at 25 centres in a phase III, multi-centre, double-blind RCT (parallel-group study) comparing Gaviscon Infant® versus placebo. Investigators assessed improvement in symptoms and quantified vomiting/regurgitation episodes over the previous 24 hours in terms of none (zero) to severe (three). This study was conducted over 14 days, and exclusions included known oesophageal/gastrointestinal disease.

Gaviscon Infant® has been changed to become aluminium-free, with different alginate content, and has been assessed in its' current form in only two studies performed since 1999. The studies below consider older forms of Gaviscon Infant®.

Please see above for Carroccio 1994.

Buts 1987 assessed 20 infants and children with characteristic symptoms of GOR (vomiting, acid regurgitation related to meals and posture, heartburn, recurrent respiratory tract disorders). Participants were randomly assigned to two groups, which were given Gaviscon® (10 participants; mean age 21 months; range two to 84 months) or placebo (lactose sachet) (10 participants; mean age 35 months; range two to 144 months). 24-Hour pH probe was assessed at baseline and on day 8; symptoms including vomiting and number of episodes of regurgitation within 24 hours during the time of the recordings were observed by staff.

Forbes 1986 assessed 10 children (mean age 68 months, range six to 168 months) given Gaviscon Infant® liquid (antacid + alginate) 10 mL every six hours (for infants) or 20 mL every six hours for older children versus placebo three times a day (mean age 71 months, range four to 168 months). Participants and parents were not blinded because of differences in the dosing regimen; however pH data were interpreted by a blinded observer. We did not consider the metoclopramide group because this is the topic of another Cochrane review. 24-Hour pH probe was performed at baseline, then consecutively with treatment: so two 24-hour pH recordings were made. Results showed no difference between Gaviscon Infant® liquid and placebo in terms of number of reflux episodes and duration of reflux episodes. No standard nursing positions were adopted, and children could move around the bed. All 20 participants had symptoms of vomiting and waterbrash at enrolment. Subgroup analysis of this group with endoscopic changes was not undertaken. The only exclusions were participants with cerebral palsy/neuromotor dysfunction.

Gaviscon®

Borrelli 2002 compared lansoprazole with alginate over eight weeks in an RCT. Thirty-six participants with a diagnosis of GORD based on symptoms, 24-hour pH probe and endoscopy were recruited (median age 5.6 years, range 12 months to 12 years).. Participants were randomly assigned to alginate alone (2 mL/kg/d in divided doses), lansoprazole 1.5 mg/kg twice daily before meals or lansoprazole and alginate. After baseline assessment and treatment, participants underwent a 24-hour pH study at one week, symptomatic assessment at four weeks and repeat symptom assessment with final endoscopy at eight weeks. If children were noted to have severe (Hetzel-Dent grade 3 to 4) oesophagitis on endoscopy, they were not enrolled but were given a high-dose PPI.

The symptom score assessed regurgitation/vomiting, chest pain/irritability, epigastric pain/bloating and nocturnal cough/postfeeding cough at baseline and at weeks four and eight. A 24-hour pH study was performed at baseline, then at week one. Endoscopy (performed at baseline, then at week eight) was scored using Hetzel-Dent scoring (grade 0 to 4).

Antispasmodics

Baclofen

Omari 2006 compared baclofen versus placebo in a randomised, double-blind, placebo-controlled trial including 30 children with resistant GORD (mean age 10.0 ± 0.8 years). All children had failed standard therapy (positioning, reassurance, feed thickener, antacids, PPI and H_2 antagonist). The only exclusions were previous GI surgery, neurological disease, cardiac/respiratory disease, peptic ulcer and cow's milk protein intolerance (CMPI)/lactose intolerance.

Children were assessed with manometry/pH at baseline for two hours after consuming 250 mL of cow's milk (control period). Baclofen 0.5 mg/kg or placebo was then administered. One hour later, 250 mL of milk was given, and measurements were performed for another two hours (test period). The incidence of transient lower oesophageal sphincter relaxation (TLESR) on impedance versus placebo was monitored after intake of baclofen. Gastric emptying was not evaluated in this review, as it was not a prespecified outcome of this review.

Side effects (causing early withdrawal but thought to be unrelated) were noted in the baclofen group, but no significant events were reported in the 48 hours following trial completion. This was a short trial, and no other studies were available in this group; further double-blind RCTs are recommended.

Excluded studies

A total of 49 studies were excluded (with reasons) from the review. More than one reason for exclusion was reported for some studies. The main reasons for exclusion were that studies were not RCTs by design (24 studies) and investigators provided only pharmacokinetic data with no clinically useful outcomes (nine studies). Studies assessing the role of cisapride (three studies) or metoclopramide (one study) were also excluded, as were studies that were not assessing medications (five studies). One study assessed dogs, and another was a taste-preference study. One study with significant methodological problems (including medication preparation changes during the study, post hoc analyses and absence of randomisation in children older than 13 years of age) was excluded. One study had adult data, and two assessed outcomes not specified in the protocol (respiratory symptoms in one study, necrotising enterocolitis in another).

Risk of bias in included studies

Risk of bias assessments per study are further detailed in Figure 2 and assign categories of high risk/unclear risk/low risk, although with many of the older studies, it was difficult to clarify methodological issues from the published protocol.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

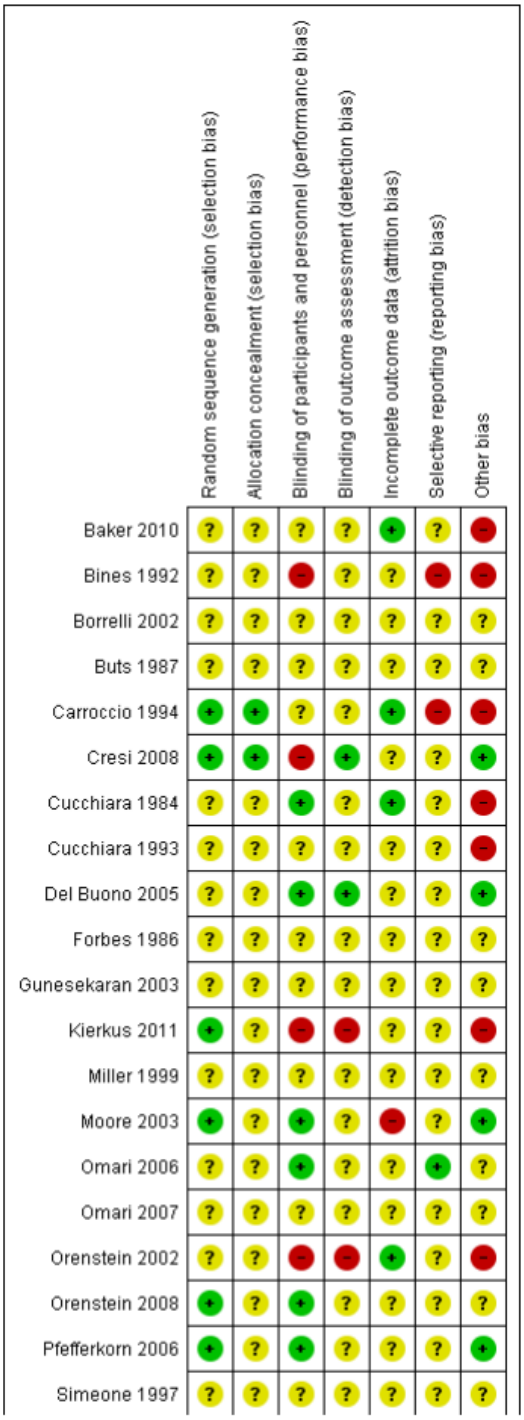
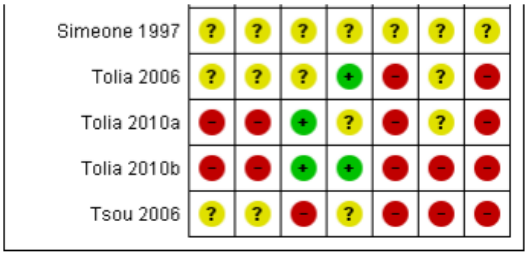


Figure 2. (Continued)



Random sequence generation (selection bias)

Method of randomisation was not stated or was unclear in 19 studies (Baker 2010; Bines 1992; Borrelli 2002: Buts 1987; Cucchiara 1984; Cucchiara 1993; Del Buono 2005; Forbes 1986; Miller 1999; Moore 2003; Omari 2006; Omari 2007; Orenstein 2008; Pfefferkorn 2006; Simeone 1997; Tolia 2006; Tolia 2010a; Tolia 2010b; Tsou 2006). Among those who did assert that a randomisation process was used, often no description revealed by which method participants were randomly assigned, particularly in studies conducted before 1998. Future studies could be more transparent regarding the use of randomisation techniques.

Allocation

The 19 studies above made no reference to or incompletely outlined the method of allocation used in the trial (Baker 2010; Bines 1992; Borrelli 2002: Buts 1987; Cucchiara 1984; Cucchiara 1993; Del Buono 2005; Forbes 1986; Miller 1999; Moore 2003; Omari 2006; Omari 2007; Orenstein 2008; Pfefferkorn 2006; Simeone 1997; Tolia 2006; Tolia 2010a; Tolia 2010b; Tsou 2006). The potential for selection bias was highlighted only by Tolia 2010a in a post hoc analysis.

Blinding

Blinding issues were potentially present in nine studies that did not outline their blinding methodology (Baker 2010; Bines 1992; Cresi 2008; Forbes 1986; Kierkus 2011; Omari 2007; Orenstein 2002; Tolia 2010a; Tsou 2006). Incomplete blinding methodology was potentially present in 10 studies (Buts 1987; Carroccio 1994; Miller 1999; Moore 2003; Orenstein 2008; Simeone 1997; Tolia 2006; Tolia 2010a; Tolia 2010b; Tsou 2006). This could affect overall symptom control outcomes, as these often rely heavily on parental reporting as with symptom recall questionnaires or symptom diaries. Endoscopic and pH outcomes would be less likely to be affected than unblinded physician assessments. Investigators in future studies using symptom control outcome measures may wish to be more rigorous regarding blinding. A mix of double-blind (Omari 2006; Orenstein 2008; Pfefferkorn 2006), single-blind and unblinded studies are included in this review. Several trials are open-label, and in studies utilising parent-reported outcomes, this introduces high risk of performance bias. Similar to randomisation, a significant number of studies claimed to be blinded and provided no description in their methodology as to how blinding was achieved.

Incomplete outcome data

Evidence of incomplete outcome data was noted in 9 studies, specifically, Bines 1992, Borrelli 2002, Cucchiara 1993, Kierkus 2011, Moore 2003, Orenstein 2008, Simeone 1997, Tolia 2010b and Tsou 2006. Further data were successfully obtained with regards to Tolia 2010a and Omari 2007.

Selective reporting

Reporting bias was potentially evident in seven studies (Bines 1992; Borrelli 2002 (excluded severe oesophagitis); Gunesekaran 2003 (no oesophageal pH data presented); Miller 1999 (no data on investigator findings at day 7 review were presented); Omari 2006; Omari 2007; Tolia 2010b).

Other potential sources of bias

Support for manuscript writing was provided by pharmaceutical companies in four studies (Baker 2010; Tolia 2010a; Tolia 2010b; Tsou 2006). Pharmaceutical funding was acknowledged in seven studies (Cucchiara 1993; Del Buono 2005; Gunesekaran 2003; Miller 1999; Omari 2006; Orenstein 2002; Orenstein 2008). No funding declarations were given for five studies (Borrelli 2002; Buts 1987; Forbes 1986; Omari 2007; Simeone 1997). Other sources of bias are diverse and are discussed below for each study. They are individual to each study, but two studies included management techniques that could also improve GOR, such as positioning and thickening (Carroccio 1994; Cucchiara 1984).

All included studies were RCTs.

Effects of interventions

Most of the studies included in the assessment provided an appraisal of improvement in clinical symptoms. However, heterogeneity of symptom assessment including composite scores was considerable, as was heterogeneity of individual symptom assessment. In infants, numbers of vomiting episodes, back arching, regurgitation, failure to thrive, feeding difficulties and abdominal pain/colic were commonly assessed, and in older children, heartburn, epigastric pain and regurgitation symptoms were examined.

In terms of investigation tools, 24-hour pH probe and/or impedance studies were utilised in several studies, with reflux index and number of reflux episodes the most commonly used endpoints. The macroscopic appearance of the oesophagus on endoscopy and histological improvement were also analysed. Results are summarised in Table 1 and Table 2.

Symptoms and symptom scores

Proton pump inhibitors

In studies assessing PPIs in children older than one year of age, good improvement in symptoms but weaker evidence for efficacy in infants was found.

Omeprazole

Pfefferkorn 2006 looked at nocturnal acid breakthrough in 16 participants (one to 13 years of age) who had recently started taking omeprazole for symptomatic GORD with endoscopic/histological changes, and compared ranitidine 4 mg/kg or placebo, whilst continuing omeprazole. Significant improvement in symptoms was noted after three weeks in participants treated with omeprazole, without benefit from additional ranitidine in those with breakthrough symptoms (see below). Cucchiara 1993 noted symptomatic improvement in symptom scores among participants treated with omeprazole (but no superiority compared with high-dose ranitidine). In studies assessing omeprazole in infants, poor-quality evidence showed symptomatic improvement of infants with likely GORD: Moore 2003 noted a non-significant improvement in cry/fuss time in both placebo and omeprazole groups.

Lansoprazole

Among older children, moderate-quality evidence showed improvement in symptomatic scores; Borrelli 2002 compared lansoprazole with alginate or lansoprazole and alginate over eight weeks in 36 children (range 12 months to 12 years) with GORD (based on symptoms, 24-hour pH probe and endoscopy). Symptom scores significantly improved in all groups (P value < 0.01), but the lansoprazole and alginate group was significantly superior to the other two groups (P value < 0.01). No significant side effects were noted. Gunesekaran 2003 similarly noted improvement in symptoms in both low-dose and high-dose groups treated with lansoprazole. However among infants with GOR based on symptoms, Orenstein 2008 showed that when treatment with lansoprazole was provided, blinded compared with placebo or open-label, rates of symptom response and treatment withdrawal were similar.

Gunesekaran 2003 assessed 63 adolescents (range 12 to 17 years of age) with symptomatic/endoscopic GORD who were randomly assigned to lansoprazole 30 mg versus 15 mg: After five days of treatment, symptom diaries in both groups noted improvements in frequency and severity of heartburn and other symptoms (P value not stated). In the 15 mg group, 69% reported that their symptoms of reflux were better, as did 74% of those in the 30 mg group, and the amount of antacid required for symptom relief in both groups was reduced (average 1.8 tablets/d to 1.05 in the lansoprazole 15 mg group, and to 1.8 to 0.63 tablets/d in the lansoprazole 30 mg group; P value not stated). Again on physician review, among participants with heartburn at baseline (n = 36), significant symptomatic improvement was reported in both groups.

However in infants, the evidence is less clear: Orenstein 2008 assessed 162 infants (range four to 51 weeks of age) randomly assigned to lansoprazole versus placebo with symptoms suggestive of reflux. No difference between lansoprazole and placebo was noted in terms of observer assessments or symptom diaries, and among participants who went on to take lansoprazole open-label (n = 55), no significant improvement in symptoms was observed. However no investigation confirmed GORD, and many of the enrolled participants may have had functional reflux.

Esomeprazole

Weak evidence of benefit may be apparent in infants and in older children: Omari 2007 compared 50 infants with symptoms of GORD and a reflux index suggestive of acid GOR (> 4%) who were given oral esomeprazole 0.25 mg/kg or 1 mg/kg for eight days. Non-significant improvement was seen in symptoms, which improved more in the low-dose group. Tolia 2010b demonstrated resolution of endoscopically proven erosive oesophagitis after eight weeks of treatment with esomeprazole among 45 of 109 children one to 11 years of age: A significant selection bias was evident. No symptom data were presented on these 45 (of 109 initially enrolled) participants, and some of the reasons for exclusions were unclear. Nevertheless a post hoc analysis of some of these participants with endoscopically confirmed GORD (12 to 36 months of age) compared esomeprazole 5 mg or 10 mg daily for eight weeks. A total of 16/19 (84.2%) had improved symptom scores by the final visit. In addition, a statistically significant reduction (P value < 0.0018) in the severity of GORD symptoms was seen within each treatment group from baseline to final assessment. No difference between low-dose and high-dose groups was noted. Omari 2007 showed symptomatic improvement among infants with reflux symptoms and an abnormal reflux index at diagnosis when treatment with esomeprazole (both low- and high-dose) was provided.

Pantoprazole

No trials assessed symptomatic improvement in infants, but three trials assessed symptom responses in children. No placebo-controlled studies were identified, but benefit was demonstrated in older children. Tsou 2006 assessed 136 children (12 to 16 years of age) with symptoms of GORD given pantoprazole 40 mg (n = 68) or pantoprazole 20 mg (n = 68) over eight weeks. In both groups, composite symptom scores improved significantly from baseline to end of trial from 177 and 174 by at least 100 points (P value < 0.001), and significant improvement was noted in numbers of vomiting episodes per day, heartburn symptom score and epigastric pain score. On physician assessment, all participants were moderately/greatly improved at eight weeks compared with baseline (P value < 0.001). No participants showed a worsened condition, but 82% reported a treatment-emergent adverse event (TEAE), mainly headache, and in the high-dose group, diarrhoea. Baker 2010 and Tolia 2006 noted symptomatic improvement in all groups treated with pantoprazole. In younger children, Baker 2010 looked at 0.3 mg/kg, 0.6 mg/kg and 1.2 mg/kg pantoprazole in 60 children (one to 5 years of age) with symptoms of GORD and endoscopic or histological signs of GORD over eight weeks. Symptoms improved among those given all dose regimens from baseline to week eight (P value < 0.001).

H2 antagonists

Ranitidine

Ranitidine was assessed by Cucchiara 1993 (see above), who found similar improvement in symptoms among those randomly assigned to eight weeks of standard doses of omeprazole (40 mg/d/1*73 m^2 surface area) or higher doses of ranitidine (20 mg/kg/d). Pfefferkorn 2006 looked at nocturnal acid breakthrough in 18 study participants (one to 13 years of age) when comparing ranitidine 4 mg/kg or placebo, whilst continuing omeprazole, recently started

for symptomatic GORD with endoscopic/histological changes. Symptom scores in both groups significantly improved, but no significant difference between ranitidine and placebo groups was observed (P value 0.31 at week three, P value 0.20 at week nine, P value 0.10 at week 17).

Cimetidine

The only RCT (Cucchiara 1984) compared cimetidine versus Maalox® over 12 weeks in 33 infants and children (two to 58 months of age) with a diagnosis of GORD based on symptoms, oesophagitis on endoscopy and acid reflux on pH probe. Investigators found that both cimetidine and Maalox® provided significant symptomatic relief (P value < 0.05).

Nizatidine

Simeone 1997 assessed 26 participants (range six months to eight years) with histological evidence of oesophagitis who were randomly assigned to nizatidine 10 mg/kg twice daily versus placebo for eight weeks. Improvement in symptoms was seen only in the nizatidine group (P value < 0.01).

Domperidone

Randomised controlled trials evaluating symptomatic improvement included Carroccio 1994, who performed an RCT in 80 participants (one to 18 months of age with symptoms of reflux) in four groups to assess symptoms through a 24-hour oesophageal pH study. Whilst no improvement in symptoms was noted between domperidone/alginate, domperidone alone and placebo, in the domperidone + Maalox® group, 16/20 participants found that their symptoms resolved, and 4/20 participants described improvement (P value < 0.001). All feeds were thickened with Medigel 1%, perhaps accounting for significant improvement in symptoms in the placebo group. Symptom improvement continued through six months of follow-up. Bines 1992 assessed the impact of domperidone over four weeks (double-blind), then over a further four weeks (open-label), versus placebo in 17 children. Gastric emptying was improved in both groups (non-significant difference). Improvement in weight and height Z scores was seen but was not significant. No individual symptom was improved after four weeks; after eight weeks of therapy, 33% of participants treated with domperidone reported improved symptoms (P value non-significant); some improvements were seen after four weeks of little symptom improvement. The small number of participants limits the applicability of this study. The second (open-label) phase may have been affected by the decision of participants who derived some benefit to remain on domperidone treatment.

Compound alginate preparations

Gaviscon Infant® was evaluated in five RCTs (Buts 1987; Carroccio 1994; Del Buono 2005; Forbes 1986; Miller 1999). Miller 1999 and Buts 1987 found significant symptomatic improvement in their studies, which were limited by short follow-up.

In the largest study, Miller 1999 assessed 90 children (birth to 12 months) at 25 centres in a phase III, multi-centre, double-blind parallel-group RCT comparing Gaviscon Infant® versus placebo. Investigators assessed improvement in symptoms and found a significant reduction in number and severity of vomiting episodes (P value 0.009); parents and investigators considered that symptoms were improved with Gaviscon Infant® (investigators P value 0.008, parents 0.002). The study was conducted over 14 days, and exclusions included known oesophageal/gastrointestinal disease. Buts 1987 noted that the number of episodes of regurgitation per day reported by parents of treated infants was reduced by three to four times during the trial. Vomiting improved in all cases; in some cases, it ceased completely (two to three episodes per day to none); in other cases, frequency and volume were decreased, although the specific numbers were not published, and the significance was not calculated. In the placebo group, no clinical improvement was noted during treatment. Carroccio 1994, as discussed above, demonstrated no symptomatic benefit in the domperidone and Gaviscon Infant® group (20 children) compared with the placebo or domperidone group, but non-significant symptomatic superiority of domperidone + Maalox® was seen. However a confounding factor may have been the thickening of all feeds in all groups by Medigel 1%. Outcomes of Del Buono 2005 and Forbes 1986 are discussed in the 24-hour pH/impedance section below.

Gaviscon® was assessed by Borrelli 2002, who, as discussed above, noted significant improvement in children (12 months to 12 years of age) with erosive oesophagitis given alginate alone, in terms of symptoms, 24-hour pH probe and endoscopy (P value < 0.01), but the most significant symptom improvement was seen in infants treated with alginate in combination with lansoprazole (P value < 0.05).

24-Hour pH/impedance probe

As a class, overall evidence shows that PPIs improve the reflux index and other pH probe markers of GORD. The correlation between pH probe results and direct symptomatic benefit was less clear, however, particularly in infants. For both infants and older children with GORD, it was not possible to combine/meta-analyse methodologically similar studies of PPIs because of heterogeneity in outcomes and in study populations.

Proton pump inhibitors

Omeprazole

In infants, Moore 2003 found significant improvement only in reflux index upon treating irritable infants with omeprazole and indicated that symptoms improved with time (and did not correlate well with reflux index on pH probe). Among older children, Cucchiara 1993 assessed participants (six months to 13.4 years of age) with symptoms refractory to low-dose ranitidine and found similar improvement in symptoms, 24-hour pH probe data and endoscopy appearances among those randomly assigned to eight weeks of standard doses of omeprazole (40 mg/d/1*73 m^2 surface area) or higher doses of ranitidine (20 mg/kg/d).

Lansoprazole

Among children older than one year of age with erosive oesophagitis, Borrelli 2002 compared lansoprazole with alginate or lansoprazole and alginate over eight weeks in 36 children with GORD (based on symptoms, 24-hour pH probe and endoscopy). A 24-hour pH study (performed at baseline, then at week one) also showed significant improvement in the reflux index (P value < 0.01) with treatment, with the lansoprazole and alginate group significantly superior to the other two groups (P value < 0.05).

Pantoprazole

Among infants, Kierkus 2011 assessed high-dose (1.2 mg/kg)/low-dose pantoprazole (0.6 mg/kg) for six weeks. The primary outcome was described in terms of pharmacokinetic data, but a 24-hour pH probe was performed at baseline, then at day five. No statistically significant difference between low-dose and high-dose groups was seen in the number of episodes of pH < 4, the number of episodes lasting longer than five minutes or the duration of episodes of pH < 4 (numerically higher in the high-dose group), but 50% to 70% of infants in each group had normal reflux indices on enrolment (reflux index < 5%, as defined by the study authors).

Esomeprazole

Omari 2007 compared 50 infants with symptoms of GORD and a reflux index suggestive of acid GOR (> 4%) who were given oral esomeprazole 0.25 mg/kg or 1 mg/kg for eight days. Reflux index significantly improved in both groups, and greater improvement was seen in the lower-dose group.

Good evidence suggests, within the limitations of study design as discussed, that PPIs are efficacious, particularly in older children with GORD, and that they appear to be efficacious and safe in infants with GORD. Less evidence was found for significant improvement in symptoms with increasing doses, but increasing the dose may increase the risk of side effects. The risk of side effects was less prominent for omeprazole and lansoprazole than for pantoprazole. No evidence has been found for the use of PPIs in functional reflux. Further studies undertaken to assess the long-term impact/safety profile of PPIs are recommended (see below).

H2-receptor antagonists

As a class overall, some evidence shows that H2-receptor antagonists improve reflux index and other pH probe markers of GORD, but the evidence base is weaker than for PPIs. For both infants and older children with GORD, it was not possible to combine/meta-analyse methodologically similar studies because of heterogeneity in outcomes and study populations.

Ranitidine

Ranitidine was assessed by Cucchiara 1993 (see above), who found similar improvements in 24-hour pH probe data indices among those randomly assigned to eight weeks of standard doses of omeprazole (40 mg/d/1*73 m^2 surface area) or higher doses of ranitidine (20 mg/kg/d). Pfefferkorn 2006 looked at nocturnal acid breakthrough in 16 participants (one to 13 years of age) when comparing ranitidine 4 mg/kg or placebo, whilst continuing omeprazole, which was recently started for symptomatic GORD with endoscopic/histological changes. On pH study, no significant differences were found between the reflux indices of the ranitidine and placebo groups (at baseline, week three (initiation of ranitidine/placebo) and week 17).

Cimetidine

The only RCT (Cucchiara 1984) compared cimetidine versus Maalox® over 12 weeks in 33 children (two to 58 months of age) with a diagnosis of GORD based on symptoms, oesophagitis on endoscopy and acid reflux on pH probe. On 24-hour pH probe, the reflux index was significantly improved in both groups (P value < 0.05).

Nizatidine

Simeone 1997 assessed 26 participants (range six months to eight years) with histological evidence of oesophagitis, who were randomly assigned to nizatidine 10 mg/kg twice daily versus placebo for eight weeks. Post-treatment pH-metry showed significant (P value < 0.01) improvement in all variables (reflux index, number of episodes of pH < 4, number of episodes > 5 minutes, duration of episodes of pH < 4) in the nizatidine group versus the placebo group.

Prokinetics

Domperidone

RCTs evaluating the use of domperidone included Cresi 2008, who randomly assigned 26 neonates to domperidone 0.3 mg/kg or placebo over 24 hours with assessment performed through a 24-hour oesophageal pH study. Reflux frequency was significantly increased but duration was significantly improved in this brief study. Carroccio 1994 performed an RCT in 80 participants (one to 18 months of age with symptoms of reflux) in four groups to assess symptoms through a 24-hour oesophageal pH study. Although no differences in improvement in symptoms were observed between domperidone/alginate, domperidone alone and placebo, in the domperidone + Maalox® group (on pH testing), the reflux index significantly improved compared with that in other treatment combinations (P value < 0.03). Other markers were also significantly improved (number of episodes of pH < 4, duration of episodes of pH < 4 and number of reflux episodes > 5 minutes; P value < 0.05). In the other groups, significant improvement in pH metrics (reflux index, duration of episodes of pH < 4 and number of reflux episodes > 5 minutes) was reported, but no benefit was apparent in group B or C compared with group D (placebo). All feeds were thickened with Medigel 1%, perhaps accounting for significant improvement in pH outcomes in the placebo group. Bines 1992 assessed the impact of domperidone over four weeks (double-blind), then over a further four weeks (open-label) versus placebo in 17 children. On pH probe, significant improvement was seen only in total reflux episodes,.and weight and height Z scores were not significantly improved. The low number of participants and the lack of full (24-hour) pH probes limit the applicability of this study. The second (open-label) phase also may have been affected by the decision of participants who derived some benefit to remain on domperidone.

Compound alginate preparations

Gaviscon Infant®

Del Buono 2005 et al noted improvement only in reflux height on manometry and no other significant differences when compared with placebo. An older formulation of Gaviscon Infant® was evaluated by Forbes 1986, who showed no differences in pH indices after 24 hours of treatment with Gaviscon Infant®; however, conclusions may be limited by the short-term nature of this study (24 hours). Given the diversity of study designs and the heterogeneity of outcomes, it was not possible to perform a meta-analysis of the efficacy of Gaviscon Infant®.

Antispasmodics

Baclofen

A single study (Omari 2006) compared baclofen versus placebo in a double-blinded RCT in 30 children with resistant GORD (mean age 10.0 ± 0.8 years). Children were assessed with manometry/pH for

two hours after 0.5 mg/kg baclofen or placebo, and the incidence of transient lower oesophageal sphincter relaxation (TLESR) was measured. Investigators found that baclofen significantly reduced the incidence of TLESR (mean 7.3 ± 1.5 vs 3.6 ± 1.2 TLESR/2 h; P value < .05) and acid GOR (mean 4.2 ± 0.7 vs 1.7 ± 1.0 TLESR + GOR/2 h; P value < .05) during the test period compared with the control period. Side effects (causing early withdrawal but thought to be unrelated) were noted in the baclofen group, but no significant events were described in the 48 hours following trial completion.

Endoscopic and histological outcomes

Proton pump inhibitors

Omeprazole

In children older than one year of age, Pfefferkorn 2006 found significant improvement in endoscopic and histological appearances after 17 weeks of treatment but improvement in reflux index and symptoms after only three weeks of treatment, and no benefit from additional ranitidine. As outlined above, Cucchiara 1993 found that endoscopic markers improved when treatment with omeprazole and ranitidine was provided.

Lansoprazole

Borrelli 2002 compared lansoprazole versus alginate or lansoprazole and alginate over eight weeks in 36 children (range 12 months to 12 years) with GORD (based on symptoms, 24-hour pH probe and endoscopy). After baseline assessment and treatment, participants underwent a 24-hour pH study at one weeksymptomatic assessment at four weeks and repeat symptom assessment with final endoscopy at eight weeks. Symptom scores and the 24-hour pH study are discussed above. Endoscopy was performed at baseline, then at week eight. In all three groups, endoscopy appearances were much improved.

Pantoprazole

Tolia 2006 performed a multi-centre, double-blind RCT comparing 10 mg, 20 mg and 40 mg pantoprazole over eight weeks in 53 children (five to 11 years of age) with symptomatic GORD. Composite symptom score (CSS) and individual symptoms (number of vomiting episodes, heartburn, epigastric pain) at week zero, week one, then week eight improved significantly in all groups. Endoscopy appearances showed no improvement in any group. Histologically though, in the 10 mg pantoprazole group, of those with non-erosive GORD, 36% improved and 52% were unchanged. No participants with erosive disease were treated within this group. Among participants receiving pantoprazole 20 mg with non-erosive GORD, 50% improved (n = 9) with 44% unchanged (n = 8). Among those with erosive disease, all 3 were healed at 8 weeks. Among those treated with pantoprazole 40 mg with non-erosive disease, 68% improved (n = 11), 25% were unchanged (n = 4) and 6.2% worsened (n = 1). The only participant with erosive disease was healed at eight weeks. However no correlation between composite symptom score changes and endoscopy/biopsy changes was observed. Statistically significant increases from baseline in mean values were noted for weight and height at week 8 in the pantoprazole 10 mg and 40 mg dose groups (P value < 0.04). Antacid use was reduced in 20 mg and 40 mg groups.

In younger children: Baker 2010 looked at 0.3 mg/kg, 0.6 mg/kg and 1.2 mg/kg pantoprazole in 60 children (one to five years of age) with symptoms of GORD and endoscopic or histological signs of GORD over eight weeks. Endoscopy was performed in four participants with erosive changes; all four healed.

Esomeprazole

Tolia 2010b demonstrated resolution of endoscopically proven erosive oesophagitis after eight weeks of esomeprazole in 45/109 children one to 11 years of age: Significant selection bias was evident: No symptom data were presented on these 45 (of 109 initially enrolled), and some of the reasons for exclusions were unclear. In all, 15/31 (48%) had erosive oesophagitis at baseline. All participants with erosive oesophagitis had healed on follow-up endoscopy (13/15). Histological appearances were graded as healed/improved/unchanged. A total of 23/31 (74.2%) had microscopic (not visible) reflux oesophagitis at baseline biopsy. All 13 participants who underwent follow-up endoscopy had healed.

H2-receptor antagonists

Ranitidine

Ranitidine was assessed by Cucchiara 1993 (see above), who found similar improvement in endoscopic appearances among those randomly assigned to eight weeks of standard doses of omeprazole (40 mg/d/1*73 m^2 surface area) or higher doses of ranitidine (20 mg/kg/d). Pfefferkorn 2006 looked at nocturnal acid breakthrough in 16 participants (one to 13 years of age) and compared ranitidine 4 mg/kg or placebo, whilst continuing omeprazole that was recently started for symptomatic GORD with endoscopic/histological changes. Endoscopic appearances (at baseline and at week 17) improved in the ranitidine group and in the placebo group: No additional benefit was noted between the ranitidine and placebo groups (P value 0.32), above that gained by taking omeprazole.

Cimetidine

The only RCT (Cucchiara 1984) compared cimetidine versus Maalox® over 12 weeks in 33 infants and children (two to 58 months of age) with a diagnosis of GORD based on symptoms, oesophagitis on endoscopy and acid reflux on pH probe. Investigators found that endoscopic appearances were significantly improved.

Nizatidine

Simeone 1997 assessed 26 participants (range six months to eight years) with histological evidence of oesophagitis who were randomly assigned to nizatidine 10 mg/kg twice daily versus placebo for eight weeks. Outcomes were assessed in terms of symptoms, pH scores and endoscopic/histological appearances. Endoscopy findings included significantly better healing in 69% of participants in the nizatidine group (P value < 0.007 by Fisher's exact test).

Serious side effects/adverse events (AEs)

Proton pump inhibitors

Omeprazole: Moore 2003 and Pfefferkorn 2006 noted no side effects. Cucchiara 1993 noted no serious side effects. One participant was withdrawn as the result of having a temperature and a respiratory infection: It was uncertain to which treatment group this participant belonged (omeprazole or high-dose ranitidine).

Lansoprazole: Orenstein 2008 noted that treatment-emergent side effects were more common in those taking lansoprazole (10 participants vs two participants given placebo, of a total of 162 participants; P value 0.03). These included lower respiratory tract infection (five participants vs one given placebo; P value was non-significant), diarrhoea (two participants), ileus (one participant) and dehydration (one participant): No serious adverse events were thought to be treatment related. Borrelli 2002 noted no serious AEs. Gunesekaran 2003 noted that pharyngitis (6%; 2/32 taking lansoprazole 15 mg) and headache (16%; 4/31) were the most commonly reported side effects among adolescents treated with lansoprazole15 mg and 30 mg, respectively.

Esomeprazole: Omari 2007 noted no serious side effects in only one infant with preexisting colic withdrawn because of excessive irritability. Tolia 2010a noted no serious AEs among infants one to 12 months of age, but 13 AEs considered by the investigator to be related to esomeprazole treatment occurred in 10 of 108 participants (9.3%), mainly diarrhoea and headache. In their post hoc analysis, Tolia 2010b noted no serious adverse events in their cohort of 12- to 36-month-old children.

Pantoprazole: Kierkus 2011 noted no serious on-treatment side effects, but one participant was withdrawn from the study during the open-label phase with excessive vomiting, probably related to an increase in pantoprazole dose. Tsou 2006 noted that although no serious AEs occurred, 82% (110 participants) had a treatment-emergent adverse event (TEAE), mainly headache, and in the high-dose group (40 mg pantoprazole), diarrhoea. Five participants had minor derangement of their liver function tests. Baker 2010, in a study of one- to five-year-olds, noted no serious AEs, but one participant had rectal bleeding.

H2-receptor antagonists

Cimetidine: Cucchiara 1984 noted no serious side effects. Two participants taking cimetidine had diarrhoea.

Ranitidine: Cucchiara 1993 noted no serious side effects. One participant was withdrawn because of temperature and a respiratory infection. It was uncertain to which treatment group this participant had been assigned (omeprazole or high-dose ranitidine). Pfefferkorn 2006 noted no side effects.

Nizatidine: Simeone 1997 noted that a single participant taking nizatidine had an urticarial rash. Severity of the rash was not noted. No other adverse effects were reported.

Prokinetics

Domperidone: Carroccio 1994 did not comment on the presence or absence of AEs. Cresi 2008 in a short-term study on neonates noted no side effects. Bines 1992 noted no serious AEs, but six participants had self-limiting diarrhoea (four taking domperidone, two placebo).

Compound alginate preparations

Gaviscon Infant ®: Buts 1987, Forbes 1986 and Borrelli 2002 noted no AEs. Carroccio 1994 and Del Buono 2005 did not comment on the presence or absence of AEs. Miller 1999 noted no serious AEs, but 13 participants withdrew because of adverse effects, including diarrhoea and constipation, although no statistical difference was noted between alginate and placebo.

Antispasmodics

Baclofen: Omari 2006 noted no serious treatment-related side effects.

Clinical bottom line

Proton pump inhibitors

In studies assessing PPIs in children over one year of age, good improvement in symptoms but weaker evidence for efficacy in infants was found. As a class overall, evidence suggests that PPIs improve the reflux index and other pH probe markers of GORD, although correlation between pH probe results and direct symptomatic benefit was less clear, particularly in infants. For older children with GORD, moderate evidence was found for their efficacy in improving pH metrics. Moderate evidence was also found for PPI efficacy in significantly improving erosive changes on endoscopy due to GORD, particularly in older children.

H2 antagonists

With so few RCTs and no appropriate head-to-head comparisons versus PPIs, meta-analysis to further investigate the effects of treatment was not possible. Ranitidine appears to be safe in children over a year of age: RCTs evaluating the use of ranitidine in infants were not identified. A single study demonstrated that high-dose ranitidine had efficacy similar to that of omeprazole in symptom relief, pH indices and endoscopic findings. Cimetidine and nizatidine also improved symptoms and signs of GORD in older children and infants. No RCTs evaluated the use of H_2 antagonists in functional reflux. Further data are called for and head-to-head trials against PPIs are recommended, given the current high usage of H_2 antagonists for GORD.

Prokinetics

Metoclopramide is assessed elsewhere, and no RCTs evaluating the use of erythromycin in children as a prokinetic for GOR or GORD were found. Domperidone: In neonates, limited assessment of outcomes and short duration of studies make drawing wider conclusions difficult. In older children, the evidence is very weak (given the diversity of study designs and the heterogeneity of outcomes) regarding benefit and does not support prolonged trials of domperidone when initial benefit is not seen.

Compound alginate preparations

Gaviscon Infant®

Moderate evidence indicates that Gaviscon Infant® improves symptoms in infants, including those with functional reflux, but further research is recommended (see Implications for research), including follow-up until one year of age.

Antispasmodics

Baclofen

A single study showed improvement in acid reflux and transient lower oesophageal sphincter relaxations in children treated with baclofen, but this was a short-duration (2-hour) trial, and no other studies on this group are available; applicability of this study is difficult, and further double-blind RCTs are recommended to evaluate the effects of baclofen in reducing GOR, particularly in children with neurodisability, who are often prescribed baclofen for concomitant spasticity.

DISCUSSION

Summary of main results

These are discussed in turn with respect to each class of medication.

Proton pump inhibitors

As a class, proton pump inhibitors are effective in healing erosive oesophagitis, particularly in older children. For older children with GORD, it was not possible to combine methodologically similar studies because of heterogeneity in outcomes and study populations, although evidence was found for their efficacy in improving outcomes. This evidence is of moderate quality, as pharmaceutical company support in manuscript preparation was a common feature, as were RCTs comparing different doses of the same drug, rather than placebo-controlled RCTs or head-to-head comparisons. This makes it difficult to ascertain statistical superiority of one PPI over another. In infants with symptoms of GORD (compared with GOR), weak evidence shows benefit derived from treatment with PPIs, but again it was not possible to combine methodologically similar studies because of heterogeneity in outcomes and study populations.

Omeprazole

One study assessing infants only (Moore 2003) noted that crying was reduced in both omeprazole-treated and untreated irritable infants, concluding that cry/fuss time decreased spontaneously with time, and that empirical acid suppression was not indicated in this group. Another study assessing children only (Pfefferkorn 2006) and one study including infants and children (Cucchiara 1993) showed improvement when using outcomes suggesting more significant disease (endoscopic findings and reflux index). Cucchiara 1993 showed that this symptomatic improvement was similar to that seen with high-dose ranitidine. No significant side effects were noted. It was not possible to demonstrate statistical superiority of omeprazole over another PPI. Data are insufficient to allow conclusions regarding the use of omeprazole to treat functional reflux in children younger than one year of age, as are data from RCTs regarding the long-term safety of omeprazole.

Lansoprazole

Evidence for efficacy of lansoprazole in infants was weak: Orenstein 2008 assessed 162 infants (range four to 51 weeks of age) who were randomly assigned to lansoprazole versus placebo with symptoms suggestive of reflux. No difference was reported between lansoprazole and placebo in terms of observer assessments or symptom diaries, and among those who went on to take lansoprazole open-label (n = 55), no significant improvement in symptoms was described. However no investigation confirmed GORD, and many of the enrolled participants may have had functional reflux. In children over a year of age, the evidence is stronger for those with erosive oesophagitis. A significant increase in risk of adverse events was reported, including lower respiratory tract infection in infants treated with lansoprazole. Borrelli 2002 compared lansoprazole versus alginate or lansoprazole and alginate over eight weeks in 36 children (range 12 months to 12 years) with GORD (based on symptoms, 24-hour pH probe and endoscopy). Symptom scores significantly improved in all groups (P value < 0.01), but the lansoprazole and alginate group was significantly superior to the other two groups (P value < 0.01). Results show that 24-hour pH study also revealed significant improvement in the reflux index (P value < 0.01), and again the lansoprazole and alginate group was significantly superior to the other two groups (P value < 0.05). Endoscopy appearances were much improved In all three groups. No significant side effects were noted. Gunesekaran 2003 assessed 63 adolescents (range 12 to 17 years of age) with symptomatic/endoscopic GORD, who were randomly assigned to lansoprazole 30 mg versus 15 mg: After five days of treatment, symptom diaries in both groups noted improvements in frequency and severity of heartburn and other symptoms (P value not stated). In all, 69% of the 15 mg group and 74% of the 30 mg group reported that their symptoms of reflux were better, and the amount of antacid required for symptom relief was reduced in both groups (average 1.8 tablets/d to 1.05 in the lansoprazole 15 mg group, and 1.8 to 0.63 tablets/d in the lansoprazole 30 mg group; P value not stated). Again on physician review, among participants with heartburn at baseline (n = 36), symptomatic improvement was significant in both groups. Data are insufficient to permit conclusions regarding the use of lansoprazole to treat functional reflux in children younger than one year of age, and data from RCTs regarding the long-term safety of lansoprazole are insufficient.

Pantoprazole

Two studies assessed treatment of older children with GORD with pantoprazole and demonstrated significant symptomatic improvement (Tsou 2006 using composite symptom scores and Tolia 2006 at all doses), but one study (Tsou 2006) noted that 82% had a treatment-emergent adverse event (TEAE), mainly headache, and in the high-dose group (40 mg pantoprazole), diarrhoea. Further studies may be useful in evaluating the side effect profile of pantoprazole compared with other PPIs.

Esomeprazole

Weak evidence may show benefit in infants and older children: Omari 2007 compared 50 infants given low-dose and high-dose esomeprazole. Improvement (non-significant) was seen in symptoms, along with a trend toward improvement in low-dose groups. Reflux index was significantly improved in both groups, again with greater improvement evident in the lower-dose group. Tolia 2010b demonstrated resolution of endoscopically proven erosive oesophagitis after eight weeks of esomeprazole in 45/109 children one to 11 years of age, but significant selection bias was evident, and no symptom data for these 45 were presented(some of the reasons for exclusion were unclear). Nevertheless a post hoc analysis (Tolia 2010a) of participants with endoscopically confirmed GORD (12 to 36 months of age) compared 5 mg and 10 mg esomeprazole. A statistically significant reduction (P value < 0.0018) in the severity of GORD symptoms was seen within each treatment group from baseline to final assessment. No difference between low-dose and high-dose groups was reported. Among 15 participants (48%) with erosive oesophagitis at baseline, 13 had repeat endoscopy, and all 13 had healed, as confirmed on histology.

Conclusion

Moderate evidence, obtained within the limitations of study design as discussed, suggests that PPIs are efficacious, particularly in older children with GORD, and evidence of their efficacy in infants with GORD is weak. Less evidence shows significant improvement in symptoms with increasing doses, but increasing the dose may increase the risk of side effects. The risk of side effects was less

prominent for omeprazole and lansoprazole than for pantoprazole. No evidence has been found for the use of PPIs in functional reflux. Further studies assessing the long-term impact/safety profile of PPIs are recommended (see below).

H2 antagonists

Ranitidine

Ranitidine was assessed by Cucchiara 1993 (see above), who found similar improvement in symptoms, 24-hour pH probe data indices and endoscopy appearances among those randomly assigned to eight weeks of standard doses of omeprazole or high doses of ranitidine (20 mg/kg/d) in children who had not responded to standard dose ranitidine. Pfefferkorn 2006 looked at the addition of ranitidine 4 mg/kg or placebo to reduce nocturnal acid breakthrough in 16 participants (one to 13 years of age) who had recently started on omeprazole for symptomatic GORD with endoscopic/histological changes, comparing ranitidine, whilst continuing omeprazole. Symptom scores in both groups significantly improved with no significant difference noted between ranitidine and placebo groups (P value 0.31 at week three; P value 0.20 at week nine; P value 0.10 week 17). On pH study, no significant differences were observed between the reflux index of the ranitidine and placebo groups (at baseline, week three (initiation of ranitidine/placebo) and week 17). Endoscopy appearances (at baseline and at week 17) improved in the ranitidine and placebo groups: No difference was seen between the ranitidine and placebo groups (P value 0.32). Therefore no additional benefit seen was seen (in terms of symptom score, reflux index or endoscopic change) from supplementation of PPI therapy with ranitidine. No evidence for tachyphylaxis was identified in the studies assessed, but this has been identified elsewhere as a concern (Hyman 1985), as has a multi-centre observational study (Terrin 2012) that noted a 6.6-fold higher rate of necrotising enterocolitis in ranitidine-treated very low birth weight infants (95% confidence interval 1.7 to 25.0; P value .003).

Cimetidine

The only RCT (Cucchiara 1984) compared cimetidine versus Maalox® over 12 weeks in 33 infants and children (two to 58 months of age) with a diagnosis of GORD based on symptoms, oesophagitis on endoscopy and acid reflux on pH probe. Investigators found that cimetidine and Maalox® provided significant symptomatic relief (P value < 0.05). On 24-hour pH probe, reflux index was significantly improved in both groups (P value < 0.05); endoscopic appearances were also improved.

Nizatidine

Simeone 1997 assessed 26 participants (range six months to eight years) with histological evidence of oesophagitis; they were randomly assigned to nizatidine 10 mg/kg twice daily versus placebo for eight weeks. Outcomes were assessed in terms of symptoms, pH scores and endoscopic/histological appearances. Improved symptoms were seen only in the nizatidine group (P value < 0.01). Endoscopic findings included significantly better healing in 69% of participants in the nizatidine group (P value < 0.007 by Fisher's exact test). Post-treatment pH-metry showed significant (P value < 0.01) improvement in all variables (i.e. reflux index, number of episodes of pH < 4, number of episodes > 5 minutes, duration of episodes of pH < 4) in the nizatidine group versus the placebo group.

Conclusions

With so few RCTs and no appropriate head-to-head comparisons against PPIs, meta-analysis to further investigate the effects of treatment was not possible.

Ranitidine appears to be efficacious and safe in children over one year of age; RCTs evaluating the use of ranitidine in infants were not identified. Cimetidine and nizatidine also improved symptoms and signs of GORD in older children and infants. No RCTs evaluated the use of H_2 antagonists in functional reflux. Further data are called for, with a recommendation for head-to-head trials against PPIs, given the current high usage of H_2 antagonists for GORD.

Prokinetics

As was discussed earlier, metoclopramide is assessed elsewhere, and no RCTS have been conducted to evaluate the use of erythromycin in children as a prokinetic for GOR or GORD.

Domperidone

RCTs evaluating the use of domperidone included Cresi 2008, who randomly assigned 26 neonates to domperidone 0.3 mg/kg or placebo over 24 hours with assessment through 24-hour oesophageal pH study. Reflux frequency was significantly increased, but duration was significantly improved. Limited assessment of outcomes and short duration of the study make drawing conclusions difficult, yet this is the only study that is evaluating antireflux treatment in neonates. Carroccio 1994 found no improvement in symptoms between domperidone/alginate, domperidone alone and placebo, but in the domperidone + Maalox® group, 16/20 participants found that their symptoms resolved, and 4/20 participants noted improvement (P value < 0.001); on pH testing, reflux index significantly improved compared with other treatment combinations (P value < 0.03). Thickened feeds (Medigel 1%) could account for significant improvement in pH outcomes in the placebo group. Symptom improvement continued through six months of follow-up. Bines 1992 assessed the impact of domperidone over four weeks (double-blind), then over a further four weeks (open-label), versus placebo in 17 children. Gastric emptying was improved in both groups (non-significant difference). On pH probe, significant improvement was seen only in total reflux episodes, and non-significant improvement in growth metrics was noted. No individual symptom was improved after four weeks; after eight weeks of therapy, 33% of participants treated with domperidone noted improved symptoms (P value non-significant).

Evidence for the efficacy of domperidone in GOR is very poor in older children, infants and neonates as the result of limitations in study design and length of follow-up, and this evidence is too weak to permit recommendations. No evidence of efficacy was identified in children with neurodisability.

Compound alginate preparations

Gaviscon Infant®

Gaviscon Infant® was evaluated by five RCTs (Buts 1987; Carroccio 1994; Del Buono 2005; Forbes 1986; Miller 1999); the current formulation has been evaluated by Miller 1999 and Del Buono 2005. Miller 1999 found significant symptomatic improvement, which was limited by short follow-up. However Del Buono 2005 noted improvement only in reflux height on manometry, with no other significant differences observed when compared with placebo.

With older preparations, Forbes 1986 showed no difference in pH indices after 24 hours of treatment with Gaviscon Infant®; Buts 1987 showed symptomatic improvement and some improvement on pH indices. Evidence was insufficient for performance of a meta-analysis on commonly used markers of acid reflux on pH study such as reflux index, and significant conclusions based on pH indices may have limited applicability, given that Gaviscon Infant® does not intrinsically act as an antacid.

Weak evidence suggests that Gaviscon Infant® improves symptoms in infants, including those with functional reflux, but further research is recommended (see Implications for research), including follow-up to a specified age.

Antispasmodics

Baclofen

A single study showed improvement in acid reflux and transient lower oesophageal sphincter relaxations in children treated with baclofen, but this was a short-duration (two-hour) trial, and no other studies are available in this group; applicability of this study is difficult, and further double-blind RCTs are recommended to evaluate the effects of baclofen in reducing GOR, particularly in children with neurodisability, who are often prescribed baclofen for concomitant spasticity.

Overall completeness and applicability of evidence

This section aims to consider the relevance of the evidence to the review question. This review summarises available RCTs, and searches have been rerun to attempt to ensure that this review is contemporary. Review searches have been run independently by the Cochrane Upper GI Group in Canada to ensure reproducibility. Overall, as discussed, a paucity of evidence has been derived from studies on the role of medications in GORD. Several factors are involved in this, including heterogeneity of the population, lack of head-to-head trials and variation in outcome measures, with variability between how well outcome measures (e.g. symptom scores/reflux index/endoscopic appearances) correlate when the severity of GORD is estimated. Another group of infants and children have been reported to have reflux that is problematic but is not a pathological disease.

The completeness of evidence is considered for each class of medication in turn.

For proton pump inhibitors: Further evidence is needed to show which children are most likely to benefit from treatment. Subgroups including children with neurodisability would be of particular interest, as they often remain on empirical acid suppression throughout childhood. Long-term safety needs to be demonstrated, and further studies to assess the role of PPIs in infants would be welcomed. Head-to-head studies to assess the proton pump inhibitor with the best efficacy and fewest side effects would also be recommended.

For H2 antagonists: Up-to-date trials are recommended to compare individual medications, or to further assess their efficacy against PPIs. Subgroups of particular importance include neonates and premature babies, as well as children with neurodisability; evidence of efficacy in resource-limited settings would be useful to consider.

For domperidone: Studies with greater power are recommended to further elucidate whether domperidone has a role in the treatment of infants and children with GOR or GORD compared with placebo or erythromycin. Major limitations in study design and length of follow-up are apparent, and the evidence is too weak to permit recommendations. Groups of particular importance include neonates, for whom the evidence base is particularly weak, and children with neurodisability, for whom no evidence base is available.

For Gaviscon Infant®: Studies assessing the role of Gaviscon Infant® in infants with functional reflux and ensuring long-term safety would be essential.

Further studies to assess whether baclofen has a role in improving GORD among children with neurodisability, who often are prescribed baclofen for concomitant spasticity, also would be important.

Quality of the evidence

As has been discussed, evidence for proton pump inhibitors in older children is moderate, and for the remainder of the medications is poor to very poor, with significant methodological concerns regarding several studies that are summarised in the 'Risk of bias' section above. Heterogeneity is considerable: Outcomes were analysed in terms of different symptom scores, different patient groups (infants vs children, GOR vs GORD) and different dosing comparisons for PPIs, rather than comparing different agents and different indices (e.g. on 24-hour pH/impedance monitoring). Whilst our attempt to combine similar participant groups with similar outcome indices on similar medications has limited validity, it demonstrates the heterogeneity of the data both for PPIs and for Gaviscon Infant®, and shows how varied the studies are. Developing a consistent evidence-based message for clinicians and families requires further robust studies, with consistent outcomes, across subgroups with differing underlying processes.

Potential biases in the review process

Strengths of this review include the systematic nature of the literature search, including handsearching, of multiple databases and relevant reviews, using wide search terms. Each study was appraised by two review authors, and the statistical analysis was verified by a statistician. Questions about newer studies (less than 10 years old) were resolved by correspondence with the original study authors. For older studies, relevant data may not have been reviewed because of inability to contact study authors. No conflicts of interest are known.

Agreements and disagreements with other studies or reviews

The National Institute for Health and Care Excellence (NICE) guidelines on GOR are currently being developed. Other reviews, which include other papers such as case control and cohort studies, show similar conclusions regarding the paucity of evidence and call for further research, particularly into the subgroups discussed above.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence base of therapies for infants is mixed. In terms of pharmacological strategies, a clear distinction should be drawn between the treatment of infants with functional reflux and those with gastro-oesophageal reflux disease (those with sequelae of GOR, or failure to thrive). In the subgroup of infants with functional reflux, the main problem appears to be caused by the milk bolus, although acid reflux undoubtedly occurs. Underlying transient gut dysmotility, with dysfunction of the lower oesophageal sphincter, a short oesophagus, high volumes of liquid feeds and a significant proportion of time lying flat are important predisposing factors that improve with time. In such a large group, the evidence also highlights significant discrepancies between reported symptom severity scores and endoscopic/histological findings, which are potentially affected by the numbers of children with distressing symptoms but functional reflux.

In terms of efficacious treatments, the best evidence for treatment of functional reflux appears to relate to Gaviscon Infant® (Buts 1987; Miller 1999), but these are short-term studies with small numbers of participants. Orenstein demonstrated lack of symptomatic benefit from PPIs in infants with functional reflux. Evidence for strategies such as reassurance, positioning and use of thickened formula milk in appropriate volumes and frequencies is covered elsewhere. For infants with evidence of GORD on investigation (endoscopic changes or abnormal reflux index on pH probe), evidence of benefit from any medical treatment is weak. Further studies are needed to confirm whether PPIs or H_2 antagonists are superior in the group, and whether individual drugs offer superior efficacy. Weak evidence has been found for acid suppression (PPIs/H2-receptor antagonists), with consequent decreased gastric enzyme activity, allowing for healing of oesophagitis, and symptomatic improvement. As a result of the factors previously discussed, we are unable to comment as to whether H_2 antagonists are superior to PPIs, but no evidence supports concurrent use. No consistent evidence for prokinetics (such as domperidone) has been found. It is currently difficult to justify continuing prescriptions of domperidone in infants for whom no benefit from empirical use has been reported. The current MHRA (Centre of the Medicines and Healthcare Products Regulatory Agency) alert recommends restricting empirical prescriptions to two weeks and avoiding them in children with co-existing cardiac disease and in those receiving treatment with CYP3A4 inhibitors (EMA 2014).

Among older children with GORD, moderate evidence of benefit from PPIs has been found, along with weak evidence of benefit from H_2 antagonists, in providing symptomatic relief and in improving endoscopic/histological appearances and pH indices. No consistent evidence has been found for prokinetics (such as domperidone). It is currently difficult to justify prescriptions for domperidone among children for whom no benefit from empirical use is apparent. The current MHRA alert recommends restricting empirical prescriptions to two weeks and avoiding them in children with co-existing cardiac disease and in those receiving treatment with CYP3A4 inhibitors (EMA 2014).

Implications for research

Undoubtedly the burden of functional reflux and GORD on primary and secondary care is large, and further research is essential to clarify the role of medications in treating particular aspects of GOR. This review demonstrates the benefit of the Pediatric Written Request (PWR) made by the FDA in improving our knowledge of a class of medications that are widely prescribed (PPIs). This review would call for this to continue with extension to the remainder of the medications used to treat GOR (e.g. H_2 antagonists/Gaviscon Infant®). We would also call for comparisons that include a placebo or different drug arm, as well as/rather than comparisons between same-drug different dosing. It was evident that significant confounding interventions that would be likely to provide significant improvements as interventions in their own right (e.g. thickened or hydrolysed feeds to infants) were often given within trials to participants. Separate funding to support these calls would be a major step forward, and at least separating more clearly industry funding for the trial from manuscript preparation would be an improvement. Several of the recent PPI trials carried out under the PWR have declared support in manuscript writing from pharmaceutical manufacturers, and this carries inherent risks.

We would also highlight the need for specific RCTs into children with underlying oesophageal dysmotility (e.g. children with cerebral palsy), who often have difficult and protracted reflux, as most of these trials specifically excluded this subgroup. They often examine maximal medical therapies, including prokinetics, given for prolonged time periods, and treatment regimes for these groups are often extrapolated from those for other groups of children. Premature babies are often also treated empirically for gastro-oesophageal reflux, for example, causing apnoea; further RCTs in this age group, using consistent outcomes, are also recommended.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Baker 2010

Methods	Randomised double-blind study over 8 weeks of 3 doses of pantoprazole
Participants	60 children (1-5 years) with symptoms of GORD and endoscopic or histological signs of GORD at recruitment
Interventions	3 groups: pantoprazole 0.3 mg/kg once daily

Baker 2010 *(Continued)*

	Pantoprazole 0.6 mg/kg once daily, pantoprazole 1.2 mg/kg once daily delayed-release
Outcomes	Symptoms: Assessed using GOR symptom score (weekly GOR frequency scores: WGSS): mean (SD) with parents recording symptoms daily in an eDiary *Low-dose group* (n = 18): baseline symptom score 3.21 (1.56) Final week 0.84 (0.72); P value < 0.001 *Medium-dose group* (n = 19): baseline 2.43 (1.58) Final week 1.79 (1.78); P value 0.063—not significant *High-dose group*: baseline 3.36 (2.48) Final week 1.71 (1.69); P value < 0.001 Individual symptoms assessed (abdominal pain, burping, heartburn, pain after eating, difficulty swallowing): improved in all groups after 8 weeks (P value < 0.05) Endoscopy: repeat endoscopy performed in 4 participants with endoscopic changes at recruitment. All 4 participants healed (randomly assigned to medium-dose (n = 2)/high-dose (n = 2) groups). Too small for statistical significance Histological appearances: no scope after treatment in participants with histological changes only Side effects: *Low-dose group*: one participant diarrhoea and nappy rash *Medium-dose group*: one participant sleep disturbance; one participant abdominal pain *High-dose group:* one participant rectal bleeding
Notes	Followed a PWR (Pediatric Written Request) template, after widespread call from FDA for manufacturers of PPIs for children to carry out RCTs in children. Exclusions: recent ALTE, eosinophilic oesophagitis, CF, CMPA, *H pylori* infection Study authors' comments: No clear relationship between dose and response was noted. Low dose may be enough to control symptoms; higher dose may be required for those with endoscopic changes Children < 2 years have quicker dose clearance and may benefit from higher doses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No comment made re blinding. Participants recorded symptoms daily in an eDiary

Baker 2010 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data on symptom scores and on participants with erosive oesophagitis who were re-scoped were included. All participants were accounted for; analysis included those not enrolled. 37 participants were not included (17 normal biopsy, 8 eosinophilic oesophagitis, 5 withdrawal of consent, 4 *H pylori* positive, 3 used medications prohibited by protocol). Of those who withdrew or were withdrawn, 1 in low-dose, 4 in medium-dose, 3 in high-dose group.
Selective reporting (reporting bias)	Unclear risk	No comment made
Other bias	High risk	Writing support (Wyeth). Institutional support from drug companies

Bines 1992

Methods	4-Week, double-blind, placebo-controlled trial of domperidone in children with gastro-oesophageal reflux, followed by open-label trial
Participants	17 participants between the ages of 5 months and 12 years with pH probe–confirmed gastro-oesophageal reflux, rated moderate to severe on the basis of symptoms
Interventions	0.6 mg/kg of domperidone 30 minutes before meal time or placebo
Outcomes	pH study Number of episodes pH < 4—mean **Domperidone:** baseline—69 After 4 weeks—26 **Placebo:** baseline—16 After 4 weeks—28 Reduction in domperidone cohort vs placebo—P value < 0.01 Longest episode pH < 4 (minutes)—mean **Domperidone:** baseline—14.3 After 4 weeks—12.6 **Placebo:** baseline—16 After 4 weeks—20.9 Non-significant % of time pH < 4—mean **Domperidone:** baseline—15.9% After 4 weeks—11.8% **Placebo:** baseline—15.2% After 4 weeks—15.9%

Bines 1992 *(Continued)*

	Non-significant Acid clearance (minutes)—mean **Domperidone:** baseline—0.22 After 4 weeks—0.61 **Placebo:** baseline—0.58 After 4 weeks—0.83 Non-significant Z score height: **Domperidone:** baseline—1.8 After 4 weeks—1.4 **Placebo:** baseline—0.1 After 4 weeks—1.2 Non-significant Z score weight: **Domperidone:** baseline—1.7 After 4 weeks—1.4 **Placebo:** baseline—0.8 After 4 weeks—0.6 Non-significant Gastric emptying scan (mean % emptied after 1 hour); **Domperidone:** baseline—64.6 After 4 weeks—49.6 **Placebo:** baseline—47.5 After 4 weeks—33.8 Non-significant
Notes	Although subjective data on infant behaviour were collected, they were not presented in a consistent manner by the study authors and do not allow for post hoc analysis Some transient, self-limiting diarrhoea was reported in 4 patients in the domperidone group and 2 in the placebo group Some reported improvement after the open-label trial (8/52 total), but again, inconsistent reporting of results makes analysis difficult Study authors' conclusions: Although reduction in number of reflux episodes was apparent, no significant change in symptomatology was noted at 4 weeks. Some possible at 8 weeks, but small and biased cohort after the open-label trial
Risk of bias	

Bines 1992 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described by study authors
Allocation concealment (selection bias)	Unclear risk	Not described by study authors
Blinding of participants and personnel (performance bias) All outcomes	High risk	Part 2 of the trial was open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described by study authors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some data not included
Selective reporting (reporting bias)	High risk	Numerous data from outcomes not presented
Other bias	High risk	Participants agreeing to open-label trial likely to be biased towards those who believed they had received initial benefit from treatment

Borrelli 2002

Methods	RCT with 24-hour pH study, symptomatic assessment and endoscopy at baseline and 24-hour pH study at 1 week, then symptomatic assessment at 4 weeks and at 8 weeks (with final endoscopy)
Participants	36 participants, median age 5.6 years (12 months to 12 years) with diagnosis of GORD based on symptoms, 24-hour pH probe and endoscopy
Interventions	Group A: alginate alone (2 mL/kg/d in divided doses) Group B: lansoprazole 1.5 mg/kg twice daily before meals Group C: lansoprazole and alginate: over 8 weeks
Outcomes	Symptoms: mean (SD) at baseline, week 4, then week 8 [Symptom score = regurgitation/vomiting, chest pain/irritability, epigastric pain/bloating, nocturnal cough/postfeeding cough] *Group A:* baseline 9.6 ± 1.8 to 5.8 ± -0.8 to 4.2 ± 0.9 (P value < 0.01) *Group B*: 10.4 ± 2.1 to 5.1 ± 1.0 to 4.3 ± 2.1 (P value < 0.01) Group C: 9.8 ± 1.7 to 5.5 ± 1.1 to 3.0 ±1.1 (P value < 0.01) Symptom score reduced between group C and A + B (P value < 0.05) 24-Hour pH study (at baseline, then at week 1): Reflux index (% of time oesophageal pH < 4) *Group A:* 11.5 ± 3.6 to 6.1 ±1.9 (after week 1) (P value < 0.01)

Borrelli 2002 *(Continued)*

Group B: 10.75 ± 2.7 to 5.5 ± 1.5 (P value < 0.01)

Group C: 11.8 ± 2.7 to 3.8 ± 0.7 (P value < 0.01)

Group C better than A + B (P value < 0.05)

Endoscopy appearances: (performed at baseline, then week 8)

Scored using Hetzel-Dent scoring: grade 0-4. Children with grade 3-4 oesophagitis on endoscopy not enrolled but given high-dose lansoprazole. Participants without erosions had hyperaemia and granularity

Group A: grade 2 oesophagitis in 5 participants: Erosions healed completely. Hyperaemia and granularity in only 2 participants

Group B: grade 2 oesophagitis in 5 participants: Erosions healed completely. Hyperaemia and granularity in only 3 participants

Group C: grade 2 oesophagitis in 6 participants: Erosions healed completely at 8 weeks. Hyperaemia and granularity in only 2 participants

Side effects: none significant

Notes	4 participants lost: 2 had URTI with fever, 2 had poor drug compliance. No list of excluded participants, but infectious diseases, CMPA, neurometabolic conditions and structural gut abnormalities were excluded on investigations as part of workup Children with grade 3 to 4 oesophagitis on endoscopy not enrolled but given high-dose PPI Lansoprazole + Gaviscon® superior to lansoprazole alone or Gaviscon® alone in terms of reflux index and symptom score. All erosions healed in all groups, and significant improvements in symptom score, reflux index and endoscopy were seen in all groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No comment made
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment made
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No comment made
Selective reporting (reporting bias)	Unclear risk	Children with severe erosive oesophagitis excluded from trial
Other bias	Unclear risk	No comment about funding

Buts 1987

Methods	Blinded RCT, single-centre study
Participants	20 infants and children with characteristic symptoms of GOR (vomiting, acid regurgitation related to meals and posture, heartburn, recurrent respiratory tract disorders)
Interventions	Gaviscon® (10 participants, mean age 21 months) or placebo (10 participants, mean age 35 months). 24-Hour pH probe at baseline and day 8; symptom assessment performed by staff during this time
Outcomes	Gaviscon® (a) (baseline, treatment, P value) versus Placebo (b) (baseline, treatment, P value) • Total number of episodes: a) 131.6 ± 29.5, 56.0 ± 16.8, P < 0.05, b) 87.2 ± 15.5, 90.6 ± 14.7, P = NS • Number of episodes > 5 minutes: a) 5.5 ± 0.5, 1.2 ± 0.2, P < 0.05, b) 5.2 ± 0.8 4.6 ± 0.9, P = NS • Euler-Byrne Index: a) 153.7 ± 32.7, 61.0 ± 16.6, P < 0.05, b) 108.0 ± 14.3, 97.8 ± 13.0, P = NS • Reflux Index: a) 3.4 ± 2.3, 6.1 ± 0.3, P < 0.05, b) 10.4 ± 0.4, 10.1 ± 1.4, P = NS • Mean duration of reflux sleep(min): a) 3.4 ± 1.07, 1.3 ± 0.23, P < 0.05, b) 2.30 ± 0.3, 2.28 ± 0.56, P = NS • Number of reflux episodes (2 hours post feed): a) 71.7 ± 13.4, 32.3 ± 7.9, P < 0.05, b) 55.3 ± 10.8, 54.1 ± 9.0, P = NS • % reflux time in sleep: a) 9.49 ± 1.47, 6.18 ± 2.58, P < 0.05, b) 7.76 ± 1.17, 8.4 ± 1.4, P = NS 24-Hour pH probe was assessed at baseline and at day 8; symptoms including vomiting and number of episodes of regurgitation within 24 hours during the time of the recordings were observed by staff. All pH monitoring variables were significantly reduced after 8 days of Gaviscon® treatment, including reflux index, compared with baseline values (P value < 0.05) Symptoms: After Gaviscon® treatment, symptoms were reported to have improved (number of episodes of regurgitation per day: reduced by 3 to 4 times), and vomiting improved in all cases, ceasing completely (2 to 3 episodes per day to none); or at least frequency and volume were decreased. No further evaluation of symptoms was given
Notes	No oesophagitis was seen on endoscopy of 14 participants (6 treated with Gaviscon®, 8 with placebo)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no methodological comment made as to blinding technique and who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment made
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only 14 participants were endoscoped, none had oesophagitis. Further details on symptom evaluation required

Buts 1987 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No evidence of selective reporting
Other bias	Unclear risk	No funding/competing interests declared

Carroccio 1994

Methods	RCT comparing combinations of domperidone, Maalox® and Gaviscon®
Participants	80 participants (45 male, 35 female: 1-18 months of age; median 4.5 months) with symptoms of reflux: 50 had vomiting and slowed growth, 20 had weight loss, 4 had recurrent bronchopneumonia, 5 had prolonged crying worse after feeding, 1 had apnoeas
Interventions	Group A: domperidone (0.3 mg/kg/dose) - Gaviscon® (0.7 mL/kg/dose). Group B: domperidone (0.3 mg/kg/dose) - Maalox® (41 g/1.73 mg/d). Group C: domperidone (0.3 mg/kg/dose). Group D: placebo
Outcomes	Symptoms: In domperidone + Maalox® group: 16/20 participants found their symptoms resolved, and 4/20 participants improved (P value < 0.001). Also on pH testing, reflux index significantly improved compared with other treatment combinations. Baseline reflux index 9% (6 to 43): improved to 4.5 (1 to 10) after treatment (P value < 0.03). Other markers were also significantly improved (number of episodes of pH < 4, duration of episodes of pH < 4 and number of reflux episodes > 5 minutes; P value < 0.05). In other groups, no improvement in symptoms was noted between domperidone/alginate, domperidone alone and placebo. In Groups B, C and D, improvement in pH metrics was significant (reflux index, duration of episodes of pH < 4 and number of reflux episodes > 5 minutes), but no benefit in Group B or C compared with Group D (placebo). All children had their feeds thickened with Medigel 1%, potentially reducing the impact of alginate, and explaining the significant improvement in pH outcomes in the placebo group. Symptom improvement was confirmed on monthly follow-up for 6 months. All participants who were not cured (n = 40) were treated with cisapride/ranitidine (36 responded)
Notes	Short-term study in young children: No child had erosions/ulcers on endoscopy before treatment. 80 were divided into small groups, limiting the power of the study. Participants were stratified by age (< 12 months, > 12 months) and by reflux index (< 10%, > 10%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratification and successive block randomisation
Allocation concealment (selection bias)	Low risk	Strata 1: age < 12 months, or > 12 months, then dependent on results of baseline pH probe (reflux index < 10% or > 10%)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reportedly double-blind (participants, parents, observers) but no comment made as to method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment made as to blinding method

Carroccio 1994 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants also reviewed at 6 months; all those who were cured at 8 weeks remained well. 40 participants with persistent symptoms required cisapride and ranitidine: 36 improved, but 4 went on to require surgery
Selective reporting (reporting bias)	High risk	No evidence of this
Other bias	High risk	All children received frequent short feeds and positioning advice, and formula milk was thickened with Medigel 1%

Cresi 2008

Methods	Neonates assessed over 24 hours by pH probe and impedance
Participants	26 neonates (mean age (SD): control group 29.5 days (7.4) vs treatment group 24.7 days (13.7))
Interventions	Domperidone 0.3 mg/kg 2 doses in 24 hours. P0 = 8 hours baseline. Time from 1st dose to 2nd dose (8 hours) = P1. Time from second dose to end of study (8 hours) = P2
Outcomes	Reflux frequency P1 + P2 vs P0: 4.06 ± 1.16 vs 2.8 ± 1.42 (95% CI; P value 0.001) Reflux duration 16.68 ± 4.49 vs 20.18 ± 7.83 (P value 0.043) Reflux height 3.37 ± 0.45 vs 3.34 ± 0.94 (P value 0.89) Reflux pH 4.72 ± 0.69 vs 4.6 ± 1.17 (P value 0.634)
Notes	No placebo. Short follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Consecutive recruitment
Allocation concealment (selection bias)	Low risk	Random allocation from odds-on pair from random-number table. Pairing occurred after treatment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, for participants/parents, operator/analyser nor study authors
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant's pH/impedance recording was stopped early: That period was discarded in the analysis. 8% data within pH probes also discarded because of interruptions
Selective reporting (reporting bias)	Unclear risk	No evidence of selective reporting
Other bias	Low risk	No funding issues/conflicts of interest

Cucchiara 1984

Methods	12-Week RCT of cimetidine vs Maalox® (liquid MgOH/AlOH)
Participants	46 children (29 boys and 17 girls) 2 to 58 months of age (mean 10.3 months) with symptoms of GORD 33 children (20 boys and 13 girls) 2 to 42 months of age (mean 9 months) met the criteria for gastro-oesophageal reflux with oesophagitis: with symptoms, oesophagitis on endoscopy and acid reflux on pH probe
Interventions	Randomly assigned to cimetidine 20 mg/kg/d or Maalox® 700 mmol/1.73 m^2/d 7× a day
Outcomes	Cimetidine and Maalox® provided significant symptomatic relief and endoscopic and pH improvement Symptom score: based on vomiting/regurgitation (no episodes/wk), weight loss, pneumonia/apnoea, anaemia Weight:height ratio (centiles), endoscopy findings, pH study (number of episodes of gastro-oesophageal reflux) Mean (SD) at baseline and at 12 weeks *Cimetidine group* (n = 14): 13 (2.9) to 4.01 (3.86) (P value < 0.05) Maalox® *group* (n = 15): 17.3 (3.7) to 3.72 (3.88) (P value < 0.05) 24-Hour pH probe: reflux index: mean (SD) *Cimetidine group:* 7.6 (3.4) to 0.61 (2.2) (P value < 0.05) Maalox® *group:* 6.45 (3.07) 0.92 (2.4) (P value < 0.05) Endoscopy: graded as healed, improved, unchanged/worsened: number (%) *Cimetidine group:* 7 (50) to 6 (42) to 1 (7 to 15) Maalox® *group:* 8 (53 to 5) to 5 (33 to 3) to 2 (13 to 3)
Notes	Exclusions: 13 had an alternative diagnosis, including GOR without oesophagitis (5), cow's milk protein intolerance (3), coeliac disease (2), intestinal malrotation (1) and urinary tract infection (2). Of those included, 4 did not complete the study: 2 in the cimetidine group were excluded (poor drug compliance), and 2 in the antacid group were excluded (diarrhoea and subsequent reduced antacid intake)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation technique or allocation not stated
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Observers of pH probe, endoscopy and manometry blinded as to treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated

Cucchiara 1984 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Unclear risk	Not stated
Other bias	High risk	All children received positioning advice, and infants had thickener added (Nestargel 1%). Respiratory complications (e.g. recurrent pneumonia, apnoea) were present in 18% of the children studied

Cucchiara 1993

Methods	Single-centre RCT
Participants	32 children (6 months to 13.4 years) with GOR based on symptomatology, pH probe and endoscopic findings. All had been unresponsive to an antireflux treatment, including combined administration of ranitidine (8 mg/kg/d, given in 2 doses) and cisapride (0-8 mg/kg/d, given in 3 doses) for 8 weeks (unresponsiveness defined as persistent symptoms and absence of resolution on endoscopy)
Interventions	8 weeks of standard doses of omeprazole (40 mg/d/1*73 m^2 surface area) or high doses of ranitidine (20 mg/kg/d)
Outcomes	Improvement was assessed using symptoms, 24-hour pH probe data and endoscopy. Reflux symptoms were recorded at baseline by parents through a diary card, then weekly throughout the study. In the omeprazole group, severity score significantly improved from a median of 24.0 (range 15 to 33) to 9.0 (0 to 18) (P value < 0.01), with marked symptom relief (decrease in symptom score > 60%) in 10 participants taking omeprazole. In the high-dose ranitidine group, severity score also significantly improved from a median of 19.5 (12 to 33) to 9.0 (6 to12) (P value < 0.01), with marked symptom relief (decrease in symptom score > 60%) in 9 participants given high doses of ranitidine. No significant difference was noted between groups. In the omeprazole group, 24-hour pH probe results again showed significant improvement in the time of oesophageal pH < 4: improving from baseline median 129.4 minutes (range 84 to 217) to 44.6 minutes (0.16 to 128) (P value < 0.05). Baseline reflux index also improved from 8.9% (5.8 to 15.6) to 3.0% (0.0001 to 8.8). Significant improvements were also seen in the high-dose ranitidine group, in the time of oesophageal pH < 4—improving from baseline median 207.3 minutes (66 to 306) to 58.4 minutes (32 to 128) (P value < 0.05), and baseline reflux index improved from 14.3 (4.5 to 21.2) to 4.0 (2.2 to 8.8). At baseline endoscopy, 8 participants taking omeprazole and 9 given high-dose ranitidine had erosions affecting the entire circumference of the distal oesophagus at baseline; with 3 other participants, isolated rounded or linear erosions affected the most distal oesophagus—not the entire circumference. Repeat endoscopies were performed within 48 hours of completion of the 8-week trial; at the end in the omeprazole group, mucosal healing was seen in 4 participants; isolated small erosions affecting the distal oesophagus in 3 participants; and erythema and oedema of the distal oesophageal mucosa in 5 participants. In the high-dose ranitidine group, healing was seen in 2 participants; small erosions affecting the distal oesophagus in 5 participants; and erythema and oedema of the distal oesophageal mucosa in 6 participants, with no statistical difference observed between groups. In terms of histological improvement, healing of oesophagitis (return to grade 0 or grade 2 of histological score) occurred in 9 participants taking omeprazole and in 8 participants given high-dose ranitidine (no significant difference)
Notes	Exclusions were oesophageal strictures, neurological pathology and systemic extraintestinal disease

Risk of bias

Bias	Authors' judgement	Support for judgement

Cucchiara 1993 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No comment made
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment made
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7 withdrew—3 taking ranitidine and 4 omeprazole. Of these participants, 4 were excluded as a result of non-compliance with the protocol, 2 were lost to follow-up and 1 was withdrawn because of prolonged fever and upper respiratory infection
Selective reporting (reporting bias)	Unclear risk	No evidence of this
Other bias	High risk	No funding disclosures were made, and 1 study author worked for Schering-Plough

Del Buono 2005

Methods	Double-blind, single-centre RCT
Participants	20 infants (mean age 163.5 days, range 34 to 319 days) exclusively bottle-fed, with symptoms of GOR
Interventions	6 random administrations (3 + 3) of Gaviscon Infant® (625 mg in 225 mL milk) or placebo (mannitol and Solvito N, 625 mg in 225 mL milk) were given (double-blind)
Outcomes	24-Hour studies of intra-oesophageal impedance/dual-channel pH monitoring. Median number of reflux events/h (1.58 vs 1.68), acid reflux events/h (0.26 vs 0.43), minimum distal or proximal pH, total acid clearance time per hour (time with pH below pH 4) and total reflux duration/h were not significantly different after GI than after placebo. Average reflux height was significantly improved compared with placebo: median -0.56, range -1.40 to 0.17 (P value 0.001)
Notes	Inclusions: Infants younger than 12 months of age had symptoms clinically suggestive of GOR (e.g. regurgitation > 3× a day any amount or more than once a day half the feed), weighed > 2 kg, were exclusively bottle-fed formula milk or expressed breast milk and had no signs of infection A total of 747 reflux events were detected by impedance, of which 518 were non-acid and 229 were acidic (pH < 4), suggesting that a significant number of episodes were non-acid reflux, particularly up to 2 hours after feeds. Very short-term study

Risk of bias

Bias	Authors' judgement	Support for judgement

Del Buono 2005 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	Identical preparations given to infants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants/parents reportedly blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded observer interpreted pH data
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No evidence of this
Selective reporting (reporting bias)	Unclear risk	No evidence of this
Other bias	Low risk	Reckitt Benckiser Healthcare (UK) Ltd, the producers of Gaviscon Infant®, funded 1 of the authors (Dr R Del Buono)

Forbes 1986

Methods	Single-centre, observer-blinded RCT
Participants	10 children (mean age 68 months, range 6 to 168 months) given Gaviscon Infant® liquid (antacid + alginate) 10 mL every 6 hours (for infants) or 20 mL every 6 hours for older children vs placebo 3 times a day (mean age 71 months, range 4 to 168 months). All 20 had symptoms of vomiting and waterbrash at enrolment
Interventions	As above. 24-Hour pH probe at baseline, then consecutively during 24 hours of treatment
Outcomes	No difference between Gaviscon Infant® liquid and placebo in terms of number of reflux episodes (mean 87 ± 17 (SE) at baseline compared with 81 ± 23 on treatment; placebo 70 ± 13.5 at baseline compared with 49 ± 11 on treatment) and total duration of reflux episodes (mean 90 ± 39 (SE) at baseline compared with 74 ± 39 on treatment; placebo 120 ± 10 at baseline compared with 96 ± 11 on treatment). No standard nursing positions were adopted, and children could move around the bed. No side effects were reported
Notes	Observer interpreting pH results was blinded. We did not consider the metoclopramide group (also 10 children) because they are discussed in another Cochrane review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	No comment made

Forbes 1986 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and parents not blinded as placebo 3 times a day and Gaviscon® liquid 4 times a day for infants and children
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	pH data interpreted by blinded observer
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No subgroup analysis of those with endoscopic evidence of oesophagitis
Selective reporting (reporting bias)	Unclear risk	No evidence of this
Other bias	Unclear risk	No funding declarations

Gunesekaran 2003

Methods	Phase I, multi-centre, double-blind study randomly assigned to 2 arms: 7-day pretreatment, then 5 days of treatment
Participants	63 adolescents with symptomatic/endoscopic GORD, or histological changes. Mean age 14.1 years (12 to 17 years)
Interventions	Lansoprazole 15 mg vs 30 mg In the pretreatment phase, physician assessment was followed by 24-hour intragastric pH probe, endoscopy and biopsy, *H pylori* testing and a symptom diary for 1 week. After 5 days of treatment, participants underwent physician assessment and analysis of symptom diaries. Pharmacokinetics and intragastric pH monitoring are not considered here, as intragastric pH is not an outcome relevant in oesophagitis, and pharmacokinetics is not a clinical outcome considered within the remits of this review
Outcomes	The symptom diary showed that 39/63 (62%) of participants at baseline reported symptoms of heartburn, with 13% abdominal pain, 6% regurgitation symptoms, dysphagia in 6%, nausea in 3% and vomiting in 3%. After 5 days, both groups reported improvement in frequency and severity of heartburn and other symptoms (P value not stated). 69% of 15 mg group and 74% of 30 mg group reported that their symptoms of reflux were better, and the amount of antacid required for symptom relief was reduced in both groups (average 1.8 tablets/d to 1.05 in lansoprazole 15 mg group, and 1.8 to 0.63 tablets/d in lansoprazole 30 mg group; P value not stated). On physician review, among participants with heartburn at baseline (n = 36), symptomatic improvement was noted in both groups—56% (n = 16) in the 15 mg group and 70% (n = 20) in the 30 mg group (P value 0.02 and 0.01, respectively) Side effects: Pharyngitis (6%; 2/32 in lansoprazole 15 mg) and headache (16%; 4/31) were the most commonly reported side effects among adolescents treated with lansoprazole 15 mg and 30 mg, respectively. Five participants experienced adverse events considered possibly treatment-related. One participant with a history of environmental allergies experienced a mild allergic reaction after 3 days of treatment with lansoprazole 15 mg. Among those treated with lansoprazole 30 mg, 4 participants each reported 1 occurrence of pain (toothache), diarrhoea, dizziness and rash
Notes	Exclusions: systemic disease (e.g. scleroderma)/infection of oesophagus/long-term use of ulcerogenic drugs/use of PPIs
Risk of bias	

Gunesekaran 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned in 1:1 fashion to each group
Allocation concealment (selection bias)	Unclear risk	Difference between treatments concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants/carers blinded. Pathologist examining histological specimens blinded (but not an outcome measure). No discussion of blinding of clinical observers
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No evidence of this
Selective reporting (reporting bias)	Unclear risk	No oesophageal data on pH probe reported.
Other bias	Unclear risk	Short-term follow-up study; however, participants who demonstrated a positive response were offered 3 months of treatment with lansoprazole. Study was supported by a grant from TAP Pharmaceuticals

Kierkus 2011

Methods	Study 1: neonates/preterm infants pantoprazole 2.5 mg (approximately 1.2 mg/kg once a day)—not analysed, as not randomised Study 2: infants 1 to 11 months of age randomly assigned high-dose (1.2 mg/kg)/low-dose pantoprazole (0.6 mg/kg). Mainly pharmacokinetic data but 24-hour pH probe at baseline, then at day 5. Treatment for 6 weeks
Participants	Study 2: 24 participants (mean age 6.9 months (range 1.3 to 11 months including 1 ex-premature baby) in low-dose treatment group and 3.6 months (1.1 to 12.1 months—2 ex-premature babies) in high-dose treatment group)
Interventions	High-dose (1.2 mg/kg) versus low-dose pantoprazole (0.6 mg/kg) for 6 weeks
Outcomes	High-dose group: pH data: baseline reflux index (mean ± SD) 4.6 ± 3.9 to steady state (day 5) reflux index 4.6 ± 5.6 (P value ns) Low-dose group: baseline reflux index (mean ± SD) 8.0 ± 5.6 to steady state (day 5) reflux index 9.0 ± 5.8 (P value ns) No statistical difference between low-dose and high-dose groups in number of episodes pH < 4, number of episodes lasting longer than 5 minutes or duration of episodes of pH < 4 (numerically higher in high-dose group) No related serious adverse events after 6 weeks of treatment, although 58% of the 24 participants reported at least 1 adverse event (unrelated)

Kierkus 2011 *(Continued)*

Notes	Funded by Wyeth, including funding for writing assistance

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocks of randomly assigned numbers in strict ascending sequential order
Allocation concealment (selection bias)	Unclear risk	At end of trial, participants could continue on same or higher dose for 6 weeks
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One participant excluded in low-dose Rx group error on pH probe. Two excluded in high-dose group: 1 pH probe error, 1 at investigator request
Selective reporting (reporting bias)	Unclear risk	No evidence found, although no symptom change reported
Other bias	High risk	Funded by Wyeth, including funding for writing assistance

Miller 1999

Methods	Double-blind, placebo-controlled RCT across 25 centres in UK
Participants	90 participants with symptoms of GOR at least twice a day for 2 days before start of study
Interventions	Sodium alginate (aluminium-free Infant Gaviscon®) 312.5 mg/sachet, 1 to 2 sachets per feed vs placebo
Outcomes	Improvement in symptoms assessed by parents (daily diary and investigators, at baseline, day 7 and day 14) Significant reduction in number and severity of vomiting episodes (P value 0.009) in those taking alginate, and parents and investigators considered that symptoms were improved in those given alginate (investigators P value 0.008, parents 0.002) Number of vomiting episodes: In alginate group (n = 42): baseline 8.5 (2 to 50) to day 14, 3.0 (0 to 22) In placebo group (n = 48): baseline 7.0 (2 to 36) to day 14, 5.0 (0-37) P value < 0.009 Assessment of vomiting severity: *In alginate group*: (n= (% in brackets)) Baseline: none 0 (0); mild 3 (7.2); moderate 30 (71.4); severe 9 (21.4) End of treatment: none 9 (21.4); mild 16 (38.1); moderate 12 (28.6); severe 5 (11.9)

Miller 1999 *(Continued)*

	In placebo group: Baseline: none 0 (0); mild 3 (7.2); moderate 30 (71.4); severe 9 (21.4) Treatment: none 5 (10.9); mild 15 (32.6); moderate 14 (30.4); severe 12 (26.1) Overall: trend in severity less in participants receiving alginate compared with placebo (P value 0.061) Global assessment of improvement at day 14: 48% of parents assessed their children as 'much better' on alginate, compared with 24% of parents on placebo (P value 0.002). Investigators' assessment of alginate was significantly better for alginate than for placebo (P value 0.002) **Investigator assessment:** Alginate group: not recorded 1 (2.4); very good 15 (35.7); good 10 (23.8); acceptable 6 (14.3); poor 7 (16.7); very poor 3 (7.1) Placebo: not recorded 2 (4.4); very good 7 (15.2); good 10 (21.7); acceptable 4 (8.7); poor 16 (34.8); very poor 7 (15.2) **Parent assessment:** Alginate group: not recorded 1 (2.4); very good 20 (47.6); good 13 (30.9); acceptable 6 (14.3); poor 1 (2.4); very poor 1 (2.4) Placebo: not recorded 2 (4.4); very good 11 (23.9); good 10 (21.7); acceptable 12 (26.1); poor 8 (17.4); very poor 3 (6.5)
Notes	Equal side effect profile Exclusions: oesophageal/neuro/cardiac/resp/metabolic/hepatic/renal disease, wt < 2.5 kg, < 37 weeks' gestation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reportedly double-blind but technique not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Technique not described

Miller 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	From 90 participants: 2 in placebo group did not receive Rx = ITT population 88. During study, 20 withdrawals (alginate 7, placebo 13; P value > 0.2) due to adverse events (alginate 4, placebo 7) and lack of efficacy (alginate 2, placebo 3). ITT analysis included withdrawals
Selective reporting (reporting bias)	Unclear risk	No evidence found, but data at day 7 of investigator assessment not presented
Other bias	Unclear risk	Funded by Reckitt + Colman and Parexel International

Moore 2003

Methods	Irritable infants completed a 4-week, randomised, double-blind, placebo-controlled, cross-over trial of omeprazole
Participants	30 children between 3 and 12 months of age, who had previous empirical gastro-oesophageal reflux treatment, excluding PPI therapy with reflux index over 5% OR biopsy evidence of oesophagitis
Interventions	Omeprazole therapy for 2 weeks vs placebo, followed by cross-over period of 2 weeks
Outcomes	Crying/fuss time; mean (SD)—symptom diary as reported by Barr et al **Omeprazole** (n = 15): baseline—246 (105) At 2 weeks—203 (113) Switched to placebo for 2 weeks—179 (129) **Placebo** (n = 15): baseline—286 (132) At 2 weeks—204 (87) Swtiched to omeprazole for 2 weeks—198 (115) No significant difference between placebo and omeprazole, but overall reduction in crying/fuss time over the 4 weeks was significant (P value 0.008) Visual analogue score; mean (SD)—slide from 0-10, assessing irritability reported by parent **Omeprazole** (n = 15): baseline—7.1 (1.4) At 2 weeks—5.9 (2.6) Switched to placebo for 2 weeks—4.0 (3.3) **Placebo** (n = 15): baseline—6.6 (1.7) At 2 weeks—6.0 (2.1) Switched to omeprazole for 2 weeks—5.7 (2.2) No significant difference between placebo and omeprazole, but overall reduction in VAS over the 4 weeks was significant (P value 0.008) Change in reflux index; mean (SD)—% of time spent with oesophageal pH < 4 **Omeprazole** (n = 15): baseline—9.9 (5.8) At 2 weeks—1.0 (1.3) Change in RI—8.9 (5.6)

Moore 2003 *(Continued)*

	Placebo (n = 15): baseline—7.2 (6.0) At 2 weeks—5.3 (4.9) Change in RI—1.9 (2.0) Change in RI omeprazole versus placebo (P value < 0.001)
Notes	Authors' conclusion: PPI caused significant reduction in RI with no additional effect on crying/fussing compared with placebo. Of note, significant reduction IN BOTH was noted over the 4-week study period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not described by study authors, but randomisation code used
Allocation concealment (selection bias)	Unclear risk	Not described by study authors
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded: parents/infants and observers; code broken at end of study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes expressed in behaviour diary (potential for recall bias) and visual analogue scale (potential for parental observer bias), but no evidence of bias identified
Incomplete outcome data (attrition bias) All outcomes	High risk	No table of baseline characteristics
Selective reporting (reporting bias)	Unclear risk	No comment made
Other bias	Low risk	Independent funding: AstraZeneca provided the placebo and omeprazole free of charge

Omari 2006

Methods	Randomised, double-blind, placebo-controlled trial. Assessed with manometry/pH at baseline for 2 hours after 250 mL of cow's milk (control period). Baclofen or placebo was then administered. One hour later, 250 mL of milk was given, and measurements were performed for another 2 hours (test period)
Participants	30 children with resistant GORD. Mean age 10.0 ± 0.8 years
Interventions	0.5 mg/kg baclofen vs placebo
Outcomes	Impedance: Baclofen significantly reduced the incidence of transient lower oesophageal sphincter relaxations (TLESR) (mean ± CI) vs placebo: 7.3 ± 1.5 vs 3.6 ± 1.2 TLESR/2 h; P value < 0.05) and acid GOR (mean 4.2 ± 0.7 vs 1.7 ± 1.0 TLESR + GOR/2 h; P value < 0.05) during test period compared with control period

Omari 2006 *(Continued)*

	pH: 130 acid reflux episodes detected: 80% caused by TLESRs *Baclofen group*: baseline 5.2 ± 1.1 to 2.3 ± 1.3 (P value 0.054) *Placebo*: 2.5 ± 0.5 to 2.1 ± 0.5 (P value ns) Side effects (causing early withdrawal but thought to be unrelated): *Baclofen group*: during treatment: tiredness (n = 2), nausea, vomiting, sore throat, epistaxis, headache, irritability (n = 1 each) No significant events in 48 hours following trial
Notes	Inclusions: All children had failed standard therapy (positioning, reassurance, feed thickener, antacids, PPI and H_2 antagonist) Exclusions: previous GI surgery, neurological disease, cardiac/respiratory disease, peptic ulcers or CM-PI/lactose intolerance Significantly higher number of acid reflux episodes and TLESRs at baseline in control group. Very short trial period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No evidence provided
Allocation concealment (selection bias)	Unclear risk	No evidence provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents and staff remained blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No evidence provided
Selective reporting (reporting bias)	Low risk	All participants had initially received a test dose to assess tolerability; no data on children who had not tolerated the initial test dose
Other bias	Unclear risk	Funded by Women and Children's Research Foundation, the JH&JD Gunn Medical Research Foundation and AstraZeneca R&D

Omari 2007

Methods	Single-centre, randomised, single-blind study (SH-NEC-0001)
Participants	50 infants with symptoms of GORD (irritability/crying, vomiting, choking/gagging) and % time with intraoesophageal pH < 4

Omari 2007 *(Continued)*

Interventions	Oral esomeprazole 0.25 mg/kg or 1 mg/kg for 8 days
Outcomes	Non-significant improvement in symptoms (irritability/crying, vomiting, choking/gagging): improved more in 0.25 mg/kg group Reflux index improved in both groups (1 mg/kg group: 11.6% to 8.4%; P value < 0.05; 0.25 mg/kg: 12.5% to 5.5%; P value < 0.001)
Notes	Published in abstract form in 2006: data confirmed in communication. Formally published in full in *Journal of Pediatric Gastroenterology and Nutrition* 2007;45:530-7. Exclusion criteria were any current/previous clinically significant illness that may interfere with study procedures or with the metabolism of esomeprazole, or that may jeopardise infant safety; any experimental drug or device in the 8-week period before screening; history of surgery of the oesophagus, stomach, duodenum or jejunum; and congenital drug addiction. Use of any pharmacological antireflux therapy up to 24 hours before, or any PPI up to 72 hours before, the first dose of study medication was not permitted. Rx with anticholinergics, antineoplastic agents, H_2-receptor antagonists, sucralfate, bismuth-containing compounds, methylxanthines, promotility drugs, macrolide antibiotics or barbiturates was not permitted. Known hypersensitivity to esomeprazole, substituted benzimidazoles or any constituents of the esomeprazole formulation also excluded infants from the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No evidence provided
Allocation concealment (selection bias)	Unclear risk	No evidence provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Staff became aware of which treatment a participant was receiving based on the weight. Parents remained blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No evidence provided
Selective reporting (reporting bias)	Unclear risk	No evidence provided
Other bias	Unclear risk	No funding statement

Orenstein 2002

Methods	8-Week, multi-centre, randomised, placebo-controlled 2-phase trial. First 4-weeks: observer-blind trial of famotidine 0.5 mg/kg; second 4 weeks: double-blind withdrawal comparison of each dose with placebo
Participants	35 infants, mean age 5.5 months (range 1.3 to 10.5 months), male:female 12:14, previous H_2 antagonist therapy in 57%, previous prokinetic use in 37%. All with clinical diagnosis of GORD

Orenstein 2002 *(Continued)*

Interventions	Phase 1—famotidine 0.5 mg/kg dose vs famotidine 1 mg/kg dose Phase 2—each dose category split to continue on dose or receive placebo
Outcomes	**Phase 1** **Improvement in regurgitation frequency** Famotidine 0.5 mg/kg (n = 15)—53% (P value 0.040) Famotidine 1 mg/kg (n = 15)—69% (P value 0.004) **Improvement in regurgitation volume** Famotidine 0.5 mg/kg—53% (NS) Famotidine 1 mg/kg—69% (P value 0.010) **Improvement in crying time** Famotidine 0.5 mg/kg—32% (NS) Famotidine 1 mg/kg—67% (P value 0.027) **Global assessment by parents as completely well** Famotidine 0.5 mg/kg—13% Famotidine 1 mg/kg—25% **Global assessment by physicians as completely well** Famotidine 0.5 mg/kg—13% Famotidine 1 mg/kg—25% *NS = not significant and P value not reported. **Phase 2** Insufficient participants completed withdrawal phase for meaningful comparison
Notes	Six participants given famotidine experienced new agitation/irritability. Two of these had accompanying head rubbing. All resolved within days of ending therapy. No breakdown as to which group Exclusion criteria: respiratory complications, previous GI surgery; CV, renal, hepatic, neoplastic or diabetic disease; inability to discontinue previous proton pump inhibitor therapy, sensitivity to famotidine or H_2 antagonists Study supported by a grant provided by Merck & Co., Inc., to each of the 3 sites

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described by study authors
Allocation concealment (selection bias)	Unclear risk	Not described by study authors
Blinding of participants and personnel (performance bias)	High risk	Parents unblinded to intervention in part 1

Orenstein 2002 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Parents unblinded to intervention in part 1, with parental assessment a key outcome measure
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for, all outcomes clearly defined and reported
Selective reporting (reporting bias)	Unclear risk	No evidence of this, although children with previous sensitivity to famotidine were excluded
Other bias	High risk	In selection, children with previously failed GORD treatment were far more likely to be enrolled. Study supported by a grant by Merck & Co., Inc., to each of the 3 sites

Orenstein 2008

Methods	Multi-centre, double-blind, randomised, placebo-controlled trial
Participants	162 infants (mean age 16 weeks, range 4 to 51 weeks) randomly assigned to lansoprazole vs placebo
Interventions	Infants were included if symptomatic of GORD—'crying, fussing or irritability' within 1 hour after feeding (specifically, daily crying noted in diary in > 25% of feeds over 4 days), after 1 week of non-pharmacological treatment. Sixteen centres participated. Infants were excluded if PPI was taken in previous 30 days or H_2-receptor antagonists within 7 days. The trial occurred in 3 phases. In the pretreatment phase, small frequent feeds were recommended, as was reduction in smoking, hypoallergenic feeds (or if breast-fed, mothers started dairy-free diet) and positioning advice. The treatment phase lasted 4 weeks, and participants were randomly assigned to lansoprazole 1:1 (0.2 to 0.3 mg/kg/d in those < 10 weeks, 1 to 1.5 mg/kg/d in those > 10 weeks) vs placebo. In the post-treatment phase, investigators can choose to put children on lansoprazole
Outcomes	Symptom assessment was performed for 30 days following the study. Parent diaries were assessed for symptom scores and individual symptoms (crying/regurgitation/back arching/hoarseness/feed refusal or early stopping/cough or wheeze). Of 81 participants given lansoprazole, 44 (54%) responded to Rx, 28 discontinued treatment compared with placebo (72 participants), 44 (54%) responded to treatment and 29 (36%) discontinued treatment). No difference between lansoprazole and placebo was noted, and of those who went on to take lansoprazole open-label (n = 55), no significant improvement in symptoms was described
Notes	No investigation confirmed GORD, and many of the participants enrolled may have had functional reflux

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation 1:1 lansoprazole:placebo
Allocation concealment (selection bias)	Unclear risk	No evidence of this

Orenstein 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding reported: randomisation blinded and parents blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Investigators able to find out after 4 weeks who was taking which Rx
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One participant in lansoprazole group: data missing
Selective reporting (reporting bias)	Unclear risk	No evidence of this
Other bias	Unclear risk	Takeda funded the trial and data analysis but took no part in manuscript preparation

Pfefferkorn 2006

Methods	Prospective, double-blind study
Participants	18 participants, ages one to 13 years (mean = 10.3 years) with symptomatic GORD with endoscopic/histological changes
Interventions	Of the 18 participants who received omeprazole (1.4 mg/kg once daily, maximum 60 mg) for the first 3 weeks (see above for discussion of improvement on omeprazole), 16 (89%) had nocturnal acid breakthrough on pH monitoring and were randomly assigned to ranitidine 4 mg/kg or placebo, whilst continuing omeprazole
Outcomes	Participants were evaluated for symptoms and adverse events during follow-up at 3 weeks, 9 weeks and 17 weeks. Symptoms (heartburn, abdominal pain, vomiting, dysphagia and "others") were recorded (none, same, better, worse) at follow-up. At week 17, all participants underwent repeat endoscopy and 24-hour pH monitoring. Omeprazole analysis: Symptom scores improved from 2.0 ± 0 at baseline to 0.6 ± 0.4 at week 3 to 0.4 ± 0.45 at week 9 (P value 0.0001) and 0.4 ± 0.5 at week 17 (P value 0.0002). pH studies were performed at baseline, week 3 and week 17, with reflux index significantly improved following initiation of therapy, from 14.3 ± 11.5 at baseline to 2.0 ± 2.9 at week 3 (P value 0.0001). The RI did not change from week 3 (2.0 ± 2.9) to week 17 (5.1 ± 5.1) (P value 0.09). Endoscopic appearances at baseline and at week 17 were assessed using Herzel-Dent score (grade 0 to 4). Improvement in grade from 3.1 ± 1.4 to 1.6 ± 1.8 (P value < 0.001). Improvement in mean histology scores of all participants from baseline (1.8 ± 0.7) to week 17 (0.8 ± 0.9) (P value 0.0013) was also seen Ranitidine vs placebo analysis: Symptom scores in the ranitidine group improved from 2.0 ± 0 at baseline, to 0.4 at week 3, to 0.3 at week 9, to 0 at week 17 (no range given) (P value 0.0001 at weeks 3 and 9; P value 0.0002 at week 17). Symptom scores in the placebo group improved from 2.0 ± 0 at baseline, to 0.7 at week 3, to 0.6 at week 9, to 0.5 at week 17 (P value 0.0001 at weeks 3 and 9; P value 0.0002 at week 17). No significant difference was noted between ranitidine and placebo groups (P value 0.31 at week 3; P value 0.20 at 9 weeks; P value 0.10 at week 17). pH study was performed at baseline, at week 3 (initiation of ranitidine and placebo) and at week 17. Reflux index in the ranitidine group improved from 17 at baseline to 2.0 at week 3 (P value 0.0001). The RI did not change from week 3 (2.0) to week 17 (4). Reflux index in the placebo group improved from baseline (12) to 3 at week 3 (P value 0.0001). The RI did not then alter from week 3 (3.0 ± 2.9) to week 17 (6). No significant differences were noted between the RI of the ranitidine and placebo groups. Endoscopic appearances at baseline and at week 17 were assessed using Herzel-Dent score (grade 0 to 4). In the ranitidine group, improvement in scores

Pfefferkorn 2006 *(Continued)*

	from 1.7 to 0.5 was seen, and in the placebo group, from 1.7 to 0.9. No difference in degree of improvement was reported between the ranitidine and placebo groups (P value 0.32). Therefore no additional benefit was seen (in terms of symptom score, reflux index or endoscopic change) to be had from supplementation of PPI therapy with ranitidine
Notes	One participant received esomeprazole 40 mg twice daily. Two participants in the ranitidine group withdrew, and 1 was lost to follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Statistician provided a randomisation table
Allocation concealment (selection bias)	Unclear risk	Not clear whether block allocation was performed, or how participants were randomly assigned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Ranges are not included for some data. Two participants in the ranitidine group withdrew, and 1 was lost to follow-up
Selective reporting (reporting bias)	Unclear risk	None
Other bias	Low risk	One participant received esomeprazole 40 mg twice daily. Funded by a Grant-in-Aid from the Riley Children's Foundation

Simeone 1997

Methods	26 participants were randomly assigned to double-blind treatment with nizatidine or placebo (10 mg/kg/d in 2 doses) for 8 weeks. A symptomatic score assessment was evaluated during the study. Baseline evaluation included endoscopy and a 24-hour pH study. A daily diary card was kept by parents to record the frequency/severity of GOR symptoms during the treatment period. A physical and symptomatologic assessment was performed after 4 weeks of therapy After 8 weeks of treatment, 48 hours before the end of therapy, clinical evaluation, laboratory tests, pH probe study and endoscopy with biopsy were again performed in all children who completed the treatment period
Participants	26 children with histological features of oesophagitis (mild to moderate): 17 boys and 9 girls (median age 1.66 years; range 6 months to 8 years) were recruited
Interventions	Nizatidine 10 mg/kg twice daily vs placebo. All participants received positional therapy and dietary manipulation with thickened feeds (dry rice cereal)
Outcomes	Outcomes were assessed in terms of symptoms, pH scores and endoscopic/histological appearance. Clinical score analysis showed improvement in symptoms only in the nizatidine group (P value < 0.01),

Simeone 1997 *(Continued)*

	except for vomiting, which was reduced in both groups. Marked reduction in symptoms (> 80%) after 8 weeks of therapy in comparison with the baseline period was observed in 8 participants taking nizatidine (66.6%) and in 3 given placebo (25%). Endoscopic findings in the nizatidine group included healing in 9/13 (69%) participants, improvement in 2 (16.7%) participants and no change in 1 (8.3%). In the placebo group, healing was seen in 2/13 (15%) participants, improvement in 3 (25%) and no change in 6 (50%), which was worse in 1 (8.3%) (P value < 0.007 by Fisher's exact test) Post-treatment pH-metry was repeated in only 10 participants in the nizatidine group (83.3%) and 9 in the placebo group (75%). The pH-metry parameters of evaluation showed significant (P value < 0.01) improvement in all variables (reflux index, number of episodes of pH < 4, number of episodes > 5 minutes, duration of episodes of pH < 4) in the nizatidine group vs placebo
Notes	Children receiving ulcerogenic drugs alone or with an antireflux agent were excluded from the study. Also excluded were participants with systemic extraintestinal disease, neurological disorders or a history of previous surgery. One participant developed urticaria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No comment made
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment made
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	pH-metry was repeated in 10 participants in the nizatidine group (83.3%) and in 9 in the placebo group (75%). Five participants refused reevaluation
Selective reporting (reporting bias)	Unclear risk	No evidence of this
Other bias	Unclear risk	No comment made. Funding not stated

Tolia 2006

Methods	Multi-centre, double-blind RCT
Participants	53 children (5 to 11 years of age) with symptomatic GORD
Interventions	Comparison of 10 mg, 20 mg and 40 mg pantoprazole for 8 weeks. Symptom score, endoscopic appearance and histological assessment, side effects

Tolia 2006 *(Continued)*

Outcomes	Overall symptom score assessed using GASP-Q to produce a composite symptom score (CSS). Also individual symptoms assessed (number of vomiting episodes, heartburn, epigastric pain) at week 0, then at week 1 and week 8 Pantoprazole 10 mg group: CSS score improved from 128 to 28 to 28 (P value < 0.001, and number of vomiting episodes improved from 25 to 19 to 5 (P value < 0.001), with heartburn scores changing from 5 to 10 to 1 (P value < 0.006), and epigastric pain improving from 17 to 7 to 2 (P value < 0.001). Pantoprazole 20 mg group: CSS score improved from 134 to 78 to 32 (P value < 0.001), and number of vomiting episodes improved from 17 to 10 to 2 (P value < 0.001), with heartburn scores changing from 15 to 20 to 5 (P value < 0.006), and epigastric pain improving from 16 to 3 to 1 (P value < 0.001) Pantoprazole 40 mg group: CSS score improved from 132 to 48 to 43 (P value < 0.001), and number of vomiting episodes improved from 10 to 3 to 2 (P value < 0.001), with heartburn scores changing from 23 to 4 to 7 (P value < 0.006) and epigastric pain improving from 13 to 4 to 1 (P value < 0.001) Endoscopic appearances were assessed using Hetzel-Dent scoring, and no improvement was seen in the 10 mg, 20 mg and 40 mg groups (no further details were given). In terms of histology though, in the 10 mg pantoprazole group: among those with non-erosive GORD, 36% improved (n = 7), 52% were unchanged (n = 10), 5.2% worsened (n = 1) and 5.2% were not done (n = 1). No participants with erosive disease were treated within this group. Among those treated with pantoprazole 20 mg, those with non-erosive GORD, 50% improved (n = 9), 44% were unchanged (n = 8), 0% worsened and 5.5% were not done (n = 1). In those with erosive disease (3 participants): All were healed at 8 weeks. Among those treated with pantoprazole 40 mg, those with non-erosive disease, 68% improved (n = 11), 25% were unchanged (n = 4) and 6.2% worsened (1). One participant with erosive disease was healed at 8 weeks Side effects: pantoprazole 10 mg group: headache (7 participants; 36.8%), rhinitis (5 participants; 26.3%) and nausea (3 participants; 15.8%). Pantoprazole 20 mg group: headache (5 participants; 27.8%), rhinitis (3 participants; 16.7%). Pantoprazole 40 mg group: headache (4 participants; 25%), abdominal pain, asthma and pharyngitis (3 participants each; 18.8%)
Notes	No correlation was noted between composite symptom score changes and endoscopy/biopsy changes. Statistically significant increases from baseline were noted in mean values for weight and height at week 8 in the pantoprazole 10 and 40 mg dose groups (P value < 0.04). Participants in the 20 mg group had a significant mean increase in weight at week 8 (P value 0.023). Antacid use was reduced in 20 mg and 40 mg groups at end of treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No comment on randomisation technique
Allocation concealment (selection bias)	Unclear risk	No comment on this
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no comment as to technique. Physician not blinded, but endoscopic findings read by blinded observer. No comment as to how participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No analysis of endoscopic appearances after treatment was given
Incomplete outcome data (attrition bias)	High risk	All enrolled participants accounted for. No evidence of consecutive enrolment and no discussion of children who refused consent or who were excluded

Tolia 2006 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	No evidence of this
Other bias	High risk	Wyeth Research involved in preparation of the manuscript

Tolia 2010a

Methods	Post hoc analysis of subgroup of participants with GORD 12 to 36 months of age
Participants	109 participants weighing 8 to < 20 kg were randomly assigned 1:1 to receive esomeprazole 5 mg or 10 mg daily
Interventions	Esomeprazole 10 mg once daily for 8 weeks vs esomeprazole 5 mg once daily
Outcomes	Symptom scores: Symptoms were measured by physician and by parents telephoning daily to report preceding 24 hours' symptoms. Symptoms were graded as none/mild/moderate/severe (PGA—Physicians Global Assessment) Also number of vomiting episodes and use of antacids were assessed Results: 19 participants with moderate or severe baseline PGA symptom scores; 16 (84.2%) had improved scores by the final visit. In addition, a statistically significant reduction (P value < 0.0018) was seen in the severity of GORD symptoms within each treatment group from baseline to final PGA assessment. No difference between low-dose and high-dose groups Endoscopic appearances: Endoscopic findings were graded using the Los Angeles (LA) classification for erosive oesophagitis Grade A is > 1 mucosal break < 5 mm that does not extend between the tops of 2 mucosal folds Grade B is > 1 mucosal break > 5 mm that does not extend between the tops of 2 mucosal folds Grade C is > 1 mucosal break that is continuous between the tops of > 2 mucosal folds but involves < 75% of the circumference of the oesophagus Grade D is > 1 mucosal break that involves > 75% of the circumference Results: 15/31 (48%) had erosive oesophagitis. All participants with erosive oesophagitis healed on follow-up endoscopy (13/15) Histological appearances: graded as healed/improved/unchanged 23/31 (74.2%) had microscopic (not visible) reflux oesophagitis at baseline biopsy. All 13 participants who had follow-up endoscopy had healed at follow-up
Notes	Study supported by AstraZeneca LP. Medical writing services provided by Scientific Connexions, Newtown, PA, on behalf of AstraZeneca LP

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	See study below; no comment made; higher risk as post hoc analysis

Tolia 2010a *(Continued)*

Allocation concealment (selection bias)	High risk	See study below; no comment made; higher risk as post hoc analysis
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind by dose strata
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment made
Incomplete outcome data (attrition bias) All outcomes	High risk	Higher risk as post hoc analysis
Selective reporting (reporting bias)	Unclear risk	ITT analysis of all participants with oesophagitis. Study authors wondered about selection bias of children with oesophagitis (sicker children); 2 children with erosive oesophagitis did not have follow-up endoscopy
Other bias	High risk	See funding comments above

Tolia 2010b

Methods	Randomised, double-blind (for dose), parallel-group study
Participants	52 children 1 to 11 years of age with endoscopically/histologically confirmed erosive oesophagitis
Interventions	5 mg or 10 mg of esomeprazole (8 to 20 kg children), 10 mg or 20 mg esomeprazole (> 20 kg children) for 8 weeks
Outcomes	Endoscopic appearance—presence/absence of erosive oesophagitis **Children 8 to 20 kg** **Esomeprazole 5 mg** (n = 26) Baseline oesophagitis n (%)—12(46) At 8 weeks: Examined at follow-up—n = 11 % healed at follow-up—100% **Esomeprazole 10 mg** (n = 23) Baseline oesophagitis n (%)—12(52) At 8 weeks: Examined at follow-up—n = 11 % healed at follow-up—82% **Children > 20 kg** **Esomeprazole 10 mg** (n = 31) Baseline oesophagitis n (%)—16(52)

Tolia 2010b *(Continued)*

	At 8 weeks: Examined at follow-up—n = 10 % healed at follow-up—90% **Esomeprazole 20 mg** (n = 29) Baseline oesophagitis n (%)—13(45) At 8 weeks: Examined at follow-up—n = 13 % healed at follow-up—85% Baseline symptom characteristics recorded and mention of record at follow-up, but no follow-up data available Baseline histological appearance recorded and mention of record at follow-up, but no follow-up data available
Notes	Study funded by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described by study authors
Allocation concealment (selection bias)	High risk	Not described by study authors
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents report outcomes but blinded to dose
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endoscopy performed by blinded examiners
Incomplete outcome data (attrition bias) All outcomes	High risk	A large number of participants did not undergo follow-up endoscopic examination (> 50%)
Selective reporting (reporting bias)	High risk	Of 3 potential outcome measures (endoscopic appearance, histological appearance and symptoms), only 1 had follow-up data recorded despite the fact that all 3 were recorded at baseline and follow-up measurement as described by study authors
Other bias	High risk	Study funded by AstraZeneca with pharmaceutical writing support noted

Tsou 2006

Methods	Outpatient, multi-centre, randomised, double-blind, multi-dose, parallel-treatment group study

Tsou 2006 *(Continued)*

Participants	112 children 12 to 16 years of age with symptomatic GORD
Interventions	Pantoprazole 40 mg (n = 68) vs pantoprazole 20 mg (n = 68)
Outcomes	Improvements were assessed using the GORD Assessment of Symptoms-Pediatric (GASP-Q) questionnaire: outcomes expressed as composite symptom score and individual symptom score, through participant/parent records and physician assessment at baseline and at week 8 (Likert score) In the 40 mg group, overall symptom score improved significantly from baseline (177) to end of trial (62.5) (P value < 0.001). Significant improvement was also seen in number of vomiting episodes per day (17.1 to 9.2; P value < 0.002); heartburn symptom score (30 to 7.4; P value < 0.002); and epigastric pain score (30 to 11.5; P value < 0.002). In the 20 mg group, overall symptom score again improved significantly from baseline to end of trial (174 to 58.2; P value < 0.001). Significant improvement was also seen in number of vomiting episodes per day (20.4 to 4.7; P value < 0.002); heartburn symptom score (30 to 7.4; P value < 0.002); and epigastric pain score (30 to 17.4; P value < 0.002). On physician assessment, all participants were moderately/greatly improved at 8 weeks compared with baseline (P value < 0.001). No participants were worse
Notes	In terms of adverse events, a total of 112 participants (82.4%) had a treatment-associated adverse event: 1 or more TEAEs—59 participants (86.8%) in the 20 mg group, 53 (77.9%) in the 40 mg group. No serious AEs/deaths occurred. The most common TEAE was headache: 25 participants in 20 mg group; 22 in 40 mg group. Most cases were mild. Headache led to early withdrawal of 3 participants in the 40 mg group. One participant in the 20 mg group and 7 in the 40 mg group reported diarrhoea. LFT fluctuation in 5 participants, mild uric acid rise in 15

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No evidence provided
Allocation concealment (selection bias)	Unclear risk	No evidence provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No evidence provided as to method of blinding. No true control arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence provided as to blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	159 patients screened and 139 participants entered the study; reasons for exclusion of the other 20 not given. Otherwise results analysed on intention-to-treat. Good assessment of compliance in teenagers
Selective reporting (reporting bias)	High risk	Participants may not have been seen at trial entry by physician, potentially causing recall bias
Other bias	High risk	Final study author employed by Wyeth, which funded the research

ALTE: acute life-threatening event.
CF: cystic fibrosis.
CI: confidence interval.
CMPA:cow's milk protein allergy.
CSS: composite symptom score.

CV: cardiovascular
GASP-Q: GORD Assessment of Symptoms-Pediatric Questionnaire.
GOR: gastro-oesophageal reflux.
GORD: gastro-oesophageal reflux disease.
ITT: intention-to-treat.
PGA: Physicians Global Assessment.
PPI: proton pump inhibitor.
PWR: Pediatric Written Request.
RCT: randomised controlled trial.
RI: reflux index.
SD: standard deviation.
TLESR: transient lower oesophageal sphincter relaxation.
URTI: upper respiratory tract infection.
WGSS: weekly GOR frequency scores.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdel-Rahman 2004	Discounted as PK data
Alliët 1998	Discounted as not an RCT
Ameen 2006	Discounted as outcome of taste preference. Unable to contact study authors to confirm no GORD-related clinical outcome data collected.
Arguelles-Martin 1989	Discounted as not an RCT
Bar-Oz 2004	Discounted as not pharmacological trial
Bellisant 1997	Discounted as metoclopramide
Clara 1979	Discounted as concerns with randomisation and participants not diagnosed with reflux
Cohn 1999	Discounted as cisapride
Corvaglia 2010	Discounted as not an RCT
De Giacomo 1997	Discounted as not an RCT
De Loore 1979	Discounted as participants not defined as having reflux/reflux disease
Dhillon 2004	Discounted as not a pharmacological trial
Fiedorek 2005	Discounted as not an RCT
Franco 2000	Discounted as not an RCT
Greally 1992	Excluded as one group given cisapride
Grill 1985	Discounted as not an RCT
Gunesekaran 1993	Discounted as not an RCT
Hassall 2000	Discounted as not an RCT

Study	Reason for exclusion
Hassall 2012	Discounted as not RCT, but participants tolerated omeprazole well in maintenance for 21 months (60% needed at least 50% of dose required for healing as maintenance)
Hyams 1986	Discounted as not an RCT
James 2007	Discounted as pharmacokinetic data. Unable to contact data holder to confirm absence of GORD-related clinical/symptom data.
Jordan 2006	Excluded as treatment group given ranitidine and cisapride
Karjoo 1995	Discounted as not an RCT
Kato 1996	Discounted as not an RCT
Kodama 2010	Discounted as assessment performed on dogs
Kukulka 2012	Discounted as pharmacokinetic data. Study author contacted and confirmed no clinical outcome data were collected
Li 2006a	Discounted as pharmacokinetic data. Study author contacted and confirmed no clinical outcome data were collected
Loots 2011	Discounted as infants recruited after RCT were given first placebo, then antacid, then PPI for 2 weeks each: not RCT
Madrazo-de la Garza 2003	Excluded as not an RCT
Mallet 1989	Discounted as not an RCT
Martin 1996	Discounted as not an RCT
Martin 2006	Discounted as not pharmacological trial
Nelson 1998	Discounted as not assessing pharmacological treatment
Nielsen 2004	Discounted as treatment was a dairy exclusion diet. However 18 of 42 investigated participants had severe GORD, defined as endoscopic oesophagitis and/or a reflux index > 10%. Among these participants, a group of 10 with GORD and CMPI was identified. This group had a significantly higher reflux index compared with children with primary GORD
Omari 2009	Not an RCT
Orenstein 2005	Discounted because of unclear randomisation and absence of randomisation in those over 13. Also multiple dose preparations (the last 44 participants received a new preparation at the request of the FDA) and post hoc analyses
Orsi 2011	Discounted as not an RCT
Salvatore 2006	Discounted as not an RCT
Størdal 2005	Excluded as respiratory symptoms, not pH probe/GORD symptoms, main endpoint. However on contact with study authors, they kindly provided available clinical data. Symptoms suggestive of gastro-oesophageal reflux disease were recorded as present/not present the last week before recruitment, and after 12 weeks, treatment with omeprazole 20 mg once daily. Changes from enrolment to 12 weeks were calculated (improved, unchanged, worsening) and analysed by Chi^2 tests comparing placebo and omeprazole. No significant differences between

Study	Reason for exclusion
	placebo and omeprazole groups were observed for any of these symptoms: regurgitation/vomiting (P value 1.0), nausea (P value 0.31), heartburn (P value 0.55), abdominal pain (P value 0.12), upper abdominal pain (P value 0.66), sour taste (P value 0.51), painful swallowing (P value 0.44) The study was not powered to assess changes in symptoms of reflux disease, and the study authors caution that enrolled participants had asthma as the primary complaint; therefore study results have limited external validity
Tammara 2011	Discounted as outcome pharmacokinetic data. Study author confirms no clinical/symptom outcome data available
Terrin 2012	Discounted as outcomes, not symptom improvement/pH probe improvement or endoscopic improvement. Unable to contact study author to confirm that these data were not collected However study showed that ranitidine therapy is associated with increased risk of infection, NEC and fatal outcome in VLBW infants. Investigators prospectively assessed 274 VLBW infants: 91 receiving ranitidine and 183 not (birth weight between 401 and 1500 g, or gestational age between 24 and 32 weeks at enrolment). 34/91 (37.4%) of the ranitidine group and 18/183 (9.8%) of the placebo group had contracted infection (OR 5.5, 95% confidence interval 2.9 to 10.4; P value < 0.001). NEC risk was 6.6-fold higher in the ranitidine group (95% confidence interval 1.7 to 25.0; P value 0.003) than in the control group. Mortality rate was significantly higher in newborns receiving ranitidine (9.9% vs 1.6%; P value 0.003)
Thjodleifsson 2003	Excluded as adult data
Tolia 2002	Excluded as not an RCT
Tran 2002	Discounted as pharmacokinetic data. Unable to contact study author to confirm that no clinical outcome data were collected
Treepongkaruna 2011	Discounted as not an RCT
Ward 2011	Discounted as pharmacokinetic data. Study author still awaiting reply from drug company at time of submission regarding presence/absence of clinical/symptom outcome data
Winter 2010	Winter looked at 128 infants 1 to 11 months of age with GORD symptoms after 2 weeks of conservative treatment received open-label pantoprazole 1.2 mg/kg/d for 4 weeks, followed by a 4-week randomised, double-blind (DB), placebo-controlled, withdrawal phase. The open-label phase was not considered, as it was not an RCT. The primary endpoint in the withdrawal phase was withdrawal due to lack of efficacy. Given that the primary endpoint was not within the primary endpoints considered above, and the study design and resultant findings would be difficult to directly extrapolate to clinical practise, we have decided to exclude this study from the analysis
Winter 2012	Winter 2012 assessed 98 infants (1 to 11 months of age) with symptoms/endoscopic findings diagnostic of GORD, who underwent an initial 2-week open-label treatment phase of esomeprazole (not assessed here, except for safety data), then a 4-week randomised, double-blind, placebo-controlled treatment withdrawal of esomeprazole 2.5 mg to 10 mg vs placebo for 4 weeks. The open-label phase was not considered, as this was not an RCT. The primary endpoint in the withdrawal phase was withdrawal due to lack of efficacy. Given that the primary endpoint (withdrawal) was not within the primary endpoints considered above, and the study design and consequent findings would be difficult to directly extrapolate to clinical practise, we have decided to exclude this study from the analysis
Zannikos 2011	Only second part of the trial was randomised, yielding only pharmacokinetic data. No valid contact available to determine presence/absence of clinical/symptom outcome data
Zhao 2006	Discounted as pharmacokinetic data. No valid contact available to determine presence/absence of clinical/symptom outcome data

CMPI: cow's milk protein intolerance.
GORD: gastro-oesophageal reflux disease.
NEC: necrotising enterocolitis.
OR: odds ratio.
RCT: randomised controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Davidson 2013

Methods	RCT, multi-centre study
Participants	52 neonates (premature to 1 month corrected age), with signs and symptoms of GERD
Interventions	0.5 mg/kg esomeprazole once daily for up to 14 days vs placebo
Outcomes	Change from baseline in the total number of GERD symptoms (from video monitoring) and GERD-related signs (from cardiorespiratory monitoring) was assessed with simultaneous esophageal pH, impedance, cardiorespiratory and 8-hour video monitoring
Notes	

Haddad 2013

Methods	Unknown
Participants	108 children (1 year to 11 years old) with endoscopically/histologically proven GERD
Interventions	0.5 or 1.0 mg/kg rabeprazole granule formulation for 12 weeks. The dose was further determined by weight: children 6 to 14.9 kg (low-weight cohort) received 5 mg or 10 mg, and children ≥ 15 kg (high-weight cohort) received 10 mg or 20 mg
Outcomes	Endoscopic/histological healing at week 12 (defined as grade 0 on the Hetzel-Dent classification scale and/or grade 0 on the Histological Features of Reflux Esophagitis Scale)
Notes	Efficacy and safety study

Haddad 2014

Methods	Prospective
Participants	Children 1 to 11 years of age who achieved endoscopic/histological healing of reflux esophagitis during 12 weeks of treatment
Interventions	Maintenance therapy (same dose) of rabeprazole for 24 additional weeks. Dose was determined by weight; 5 mg or 10 mg for children weighing between 6 and 14.9 kg, 10 mg or 20 mg for children weighing 15 kg or greater
Outcomes	Maintainance of healing, GERD symptom and severity score, GERD symptom relief score, adverse events
Notes	

Hassall 2012b

Methods	Prospective study
Participants	46 participants 1 to 16 years of age with healed erosive reflux oesophagitis after omeprazole treatment
Interventions	21-Month maintenance phase during which participants initially received half the dose of omeprazole required to heal. Endoscopy was performed after 3, 12 and 21 months. The omeprazole dose was increased if erosive oesophagitis or reflux symptoms recurred
Outcomes	Change in maintenance dose, relapse of symptoms
Notes	32 participants completed the study

Ummarino 2013

Methods	Prospective, comparative RCT
Participants	35 participants younger than 1 year old, affected by symptoms of GERD
Interventions	8 weeks of treatment with Mg-alginate, thickened formula feeding or reassurance (lifestyle changes and reassurance about the condition)
Outcomes	Change in symptoms, as measured by a validated questionnaire (I-GERQ)
Notes	

GERD: gastro-oesophageal reflex disease.
I-GERQ: Infant Gastroesophageal Reflux Questionnaire.
RCT: randomised controlled trial.

ADDITIONAL TABLES

Table 1. Summary of study results and quality of evidence

Medical treatment compared with no treatment for gastro-oesophageal reflux disease

Patient or population: children 1 to 16 years of age with erosive oesophagitis

Settings: paediatric outpatients

Intervention: medical treatment: proton pump inhibitors (omeprazole, lansoprazole, esomeprazole and pantoprazole) or H_2-antagonists (ranitidine, cimetidine or nizatidine) or prokinetics (domperidone, erythromycin) or alginates (Gaviscon Infant®)

Comparison: placebo or no treatment

Outcomes	Age group	Medication	Effect	Number of participants (studies)	Quality of the evidence (GRADE)	Comments

Table 1. Summary of study results and quality of evidence *(Continued)*

Improvement in symptom score (primary outcome)	**Older children**	PPIs	PPIs (omeprazole—50 children (2 studies), lansoprazole—46 children (2 studies) Esomeprazole—153 children (2 studies) and pantoprazole—225 children (3 studies) had **moderate** evidence of symptom relief	474 children (9 studies)	⊕⊕⊕⊖ **Moderate**	Most studies compared same drug, different doses
		H2-antagonists	H_2-antagonists had **weak** evidence of efficacy, with 1 study (32 children, 1 study) showing equal efficacy of high-dose ranitidine compared with PPIs, and 1 study (18 children) showing evidence for absence of effect when ranitidine was added to PPI. Cimetidine (33 infants and children) also had very weak evidence for efficacy in delivering symptom relief	83 children (3 studies)	⊕⊕⊖⊖ **Low**	
		Prokinetics	Very weak evidence of efficacy was found for domperidone, with non-significant improvement in symptoms in only 33% of participants in one study of 17 children	17 patients (1 studies)	⊕⊖⊖⊖ **Very low**	
	Infants	PPIs	**Weak** evidence has been found to support the use of PPIs in infants with GORD (30.infants, 1 study)	30 infants (1 study)	⊕⊖⊖⊖ **Very low**	
		H2-antagonists	**No** evidence shows the efficacy of ranitidine; however nizatidine (26 infants and children, 1 study) and cimetidine (33 infants and children, 1 study) improved symptoms of GORD	59 infants (2 studies)	⊕⊖⊖⊖ **Very low**	
		Alginates	**Weak** evidence suggests that Gaviscon Infant® improves symptoms in infants with GOR and GORD. The largest study (90 infants) showed significant symptomatic improvement, but another study (20 infants) showed no significant symptom relief	110 infants (2 studies)	⊕⊕⊖⊖ **Low**	Gaviscon Infant® has changed to become aluminium-free, and has been assessed in its' current form in only 2 studies since 1999
		Prokinetics	**Very weak** evidence of efficacy was found for domperidone, with no improvement compared with placebo, and a significant improvement in symptoms only when combined with Maalox® in 1 study of 80 infants. Symptom improvement was still present at 6 months	80 patients (1 studies)	⊕⊖⊖⊖ **Very low**	All feeds were thickened
	Preterm babies	No robust RCT evidence has been found regarding the efficacy of treatment of patients with GOR/GORD in improving symptoms				
	Children with neu-	No RCT evidence was identified				

Table 1. Summary of study results and quality of evidence *(Continued)*

	rodisabilities					
Adverse events (AEs)	**Older children + Infants + Preterm babies**	PPIs	**Weak** evidence shows that increasing the dose may increase the risk of side effects. The risk of side effects was less prominent for omeprazole, lansoprazole and esomeprazole than for pantoprazole	748 children (12 studies)	⊕⊕⊖⊖ **Low**	82% of participants taking pantoprazole in one study had an adverse event (mainly headache and diarrhoea)
		H2-antagonists	No serious AEs were noted, although 2 participants given cimetidine had diarrhoea, and 1 participant taking nizatidine had an urticarial rash	109 children (4 studies)	⊕⊕⊖⊖ **Low**	
		Prokinetics	No significant adverse events were noted, although 1 study did not comment on AEs	97 children (3 studies)	⊕⊖⊖⊖ **Very low**	The recent MHRA alert is noted
		Alginates	No serious AEs were noted, although in 1 study, 13 participants had constipation and diarrhoea (but no difference between alginate and placebo)	156 children (5 studies	⊕⊕⊖⊖ **Low**	
Improvement in reflux index	**Older children**	PPIs	1 study assessing omeprazole and 1 study assessing lansoprazole, noted a significant improvement in reflux index	68 children (2 studies)	⊕⊕⊖⊖ **Low**	
		H2-antagonists	2 studies assessing ranitidine, 1 study assessing cimetidine and 1 study assessing nizatidine noted significant improvements in reflux index. 1 study (32 children) showed equal efficacy of high-dose ranitidine compared with PPIs, and 1 study (18 children) showed evidence for absence of additional effect when ranitidine was added to PPI	109 children (4 studies)	⊕⊕⊖⊖ **Low**	
	Infants	PPIs	1 study assessing omeprazole and 1 study assessing esomeprazole noted a significant improvement in reflux index in infants with GORD; in the only study of infants treated with pantoprazole, no improvement in reflux index was noted, but 50% to 70% had a normal reflux index at baseline	104 infants (3 studies)	⊕⊕⊖⊖ **Low**	
		H2-antagonists	**No** evidence shows the efficacy of ranitidine; however nizatidine (26 infants and children, 1 study) and cimetidine (33 infants and children, 1 study) improved symptoms of GORD	59 infants and children (2 studies)	⊕⊖⊖⊖ **Very low**	

Table 1. Summary of study results and quality of evidence *(Continued)*

	Preterm babies	Domperidone	A single study of domperidone showed a significant increase in reflux frequency, but duration of reflux significantly improved	26 babies (1 study)	⊕⊝⊝⊝ **Very low**	Short-duration study (24 hours)
Improvement in endoscopic and histological findings	**Older children**	PPIs	Moderate evidence showed improvement in endoscopic findings in children given PPIs (omeprazole 50 children—2 studies, lansoprazole 36 participants, 103 children—1 study and esomeprazole 109 children—1 study)	195 children (4 studies)	⊕⊕⊕⊝ **Moderate**	
		H2-antagonists	Weak evidence showed benefit in H2-antagonists improving endoscopic findings in 4 studies, with 1 study showing equal benefit compared with PPI, but another study showing no benefit derived from adding H2 antagonist to PPI	109 children (4 studies)	⊕⊕⊝⊝ **Low**	
	Infants	PPIs	No studies of PPIs evaluated endoscopic evidence of improvement		⊕⊝⊝⊝ **Very low**	
		H2-antagonists	**Weak** evidence showed benefit derived from H2-antagonists improving endoscopic findings in 2 studies, with 2 studies showing significant improvement: 1 with nizatidine (26 infants and children) and another with cimetidine (33 infants and children)	59 infants and children (2 studies)	⊕⊕⊝⊝ **Low**	
	Infants + Children	Prokinetics	No evidence was identified to ascertain efficacy of domperidone in improving endoscopic findings		⊕⊝⊝⊝ **Very low**	
	Children with neurodisabilities	No evidence was identified for children with neurodisabilities. No evidence was available from which to evaluate erythromycin				

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Table 2. Summary of study results and quality of the evidence

Medical treatment compared with no treatment or reassurance for gastro-oesophageal reflux

Patient or population: infants with gastro-oesophageal reflux

Settings: paediatric outpatients

Intervention: medical treatment

Comparison: no treatment or reassurance

Table 2. Summary of study results and quality of the evidence *(Continued)*

Outcomes	Age group	Effect	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Improvement in symptom score	**Infants**	1 study of the current formulation of Gaviscon Infant® in GOR showed weak evidence of symptomatic improvement (90 participants). 1 study of 20 children showed no symptomatic improvement	110 participants (2 studies)	⊕⊕⊖⊖ **Low**	Gaviscon Infant® has changed to become aluminium-free, and has been assessed in its current form in only 2 studies since 1999
		1 study of 162 infants with GOR showed no symptomatic improvement with PPI	162 infants (1 study)	⊕⊕⊖⊖ **Low**	
		2 studies showed very poor evidence of symptomatic improvement with domperidone	97 infants (2 studies)	⊕⊖⊖⊖ **Very low**	

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

APPENDICES

Appendix 1. CENTRAL search strategy

1. exp Gastroesophageal Reflux/

2. (GER or GOR).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

3. ((gastro-oesophag* or gastroesophag*) adj reflux).tw.

4. (GERD or GORD).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

5. infant, newborn, diseases/ or infant, premature, diseases/

6. Esophageal Sphincter, Lower/gd, pa, pp [Growth & Development, Pathology, Physiopathology]

7. child nutritional physiological phenomena/ or adolescent nutritional physiological phenomena/ or exp infant nutritional physiological phenomena/

8. or/1-7

9. Alginates/

10. (gaviscon or alenic alka or almagate or almax or aluminum-magnesium hydroxide carbonate or aluminum-magnesium hydroxycarbonate or deprece or genaton or obetine or tisacid).mp.

11. antacid*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

12. exp antacids/

13. (magnesium hydroxide or brucite or magnesium hydrate or mil-par or milk of magnesia).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

14. (aluminum hydroxide or aldrox or algeldrate or alhydrogel or aloh-gel or alternagel or alu-cap or alu-tab or alugel or amphojel or andursil or basalgel or brasivil or brimos or dialume or hydrated alumina or pepsamer or rocgel).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

15. (Maalox$ or alamag or alucol or (alumina and magnesia) or aluminum hydroxide-magnesium hydroxide or aluminum magnesium hydroxide or co-magaldrox or gen-alox or kudrox or magagel or magnalox or magnesium aluminum hydroxide or maldroxal or mintox or mucogel or mylanta ultimate or novalucol or ri-mox or rulox or supralox).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

16. H2 antagonist*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

17. histamine h2 antagonists/ or cimetidine/ or famotidine/ or ranitidine/

18. (Ranitidin$ or azanplus or biotidin or pylorid or raciran or raniberl or ranisen or rantec or sostril or taladine or tritec or wal-zan or zantac).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

19. (Cimetidine or acitak or altramet or biomet or dyspamet or eureceptor or galenamet or histodil or peptimax or phimetin or tagamet or ultec or zita).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

20. (Famotidine or fluxid or mylanta ar or pepcid or ym 11170).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

21. Proton Pump Inhibitors/ or PPI.tw.

22. (lansoprazol$ or agopton or bamalite or lanzoprazol$ or lanzor or monolitum or ogast or ogastro or opiren or prevacid or prezal or pro ulco or promeco or takepron or ulpax or zoton).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

23. (Pantoprazole or "protium iv" or protonix or "skf-96022" or Pantotab or Pantopan or Pantozol or Pantor or Pantoloc or Astropan or Controloc or Pantecta or Inipomp or Somac or Ulcepraz or Pantodac).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

24. (omeprazole or losec or nexium or prilosec or rapinex or zegerid or OMEZ or Antra or Gastroloc or Mopral or Omepral).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

25. (Rabeprazole or aciphex or dexrabeprazole or "e 3810" or "ly-307640" or pariet).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

26. (Esomeprazole or Sompraz or Zoleri or Nexium or Lucen or Esopral or Axagon or Nexiam).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

27. (metoclopramide or cerucal or clopra or degan or gastrobid continus or gastroflux or gastromax or maxolon or maxeran or metaclopramide or metozolv or migravess forte or mygdalon or octamide or primperan or pylomid or reglan or reliveran or rimetin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

28. (domperidon$ or domidon or domperidona gamir or gastrocure or "kw 5338" or motilium or Motillium or Motinorm or nauzelin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

29. (erythromycin or aknemycin or del-mycin or e-base or emycin or "e-solve 2" or emcin clear or emgel or ery-sol or ery-tab or eryacne or eryc or erycen or erycette or eryderm or erygel or erymax or erymin or eryped or erythra-derm or erythro or erythrocot or erythroped or eyemycin or "eyrthromycin ethyl succinate" or gallimycin or ilosone or ilotycin or lauromicina or monomycin or pediamycin or retcin or rommix or romycin or roymicin or rp-mycin or staticin or stiemycin or "t stat" or theramycin or tiloryth or "vcp-1" or wyamycin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

30. (bethanechol or bethanecol or duvoid or myo hermes or myocholine or myotonachol or myotonine or pmsbethanechol chloride or urecholine or urocarb).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

31. Sucralfate/

32. (sucralfate or aluminum sucrose sulfate or antepsin or carafate or Sucramal or Pepsigard or Sucral or sucrafil or Sutra or Sulcrate or ulcerban or ulcogant or ulsanic or xactdose).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

33. or/9-32

34. (exp Adult/ or exp Aged/ or exp Middle Aged/ or exp Young Adult/) not (exp infant/ or exp Infant, Newborn/ or exp Pediatrics/ or exp child/ or exp Adolescent/)

35. 8 and 33

36. 35 not 34

Appendix 2. MEDLINE search strategy

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. clinical trials as topic.sh.

6. randomly.ab.

7. trial.ti.

8. or/1-7

9. exp animals/ not humans.sh.

10. 8 not 9

11. exp Gastroesophageal Reflux/

12. (GER or GOR).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

13. ((gastro-oesophag* or gastroesophag*) adj reflux).tw.

14. (GERD or GORD).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

15. infant, newborn, diseases/ or infant, premature, diseases/

16. Esophageal Sphincter, Lower/gd, pa, pp [Growth & Development, Pathology, Physiopathology]

17. child nutritional physiological phenomena/ or adolescent nutritional physiological phenomena/ or exp infant nutritional physiological phenomena/

18. or/11-17

19. Alginates/

20. (gaviscon or alenic alka or almagate or almax or aluminum-magnesium hydroxide carbonate or aluminum-magnesium hydroxycarbonate or deprece or genaton or obetine or tisacid).mp.

21. antacid*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

22. exp antacids/

23. (magnesium hydroxide or brucite or magnesium hydrate or mil-par or milk of magnesia).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

24. (aluminum hydroxide or aldrox or algeldrate or alhydrogel or aloh-gel or alternagel or alu-cap or alu-tab or alugel or amphojel or andursil or basalgel or brasivil or brimos or dialume or hydrated alumina or pepsamer or rocgel).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

25. (Maalox$ or alamag or alucol or (alumina and magnesia) or aluminum hydroxide-magnesium hydroxide or aluminum magnesium hydroxide or co-magaldrox or gen-alox or kudrox or magagel or magnalox or magnesium aluminum hydroxide or maldroxal or mintox or mucogel or mylanta ultimate or novalucol or ri-mox or rulox or supralox).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

26. H2 antagonist*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

27. histamine h2 antagonists/ or cimetidine/ or famotidine/ or ranitidine/

28. (Ranitidin$ or azanplus or biotidin or pylorid or raciran or raniberl or ranisen or rantec or sostril or taladine or tritec or wal-zan or zantac).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

29. (Cimetidine or acitak or altramet or biomet or dyspamet or eureceptor or galenamet or histodil or peptimax or phimetin or tagamet or ultec or zita).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

30. (Famotidine or fluxid or mylanta ar or pepcid or ym 11170).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

31. Proton Pump Inhibitors/ or PPI.tw.

32. (lansoprazol$ or agopton or bamalite or lanzoprazol$ or lanzor or monolitum or ogast or ogastro or opiren or prevacid or prezal or pro ulco or promeco or takepron or ulpax or zoton).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

33. (Pantoprazole or "protium iv" or protonix or "skf-96022" or Pantotab or Pantopan or Pantozol or Pantor or Pantoloc or Astropan or Controloc or Pantecta or Inipomp or Somac or Ulcepraz or Pantodac).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

34. (omeprazole or losec or nexium or prilosec or rapinex or zegerid or OMEZ or Antra or Gastroloc or Mopral or Omepral).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

35. (Rabeprazole or aciphex or dexrabeprazole or "e 3810" or "ly-307640" or pariet).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

36. (Esomeprazole or Sompraz or Zoleri or Nexium or Lucen or Esopral or Axagon or Nexiam).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

37. (metoclopramide or cerucal or clopra or degan or gastrobid continus or gastroflux or gastromax or maxolon or maxeran or metaclopramide or metozolv or migravess forte or mygdalon or octamide or primperan or pylomid or reglan or reliveran or rimetin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

38. (domperidon$ or domidon or domperidona gamir or gastrocure or "kw 5338" or motilium or Motillium or Motinorm or nauzelin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

39. (erythromycin or aknemycin or del-mycin or e-base or emycin or "e-solve 2" or emcin clear or emgel or ery-sol or ery-tab or eryacne or eryc or erycen or erycette or eryderm or erygel or erymax or erymin or eryped or erythra-derm or erythro or erythrocot or erythroped or eyemycin or "eyrthromycin ethyl succinate" or gallimycin or ilosone or ilotycin or lauromicina or monomycin or pediamycin or retcin or rommix or romycin or roymicin or rp-mycin or staticin or stiemycin or "t stat" or theramycin or tiloryth or "vcp-1" or wyamycin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

40. (bethanechol or bethanecol or duvoid or myo hermes or myocholine or myotonachol or myotonine or pmsbethanechol chloride or urecholine or urocarb).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

41. Sucralfate/

42. (sucralfate or aluminum sucrose sulfate or antepsin or carafate or Sucramal or Pepsigard or Sucral or sucrafil or Sutra or Sulcrate or ulcerban or ulcogant or ulsanic or xactdose).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

43. or/19-42

44. (exp Adult/ or exp Aged/ or exp Middle Aged/ or exp Young Adult/) not (exp infant/ or exp Infant, Newborn/ or exp Pediatrics/ or exp child/ or exp Adolescent/)

45. 10 and 18 and 43

46. 45 not 44

Appendix 3. EMBASE search strategy

1. Clinical trial/

2. Randomized controlled trial/

3. Randomization/

4. Single-Blind Method/

5. Double-Blind Method/

6. Cross-Over Studies/

7. Random Allocation/

8. Placebo/

9. Randomi?ed controlled trial$.tw.

10. Rct.tw.

11. Random allocation.tw.

12. Randomly allocated.tw.

13. Allocated randomly.tw.

14. (allocated adj2 random).tw.

15. Single blind$.tw.

16. Double blind$.tw.

17. ((treble or triple) adj blind$).tw.

18. Placebo$.tw.

19. Prospective study/

20. or/1-19

21. Case study/

22. Case report.tw.

23. Abstract report/ or letter/

24. or/21-23

25. 20 not 24

26. exp Gastroesophageal Reflux/

27. (GER or GOR).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

28. ((gastro-oesophag* or gastroesophag*) adj reflux).tw.

29. (GERD or GORD).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

30. or/26-29

31. Alginates/

32. (gaviscon or alenic alka or almagate or almax or aluminum-magnesium hydroxide carbonate or aluminum-magnesium hydroxycarbonate or deprece or genaton or obetine or tisacid).mp.

33. antacid*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

34. exp antacids/

35. (magnesium hydroxide or brucite or magnesium hydrate or mil-par).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

36. (aluminum hydroxide or aldrox or algeldrate or alhydrogel or aloh-gel or alternagel or alu-cap or alu-tab or alugel or amphojel or andursil or basalgel or brasivil or brimos or dialume or hydrated alumina or pepsamer or rocgel).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

37. (Maalox$ or alamag or alucol or (alumina and magnesia) or aluminum hydroxide-magnesium hydroxide or aluminum magnesium hydroxide or co-magaldrox or gen-alox or kudrox or magagel or magnalox or magnesium aluminum hydroxide or maldroxal or mintox or mucogel or mylanta ultimate or novalucol or ri-mox or rulox or supralox).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

38. H2 antagonist*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

39. histamine h2 antagonists/ or cimetidine/ or famotidine/ or ranitidine/

40. (Ranitidin$ or azanplus or biotidin or pylorid or raciran or raniberl or ranisen or rantec or sostril or taladine or tritec or wal-zan or zantac).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

41. (Cimetidine or acitak or altramet or biomet or dyspamet or eureceptor or galenamet or histodil or peptimax or phimetin or tagamet or ultec or zita).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

42. (Famotidine or fluxid or mylanta ar or pepcid or ym 11170).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

43. Proton Pump Inhibitors/ or PPI.tw.

44. (lansoprazol$ or agopton or bamalite or lanzoprazol$ or lanzor or monolitum or ogast or ogastro or opiren or prevacid or prezal or pro ulco or promeco or takepron or ulpax or zoton).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

45. (Pantoprazole or "protium iv" or protonix or "skf-96022" or Pantotab or Pantopan or Pantozol or Pantor or Pantoloc or Astropan or Controloc or Pantecta or Inipomp or Somac or Ulcepraz or Pantodac).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

46. (omeprazole or losec or nexium or prilosec or rapinex or zegerid or OMEZ or Antra or Gastroloc or Mopral or Omepral).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

47. (Rabeprazole or aciphex or dexrabeprazole or "e 3810" or "ly-307640" or pariet).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

48. (Esomeprazole or Sompraz or Zoleri or Nexium or Lucen or Esopral or Axagon or Nexiam).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

49. (metoclopramide or cerucal or clopra or degan or gastrobid continus or gastroflux or gastromax or maxolon or maxeran or metaclopramide or metozolv or migravess forte or mygdalon or octamide or primperan or pylomid or reglan or reliveran or rimetin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

50. (domperidon$ or domidon or domperidona gamir or gastrocure or "kw 5338" or motilium or Motillium or Motinorm or nauzelin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

51. (erythromycin or aknemycin or del-mycin or e-base or emycin or "e-solve 2" or emcin clear or emgel or ery-sol or ery-tab or eryacne or eryc or erycen or erycette or eryderm or erygel or erymax or erymin or eryped or erythra-derm or erythro or erythrocot or erythroped or eyemycin or "eyrthromycin ethyl succinate" or gallimycin or ilosone or ilotycin or lauromicina or monomycin or pediamycin or retcin or rommix or romycin or roymicin or rp-mycin or staticin or stiemycin or "t stat" or theramycin or tiloryth or "vcp-1" or wyamycin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

52. (bethanechol or bethanecol or duvoid or myo hermes or myocholine or myotonachol or myotonine or pmsbethanechol chloride or urecholine or urocarb).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

53. Sucralfate/

54. (sucralfate or aluminum sucrose sulfate or antepsin or carafate or Sucramal or Pepsigard or Sucral or sucrafil or Sutra or Sulcrate or ulcerban or ulcogant or ulsanic or xactdose).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

55. or/31-54

56. (exp Adult/ or exp Aged/ or exp Middle Aged/ or exp Young Adult/) not (exp infant/ or exp Infant, Newborn/ or exp Pediatrics/ or exp child/ or exp Adolescent/)

57. 25 and 30 and 55

58. 57 not 56

Appendix 4. Science Citation Index search strategy

# 16	#15 AND #14 *Databases=SCI-EXPANDED Timespan=All Years*
# 15	Topic=(single blind*) OR Topic=(double blind*) OR Topic=(clinical trial*) OR Topic=(placebo*) OR Topic=(random*) OR Topic=(controlled clinical trial) OR Topic=(research design) OR Topic=(comparative stud*) OR Topic=(controlled trial) OR Topic=(follow up stud*) OR Topic=(prospective stud*) *Databases=SCI-EXPANDED Timespan=All Years*
# 14	#13 NOT #11 *Databases=SCI-EXPANDED Timespan=All Years*
# 13	#12 AND #1 *Databases=SCI-EXPANDED Timespan=All Years*
# 12	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 *Databases=SCI-EXPANDED Timespan=All Years*
# 11	Topic=(Adult* or Elderly or Middle Aged or Aged) NOT Topic=(infant* or Newborn* or Pediatric* or child* or baby or babies or babe or Adolescent) *Databases=SCI-EXPANDED Timespan=All Years*
# 10	Topic=(Rabeprazole or Esomeprazole or metoclopramide or domperidon* or bethanechol) OR Topic=(Sucralfate) *Databases=SCI-EXPANDED Timespan=All Years*
# 9	Topic=(lansoprazol* or Pantoprazole or omeprazole) *Databases=SCI-EXPANDED Timespan=All Years*
# 8	Topic=(Proton Pump Inhibitor* OR PPI) *Databases=SCI-EXPANDED Timespan=All Years*
# 7	Topic=(Ranitidin*) OR Topic=(Cimetidine) OR Topic=(Famotidine) *Databases=SCI-EXPANDED Timespan=All Years*
# 6	Topic=(H2 antagonist*) *Databases=SCI-EXPANDED Timespan=All Years*
# 5	Topic=(Maalox*) *Databases=SCI-EXPANDED Timespan=All Years*

(Continued)

# 4	Topic=(antacid*) *Databases=SCI-EXPANDED Timespan=All Years*
# 3	Topic=(Gaviscon) *Databases=SCI-EXPANDED Timespan=All Years*
# 2	Topic=(Alginate*) *Databases=SCI-EXPANDED Timespan=All Years*
# 1	Topic=(Gastroesophageal Reflux) OR Topic=(GER or GOR) OR Topic=(GERD or GORD) *Databases=SCI-EXPANDED Timespan=All Years*

WHAT'S NEW

Date	Event	Description
3 November 2016	Amended	Typographic edits made to remove hyperlinks from abstract. No other changes made.

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities

Draft the protocol: Mark Tighe, Mark Beattie.
Develop a search strategy: Mark Tighe, Mark Beattie.
Search for trials (usually two people): Mark Tighe, Alasdair Munro.
Obtain copies of trials: Mark Tighe, Alasdair Munro.
Select which trials to include (two + one arbiter): Mark Tighe, Alasdair Munro, Nadeem Afzal.
Extract data from trials (two people): Mark Tighe, Alasdair Munro.
Enter data into RevMan: Mark Tighe, Alasdair Munro.
Carry out the analysis: Mark Tighe, Alasdair Munro, Andrew Hayen.
Interpret the analysis: Mark Tighe, Nadeem Afzal, Mark Beattie, Amanda Bevan, Alasdair Munro, Andrew Hayen.
Draft the final review: Mark Tighe, Nadeem Afzal, Mark Beattie, Amanda Bevan, Alasdair Munro, Andrew Hayen.
Update the review: Mark Tighe.

DECLARATIONS OF INTEREST

MT: none known.

NAA: none known.

AB has received support to attend unrelated educational activities from Abbvie and Forest inc.

AH: none known.

AM: none known.

RMB had previously received an educational research grant from GlaxoSmithKline in 2012/3, and speakers fees from Nestle, Nutricia and GlaxoSmithKline in 2011-3. However, RMB's participation in the development of this review was not sponsored by any of these companies.

A review of the medical treatment of gastro-oesophageal reflux was completed for *Paediatric Drugs* (publishers: 'Adis') and was published in early 2009. However, that article is substantially different from the Cochrane review. The *Paediatric Drugs* article was not funded.

SOURCES OF SUPPORT

Internal sources

- Statistical support from Portsmouth Hospitals Research and Development Support Unit, UK.
- Library, Poole Hospitals NHS Foundation Trust, UK.

Obtaining manuscripts

- Library, University Hospital Southampton, UK.

Obtaining original papers

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We noted that metoclopramide and thickened feeds had already been assessed in 2007, so a re-review was not considered to be required (Craig 2007). In one trial, the methodology aroused such concern that clear consensus was reached indicating that the trial should not be included.

INDEX TERMS

Medical Subject Headings (MeSH)

Alginates [therapeutic use]; Aluminum Hydroxide [therapeutic use]; Domperidone [therapeutic use]; Drug Combinations; Gastroesophageal Reflux [*drug therapy]; Gastrointestinal Agents [*therapeutic use]; Histamine H2 Antagonists [*therapeutic use]; Magnesium Hydroxide [therapeutic use]; Proton Pump Inhibitors [*therapeutic use]; Randomized Controlled Trials as Topic; Silicic Acid [therapeutic use]; Sodium Bicarbonate [therapeutic use]

MeSH check words

Child; Child, Preschool; Humans; Infant; Infant, Newborn

Article IV: NICE guidance (NG1) leading to NICE audit tool and NICE Quality standards (QS112)

National Institute for Health and Care Excellence, 2015. *Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people*. London: NICE. NG1. https://www.nice.org.uk/guidance/ng1

National Institute for Health and Care Excellence, 2016. Quality Standard 112: Gastro-oesophageal reflux in children and young people: London: NICE. https://www.nice.org.uk/guidance/QS112

What does this group of publications achieve?

NICE guidance aims to integrate the existing evidence-base to form evidence-based recommendations involving invited experts, statisticians and health economists and lay representatives. The guidance comes with a suite of supporting materials including patient/parent information, economic evaluation of recommendations, and an audit tool to assess compliance, and is followed 2-3 years later by supporting Quality Standards. The initial scoping and subsequent guidance was commissioned by NICE and created by the NCC-Women and Children's group. I joined the Guideline Development Group (GDG) at the scoping stage as an invited expert given articles I, II and III. The GDG defined the title and key clinical areas of work (see scope below) and participated in stakeholder work as part of the assurance process. The full Guideline Development Group (see Appendix 1) also comprised two paediatric gastroenterologists (including the chair); a neonatologist; a consultant in paediatric neurodisability; a paediatric surgeon; two general practitioners; an advanced paediatric nurse practitioner; a paediatric dietitian; a pharmacist, a health visitor; lay members with experience of caring for such infants, children, or young people; and experts in guideline methodology. As well as monthly meetings over a 4-year period, I led sub-groups focusing on topic areas, supported detailed communication between meetings to evaluate papers, and discussed wording of recommendations based on the evidence graded according to GRADE criteria. While the data were sourced and analysed by the NCC statisticians and economists, as part of the GDG, I helped appraise and provide clinical context to the evidence and learnt a lot through this process.

The NICE guidance (NG1) was published in January 2015, and I received a detailed letter of thanks highlighting my degree of contribution to the guideline, and I helped draft and develop the nationally-used patient information, costing statement and NICE-adopted clinical audit tool (leading to Article V), as well as research recommendations including highlighting the need for an evidence-

base in children with neurodisability and GORD (Articles VII and VIII). This summary of NICE guidance, using wording agreed by the GDG, was also published in the BMJ (Davies et al 2014).
I then participated in the development of the NICE quality standard (QS112) which has helped benchmark care for infants and children with reflux. The development of the quality standards took place in 2015, following the publication of NICE guidelines (NG1) in 2014. Over 2 meetings and during subsequent edits, I was one of 3 invited experts participating in the discussion and creation of NICE guidance to form 9 quality standards that clinicians must deliver (and NHS funding should be made available to enable implementation of the quality standards).

How does it contribute to the evidence-base?

The NICE guidance enabled evidence-based recommendations which integrated the views of a wide range of health professionals and, significantly, parental views and health economic data. In September 2023, NG1 is being viewed 4000 times per month and being downloaded 65 times per month. QS112 is being viewed 400 times per month (information kindly provided by NICE). The process led to a more systematic approach to care of children with reflux which had been highly individualised until that point. Many families found the linked patient information useful, and these children are also being managed with less investigations and less off-license medications, as recommended by QS112. Based on the National Patient Dose Database: the number of barium swallows performed in children dropped from 594 in 2005 to 190 in 2010 (the year following the release of the guidance) (Hart 2007, 2010). One audit estimated the empirical prescribing of domperidone for GORD prior to NICE guidance accounted for 64% of overall prescribing of domperidone in infants and children, and that prescribing for this indication had dropped five-fold in one hospital (17 prescriptions to 3 prescriptions) by 2015 (Williams 2018).

What were the next steps?

I then audited the Red Flags table of concerning symptoms (in Article V), using the NICE audit tool. I also participated in the NICE surveillance report appraising the new evidence in 2018.
I was also able to take the experience gained from working as part of such a widely skilled team into the Cochrane re-review (Article VI) including developing familiarity with GRADE recommendations, and minimal clinically important differences. The research recommendation derived from NG1 directly led to article VII and VIII, as well as listening to the experiences of the parent representatives and their children's treatment journeys.

I also developed publications to raise awareness of the issue and evidence-base in primary care (Tighe et al, Pulse, 2014). I also evaluated the NICE audit tool and presented this at the RCPCH meeting, then published this, as well as an evaluation of treatment of GORD in children with neurodisability in 2017 (article VII).

Initial NICE scoping guidance for NG1: (published 2015)

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Gastro-oesophageal reflux in children and young people: diagnosis, investigation and management of gastro-oesophageal reflux in children and young people.

Short title

Gastro-oesophageal reflux in children and young people.

2 The remit

The Department of Health has asked NICE: 'To produce a clinical guideline on the investigation and management of gastro-oesophageal reflux disease in children'.

3 Clinical need for the guideline

3.1 Epidemiology

a) Gastro-oesophageal reflux (GOR) is a normal bodily process. It usually happens after eating in healthy infants, children, young people and adults. In contrast, gastro-oesophageal reflux disease (GORD) is present when GOR causes symptoms (for example, frequency of regurgitation) and/or complications (for example, oesophagitis) that have a significant effect on the person and require treatment. However, there is no exact distinction of when GOR becomes GORD, and the terms are used to cover a range of severity.

b) All children and young people have GOR, however, the prevalence of GORD in children and young people in the UK is uncertain. Data

from the USA shows that 'problematic' regurgitation was reported in 23% of infants aged 6 months but decreased to 14% by the age of 7 months.

c) English NHS hospital episode statistics data for 2010–11 show that there were 8943 consultant episodes for GORD with or without oesophagitis in children and young people aged 0–14 years.

d) The prevalence of GORD is higher in children and young people with neurodevelopmental disorders, oesophageal atresia repair, cystic fibrosis, hiatal hernia, repaired achalasia or a family history of complex GORD.

3.2 Current practice

a) Many infants and young children present in primary care with regurgitation caused byGOR/GORD. Advice may be sought from health visitors and GPs about this condition. In cases where symptoms are mild and there is no reason to suspect the presence of GORD, reassurance may be all that is given. Frequently, however, treatment is prescribed including feeding changes or drug therapy with antacids. In addition, some children are referred to a specialist for assessment and possible treatment, especially those with severe symptoms (for example, in a child with overt regurgitation the presence of blood might indicate erosive oesophagitis, or recurrent respiratory symptoms might be attributed to occult reflux) or other risk-factors, such as neurodevelopmental disorders.

b) As well as assessing symptoms, a specialist may want to carry out diagnostic tests to demonstrate the presence of reflux or to establish its impact, such as:

- oesophageal pH monitoring
- combined use of multiple intraluminal impedance (MII)
- barium meal and other forms of contrast radiography

- upper gastrointestinal endoscopy and mucosal biopsy
- empirical trials of acid suppression.

c) In addition to the treatments used in primary care, specialists may prescribe drugs to suppress gastric acid production, and some children may also undergo surgery.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will not be covered

a) Children and young people under 18 years of age.

b) Specific consideration will be given to children and young people with neurodevelopmental disorders.

4.1.2 Groups that will not be covered

a) People aged 18 years or over.

b) Children and young people with Barrett's oesophagus.

c) Preterm babies in neonatal intensive care units.

4.2 Healthcare setting

a) All settings where NHS healthcare is provided or commissioned.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a) The natural history of physiological gastro-oesophageal reflux.

b) The distinction between physiological gastro-oesophageal reflux and gastro-oesophageal reflux disease.

c) Indications for investigations.

d) Indications for treatment.

e) Effectiveness of treatments for GOR/GORD:

- positional management
- changes to feeds (including composition and regimens)
- antacids (including products with alginate)
- H2 receptor antagonists
- proton pump inhibitors
- prokinetic agents
- jejunal feeding
- surgery.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

4.3.2 Clinical issues that will not be covered

Clinical areas that will not be covered by the guideline are:

a) Diagnosis and management of Barrett's oesophagus.

b) Reflux associated with pregnancy.

c) The management of conditions associated with GOR, for example, management of obesity.

4.4 Main outcomes

The following outcomes will be assessed where relevant:

a) Health-related quality of life (measured using EQ-5D and/or disease-specific tools, if available).

b) Change in symptoms and signs, for example:

- cessation or reduction (volume or frequency) of regurgitation
- reduction in crying and distress
- improved feeding
- improved nutritional status.

c) Improvement in investigative findings, including:

- healing of erosive oesophagitis.

d) Adverse events of interventions (diagnostic or treatment).

e) Resource use and cost.

4.5 Review questions

Review questions guide a systematic review of the literature. They address only the key clinical issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

a) What clinical features indicate or suggest the presence of GORD? For example:

- duration of persisting overt reflux
- excessive crying or distressed behaviour ('infant colic')

- feeding difficulties or feed refusal.

b) Is there an association between GOR and:

- apnoeic episodes
- respiratory disease
- dental erosion
- sinusitis
- asthma.

c) What are the clinical indications for endoscopy?

d) What are the clinical indications for pH monitoring?

e) What are the clinical indications for impedance monitoring?

f) How effective is positional management in infants with GOR/GORD?

g) How effective are changes to feeding (including composition and regimens) in infants with GOR/GORD?

h) How effective are antacids compared to placebo in the treatment of GOR/GORD?

i) How effective are H2-receptor antagonists compared to placebo in the treatment of GOR/GORD?

j) How effective are proton pump inhibitors compared to placebo and one another in the treatment of GOR/GORD?

k) How effective are H2-receptor antagonists compared to proton pump inhibitors in the treatment of GOR/GORD?

l) How effective are prokinetic agents compared to placebo in the treatment of GOR/GORD?

m) Which, if any, combinations of treatments should be used to alleviate symptoms in children and young people with GOR/GORD?

n) How effective are naso-gastric, gastrostomy and jejunal feeding in the management of GOR/GORD?

o) What are the clinical indications for offering surgery?

p) How effective is surgery in the treatment of GOR/GORD?

4.6 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.7 Status

4.7.1 Scope

This is the consultation draft of the scope. The consultation dates are 21 December 2012 to 25 January 2013.

4.7.2 Timing

The development of the guideline recommendations will begin in April 2013.

NICE guidance (NG1) is available at https://www.nice.org.uk/guidance/ng1

NICE Quality standards: QS112 (published in 2022)

Statement 1 Parents and carers attending postnatal appointments are given information about gastro-oesophageal reflux (GOR) in infants.

Statement 2 Breast-fed infants with frequent regurgitation associated with marked distress have their feeding assessed.

Statement 3 Formula-fed infants with frequent regurgitation associated with marked distress have their symptoms managed using a stepped-care approach.

Statement 4 Infants with frequent regurgitation associated with marked distress have a trial of alginate therapy if first-line management is unsuccessful.

Statement 5 Infants and children are not investigated or treated for gastro-oesophageal reflux disease (GORD) if they have no visible regurgitation and only 1 associated symptom.

Statement 6 Infants and children are not prescribed acid-suppressing drugs if visible regurgitation is an isolated symptom.

Statement 7 Infants, children and young people do not have an upper gastrointestinal (GI) contrast study to diagnose or assess the severity of gastro-oesophageal reflux disease (GORD).

Statement 8 Infants, children and young people are not prescribed domperidone, metoclopramide or erythromycin to manage gastro-oesophageal reflux (GOR) or gastro-oesophageal reflux disease (GORD) without specialist paediatric advice.

Statement 9 Infants, children and young people with vomiting or regurgitation and any 'red flag' symptoms are referred to specialist care with investigations as appropriate.

NICE Quality standards (QS112): statement 9 leading to article V.

Quality statement 9: 'Red flag' symptoms and suggested actions

Quality statement

Infants, children and young people with vomiting or regurgitation and any 'red flag' symptoms are referred to specialist care with investigations as appropriate.

Rationale

Some symptoms that are commonly mistaken for gastro-oesophageal reflux disease (GORD) may be 'red flag' symptoms for other problems. These problems need action to be taken, such as further investigations or specialist referral.

Quality measures

The following measures can be used to assess the quality of care or service provision specified in the statement. They are examples of how the statement can be measured, and can be adapted and used flexibly.

Structure

Evidence of local arrangements to ensure that infants, children and young people with vomiting or regurgitation and any 'red flag' symptoms are further investigated or referred to specialist care with investigations as appropriate.

Data source: Local data collection.

Process

a) Proportion of infants, children and young people with vomiting or regurgitation and any 'red flag' symptoms who had further investigations and specialist referral.

Numerator – number in the denominator who had further investigations and specialist

referral.

Denominator – number of infants, children and young people presenting with vomiting or regurgitation and any 'red flag' symptoms.

Data source: Local data collection.

b) Proportion of infants, children and young people with vomiting or regurgitation and any 'red flag' symptoms who had appropriate investigations and specialist referral.

Numerator – number in the denominator who had appropriate investigations and specialist referral.

Denominator – number of infants, children and young people with vomiting or regurgitation and any 'red flag' symptoms who had further investigations and specialist referral.

Data source: Local data collection.

What the quality statement means for different audiences

Service providers ensure that there are practice arrangements and written clinical protocols to ensure that healthcare professionals look out for 'red flag' symptoms in infants, children and young people with vomiting or regurgitation, and carry out further investigations or arrange specialist referrals depending on the symptoms.

Healthcare professionals (midwives, paediatric nurses or GPs) look out for 'red flag' symptoms in infants, children and young people with vomiting or regurgitation and carry out further investigations or arrange specialist referrals depending on the symptoms.

Commissioners (clinical commissioning groups and NHS England) ensure that services they commission have pathways for healthcare professionals to carry out further investigations or arrange specialist referrals for infants, children and young people with vomiting or regurgitation and 'red flag' symptoms.

Infants, childrenand young people have tests or are referred to a specialist if their symptoms show that they might have another problem than reflux.

Source guidance

Gastro-oesophageal reflux disease in children and young people. NICE guideline NG1 (2015, updated 2019), recommendation 1.1.5 (key priority for implementation)

Definitions of terms used in this quality statement

'Red flag' symptoms and suggested actions

Gastrointestinal symptoms and signs	Possible diagnostic implications	Suggested actions
Frequent, forceful (projectile) vomiting	May suggest hypertrophic pyloric stenosis in infants up to 2 months old	Paediatric surgery referral
Bile–stained (green or yellow–green) vomit	May suggest intestinal obstruction	Paediatric surgery referral
Haematemesis (blood in vomit) with the exception of swallowed blood, for example, following a nose bleed or ingested blood from a cracked nipple in some breast-fed infants	May suggest an important and potentially serious bleed from the oesophagus, stomach or upper gut	Specialist referral
Onset of regurgitation and/or vomiting after 6 months or persisting after 1 year	Late onset suggests a cause other than reflux, for example a urinary tract infection (also see the NICE guideline on urinary tract infection in under 16s) Persistence suggests an alternative diagnosis	Urine microbiology investigation Specialist referral

Gastrointestinal symptoms and signs	Possible diagnostic implications	Suggested actions
Blood in stool	May suggest a variety of conditions, including bacterial gastroenteritis, infant cows' milk protein allergy (also see the NICE guideline on food allergy in under 19s) or an acute surgical condition	Stool microbiology investigation Specialist referral
Abdominal distension, tenderness or palpable mass	May suggest intestinal obstruction or another acute surgical condition	Paediatric surgery referral
Chronic diarrhoea	May suggest cows' milk protein allergy (also see the NICE guideline on food allergy in under 19s)	Specialist referral
Systemic symptoms and signs	**Possible diagnostic implications**	**Suggested actions**
Appearing unwell Fever	May suggest infection (also see the NICE guideline on fever in under 5s)	Clinical assessment and urine microbiology investigation Specialist referral
Dysuria	May suggest urinary tract infection (also see the NICE guideline on urinary tract infection in under 16s)	Clinical assessment and urine microbiology investigation Specialist referral

Gastrointestinal symptoms and signs	Possible diagnostic implications	Suggested actions
Bulging fontanelle	May suggest raised intracranial pressure, for example, due to meningitis (also see the NICE guideline on meningitis (bacterial) and meningococcal septicaemia in under 16s)	Specialist referral
Rapidly increasing head circumference (more than 1 cm per week) Persistent morning headache, and vomiting worse in the morning	May suggest raised intracranial pressure, for example, due to hydrocephalus or a brain tumour	Specialist referral
Altered responsiveness, for example, lethargy or irritability	May suggest an illness such as meningitis (also see the NICE guideline on meningitis (bacterial) and meningococcal septicaemia in under 16s)	Specialist referral
Infants and children with, or at high risk of, atopy	May suggest cows' milk protein allergy (also see the NICE guideline on food allergy in under 19s)	Specialist referral

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<u>Article V: Red Flags Audit</u> using the NICE audit tool (**NG1:** Gastro-oesophageal reflux in children)

Greig RJE, Tighe MP, 2017. G188(P) Gastro-oesophageal reflux disease in children: 'Red flags' clinical audit. *Archives of Disease in Childhood*, 102 (Suppl 1), A75. https://doi.org/10.1136/archdischild-2017-313087.186

What does this paper achieve?

Having participated in the design of the NICE audit tool in Article IV, I undertook this study of UHD patients to ascertain whether the NICE audit tool was suitable in evaluating a paediatric service and helped to improve the robustness of assessment of vomiting children, which may have causes other than GOR. Our cohort included a random sample of 30 paediatric inpatients aged <1 year with a new diagnosis of GORD (April 2015 to April 2016) presenting to a moderate sized DGH (6000 paediatric admissions per annum). The paper and computer notes were reviewed, and the NICE audit tool completed.

The NICE audit tool for GORD was easy to use and helpful in analysing results. Generally, there was good documentation of red flags for GORD: recommendations for change included checking head circumference routinely. There were differing managements in the assessment of projectile vomiting and dysuria in infants: including variable use of routine urine dips and head circumferences in vomiting babies. This was the first published audit using the NICE audit tool for GORD, and first assessment of how a moderate-sized DGH assesses for red-flags in GORD. This was presented at the RCPCH annual meeting (2017) The posters received feedback from a panel of 3 consultant paediatricians and paediatric gastroenterologists and was highly commended. Additional data was presented at the regional paediatric gastroenterology conference (WESPGHAN): in figure 5.3.

How does it contribute to the evidence-base?

On a local level, this audit allowed us to make practical improvements to patient care and was the first to evaluate the NICE audit tool, which was found to be usable and practical. Recommendations included improvements regarding the frequency of head circumference management and testing for UTIs. On a national level, the NICE audit tool allowed the demonstration of implementation of quality standards and also ensured that many babies with conditions other than GOR had appropriate assessments, and were identified early. As part of NICE surveillance, paediatric departments including UHD had to demonstrate compliance with QS112, and so this audit helps validate clinical care, as well as assessing the utility of the audit tool.

What were the next steps?

This work was useful to translate national work to improve care of infants and children with GOR at a local level. I was then able to progress with the Cochrane re-review (Article VI).

usual fasting limit. His blood sugar was 0.8 mmol/L and this was treated appropriately.

Hypoglycaemia screen done during this episode was normal except for low serum Carnitine of 3 umol/L (normal 15–53), suggesting diagnosis of Carnitine deficiency. Further paired serum Carnitine and urine Carnitine ruled out primary Carnitine deficiency with low serum Carnitine of 5 umol/L and free urinary Carnitine of 2 umol/L. His serum Lysine (precursor of Carnitine) level was also low at 75 umol/L (normal level 101–246). This was thought to be consistent with secondary (nutritional) Carnitine deficiency. He was started on enteral carnitine supplementation via gastrostomy with Carnitine level normalising (49 umol/L)within two weeks.

Discussion and Conclusion Carnitine plays a key role in the beta oxidation of fatty acids and its deficiency can lead to poor fasting tolerance. Endogenous Carnitine synthesis depends on its precursor lysine and is insufficient in children on minimal enteral nutrition. Most solutions for parenteral nutrition do not contain Carnitine. This makes PN dependent patients prone to develop nutritional Carnitine deficiency especially with minimal enteral feeding tolerance.

Enteral supplementation of Carnitine normalised Carnitine level in our patient within two weeks and also improved fasting tolerance when prospectively monitored. He tolerated Carnitine supplementation well and is currently monitored for serum Carnitine levels regularly.

We are currently screening our cohort of intestinal failure patients on PN for serum Carnitine levels and trying to co-relate this with their enteral intake. Low Caritine level in these patients may suggest routine screening for serum Carnitine in these patients to actively look for development of nutritional Carnitine deficiency.

G186(P) THE SWIM DRINK STUDY: A RANDOMISED CONTROLLED TRIAL OF DURING-EXERCISE REHYDRATION TO ENHANCE PERFORMANCE

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10.1136/archdischild-2017-313087.185

Sports drinks are widely used with the aim of improving hydration and performance, but the supporting evidence for claims of enhanced performance has not been of high quality. There are however clear health risks from overhydration.

Aims To answer 3 questions: Does drinking during swimming Improve performance? Is isotonic sports drink better than water? Are there idiosyncratic responses in individual swimmers?

Method 19 competitive swimmers aged 11–17 drank *ad-libitum* sports drink (x3 sessions), Water (x3 sessions) or no drink (x6 sessions) in the course of twelve 75 min training sessions, each followed by ten 100m maximum effort freestyle sprints at 3 min intervals. Electronic timing equipment recorded times for the middle 50m of each sprint. Each athlete used the rehydration regimes in an individually randomised order and was blinded to drink allocation. To blind the observers a block randomised analysis subset of data from 8 sessions was selected after data collection. Percentage dehydration was determined from weight measurements. Repeated measures t-tests assessed primary outcome measures.

Results The analysis data comprised 1118 swims. Sprint times after not drinking were 0.027 s faster than after drinking (95% CI 0.186s faster to 0.113s slower). Times after drinking water were 0.151s faster than after sports drink (95% CI 0.309s faster to 0.002s slower) There was no performance difference between drinking regimes. Mean (SEM) 50 m time for no drink swims was 38.077 (0.128)s and 38.105 (0.131)s for drink swims, p=0.701. Mean 50m times were 38.031 (0.184)s for drinking water and 38.182 (0.186)s for drinking sports drink, p=0.073. No individual athlete had progressive performance improvement with drinking water and sports drink. The exercise generated 0.42% dehydration which was over-corrected by drinking to +0.27%.

Conclusions Drinking sports drink or water over 105 min of sustained effort swimming (typically 3300 to 4200m) has no benefit on swimming performance in a non-elite athlete population. Sports drinks can be considered as sugar sweetened beverages.

G187(P) ABSTRACT WITHDRAWN

G188(P) GASTRO-OESOPHAGEAL REFLUX DISEASE IN CHILDREN: 'RED FLAGS' CLINICAL AUDIT

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10.1136/archdischild-2017-313087.186

Aims 1) To determine whether infants presenting with a new diagnosis of regurgitation plus 'red flag' symptoms are appropriately investigated and managed in accordance with NICE NG1 guidelines and NICE quality standards. 2) To ascertain if the NICE audit tool is useful in clinical practice.

Method Cohort consisted of a random sample of 30 paediatric inpatients aged <1 year with a new diagnosis of GORD (April 2015 to April 2016) presenting to a moderate sized DGH (6000 paediatric admissions per annum). Paper and computer notes reviewed.

Results

Abstract G188(P) Table 1

Red Flags	Results
1. Projectile vomiting.	67% non-projectile. **27% projectile – none referred to surgeons.** **6% not documented.**
2. Bile stained vomit.	94% non-bilious. **6% colour not documented.**
3. Haematemesis	**3% - streaks of blood in vomit (Mallory Weiss) – local OPD follow-up arranged.**
4. Onset of regurgitation and/or vomiting>6 months old or persisting>1 year old.	**0%**
5. Blood in stool.	88% no blood in stool. **6% colour not documented.** **6% bowel habit not documented.**
6. Abdominal distension, tenderness or palpable mass.	97% normal abdomen. **3% distended abdomen – admitted but not referred to surgeons.**

7. Chronic diarrhoea.	94% normal stool. **6% bowel habit not documented.**
8. Appearing unwell/fever.	**0%**
9. Dysuria.	10% no dysuria. **90% no documentation (50% urinalysis performed).**
10. Bulging fontanelle.	94% normal fontanelle. **6% examination of fontanelle not documented.**
11. Rapidly increasing head circumference/ morning headache and vomiting worse in the morning.	**0% head circumference documented.** **0% documentation of headache/morning vomiting.**
12. Altered responsiveness.	**88% normal responsiveness.** **12% altered consciousness – 6% discharged after observation, 6% admitted overnight for further investigation/observation.**
13. Infants and children with/high risk of atopy.	**20% high risk of atopy – 10% outpatient clinic follow-up.**

Conclusions The NICE audit tool for GORD was easy to use and helpful in analysing results. Generally there was good documentation of red flags for GORD: recommendations for change included checking head circumference routinely. There were differing managements in the assessment of projectile vomiting and dysuria in infants which is further discussed. This is the first published audit using the NICE audit tool for GORD, and first assessment of how a moderate-sized DGH looks for red-flags in GORD.

G189(P) DEVELOPMENT OF AN ANNUAL ENDOSCOPY AUDIT PLAN USING MEASURES IN THE P-GRS(PAEDIATRIC GLOBAL RATING SCALE FOR ENDOSCOPY) IN A TERTIARY PAEDIATRIC ENDOSCOPY SERVICE TO FACILITATE QUALITY IMPROVEMENT

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10.1136/archdischild-2017-313087.187

Background A paediatric global ratings scale for endoscopy(P-GRS) is currently being piloted nationally, and this will provide a quality and safety framework for service improvement in Paediatric endoscopy units. An annual endoscopy audit plan is essential to help units identify that they are meeting the required measures and identifying areas of improvement.
Aim To develop an annual endoscopy audit plan to facilitate quality improvement in the endoscopy service in a tertiary centre.
Subjects and Methods A retrospective audit of all procedures done by the Paediatric gastroenterology team during 1/10/16–15/10/16 was done. We used measures from the P-GRS to develop standards for the audit plan. Letters of correspondence, consent, operation notes, anaesthetic charts, nursing documentation and biopsy reports were reviewed. Patient feedback questionnaires were also included.
Results 46 patients(age range 8 months to 17 years) had endoscopies during the study period. 78%(36) of these had elective procedures. Out of the 22%(10) who had non-elective procedures, 18%(8) were urgent and 4%(2) were emergency procedures. 100% of procedures had a clearly documented indication, and had completed consent forms, all of which were 2-stage. The procedure completion rate was 100%, and bowel preparation was adequate in 98%. One patient developed post-operative oxygen requirement; otherwise there were no other post-procedure complications. There were no deaths within 30 days of the procedure. Patient feedback questionnaires showed 78% of respondents rated their overall endoscopy experience as 'excellent' or 'good'. One patient had an endoscopic assessment for Upper GI bleeding during the audit period. This patient was risk assessed and had an endoscopic assessment appropriately.
Summary and conclusion The audit showed that our Unit is performing well against a number of the quality and safety measures in the P-GRS. Areas that require improvement include developing procedure-specific after care patient information leaflets, better documentation on patients' anaesthetic needs, and procuring an endoscopy reporting system(ERS). This also highlighted the need for close collaboration with other stakeholders such as anaesthetics and theatre admissions staff to share findings and implement change.

G190(P) PATIENT AND FAMILY EXPERIENCE OF ENDOSCOPY AT A TERTIARY PAEDIATRIC GASTROENTEROLOGY UNIT

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10.1136/archdischild-2017-313087.188

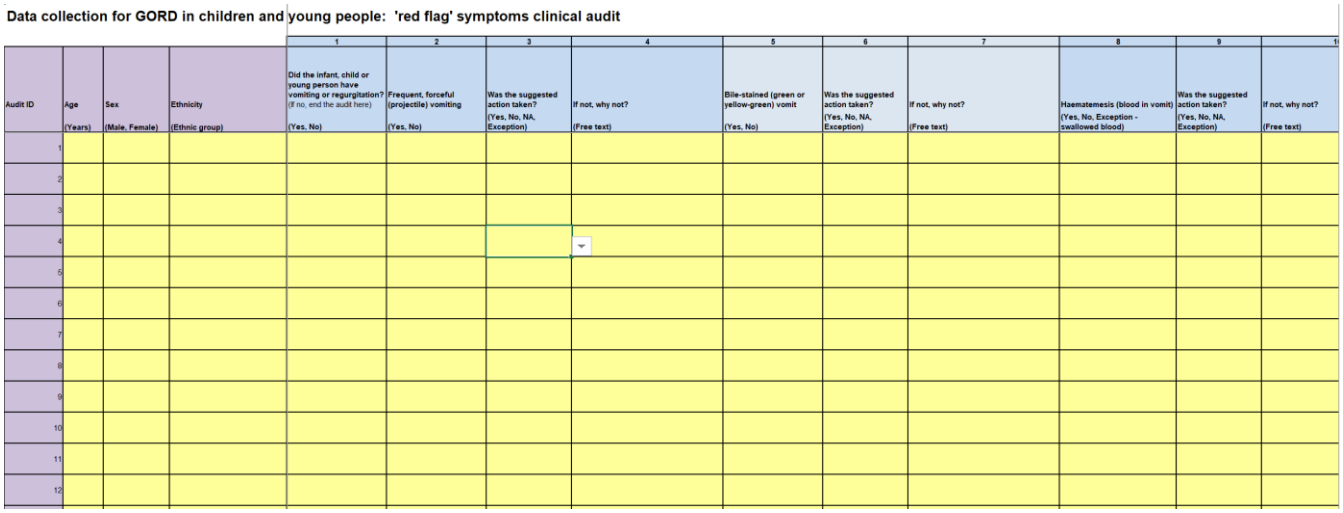
Background A paediatric global ratings scale for endoscopy(P-GRS) is currently being piloted and this will provide a quality and safety framework for service improvement in Paediatric endoscopy units. An important aspect of this is patient involvement and an annual survey on the patient's experience.
Aim A patient/parent feedback survey was used to evaluate the endoscopy experience for our patients and family, as part of an annual endoscopy audit plan.
Method A questionnaire that has previously been approved by our clinical governance team in 2013 was used. Questionnaires were distributed to patients and parents over a 3 week period (24/10/16–11/11/16).
Results 28 questionnaires were returned, including an even spread between age groups. The results are illustrated in Table 1.

Abstract G190(P) Table 1: Results of patient/parent questionnaire

Preparation before procedure	Yes (%)	No (%)	Not recorded (%)
Was the procedure explained during consent?	100	0	0
Did you feel you had opportunity to ask questions?	100	0	0
Were you given information leaflets about the procedure?	75	18	7
In those who had colonoscopies, were you explained the importance of bowel preparation?	100	0	0
Were you informed of waiting time in advance?	71	25	4
Did you have an opportunity to discuss options with the Anaesthetist?	82	11	7
Overall preparation rated as 'excellent' or 'good'	79	14	7
Experience post procedure			
Did the patient experience post-operative pain?	29	61	10
Did the patient experience post-operative bleeding?	4	86	10
Were the endoscopy findings discussed and explained?	71	11	17
Were follow up arrangements given at discharge?	71	4	25
Was advice given about complications after discharge?	46	7	47

Figure 5.2: NICE Audit tool: editable and freely downloadable Excel spreadsheet:

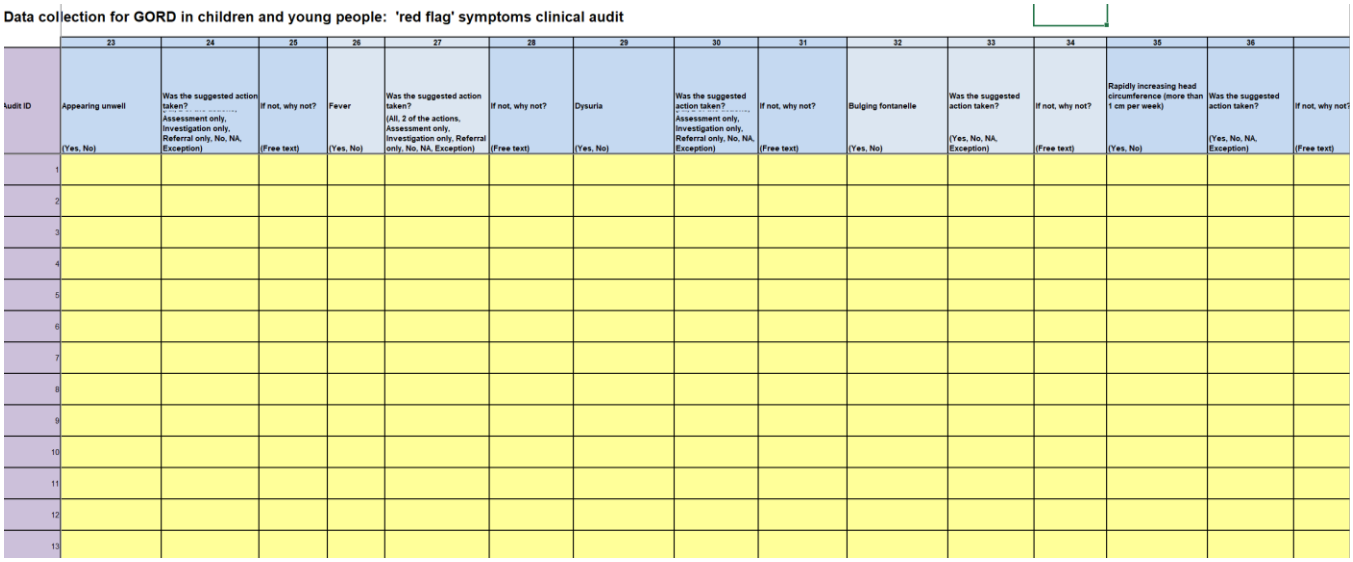
a) Gastrointestinal red flags (screenshot)



Data collection for GORD in children and young people: 'red flag' symptoms clinical audit

	1	2	3	4	5	6	7	8	9	1
Audit ID	Age (Years)	Sex (Male, Female)	Ethnicity (Ethnic group)	Did the infant, child or young person have vomiting or regurgitation? (If no, end the audit here) (Yes, No)	Frequent, forceful (projectile) vomiting (Yes, No)	Was the suggested action taken? (Yes, No, NA, Exception)	If not, why not? (Free text)	Bile-stained (green or yellow-green) vomit (Yes, No)	Was the suggested action taken? (Yes, No, NA, Exception)	If not, why not? (Free text)	Haematemesis (blood in vomit) (Yes, No, Exception - swallowed blood)	Was the suggested action taken? (Yes, No, NA, Exception)	If not, why not? (Free text)
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													

b) Systemic red flags (screenshot)



Data collection for GORD in children and young people: 'red flag' symptoms clinical audit

	23	24	25	26	27	28	29	30	31	32	33	34	35	36	
udit ID	Appearing unwell (Yes, No)	Was the suggested action taken? ... (Assesment only, Investigation only, Referral only, No, NA, Exception)	If not, why not? (Free text)	Fever (Yes, No)	Was the suggested action taken? (All, 2 of the actions, Assessment only, Investigation only, Referral only, No, NA, Exception)	If not, why not? (Free text)	Dysuria (Yes, No)	Was the suggested action taken? ... (Assesment only, Investigation only, Referral only, No, NA, Exception)	If not, why not? (Free text)	Bulging fontanelle (Yes, No)	Was the suggested action taken? (Yes, No, NA, Exception)	If not, why not? (Free text)	Rapidly increasing head circumference (more than 1 cm per week) (Yes, No)	Was the suggested action taken? (Yes, No, NA, Exception)	If not, why not? (Free text)
1															
2															
3															
4															
5															
6															
7															
8															
9															
10															
11															
12															
13															

c) Audit report (autopopulates: screenshot)

GORD in children and young people: 'red flag' symptoms clinical audit report

Project title
GORD in children and young people: 'red flag' symptoms clinical audit.

Aim
The aim of this clinical audit is to ensure that infants, children and young people with vomiting or regurgitation and 'red flag' symptoms suggestive of disorders other than GORD have been followed up appropriately.

Audit standards
The audit standards are based on Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people. NICE clinical guideline NG1 (2015).

Sample
The audit sample includes infants, children and young people aged under 18 years who present with vomiting and regurgitation and 'red flag' symptoms.

Results

Audit N= 0 **Re-audit N= 0**

Audit standards	Audit results		Re-audit results	
1. Where 'red flag' symptoms are present that suggest disorders other than GORD, along with vomiting or regurgitation, they are investigated and/or the infant, child or young person is referred, according to the table below.	Number identified	Number where suggested action was taken	Number identified	Number where suggested action was taken
Gastrointestinal				
Frequent, forceful (projectile) vomiting	0	0	0	0
Bile-stained (green or yellow-green) vomit	0	0	0	0
Haematemesis (blood in vomit) with the exception of swallowed blood, for example, following a nose bleed or ingested blood from a cracked nipple in some breast fed infants	0	0	0	0
Onset of regurgitation and/or vomiting after 6 months old or persisting after 1 year old (both actions)	0	0	0	0
• Urine microbiology investigation only		0		0

d) Action plan (screenshot)

Action plan for GORD in children and young people: 'red flag' symptoms clinical audit

Action plan lead	Name:	Title:	Contact details:

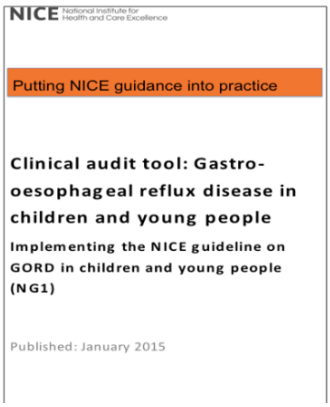
In 'Actions required', specifically state what needs to be done to achieve the recommendations. Include all updates to the action plan in the 'Comments' section.

Recommendation	Actions required (specify 'None', if none required)	Deadline for action (dd/mm/yyyy)	Person responsible	Progress (Provide examples of actions practices etc.)

When making improvements to practice, you may like to use the tools developed by NICE to help implement its guideline on GORD in children and young people

NICE has adapted the action plan template produced by the Healthcare Quality Improvement Partnership (HQIP) in their template clinical audit report.

Figure 5.3: NICE audit results presented to WESPGHAN as Powerpoint.


NICE National Institute for Health and Care Excellence

Putting NICE guidance into practice

Clinical audit tool: Gastro-oesophageal reflux disease in children and young people

Implementing the NICE guideline on GORD in children and young people (NG1)

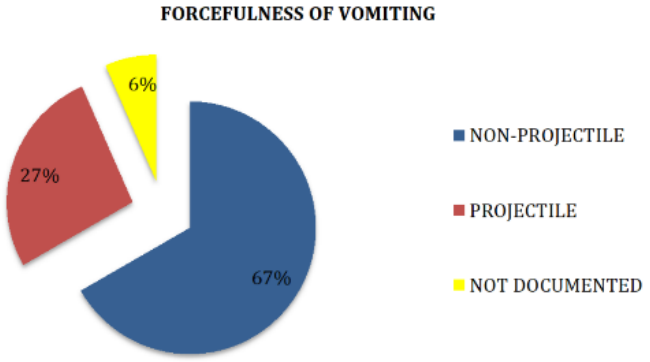
Published: January 2015

Demographics of 30 patients

- Age range 4 days to 6 months. Mean 6.8 weeks.
- Gender 15 males, 15 females.
- Ethnicity
  - White British 22
  - White Irish 1
  - Any other white background 2
  - Mixed White and black caribbean 1
  - Any other mixed background 1
  - Asian or Asian British: Bangladeshi 1
  - Any other asian background 1
  - Chinese 1

Results

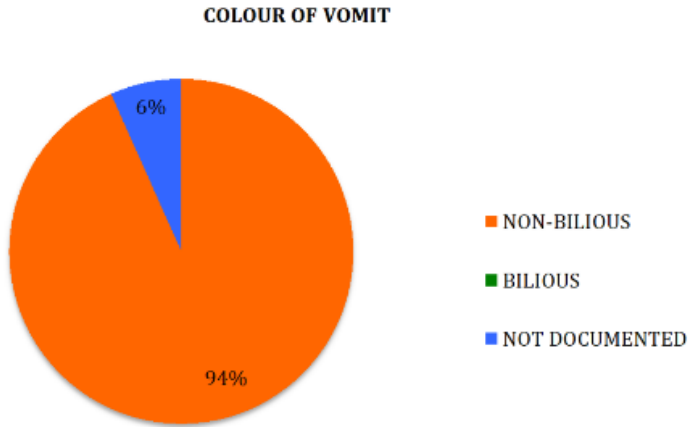
GI symptoms and signs	Possible diagnostic implications	Suggested actions
1. Frequent, forceful (projectile) vomiting.	May suggest hypertrophic pyloric stenosis (infants up to 2 months old).	Paediatric surgery referral.



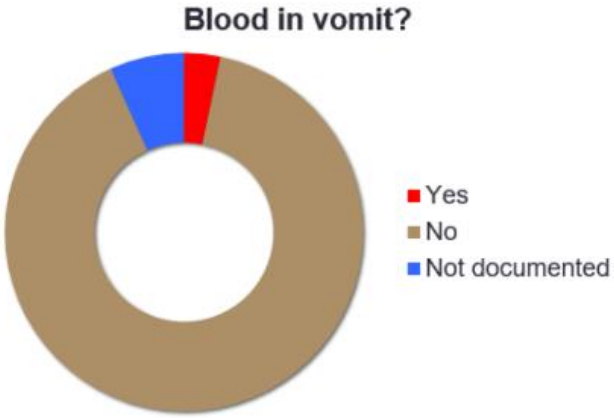
8/30 documented to have projectile vomiting:
1/8 thought to be overfeeding, sent home on Gaviscon. Represented 2 weeks later with similar presentation & admitted overnight for observation. No vomiting witnessed so discharged on Ranitidine & Gaviscon.
1/8 no vomiting witnessed during assessment, given safety net advice & OA 48 hours, asked to f/u with GP.
1/8 period of observation on Elmwood, senior thought not projectile but arranged OP USS within 72 hours – normal.
3/8 admitted for period of observation overnight. No further vomiting, 1 had normal venous gas, 1 discharged with OPC f/u.
2/8 venous gas performed – normal, sent home with safety net advice.

NB no referrals to paediatric surgeons.
2/30 no documentation of forcefulness of vomiting.

2. Bile stained (green or yellow-green) vomit.	May suggest intestinal obstruction.	Paediatric surgery referral.



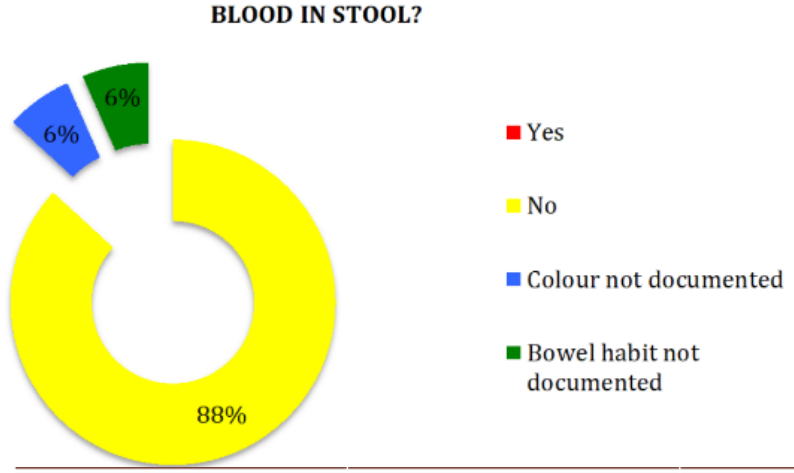
3. Haematemesis (blood in vomit) with the exception of swallowed blood.	May suggest potentially serious bleed from oesophagus, stomach or upper gut.	Specialist referral.



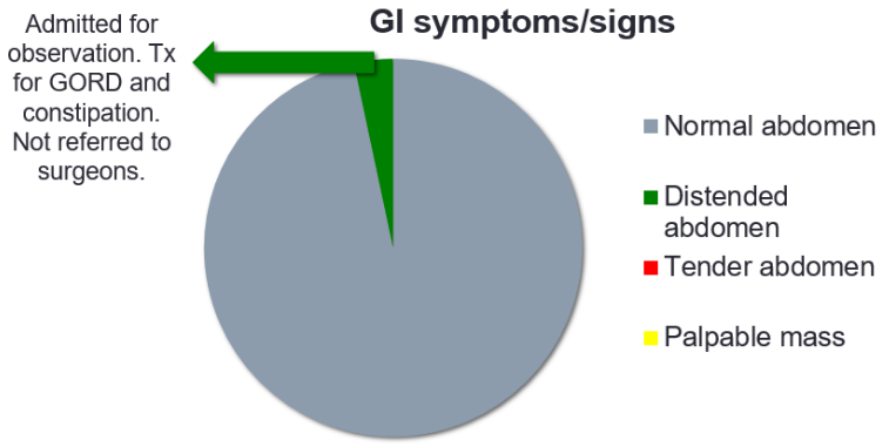
4. Onset of regurgitation and/or vomiting after 6 months old or persisting after 1 year old.	Late onset suggests cause other than reflux, e.g. UTI. Persistence suggests alternative diagnosis.	Urine microbiology Ix. Specialist referral.

0/30 onset of regurgitation/vomiting after 6 months or persisting after 1 year.

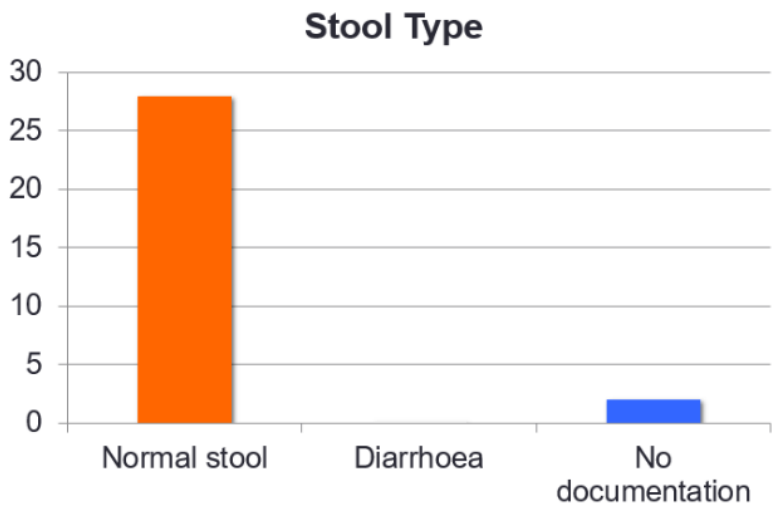
5. Blood in stool.	May suggest variety of conditions, e.g. bacterial gastroenteritis, infant CMPA or acute surgical condition.	Stool microbiology Ix. Specialist referral.



6. Abdominal distension, tenderness or palpable mass.	May suggest intestinal obstruction or another acute surgical condition.	Paediatric surgery referral.



7. Chronic diarrhoea.	May suggest CMPA.	Specialist referral.



8. Appearing unwell/fever.	May suggest infection.	Clinical assessment and urine microbiology Ix. Specialist referral.

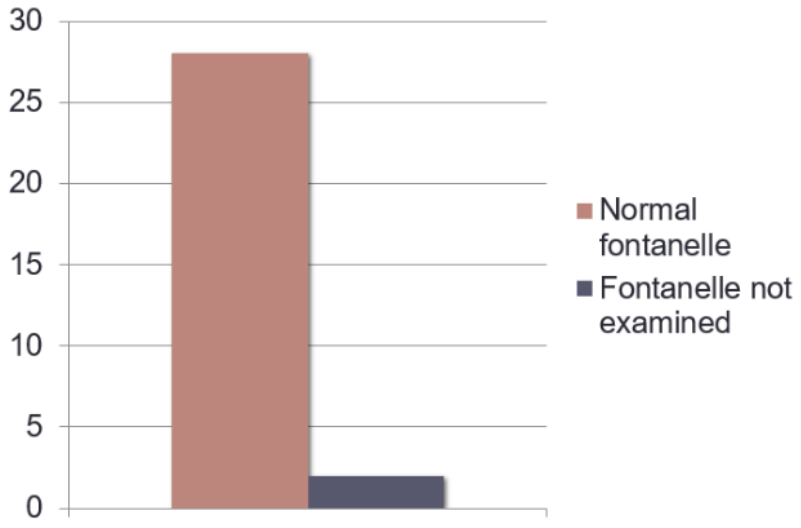
0/30 appeared unwell/pyrexial.

9. Dysuria.	May suggest UTI	Clinical assessment and urine microbiology Ix. Specialist referral.

3/30 documented as no dysuria.
27/30 no documentation ?due to age (unable to comment)
13/27 no urinalysis performed (well, afebrile).

14/27 had urine dipstick: 13/14 NAD,
1/14 2+ leucocytes, 1+ protein.

10. Bulging fontanelle.	May suggest raised ICP, e.g. due to meningitis.	Specialist referral.



11. Rapidly increasing head circumference (more than 1 cm per week). Persistent morning headache & vomiting worse in the morning.	May suggest rasied ICP, e.g. due to hydrocephalus or brain tumour.	Specialist referral.

0/30 had head circumference documented in notes.

0/30 had persistent morning headache and/or vomiting worse in morning
?unable to comment on headache due to age.

12. Altered responsiveness, e.g. lethargy or irritability.	May suggest an illness such as meningitis.	Specialist referral.

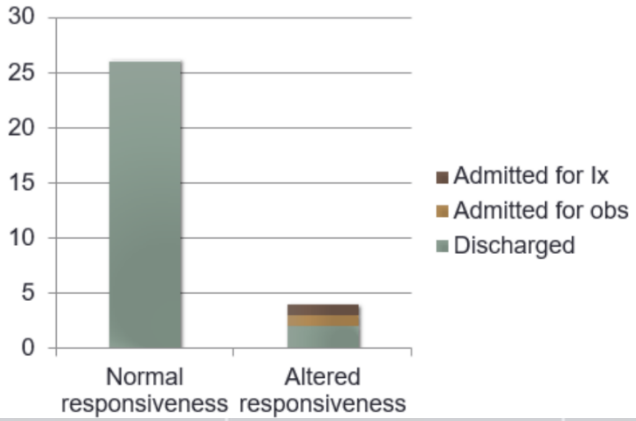
4/30 has altered responsiveness

1 lethargic but rousable, admitted for bloods and NGT feeds. Commenced Ranitidine, Domperidone and Omeprazole.

1 admitted for observation overnight as 'unsettled'.

1 floppy episode at home associated with apnoea, no episodes in hospital and normal oxygen saturations so discharged home.

1 floppy episode for a few seconds following large milky vomit, back to normal when seen by paediatricians, not admitted.



13. Infants and children with/high risk of atopy.	May suggest CMPA.	Specialist referral.

6/30 infants with/high risk of atopy:

2 admitted overnight for observation – 1 seen by dietitian and further Ix arranged, 1 sent home once tolerating feeds.

3 arranged f/u in OPC – 1 had bloods incl RAST food panel prior to clinic.

1 Fhx of CMPI & nut allergy, parents advised low threshold for cows milk free formula if no improvement on Omeprazole.

Summary

- Generally fairly good documentation of red flags in notes when assessing infants with vomiting/regurgitation.
- Areas for improvement as previously mentioned.
- Need to highlight NICE guideline NG1 to paediatric team.
  - Aim to produce posters and send out memo to team.
  - Re-audit following education on red flags.

Article VI: Cochrane review (2023): Pharmacological treatment of children with gastro-oesophageal reflux

Tighe MP, Andrews E, Liddicoat I, Afzal NA, Hayen A, Beattie RM, 2023. Pharmacological treatment of gastro-oesophageal reflux in children. *Cochrane Database of Systematic Reviews*, 8 (8), CD008550. https://doi.org/10.1002/14651858.CD008550.pub3

What does this paper achieve?

This article allowed newer papers to be evaluated, as well as the newer Cochrane processes to be integrated (e.g. GRADE criteria, MECIR recommendations and independent data extraction). This allowed a broader evidence-base to be considered, in the light of a slight shift in the diagnostic definition of GORD vs GOR, and a more robust appraisal of the evidence.

How did this differ from Article III?

This review was separated by 6 years from the previous Cochrane review and was significantly different, with different software platforms, independent extraction of relevant data, use of GRADE criteria to assess the quality of evidence, and adoption of MECIR recommendations. More detailed methodology is contained within the article. New evidence on other medicines were included, such as quince syrup, which is thought to have ulcer-healing properties and increase the tone of the lower oesophageal sphincter (reducing GORD) as well as new alginate formulations such as Refluxsan Nipio and Gastrotuss. This review was more precise regarding the age cut-offs for subgroup analysis. As infants (defined as children under the age of 12months) have a trend towards symptom improvement after the age of 12 months, I focused more in Article VI data extraction on only including data on infants, rather than allowing some data using children between 12-18months in this subgroup analysis by considering them as part of an infant GOR continuum or spectrum, as the Cochrane editorial team was clear regarding the importance of this cut-off, which may however mean that the evidence-base for 1-2year olds is affected.

Differences between the Article VI protocol and previous review protocol included:

The data collection and analysis: Review Manager 5.4 and RevMan Web was used for data collection and analysis, updated from RevMan 5.1. GRADEPro was a new software package to evaluate the certainty of evidence.

For the selection of studies: Reprints of articles were added to the reference list of included studies but not separately considered if they contained no new data. In the previous review articles

reprints were discounted. Studies that are only in abstract form, or were only identified in the ISRCTN register were entered into ‘Characteristics of studies awaiting classification’.

The participants were slightly altered compared to the previous review as the definition of GORD changed in 2018 to 'GOR associated with bothersome symptoms or complications' NASPGHAN-ESPGHAN guidelines 2018.

For outcomes: The outcome of 'pH/impedance studies' to 'pH/impedance indices' was redesignated to account for the range of pH/impedance measurements described in the available literature.

For data extraction and management: Three review authors, led by myself independently extracted study data using a robust data extraction form and checked and entered the data into RevMan 5.4/RevMan Web; the data was analysed and any discrepancies highlighted. In the previous review two review authors extracted and entered study data onto RevMan 5.1.

For measures of treatment effect: Continuous data (e.g. reflux index) were extracted for summary data: means and standard deviations were used to derive a standardised mean difference (SMD) with a 95% confidence interval using a fixed-effect model. The latest NASPGHAN/ESPGHAN guidelines (NASPGHAN-ESPGHAN guidelines 2018) do not define normal values for pH-metry and pH-impedance and the values of reflux index mentioned in the previous review (>10% in infants and >4% in children >12 months) have been modified here with a judgement regarding improvement/non-improvement. Dichotomous data such as improvement/non-improvement in endoscopic appearance produced outcome data that is presented as a risk ratio, and from which 'numbers needed to treat for an additional beneficial outcome' data were derived. In the previous review, reported data rather than extracting summary data were used.

Unit of analysis issues were considered related to multiple observations for the same outcome (e.g. repeated pH/impedance measurements); and would consult the Cochrane Gut group if clarification was required. If multi-arm studies are included, multiple intervention groups were analysed in an appropriate way to prevent arbitrary omission of relevant groups or double-counting of participants. In the previous review: there was some overlap in reported data e.g. according to age criteria: corrected in this review.

In dealing with missing data, trial authors or sponsors of studies published from 2014 to 2021 were contacted to provide missing data, or clarification, where there was uncertainty about the specifics of a trial that are pertinent to analysis, could not be resolved. In the previous review: contacting authors was limited to studies less than ten years old.

Data synthesis: Studies were unable to be combined meaningfully, due to heterogeneity of studies in terms of outcomes, comparisons, and populations. For continuous measurements, weighted mean differences were intended for pooled results from studies where a common measurement scale was used, and where different measurement scales have been employed, standardised mean differences would be pooled. Instead, difference in means and 95% confidence intervals for individual agents and summary effects are presented in order: Population > Comparison > Outcome following updated guidance in the current Cochrane review, and guidance provided based on individual treatments to give better focus for decision-makers, and given the individual study differences and heterogeneity in study design. This differs from the previous review.
Had a meta-analysis been performed, a sensitivity analysis using RevMan Web was intended to ascertain whether any decisions regarding thresholds influence result reporting (e.g. choosing age thresholds at 12months influencing meta-analysis robustness) and integrate the findings into the results and conclusions. This was not considered in the previous review. However, a meta-analysis was not possible and sensitivity analysis not required.

In the summary of findings and assessment of the certainty of the evidence: two authors led by myself used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence for each outcome, and to draw conclusions about the certainty of evidence within the text of the review independently and disagreements reconciled by discussion, with all authors involved if a disagreement could not be reconciled. Two authors then reviewed the GRADE considerations in assessing the certainty of evidence and integrated this into the SoF tables using GRADEPro. The summary of findings tables distinguish results by age (infants and children aged 1-16), then comparison, and the evidence is presented by outcome measures (symptoms, adverse events, pH/impedance indices and endoscopic findings) (MECIR PR40) with clear rationales given where evidence was down or upgraded according to GRADE criteria including if the risk of bias was so great the evidence needed downgrading by two steps.

Differences in the literature search in this update version: the CRG Specialised Register was not searched as it was not updated since the previous version and the included RCTs are included in Cochrane CENTRAL that was also searched. The Centralised Information Service for Complementary Medicine (CISCOM) was not searched again. This database did not yield additional eligible studies for our review in the previous version, and it was not available to reviewers for this update. In the previous version, I handsearched published abstracts from conference proceedings. For this update, handsearching proceedings from conferences that took place after 2014 was not needed, because

EMBASE now includes proceedings from these conferences (2000 onwards); these abstracts were searched electronically through our main electronic search. In the previous version, the clinical trial register mRCT was searched. In this updated version, WHO ITCPR and clinicaltrials.gov were searched, as suggested by MECIR. The search strategies were revisited with Cochrane guidance and some new terms to reflect the current practice of treatment were added in the updated search.

Search methods: For the previous version of this review, up to May 2014 was searched. In this update, relevant published trials were identified in the Cochrane Central Register of Controlled Trials (*CENTRAL*), MEDLINE, Embase and Web of Science up to 17 September 2022, as well as ongoing trials in the clinical trial registries. I also contacted experts in the field and searched references of trials and reviews for any additional trials.

Selection criteria: I was one of two review authors who reviewed abstracts and selected relevant RCTs for all participants (birth-16 years) receiving pharmacological treatment for GOR. Analyses in children by age were grouped: aged less than 12 months (infants), in children aged 12 months to 16 years, as well as subgroups: premature infants and children with neurological impairment.

Data collection and analysis: Four review authors critically appraised the trials and data collected, including summary statistics and risk of bias. Suitable outcome data were analysed using RevMan 5.4, GRADEPro and RevMan Web, according to GRADE criteria.

How does it contribute to the evidence-base?

107 papers were identified that met our inclusion criteria and assessed them in full-text form, with 36 suitable RCTs assessing 2251 patients (12 new included studies, and 24 from the first review) suitable for inclusion. 2 studies are awaiting classification. Summary data was extracted from 14 RCTs, with the remaining studies having insufficient data for extraction. The results are presented by patient age then comparison (class of medication) then outcome and contained within the article. A high proportion of infants were found to have physiological GOR, with very low-certainty evidence about treatment efficacy regarding symptom improvements, changes in pH/impedance indices and no summary data for endoscopic changes. Medications may or may not provide additional benefit (based on very low-certainty evidence), for infants whose symptoms remain bothersome despite non-medical interventions or parental reassurance. The evidence-base includes treatments for breast- and formula-fed infants with GOR/GORD but this was not assessed as a subgroup for analysis. If a medication is required, there is no clear evidence based on summary data for

omeprazole, esomeprazole (in neonates), H_2 antagonists and alginates for symptom improvements (very low-certainty evidence); and further studies with longer follow-ups are needed.

In older children with GORD, in studies with summary data extracted, there is very low-certainty evidence that PPIs (rabeprazole and pantoprazole), may or may not improve GORD outcomes. No robust data exists for H_2 antagonists, domperidone or erythromycin.

Further evidence in all areas, including subgroups (preterm babies, and children with neurodisabilities) is required.

Article VI: Pharmacological treatment of gastro-oesophageal reflux in children (2022)

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Pharmacological treatment of gastro-oesophageal reflux in children (Review)

Tighe MP, Andrews E, Liddicoat I, Afzal NA, Hayen A, Beattie RM

Tighe MP, Andrews E, Liddicoat I, Afzal NA, Hayen A, Beattie RM.
Pharmacological treatment of gastro-oesophageal reflux in children.
Cochrane Database of Systematic Reviews 2023, Issue 8. Art. No.: CD008550.
DOI: 10.1002/14651858.CD008550.pub3.

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[Intervention Review]

Pharmacological treatment of gastro-oesophageal reflux in children

Mark P Tighe[1], Edward Andrews[1], Iona Liddicoat[1], Nadeem A Afzal[2], Andrew Hayen[3], R Mark Beattie[4]

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Contact: Mark P Tighe, mpt195@hotmail.com.

Editorial group: Cochrane Gut Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 8, 2023.

Citation: Tighe MP, Andrews E, Liddicoat I, Afzal NA, Hayen A, Beattie RM. Pharmacological treatment of gastro-oesophageal reflux in children. *Cochrane Database of Systematic Reviews* 2023, Issue 8. Art. No.: CD008550. DOI: 10.1002/14651858.CD008550.pub3.

ABSTRACT

Background

Gastro-oesophageal reflux (GOR) is characterised by the regurgitation of gastric contents into the oesophagus. GOR is a common presentation in infancy, both in primary and secondary care, affecting approximately 50% of infants under three months old. The natural history of GOR in infancy is generally of a self-limiting condition that improves with age, but older children and children with co-existing medical conditions can have more protracted symptoms. The distinction between gastro-oesophageal reflux disease (GORD) and GOR is debated. Current National Institute of Health and Care Excellence (NICE) guidelines define GORD as GOR causing symptoms severe enough to merit treatment. This is an update of a review first published in 2014.

Objectives

To assess the effects of pharmacological treatments for GOR in infants and children.

Search methods

For this update, we searched CENTRAL, MEDLINE, Embase, and Web of Science up to 17 September 2022. We also searched for ongoing trials in clinical trials registries, contacted experts in the field, and searched the reference lists of trials and reviews for any additional trials.

Selection criteria

We included randomised controlled trials (RCTs) that compared any currently-available pharmacological treatment for GOR in children with placebo or another medication. We excluded studies assessing dietary management of GORD and studies of thickened feeds. We included studies in infants and children up to 16 years old.

Data collection and analysis

We used standard methodology expected by Cochrane.

Main results

We included 36 RCTs involving 2251 children and infants. We were able to extract summary data from 14 RCTs; the remaining trials had insufficient data for extraction. We were unable to pool results in a meta-analysis due to methodological differences in the included studies (including heterogeneous outcomes, study populations, and study design).

We present the results in two groups by age: infants up to 12 months old, and children aged 12 months to 16 years old.

Infants

Omeprazole versus placebo: there is no clear effect on symptoms from omeprazole. One study (30 infants; very low-certainty evidence) showed cry/fuss time in infants aged three to 12 months had altered from 246 ± 105 minutes/day at baseline (mean +/- standard deviation (SD)) to 191 ± 120 minutes/day in the omeprazole group and from 287 ± 132 minutes/day to 201 ± 100 minutes/day in the placebo group (mean difference (MD) 10 minutes/day lower (95% confidence interval (CI) -89.1 to 69.1)). The reflux index changed in the omeprazole group from 9.9 ± 5.8% in 24 hours to 1.0 ± 1.3% and in the placebo group from 7.2 ± 6.0% to 5.3 ± 4.9% in 24 hours (MD 7% lower, 95% CI -4.7 to -9.3).

Omeprazole versus ranitidine: one study (76 infants; very low-certainty evidence) showed omeprazole may or may not provide symptomatic benefit equivalent to ranitidine. Symptom scores in the omeprazole group changed from 51.9 ± 5.4 to 2.4 ± 1.2, and in the ranitidine group from 47 ± 5.6 to 2.5 ± 0.6 after two weeks: MD -4.97 (95% CI -7.33 to -2.61).

Esomeprazole versus placebo: esomeprazole appeared to show no additional reduction in the number of GORD symptoms compared to placebo (1 study, 52 neonates; very low-certainty evidence): both the esomeprazole group (184.7 ± 78.5 to 156.7 ± 75.1) and placebo group (183.1 ± 77.5 to 158.3 ± 75.9) improved: MD -3.2 (95% CI -4.6 to -1.8).

Children

Proton pump inhibitors (PPIs) at different doses may provide little to no symptomatic and endoscopic benefit.

Rabeprazole given at different doses (0.5 mg/kg and 1 mg/kg) may provide similar symptom improvement (127 children in total; very low-certainty evidence). In the lower-dose group (0.5 mg/kg), symptom scores improved in both a low-weight group of children (< 15 kg) (mean -10.6 ± SD 11.13) and a high-weight group of children (> 15 kg) (mean -13.6 ± 13.1). In the higher-dose groups (1 mg/kg), scores improved in the low-weight (-9 ± 11.2) and higher-weight groups (-8.3 ± 9.2). For the higher-weight group, symptom score mean difference between the two different dosing regimens was 2.3 (95% CI -2 to 6.6), and for the lower-weight group, symptom score MD was 4.6 (95% CI -2.9 to 12).

Pantoprazole: pantoprazole may or may not improve symptom scores at 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg pantoprazole in children aged one to five years by week eight, with no difference between 0.3 mg/kg and 1.2 mg/kg dosing (0.3 mg/kg mean −2.4 ± 1.7; 1.2 mg/kg −1.7 ± 1.2: MD 0.7 (95% CI -0.4 to 1.8)) (one study, 60 children; very low-certainty evidence).

There were insufficient summary data to assess other medications.

Authors' conclusions

There is very low-certainty evidence about symptom improvements and changes in pH indices for infants. There are no summary data for endoscopic changes. Medications may or may not provide a benefit (based on very low-certainty evidence) for infants whose symptoms remain bothersome, despite nonmedical interventions or parental reassurance. If a medication is required, there is no clear evidence based on summary data for omeprazole, esomeprazole (in neonates), H_2antagonists, and alginates for symptom improvements (very low-certainty evidence). Further studies with longer follow-up are needed.

In older children with GORD, in studies with summary data extracted, there is very low-certainty evidence that PPIs (rabeprazole and pantoprazole) may or may not improve GORD outcomes. No robust data exist for other medications.

Further RCT evidence is required in all areas, including subgroups (preterm babies and children with neurodisabilities).

PLAIN LANGUAGE SUMMARY

Medicines for children with reflux

Review question

What is the best and safest treatment for babies and children with gastro-oesophageal reflux?

Key messages:

- the evidence for medications for babies with gastro-oesophageal reflux/reflux disease is very uncertain;

- for children with gastro-oesophageal reflux disease, the evidence is very uncertain regarding the effects of proton pump inhibitors. There was no adequate evidence to draw conclusions regarding other medications.

What is gastro-oesophageal reflux?

Gastro-oesophageal reflux happens when stomach contents come back up into the oesophagus (food pipe). Most babies (under 1 year) grow out of reflux symptoms, but does medicine help? Children (older than 1 year) can have reflux just like adults. Reflux can be normal ('physiological reflux'), but in babies and children, it can cause symptoms, including pain or weight loss, as the oesophagus becomes inflamed (oesophagitis). Bothersome symptoms of reflux are called 'gastro-oesophageal reflux disease' (GORD).

How is gastro-oesophageal reflux treated?

Medicines can thicken the stomach contents (alginates), neutralise stomach acid (ranitidine, omeprazole, lansoprazole), or help the stomach to empty faster (domperidone, erythromycin).

What did we want to find out?

We wanted to learn the best way to reduce reflux in babies and children. We wanted to see if medicines help infants and children to feel better (symptom scores), heal the oesophagus (which is checked by using endoscopy, where a tiny camera is put down the oesophagus), or lower the time the oesophagus is exposed to stomach acid. We also investigated whether the medicines were safe by considering the harmful or unwanted effects reported in the studies.

What did we do?

We searched for studies testing gastro-oesophageal reflux medicines in babies and children. We included all studies comparing these medicines, or comparing them to an inactive medicine (placebo). We assessed results which are important to doctors, nurses, and parents, and performed our own analysis of the results. We rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 36 suitable studies (involving 2251 babies and children), conducted worldwide, with most in the USA. The largest study recruited 268 babies, the smallest, 16 children. Fifteen studies compared an active medicine to placebo; 8 compared one active medication to another; and 11 studies gave the same medication at different doses. We found useable outcome information in 14 of the 36 studies. The remaining studies either did not report outcomes we were interested in or did not report them in a way we could analyse. We could not combine the results of any studies because they were too different (in terms of how long they followed participants up and the outcomes they investigated) to use in a meaningful way.

Key results

Babies. There is no clear effect on symptoms or measured acidity (one measure is reflux index, which is the percentage of time in 24 hours the oesophagus is exposed to stomach acid) between babies given omeprazole or placebo. One study (30 babies) showed cry/fuss time went down from 287 to 201 minutes/day in the placebo group and 246 to 191 minutes/day in the omeprazole group. Reflux index changed in the omeprazole group from 9.9% to 1.0% in 24 hours, and in the placebo group from 7.2% to 5.3%. One study (76 babies) showed that omeprazole and ranitidine may have a similar benefit for symptoms after 2 weeks: symptom scores (higher scores mean worse symptoms) in the omeprazole group dropped from 51.9 to 2.4, and in the ranitidine group, from 47 to 2.5. In one study of 52 newborn babies, esomeprazole appeared to show no reduction in the number of symptoms (184.7 to 156.7) compared to placebo (183.1 to 158.3). None of the studies reported harmful events or results about changes to babies' oesophaguses.

Children. In children older than 1 year of age, no studies assessed medical treatment versus placebo. Proton pump inhibitors (PPIs), which block stomach acid production, at different doses may provide little to no improvements in symptoms or oesophagus healing. In one study (127 children), both lower-weight and higher-weight children given rabeprazole at lower and higher doses had both minimal – probably unimportant – changes in symptom scores and endoscopic scores (which indicate whether healing of the oesophagus has occurred). Pantoprazole may or may not improve symptom scores in children aged 1 to 5 years by week 8: there was no difference between lower and higher dosing in one study (60 children). Studies investigating other medications did not report enough information for us to assess their results properly.

Quality of the evidence

We are not confident in the evidence, which was mainly based on single studies with few babies and children. Several studies had pharmaceutical company help with manuscript writing. The question of how best to treat children with disabilities, and whether any PPIs are better than other medicines remain. The evidence is current to 17 September 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Omeprazole compared to placebo for GORD in infants

Omeprazole compared to placebo for GORD in infants

Patient or population: infants with GORD
Setting: outpatients
Intervention: omeprazole
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with omeprazole				
Improvement in symptoms in infants assessed with: cry/fuss diary (minutes/day) Follow-up: mean 2 weeks	The mean improvement in symptoms in infants was **-66** minutes/day	MD **10 minutes/day lower** (89.1 lower to 69.1 higher)	-	30 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]	Cry/fuss time in infants between 3 and 12 months of age (mean 5.4 months) improved from 246 ± 105 minutes/day at baseline (mean +/- SD) to 191 ± 120 minutes/day in the omeprazole group and from 287 ± 132 minutes/day to 201 ± 100 minutes/day in the placebo group (mean difference (MD) 10 minutes/day lower (95% confidence interval (CI) -89.1 to 69.1))
Adverse events - not reported	There were no reports of adverse events in either the omeprazole or placebo group			-	-	
Improvement in pH metrics in infants assessed with: reflux index Follow-up: mean 2 weeks	The mean improvement in pH metrics in infants was **1.9** % of time in 24 hours	MD **7% of time in 24 hours lower** (4.66 lower to 9.34 lower)	-	30 (1 RCT)	⊕⊖⊖⊖ Very low[b,c]	In the omeprazole group, the reflux index improved from 9.9 ± 5.8% in 24 hours to 1.0 ± 1.3% in 24 hours. In the placebo group, the reflux index improved from 7.2 ± 6.0% in 24 hours to 5.3 ± 4.9% in 24 hours.
Endoscopic metrics - not measured	-	-	-	-	-	There were no data to assess this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_429021146969853213.

[a]Risk of bias: outcomes were assessed with behaviour diary (potential for recall bias) and visual analogue score (potential for parental observer bias). There were concerns that some of these infants may not have had significant endoscopic or reflux index changes at inclusion. North American Society of Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidance in place at the time considered reflux index > 10% to be pathological in infants, and no evidence of reflux oesophagitis was seen (erosions or ulcers) at entry endoscopy. The inclusion criteria considered loss of vascular pattern or friability enough for inclusion. Only seven infants had both endoscopic changes and reflux index > 5%. With these concerns, we have downgraded the evidence by one step.
[b]Imprecision: for Moore 2003, there was a wide confidence interval crossing the clinical decision threshold and only 15 infants in each group so we have downgraded the evidence by two steps.
[c]Risk of bias: there were concerns that some of these infants may not have had significant endoscopic or reflux index changes at inclusion. NASPGHAN guidance in place at the time considered reflux index > 10% to be pathological in infants, and no evidence of reflux oesophagitis was seen (erosions or ulcers) at entry endoscopy. The inclusion criteria considered loss of vascular pattern or friability enough for inclusion. Only seven infants had both endoscopic changes and reflux index.

Summary of findings 2. Omeprazole compared to ranitidine for GORD in infants

Omeprazole compared to ranitidine for GORD in infants

Patient or population: GORD in infants
Setting: outpatients
Intervention: omeprazole
Comparison: ranitidine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ranitidine	Risk with omeprazole				
Improvement in symptoms in infants assessed with: weekly gastro-oesophageal reflux score (WGSS) Follow-up: mean 2 weeks	The mean improvement in symptoms in infants was **-44.5** points	MD **4.97 points lower** (2.47 lower to 7.33 lower)	-	60 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]	Omeprazole (0.5 mg/kg/day) appears to provide some symptomatic benefit in infants between 2 and 12 months old, with improved scores after 2 weeks (51.93 ± 5.42 to 2.43 ± 1.15) equivalent to ranitidine (2 to 4 mg/kg/day) with scores improving (47 ± 5.6 to 2.47 ± 0.58): no differences between omeprazole

					and ranitidine were noted: MD -4.97 (95% CI -2.47 to -7.33).
Adverse events in infants - not measured			-	-	No data were available for this outcome
Improvement in pH metrics in infants - not measured			-	-	No data were available for this outcome
Improvement in endoscopic findings in infants - not measured			-	-	No data were available for this outcome

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_429020868699799221.

[a]Risk of bias: the certainty of evidence was downgraded by two steps due to issues with blinding (performance bias) as omeprazole was delivered as a capsule and ranitidine as a syrup so parents would be aware which medication was being offered. In addition, 16 infants were lost to follow-up (attrition bias), severe pneumonia, premature discontinued drugs, and parental issues with the questionnaire
[b]Imprecision: as the confidence intervals do not overlap the clinical decision threshold between recommending and not recommending treatment, and the study had very small numbers, we downgraded the certainty of evidence by two steps (very serious), but the certainty of evidence was already very low.

Summary of findings 3. Esomeprazole compared to placebo for GORD in infants

Esomeprazole compared to placebo for GORD in infants

Patient or population: GORD in infants
Setting: inpatients in 3 neonatal intensive care units
Intervention: esomeprazole
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with esomeprazole				
Improvement in symptoms and signs in infants assessed with: total number of gastro-oesophageal reflux disease (GORD) symptoms Follow-up: mean 2 weeks	The mean improvement in symptoms and signs in infants was **-24.5** episodes	MD **3.2 episodes fewer** (4.6 fewer to 1.8 fewer)	-	52 (1 RCT)	⨁◯◯◯ **Very low**[a,b,c,d]	Included data from premature babies to 1 m corrected gestational age. No data in older infants. For total number of GORD symptoms (from video monitoring) and GORD-related signs (from cardiorespiratory monitoring), the esomeprazole group improved from baseline 184.7 (78.5) to 156.7 (75.1) and placebo group improved from 183.1 (77.5) to 158.3 (75.9).
Adverse events - not reported	-	-	-	-	-	It was not possible to extract summary data, although there were no reported differences between the placebo and esomeprazole groups.
pH indices - not measured				-	-	No data were available for this outcome
Endoscopic metrics - not measured				-	-	No data were available for this outcome

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_429020489057615413.

[a]Risk of bias: the certainty of evidence was downgraded by one step as the study was terminated early due to poor recruitment (the power calculation estimated needing 38 neonates in each group).
[b]Indirectness: the certainty of evidence was downgraded by one step as the population studied (neonates) is only a part of the population under assessment (infants).
[c]Imprecision: the certainty of evidence was downgraded by two steps due to small numbers and wide confidence intervals crossing the clinical decision threshold.

[d]Publication bias: this single study was industry-funded, with support for manuscript-writing, but the certainty of evidence was not downgraded by one step, as already at 'very low'

Summary of findings 4. Rabeprazole at higher doses (1 mg/kg) compared to rabeprazole at lower doses (0.5 mg/kg) for GORD in children over 1 year of age

Rabeprazole at higher doses (1 mg/kg) compared to rabeprazole at lower doses (0.5 mg/kg) for GORD in children over 1 year of age

Patient or population: GORD in children over 1 year of age
Setting: outpatients
Intervention: rabeprazole at higher doses (1 mg/kg)
Comparison: rabeprazole at lower doses (0.5 mg/kg)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with rabeprazole at lower doses (0.5 mg/kg)	Risk with rabeprazole at higher doses (1 mg/kg)				
Improvement in symptoms assessed with: 'Total GORD Symptoms and Severity' score Follow-up: mean 12 weeks	The mean improvement in symptoms was **-9.9** points	MD **2.3 points higher** (2 lower to 6.6 higher)	-	127 (1 RCT)	⊕⊝⊝⊝ **Very low**[a,b,c]	Rabeprazole at 0.5 mg/kg and 1 mg/kg may provide similar symptom improvement: in the 0.5 mg/kg group, symptom score improved in both the low-weight (< 15 kg) (n = 21 mean -10.6 ± SD 11.13)) and high-weight (> 15 kg) groups (n = 44 mean -13.6 ± 13.1). In the 1 mg/kg group, scores improved in the low-weight (n = 19, -9 ± 11.2)) and higher-weight groups (n = 43, -8.3 ± 9.2). For the higher-weight group, MD 2.3 (95% CI -2 to 6.6), and low-weight group: 0.5 mg/kg vs 1 mg/kg: MD 4.6 (95% CI -2.9 to 12).
Adverse events assessed with: parent-reported events	Rabeprazole at 0.5 mg/kg and 1 mg/kg may lead to some adverse events: 95 (84%) children had adverse events, including abdominal pain, nausea, vomiting, bronchopneumonia, gastroenteritis, cough, and choking.			127 (1 RCT)	⊕⊝⊝⊝ **Very low**[a,b,c]	There was no difference between the groups.
Improvement in endoscopic appearances assessed with: Hetzel-Dent score Follow-up: mean 12 weeks	The mean improvement in endoscopic appearances was **-1.4** points	MD **0.1 points higher** (0.23 lower to 0.43 higher)	-	127 (1 RCT)	⊕⊝⊝⊝ **Very low**[a,b,c]	In the 0.5 mg/kg group, endoscopic appearances improved in both the low-weight (-1.4 ± 1.06) and higher-weight groups (-1.2 ± 0.75). In the 1 mg/kg group, endoscopic appearances also improved in the low-weight (-1.1 ± 0.72) and high-weight groups (-1.0 ± 0.85). In the low-weight group: 0.5 mg/kg vs 1 mg/kg: MD 0.30 (95% CI -0.27 to 0.87) and in the higher-weight group MD 0.1 (95% CI -0.23 to 0.43).
pH indices - not measured				-	-	No data were available for this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_429021824944230742.

[a]Risk of bias: the certainty of evidence was downgraded by one step for selection bias: 30% of children had already received proton pump inhibitors, 15% H2 antagonists, and 2% prokinetics. 15% of participants had also withdrawn.
[b]Imprecision: the certainty of evidence was downgraded by one step as the wide confidence intervals crossed the clinical decision threshold.
[c]Publication bias: the certainty of evidence was downgraded by one step as this was a single study and was industry-funded, with assistance in manuscript preparation, and authors were employed by a pharmaceutical company. The study design involved the same medication at different doses which is less clinically useful than comparison to placebo or an alternative medication. We do not have other studies to assess whether this would have had a material impact.

Summary of findings 5. Pantoprazole in higher doses (1.2 mg/kg) compared to pantoprazole at lower doses (0.3 mg/kg) for GORD in children over 1 year of age

Pantoprazole in higher doses (1.2 mg/kg) compared to pantoprazole at lower doses (0.3 mg/kg) for GORD in children over 1 year of age

Patient or population: GORD in children over 1 year of age
Setting: outpatients
Intervention: pantoprazole in higher doses (1.2 mg/kg)
Comparison: pantoprazole at lower doses (0.3 mg/kg)

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with pantoprazole at lower doses (0.3 mg/kg)	Risk with Pantoprazole in higher doses (1.2 mg/kg)				
Improvement in symptoms assessed with: weekly gastro-oesophageal reflux score (WGSS) Follow-up: mean 8 weeks	The mean improvement in symptoms was **-2.37** points	MD **0.7 points higher** (0.4 lower to 1.8 higher)	-	60 (1 RCT)	⊕⊝⊝⊝ **Very low**[a,b,c]	Pantoprazole appears to improve symptoms at 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg pantoprazole in 60 children aged 1 to 5 years. Symptom scores improved from baseline to week 8 (0.3 mg/kg MD -2.4, 95% CI -3.2 to -1.5; 1.2 mg/kg -1.7, 95% CI -2.9 to -0.39). There was no difference between 0.3 mg/kg and 1.2 mg/kg dosing: MD 0.7 (95% CI -0.4 to 1.8). Individual symptoms (abdominal pain, burping, heartburn, pain after eating and difficulty swallowing) improved in all groups after 8 weeks.
Adverse events assessed with: individual symptom reporting Follow-up: 8 weeks	Pantoprazole at all doses investigated may lead to adverse events: in the 0.3 mg/kg group, 1 child developed diarrhoea and nappy rash; in the 0.6 mg/kg group, 1 child had sleep disturbance and 1 developed abdominal pain; and in the 1.2 mg/kg group, 1 child had rectal bleeding.			60 (1 RCT)	⊕⊝⊝⊝ **Very low**[a,b,c]	There was no difference between the groups.
Improvement in pH indices - not measured				-	-	No data were available for this outcome.
Improvement in endoscopic metrics - not measured				-	-	No data were available for this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_429032441167302611.

[a]Risk of bias: we downgraded the certainty of evidence by one step as no comment was made about blinding and randomisation technique.
[b]Imprecision: we downgraded the certainty of evidence due to the small sample size, which would not meet the optimal information size, and confidence intervals that cross the decision-making threshold. We would have downgraded by two steps but the certainty of evidence was already 'very low'.
[c]Publication bias: we downgraded the certainty of evidence by one step as this study was industry-funded with support with manuscript writing. The study design involved the same medication at different doses which is less clinically useful than comparison to placebo or an alternative medication. It is difficult to estimate the degree of effect given other studies were not available to compare.

BACKGROUND

Description of the condition

Gastro-oesophageal reflux (GOR) occurs when gastric contents come back up into the oesophagus (NASPGHAN-ESPGHAN guidelines 2018). GOR is a very common presentation, both in primary and secondary care settings. Symptoms of GOR can affect approximately 50% of infants aged one to three months old (Miyazawa 2002; Nelson 1997). The natural history of GOR is generally of improvement with age, with less than 5% to 10% of children with vomiting or regurgitation in infancy continuing to have symptoms after the age of 12 to 14 months (Campanozzi 2009; Martin 2002). This is due to a combination of growth in length of the oesophagus, a more upright posture, increased tone of the lower oesophageal sphincter, and a more solid diet.

Gastro-oesophageal reflux disease (GORD) is defined as "GOR associated with bothersome symptoms or complications" (NASPGHAN-ESPGHAN guidelines 2018; Sherman 2009). Sherman and colleagues caution that this definition is complicated by unreliable reporting of symptoms in children under eight years of age (Sherman 2009). Gastrointestinal sequelae include oesophagitis, haematemesis, oesophageal stricture formation, and Barrett's oesophagitis. Extraintestinal sequelae can include acute life-threatening events, apnoea, chronic otitis media, sinusitis, secondary anaemia, and chronic respiratory disease (chronic wheezing/coughing or aspiration), as well as failure to thrive. The presence of severe oesophagitis has historically been shown to predict the need for surgical reconstruction (Hyams 1988).

GOR is distinguished from vomiting physiologically by the absence of (1) a central nervous system emetic reflex, (2) retrograde upper intestinal contractions, (3) nausea, and (4) retching. GOR is generally characterised as effortless and non-projectile, although it may be forceful in infants (Sherman 2009). Other conditions, such as rumination syndrome, are distinguished by the absence of nighttime symptoms, and features such as early satiety and bloating may point to functional dyspepsia (Hyams 2016).

Children with certain predisposing conditions are more prone to severe GORD. These conditions include neurological impairment (e.g. cerebral palsy), repaired oesophageal atresia or congenital diaphragmatic hernia, and chronic lung disease.

Diagnosis of physiological or functional GOR (i.e. reflux symptoms that are likely to improve with gut maturation) in infants is usually made based on the symptoms alone, avoiding the need for expensive and possibly harmful investigations. Investigations to assess the severity of GORD, or in cases where GOR cannot be diagnosed on clinical grounds, include 24-hour oesophageal pH monitoring, which can be combined with impedance monitoring, upper gastrointestinal endoscopy, scintigraphy, or oesophageal manometry. All have been shown to correlate poorly with symptomatology, and may not accurately predict the degree of improvement with treatment (Augood 2003; NICE 2019).

Clinical symptoms are commonly scored and reported individually. These symptoms include:

- number of vomiting episodes, back arching, regurgitation, failure to thrive, feeding difficulties, and abdominal pain in infants;
- heartburn, epigastric pain, and regurgitation symptoms in older children.

Common scoring systems include the Paediatric Gastro-oesophageal Symptom Questionnaire (PGSQ) for older children (Kleinman 2011), the GORD Assessment of Symptoms in Pediatrics Questionnaire (GASP-Q) for younger children (Fitzgerald 2003), and the Infant Gastro-oesophageal Reflux Questionnaire Revised (I-GERQ-R) for infants (Orenstein 2010).

Normal gastric juices are acidic in nature, with a pH of approximately 1 to 3. The pH scale goes from 1 (strongly acidic) through 7 (neutral), to 14 (strongly alkaline).

Investigations to assess disease severity include:

- pH-impedance indices over 24 hours, including: reflux index on pH probe (percentage of time that oesophageal pH < 4 in 24 hours); number of acid reflux/impedance episodes; and time length of reflux episodes where oesophageal pH is less than 4;
- endoscopic findings, including macroscopic appearance of oesophagus on endoscopy, and histological appearances.

Consensus exists that there are insufficient data to recommend histology as a tool to diagnose or exclude GORD in children, but that histology is useful in confirming the presence of oesophagitis and ruling out other conditions, such as eosinophilic oesophagitis, Barrett's oesophagus, Crohn's disease, infection, and graft-versus-host disease (NICE 2019). Histological scoring scales (e.g. the Hetzel-Dent classification) are also commonly utilised to help assess improvement (NASPGHAN-ESPGHAN guidelines 2018).

Description of the intervention

Proton pump inhibitors (PPIs)

PPIs, such as omeprazole and lansoprazole, are a group of drugs that irreversibly inactivate H+/K+ ATPase, in the parietal cells of the stomach. There are five PPIs approved by the US Food and Drug Administration (FDA) in adults: omeprazole (since 1988), lansoprazole, pantoprazole, rabeprazole, and esomeprazole (the pure S-isomer of omeprazole). The current National Institute for Health and Clinical Excellence (NICE) guidelines recommend only a two-week trial of a PPI or a histamine receptor antagonist (H_2RA) for infants whose symptoms fail to improve with nonmedical interventions (NICE 2019). Omeprazole is licensed for use in children over one year of age in the UK, with a half-life of one hour, but due to the permanent receptor block, the effect can last for five to seven days. The dose range is 5 mg to 10 mg daily in infants, 10 mg to 20 mg daily in young children, and 20 mg to 40 mg daily in older children and adolescents. Lansoprazole is only recommended by the British National Formulary for children when treatment with the available formulations of omeprazole is unsuitable (BNFc 2021). It is used in doses of 7.5 mg to 15 mg in young children, and 15 mg to 30 mg in older children. The average elimination half-life is 1.5 hours in infants and young children. The inhibition of acid secretion is about 50% of maximum at 24 hours and the duration of action is approximately 72 hours (Ward 2013). Esomeprazole is also licensed for GORD: for children aged one to 11 years with a body-weight of 10 kg to 19 kg, 10 mg once daily; for children aged one to 11

years with a body-weight of 20 kg and above, 10 mg to 20 mg once daily; for children aged 12 to 17 years, 20 mg to 40 mg once daily, and a maintenance dose of generally 20 mg daily. Pantoprazole and rabeprazole are not currently licensed for use in children.

Gastric pH provides some protection against infection in children. Thus, there is evidence that potentiating the hypochlorhydria (low levels of stomach acid) in neonates further with PPIs can result in bacterial overgrowth (De Bruyne 2018). Increases in respiratory infections in critically-ill inpatients have been identified, but in infants and children who are otherwise well, no clear ill effects have been demonstrated from this overgrowth. A Medicines and Healthcare products Regulatory Agency (MHRA) alert in 2012 highlighted that PPIs used for longer than three months may be associated with hypomagnesaemia (especially in those on therapy lasting for more than five years), and a possible increased risk of fractures (Fleishmann 2021; MHRA 2012). Since then, concerns have been raised about hypergastrinaemia (but the risk of cancer is not thought to be increased), *Clostridioides difficile* colitis, vitamin B12 deficiency (due to atrophic gastritis and hypochlorhydria, which produce bacterial overgrowth promoting increased digestion of cobalamin), and acute interstitial nephritis (a hypersensitivity reaction that can occur within days to 18 months of starting treatment and resolves on discontinuing the PPI) (BNFc 2021; NICE 2019). There have been a handful of cases reported of PPI-induced systemic cutaneous lupus erythematosus, and significant drug interactions (itraconazole, ketoconazole, isoniazid, oral iron supplements) (Schoenfeld 2016). PPIs are metabolised by the cytochrome P450 system in the liver and interactions include those medications that inhibit or enhance cytochrome P450 metabolism (listed in BNFc 2021).

Histamine (H_2) receptor antagonists (H2RAs)

The most commonly used H2RA is ranitidine, which competitively blocks selective histamine receptors. Ranitidine is metabolised in the liver and renally excreted with a half-life of two to four hours and length of action of 12 to 24 hours. Ranitidine is well-tolerated and has a low incidence of side effects; these commonly include fatigue, dizziness, and diarrhoea (Tighe 2009). It also affects metabolism of other drugs by the cytochrome P450 system (BNFc 2021). Ranitidine has been withdrawn worldwide due to concerns regarding a low level of impurity of N-nitrosodimethylamine (NDMA) (MHRA 2019). Cimetidine is rarely used clinically because of concerns about its greater effects on the cytochrome P450, which cause multiple drug interactions, as well as its interference with vitamin D metabolism and endocrine function. Famotidine is a recently-developed H_2 antagonist not commonly used in children but with similar pharmacodynamics to ranitidine. Tachyphylaxis from H_2 antagonists has been reported (McRorie 2014).

Magnesium hydroxide and aluminium hydroxide (MHAH)

Magnesium hydroxide and aluminium hydroxide reduce gastric pH and are commercially available as Maalox. Aluminium should be avoided in chronic use, especially in infants and children with chronic renal failure, due to the risk of aluminium accumulation.

Prokinetics

Domperidone is a dopamine-receptor (D-2) blocker that has relatively few side effects, but case reports of extrapyramidal side effects exist (Franckx 1984; Shafrir 1985), and there is concern about the risk of cardiac side effects (EMA 2014b). Its use has declined except in specialist indications, since the publication of NICE guidance (NICE 2019). Current advice is to not use it in children with co-existing cardiac disease or in those taking CYP3A4 inhibitors, and not to exceed a daily dose of 30 mg/day in children over 12 years old and 250 micrograms/kg three times a day in younger children (EMA 2014b). Domperidone is no longer marketed in the USA (Bashashati 2016), but can be used as an investigational new drug and should not be used for nausea and vomiting for more than one week.

Erythromycin is a macrolide antibiotic; its use as a prokinetic is as an unlicensed indication (BNFc 2021).

Metoclopramide has been the subject of an FDA 'black box' warning (FDA 2009). In August 2013, the European Medicines Agency released a statement that the risk of neurological adverse events (such as short-term extrapyramidal disorders and tardive dyskinesia) with metoclopramide outweighed the benefit, when taken for a prolonged period at a high dose (EMA 2014a). Metoclopramide has also been assessed in a separate Cochrane Review (Craig 2004), so we did not review the associated literature for metoclopramide as it is not used to treat reflux in children, given the adverse event profile and NICE guidance (NICE 2019).

At its peak use, cisapride was prescribed to over 36 million children worldwide for GOR (Vandenplas 1999). However, concerns about the effect of cisapride in prolonging the QT interval led to its removal from general paediatric use (Com Safety Med 2000). A Cochrane Review found that there was no clear evidence that cisapride reduces symptoms of GOR, and found evidence of substantial publication bias favouring studies showing a positive effect of cisapride (Augood 2003). Given the known risks of toxicity and its suspension of manufacture, further trials of cisapride are unlikely.

Quince syrup (heated extract of *Cydonia oblonga* Mill.) belongs to the rose family (Rosacea) as a traditional Persian medicine to treat GORD (Zohalinezhad 2015). It is unlicensed in the UK.

Alginates

Compound alginate preparations differ from other alginate preparations, which can also contain sodium bicarbonate or potassium bicarbonate (BNFc 2021).

Caution should be used with alginates that contain aluminium (see below), and in children with vomiting or diarrhoea, or children at risk of intestinal obstruction (Gaviscon Product Information 2021). In children whose feeds are already thickened (e.g. Enfamil AR/SMA Staydown), coexistent Gaviscon Infant could potentially cause intestinal obstruction (Keady 2007). Some alginate preparations contain sodium: for example, Gaviscon Infant contains 0.92 mmol Na^+/dose, which should be considered if a child's sodium intake needs to be monitored with caution (e.g. renal impairment, congestive cardiac failure, preterm infants, or children with diarrhoea and vomiting) (BNFc 2021). Gaviscon Infant has changed to become aluminium-free, with different proportions of alginate, and other forms are now available (Gastrotuss and Refluxsan Nipio). Alginates for infants are generally prescribed at up to six doses per day with half a dual sachet in formula bottles of less than 210 mL and one dual sachet in formula bottles of more than 210 mL of milk. Breastfed babies have a dose mixed with expressed breast milk and given before or with a breastfeed by syringe.

Two other Cochrane Reviews have assessed thickened feeds (Craig 2004; Kwok 2017).

Antispasmodics

Baclofen is primarily an antispasmodic acting on gamma-aminobutyric acid (GABA) receptors, commonly used in children with neurodisability, such as cerebral palsy (Omari 2006). It is not licensed for children with GORD (BNFc 2021).

Conservative options

These include reassurance of parents, and positioning of the baby to reduce gastro-oesophageal reflux, through the effect of gravity on gastric contents. This can include elevating the head of the cot or basket in which the baby is placed to sleep, or keeping the baby upright after a feed.

Altering the feed's consistency can be achieved with feed thickeners (e.g. with rice starch/carob bean gum) and may reduce the reflux of gastric contents with increased viscosity. Some feeds are manufactured with a thickening agent added. Weaning also has a similar effect by increasing the viscosity of gastric contents, and gastro-oesophageal reflux is known to improve with weaning. We have considered compound alginates in this review, but not other feed-thickeners, which are assessed elsewhere (Craig 2004; Kwok 2017).

Changes in feeding can also improve GOR. For breastfed babies, a breastfeeding assessment by health professionals experienced in breastfeeding is recommended initially, then elimination of cow's milk from the maternal diet can be trialled. For formula-fed infants, after assessing for and correcting overfeeding, clinicians can consider recommendations supporting two to four weeks of a protein hydrolysate or amino acid-based formula (NASPGHAN-ESPGHAN guidelines 2018; NICE 2019).

Surgical options

Surgery is used to limit GORD. The most common strategy is a Nissen's fundoplication involving a 360° wrap (Hassall 2005). This aims to combine antireflux factors, including creation of a high pressure zone at the distal oesophagus and recreation of the diaphragmatic crural mechanism. However, underlying dysmotility may persist and retching may continue as a prominent feature. Comparisons of these techniques are considered elsewhere (NICE 2019). We have not assessed conservative and surgical strategies in this Cochrane Review, which seeks to assess medical treatments, to better inform medical practitioners (GPs/paediatricians). Surgery relates to a small minority of children with gastro-oesophageal reflux and is beyond the scope of this review.

How the intervention might work

Pharmacological treatments work by altering the gastric pH (e.g. PPIs, H_2 antagonists) and reducing the acidity of refluxate, by promoting gut motility (prokinetics), or by altering the viscosity of refluxate (alginates). Pharmacological treatments are considered if nonmedical measures have been ineffective. Dosing, metabolism interactions, and associated adverse events are described above.

Proton pump inhibitors (PPIs)

PPIs irreversibly inactivate H+/K+ ATPase, at the level of the parietal cell membrane transporter. This increases the pH of gastric contents and decreases the total volume of gastric secretion. Of the five PPIs approved by the FDA, three are licensed in the UK for children: omeprazole, lansoprazole, and esomeprazole. PPIs were the subject of a 'Pediatric Written Request' (PWR) made by the FDA to improve our knowledge of PPIs in children and infants. There is good clinical experience with PPIs in children, and an excellent evidence-base of efficacy in adults (NICE 2019).

H_2 receptor antagonists (H2RAs)

H_2 antagonists also aim to increase the pH of gastric contents in children, and there is good clinical experience with H_2 antagonists in infants, children, and adults (NICE 2019).

Magnesium hydroxide and aluminium hydroxide (MHAH)

MHAH is designed to reduce gastric acid, and forms water as a by-product. Its use in children is unlicensed.

Prokinetics

Prokinetics are considered when GOR fails to improve with conservative measures. There are several classes of drugs designed to increase gastrointestinal motility.

Domperidone acts to increase motility and gastric emptying through acting on dopamine receptors and decreases post-prandial reflux time (Franckx 1984; Shafrir 1985). Domperidone had been commonly used in clinical practice, either as part of empirical medical therapy of gastro-oesophageal reflux disease or if delayed gastric emptying has been demonstrated on a barium swallow or milk scan.

Erythromycin binds to motilin receptors to promote peristalsis and gastric emptying, to decrease post-prandial reflux time. Its use as a prokinetic is unlicensed.

Metoclopramide has also been assessed in a separate Cochrane Review (Craig 2004), so we did not review the associated literature for metoclopramide as it is not used to treat reflux in children, given the adverse event profile and NICE guidance (NICE 2019).

Cisapride is a gastro-oesophageal prokinetic agent which stimulates motility in the gastrointestinal tract by increasing acetylcholine release in the myenteric plexus, controlling smooth muscle. As cisapride has been the subject of a separate Cochrane Review (Augood 2003), and is now no longer manufactured, we have not reviewed the literature for this drug.

Quince syrup has ulcer-healing properties and is thought to increase the lower oesophageal sphincter tone (Zohalinezhad 2015).

Alginates

Compound alginate preparations prevent reflux in infants by increasing the viscosity of gastric contents (BNFc 2021). This contrasts with other Gaviscon preparations, which can also contain sodium bicarbonate/potassium bicarbonate that – in the presence of gastric acid – forms a gel in which carbon dioxide (derived from the breakdown of bicarbonate) is trapped. This 'foam raft' floats on top of the gastric contents and is designed to neutralise gastric acid (providing symptomatic relief), to thicken the feed (to reduce reflux), and to reduce oesophageal irritation (Mandel 2000).

Sodium and magnesium alginate (Gaviscon Infant) is a thickener, and other forms are now available (Gastrotuss and Refluxsan Nipio).

Other thickening agents, such as carob bean gum (Carobel), have been assessed separately (Craig 2004; Kwok 2017). Current NICE guidance recommends discontinuing pre-thickened formulas if alginates are trialled (NICE 2019).

Antispasmodics

Baclofen has been used to treat co-existing reflux by aiming to improve the incoordination of the lower oesophageal sphincter, reducing the number of transient lower oesophageal sphincter relaxations (TLESRs) (Omari 2006). It is not part of clinical GORD consensus guidelines (NASPGHAN-ESPGHAN guidelines 2018).

Why it is important to do this review

Gastro-oesophageal reflux in children is a common condition. Healthcare professionals frequently use pharmacological treatment of this condition for symptom relief. New studies have been published since the original version of this review (Tighe 2014), and new medicines to treat gastro-oesophageal reflux are available. Thus, an up-to-date synthesis of the evidence, including the current balance of benefits and harms of these treatments, is required.

OBJECTIVES

To assess the effects of pharmacological treatments for GOR in infants and children.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised controlled trials (RCTs) for inclusion.

Types of participants

We included all children (aged 0 to 16 years) with "GOR associated with bothersome symptoms or complications" (NASPGHAN-ESPGHAN guidelines 2018; see also Sherman 2009).

We predefined two groups organised by age: infants up to 12 months old, and children aged 12 months to 16 years old. We included studies assessing preterm neonates and children with a neurodisability.

Types of interventions

We included all currently available medical treatments for gastro-oesophageal reflux in children.

We considered all RCTs that compared a medication for GOR with a placebo or another medication. We imposed no restrictions on dosage, frequency, or duration of pharmacological treatment.

We attempted comparisons of all active treatments versus placebo, by treatment class:

- proton pump inhibitors (PPIs: omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) versus placebo;
- H_2 antagonists (ranitidine, famotidine, cimetidine) versus placebo;
- prokinetics (domperidone, erythromycin, bethanechol) versus placebo;
- compound alginate preparations versus placebo
- sucralfate versus placebo.

We included studies assessing quince syrup, a traditional Persian medicine to treat GOR. We outline the evidence base, but note that quince syrup is not currently a prescribable medicine in many countries, including the United Kingdom.

We excluded studies assessing metoclopramide, thickened feeds, or using thickened feeds as a comparator. (In a 2004 Cochrane Review, Craig and colleagues assessed metoclopramide and thickened feeds for GOR in children under two years of age (Craig 2004); this review has since been withdrawn.) We excluded studies employing conservative treatment and surgical techniques for GOR, as well as studies assessing dietary management of GORD. We excluded studies assessing pharmacological treatments for GORD in people with coexistent conditions, such as tracheo-oesophageal fistula (TOF) or asthma, that predispose them to GORD, to avoid heterogeneity between participants.

Types of outcome measures

To make this update as robust as possible, and to assist the potential for meta-analysis, we selected the same outcome measures in this updated review as in the previous version (Tighe 2014). We included all reported outcomes that are likely to be meaningful to clinicians making medical decisions about treating gastro-oesophageal reflux. We included all time points for assessments. We identified studies with very short follow-up periods (fewer than two weeks) as a potential source of bias.

We did not exclude studies based on outcomes measured. However, we excluded studies assessing purely pharmacokinetic outcomes or taste, as these were not considered as primary or secondary outcome measures of interest. Nevertheless, to exclude outcome bias, we contacted corresponding authors of such trials to establish if there were any relevant data that had not been published. In cases of uncertainty, we contacted corresponding authors for clarification.

Primary outcomes

Our primary outcome was improvement in clinical symptoms, which was usually assessed through questionnaires completed by parents and childcare providers. The symptoms monitored included:

- number of vomiting episodes (continuous data);
- episodes of back arching (continuous data);
- number of regurgitation episodes (continuous data);
- failure to thrive (binary outcome);
- feeding difficulties (binary outcome);
- abdominal pain in infants (continuous data).

In older children, the number of episodes of heartburn, epigastric pain, or regurgitation (continuous data) were again assessed through questionnaires completed by participants, parents, and health professionals. These included, for example, the Paediatric Gastro-oesophageal Symptom Questionnaire (PGSQ) and the

Infant Gastro-oesophageal Reflux Questionnaire–Revised (I-GER-Q), which were completed daily by parents and health professionals to provide quantitative data through validated symptom scores.

Secondary outcomes

Our secondary outcomes were: adverse effects, 24-hour pH-impedance indices, and endoscopic metrics.

Adverse effects

We explored all studies for any adverse effects, as defined by the Medicines Health Regulation Authority (MHRA 2012). In cases of uncertainty, we contacted corresponding authors for clarification. This exploratory approach aimed to identify unanticipated and rare adverse effects of an intervention and to look for data on possible associations between an intervention and a list of observed adverse events, to add to existing safety profiles. We assessed and reported adverse effects, and studies reporting the absence of adverse effects without separate data extraction, in line with Cochrane guidance (Higgins 2022).

24-hour pH-impedance indices

Reflux monitoring measures the amount of reflux in the oesophagus during a 24-hour period. The test is carried out by placing a catheter in the oesophagus. These indices assess:

- improvement in the reflux index (continuous data);
- number and duration of reflux episodes on a 24-hour pH-impedance probe (continuous data);
- results of non-acid impedance studies (continuous data).

Endoscopic metrics

- Improvement of oesophagitis on endoscopy (visual appearance – this can be a binary outcome or continuous data if scored (e.g. Hetzel-Dent classification));
- Histology (continuous data).

Different grading scales currently exist for classifying macroscopic appearances of the oesophagus, but no one grading scale has been demonstrated to show superior validity to the alternatives. We considered the description of histological changes, and histological scoring scales, and where relevant to help clinicians, we describe useful findings below. However, we did not include histological data in the summary of findings tables.

The number of children within a study population who failed to improve and required fundoplication was considered a potential secondary outcome (binary outcome).

Search methods for identification of studies

Electronic searches

We searched the following databases on 17 September 2022:

- Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid Evidence-Based Medicine Reviews Database (EBMR) (from inception to 2022) (Appendix 1);
- MEDLINE via Ovid (from 1946 to 17 September 2022) (Appendix 2);
- Embase via Ovid (from 1974 to 17 September 2022) (Appendix 3);
- Science Citation Index via Web of Science (from inception to 17 September 2022) (Appendix 4).

We searched the World Health Organization International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/) and ClinicalTrials.gov (www.ClinicalTrials.gov).

We developed this search strategy with assistance from the Information Specialist of the Cochrane Gut Group.

Searching other resources

We checked the reference lists of all eligible studies and relevant reviews identified by the search and published within the past five years for possible references to RCTs. We also contacted experts in the field for any additional trials.

Adverse outcomes

We did not conduct a separate search for adverse events.

Language

We did not restrict our searches by language, and translated papers as necessary.

Data collection and analysis

We used Review Manager 5.4 and RevMan Web for data collection and analysis (RevMan 2019; RevMan Web 2022).

Selection of studies

Two review authors (MT, IL) downloaded all titles and abstracts retrieved by electronic searching to a reference management database and removed duplicates. Four review authors (MT, IL, EA, RMB) independently screened titles and abstracts for inclusion. We retrieved the full-text reports/publications and independently applied the eligibility criteria to the full texts, identified studies for inclusion, and identified and recorded reasons for exclusion of ineligible studies. We resolved any disagreement through discussion or, when required, through consulting a fifth review author (NAA).

We listed studies that initially appeared to meet the inclusion criteria but that we later excluded in the Characteristics of excluded studies table, with the reasons for their exclusion. We collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We also provided any information we could obtain about ongoing studies. We entered studies that were only in abstract form, or were only identified in the ISRCTN register into the Characteristics of studies awaiting classification table. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009).

Data extraction and management

Three review authors (MT, IL, EA) independently extracted the data using a robust data extraction form (utilised in the first review), checked and entered the data into RevMan 5.4/RevMan Web, analysed the data, and highlighted any discrepancies, with statistician supervision (AH). RMB supervised data collection and acted as arbiter for any disagreements. If studies had insufficient data, we did not extract summary data. We collected and archived data in a format to facilitate future access and data sharing. Where statistical analyses were not possible (or were inappropriate), we provided a descriptive summary. We looked at all studies, performing further analysis of those employing an intention-to-

treat (ITT) analysis where such information existed, and have included single forest plots of studies with summary data extracted.

Assessment of risk of bias in included studies

As in the original review, we have described each study in a risk of bias table, and addressed the following issues, which may be associated with biased estimates of treatment effect: recruitment strategy, random sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias (Higgins 2011). We commented specifically on:

- the method of generation of the randomisation sequence;
- the method of allocation concealment – it is considered 'adequate' if the assignment could not be foreseen, and should be independent of and remote from the investigators;
- who was blinded and not blinded (participants, clinicians, outcome assessors) if this was appropriate (up to and after the point of treatment allocation);
- how many participants were lost to follow-up in each arm, and whether reasons for losses were adequately reported;
- whether all participants were analysed in the groups to which they were originally randomised (intention-to-treat principle).

We also reported on:

- the baseline assessment of the participants for age, sex, and duration of symptoms, if suggestive of bias between the groups;
- whether outcome measures were described and their assessment was standardised;
- the use and appropriateness of statistical analyses, where we could not extract tabulated data from the original publication.

Measures of treatment effect

The outcomes described above yielded both continuous and dichotomous data.

Clinical symptoms produced continuous data (e.g. number of vomiting episodes), yielding outcomes described as the mean difference (MD) and standardised mean difference (SMD). We extracted continuous data (e.g. reflux index) for summary data: we used means and standard deviations (SDs) to derive a mean difference (MD) with a 95% confidence interval (95% CI) using a fixed-effect model.

The latest guidelines of the North American Society of Paediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) and the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) do not define normal values for pH-metry and pH-impedance (NASPGHAN-ESPGHAN guidelines 2018). We therefore continued to treat reflux index as continuous data but removed consideration of whether baseline values were normal or abnormal (which had been discussed in the previous version of this review), and included any improvement/non-improvement in values compared to the other agent or dose being tested, expressed as MD ± 95% CI.

Dichotomous data, such as improvement/non-improvement in endoscopic appearance, produced outcome data we presented as risk ratios. For studies of a single pharmacological agent (e.g. omeprazole) versus either placebo or a different drug, if sufficient trials were available and participant characteristics were clinically similar, we planned to conduct meta-analyses of primary and secondary outcomes.

Unit of analysis issues

We considered unit of analysis issues for any included trials with multiple treatment groups and cluster-randomised designs. We considered cross-over trials for inclusion and assessed only the first stage of therapy prior to cross-over, but commented on results obtained after cross-over if clinically relevant. We also considered issues arising from multiple observations for the same outcome (e.g. repeated pH-impedance measurements), and planned to consult the Cochrane Gut group if clarification was required. For multi-arm studies, we analysed multiple intervention groups appropriately to prevent arbitrary omission of relevant groups or double-counting of participants.

Dealing with missing data

Where we were uncertain about the specifics of a trial pertinent to analysis, we contacted trial authors or sponsors of studies published from 2014 to 2022 to request missing data or clarification. We detailed authors' and sponsors' contribution in Characteristics of included studies.

Assessment of heterogeneity

We screened studies to assess clinical heterogeneity and planned subgroup analyses if appropriate, reporting on the extent of any heterogeneity using the I^2 statistic (Higgins 2003). Where we found evidence of significant heterogeneity (I^2 > 50%) in summary data extraction, we downgraded the evidence certainty.

Assessment of reporting biases

We assessed selective reporting of results by comparing (where available) the outcomes listed in trials' original protocols to those reported in the final papers. We also searched clinical trials registries for details of the included trials. We contacted the primary investigator(s) of included trials to determine whether they were aware of any relevant unpublished data. We aimed to identify publication bias with the construction of funnel plots (Page 2020). However, insufficient trials were eligible for inclusion in the current version of the review. We plan to undertake this analysis in future if we can include more trials.

Data synthesis

We were unable to combine studies meaningfully due to the heterogeneity of studies in terms of outcomes, comparisons, and populations. For continuous measurements, we had planned to use weighted mean differences to pool results from studies using a common measurement scale. Where studies used different measurement scales, we planned to pool standardised mean differences. Instead, we have presented difference in means and 95% confidence intervals for individual studies and summary effects, using the following order: Population > Comparison > Outcome. We assessed all individual treatments separately, given the individual study differences and heterogeneity in study design. We considered combining data – for example, on high-dose versus low-dose proton pump inhibitors (please see Effects of interventions) – to attempt to increase the population size on which conclusions were based, only where similar outcomes in similar participants were assessed. However, we were unable to undertake

this method due to the heterogeneity of study methodology. Due to the number of summary of finding tables, we limited our assessment of quince syrup, as it is not a prescribable medicine. We have not included quince syrup in the summary of findings tables, nor assessed the certainty of evidence for this intervention.

Subgroup analysis and investigation of heterogeneity

We addressed subgroup analysis in two ways. First, we have distinguished between infants (up to 12 months in age) and children (one to 16 years in age) throughout the review. These subgroups have different GOR characteristics. For example, infants with symptomatic gastro-oesophageal reflux have different symptoms from older children (who are generally on a more solid diet, and are upright). Some treatments, such as alginates, are mainly used in the infant cohort.

Secondly, we looked for studies evaluating specific subgroups: (1) preterm infants, as this group of babies can be problematic to assess and often have empirical treatment for common symptoms (e.g. apnoeas and bradycardias) that can be caused by GORD, but are more commonly caused by other issues associated with prematurity; and (2) children with neurodisability, who often have considerable gut dysmotility, and are often on long-term antireflux therapy. The results are outlined within Effects of interventions.

Where we found substantial heterogeneity (I^2 > 50%) between studies for the primary outcome, we explored the reasons for heterogeneity (including severity of reflux, demographic differences (age and comorbidity) within the age subgroups, having considered varying outcomes, different comparison agents (same drug, different dosing)) and downgraded the evidence certainty. As it was inappropriate to pool the data because of clinical or statistical heterogeneity, which we discuss in Overall completeness and applicability of evidence, we did not conduct meta-analysis. There were insufficient studies within other specific subgroups (preterm infants and children within neurodisability) to consider heterogeneity.

Sensitivity analysis

In this review update, we could not undertake meta-analysis due to the heterogeneity of the included studies' populations, comparisons, and outcomes. Thus, sensitivity analysis was not required. In future updates of the review, if meta-analysis is possible, we plan to undertake sensitivity analysis to explore whether a 12-month age threshold for subgroups influences meta-analytic robustness. We plan to integrate these findings into the results and conclusions. Additionally, if there are sufficient data in future updates of the review, we plan to explore whether endoscopic metrics, pH indices, and symptomatic outcomes are affected by either endoscopic descriptors (such as erosive or non-erosive oesophagitis) or severity markers on 24-hour pH-impedance monitoring (such as reflux index). Other possible sensitivity analyses will depend on the type of meta-analysis possible.

Summary of findings and assessment of the certainty of the evidence

Two authors (MT, EA) independently used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each outcome, and to draw conclusions about the certainty of evidence within the text of the review. We resolved any disagreements through discussion, involving all review authors if a disagreement could not be resolved.

Our summary of findings tables prioritise comparisons and outcomes that will be of use to decision-makers. We deferred the creation of summary of findings tables for treatments that are not currently available by prescription to future review updates. All review author reviewed the GRADE considerations in assessing the certainty of evidence (Schünemann 2013), and integrated judgements into the summary of findings tables.

All review authors agreed prior to data collection that the summary of findings tables should distinguish results by age (infants: 0 to 12 months; and children: aged 1 to 16 years old). The tables present these outcomes: symptoms, adverse events, pH impedance indices, and endoscopic metrics. We provide clear rationales where we downgraded evidence according to GRADE criteria.

RESULTS

Description of studies

Results of the search

The first version of this review included 24 studies (Tighe 2014). In the September 2022 update searches, we identified 1427 records through electronic database searches and supplemental search methods. After the removal of duplicates, 1034 records remained. At this stage, we discarded 978 records as clearly irrelevant. We screened the full-text publications of 54 studies (56 records). We excluded 40 studies (42 records) and listed two studies as 'awaiting classification.' We identified 12 new studies for inclusion. Thus, in this updated version, we have included a total of 36 RCTs assessing 2251 participants. We identified no ongoing studies (see Figure 1).

Figure 1. PRISMA study flow diagram

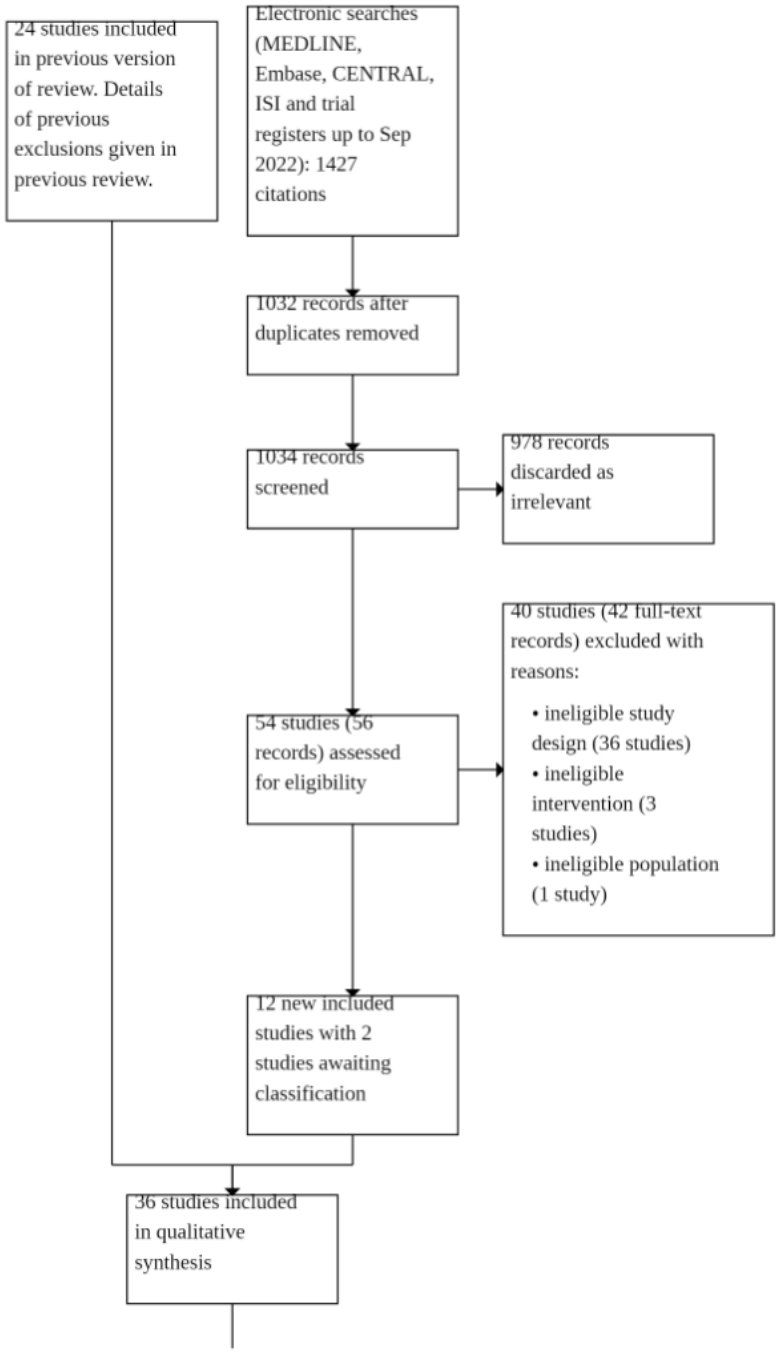
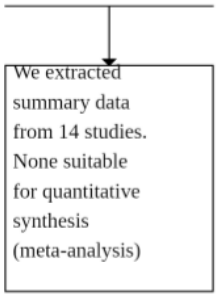


Figure 1. (Continued)



Included studies

We present the main characteristics of the included studies in the Characteristics of included studies table.

Study design

Of the 36 RCTs, most (31) were of parallel-group design (Azizollahi 2016; Baker 2010; Ballengee 2018; Bines 1992; Borrelli 2002; Buts 1987; Carroccio 1994; Cresi 2008; Cucchiara 1984; Cucchiara 1993; Davidson 2013; Famouri 2017; Forbes 1986; Gilger 2006; Gunesekaran 2003; Haddad 2013; Kierkus 2011; Loots 2014; Miller 1999; Naeimi 2019; Omari 2006; Omari 2007; Orenstein 2008; Pfefferkorn 2006; Simeone 1997; Tolia 2006; Tolia 2010a; Tolia 2010b; Tsou 2006; Ummarino 2015; Zohalinezhad 2015); two were cross-over studies (Baldassarre 2020; Moore 2003), two were withdrawal studies (Hussain 2014; Orenstein 2002), and one had a more complex design (Del Buono 2005). Twenty-two studies (61%) enroled more than 40 participants (Azizollahi 2016; Baker 2010; Baldassarre 2020; Carroccio 1994; Cucchiara 1984; Davidson 2013; Famouri 2017; Gilger 2006; Gunesekaran 2003; Haddad 2013; Hussain 2014; Loots 2014; Miller 1999; Naeimi 2019; Omari 2007; Orenstein 2008; Tolia 2006; Tolia 2010a; Tolia 2010b; Tsou 2006; Ummarino 2015; Zohalinezhad 2015), and 14 studies enroled fewer than 40 participants (Ballengee 2018; Bines 1992; Borrelli 2002; Buts 1987; Cresi 2008; Cucchiara 1993; Del Buono 2005; Forbes 1986; Kierkus 2011; Moore 2003; Omari 2006; World Bank 2022; Pfefferkorn 2006; Simeone 1997). The largest study enroled 268 participants (Hussain 2014).

Fifteen studies were multicentre (Baker 2010; Baldassarre 2020; Davidson 2013; Gilger 2006; Gunesekaran 2003; Haddad 2013; Hussain 2014; Loots 2014; Miller 1999; Orenstein 2002; Orenstein 2008; Tolia 2006; Tolia 2010a; Tolia 2010b; Tsou 2006) and 21 were single-centre (Azizollahi 2016; Ballengee 2018; Bines 1992; Borrelli 2002; Buts 1987; Carroccio 1994; Cresi 2008; Cucchiara 1984; Cucchiara 1993; Del Buono 2005; Famouri 2017; Forbes 1986; Kierkus 2011; Moore 2003; Naeimi 2019; Omari 2006; Omari 2007; Pfefferkorn 2006; Simeone 1997; Ummarino 2015; Zohalinezhad 2015). Seventeen studies had a placebo-controlled arm (Ballengee 2018; Bines 1992; Buts 1987; Carroccio 1994; Cresi 2008; Davidson 2013; Del Buono 2005; Famouri 2017; Forbes 1986; Hussain 2014; Loots 2014; Miller 1999; Moore 2003; Omari 2006; Orenstein 2002; Orenstein 2008; Simeone 1997). Ten studies compared the active medication to a comparator medication (Azizollahi 2016; Baldassarre 2020; Borrelli 2002; Carroccio 1994; Cucchiara 1984; Cucchiara 1993; Naeimi 2019; Pfefferkorn 2006; Ummarino 2015; Zohalinezhad 2015), and 10 studies used the same medication at different doses (Baker 2010; Gilger 2006; Tolia 2010b; Gunesekaran 2003; Haddad 2013; Kierkus 2011; Tolia 2006; Tolia 2010a; Tolia 2010b; Tsou 2006). One study compared improvements on the active medication to baseline (Omari 2006). All the studies were conducted on outpatients except Cresi 2008 and Davidson 2013 which were conducted on inpatients in neonatal intensive care units (NICUs). All bar four of the studies were conducted in high-income countries: Azizollahi 2016, Famouri 2017, Naeimi 2019, and Zohalinezhad 2015 were conducted in Iran, a lower-middle income country (World Bank 2022).

Participants

Nineteen studies assessed infants only, six studies assessed infants and children, and 11 assessed children aged one year or older. Of the studies that assessed infants only, 14 included infants with symptomatic GORD (Azizollahi 2016; Baldassarre 2020; Bines 1992; Cresi 2008; Davidson 2013; Del Buono 2005; Famouri 2017; Forbes 1986; Hussain 2014; Loots 2014; Miller 1999; Orenstein 2002; Orenstein 2008; Ummarino 2015), four studies included infants with symptoms and signs of GORD on 24-hour pH/impedance monitoring (Ballengee 2018; Kierkus 2011; Moore 2003; Omari 2007); one study included infants with endoscopic changes (Pfefferkorn 2006); and one study included infants with either significant pH indices or endoscopic changes (Moore 2003). Of those studies in both infants and children, one study included participants with symptomatic GORD (Zohalinezhad 2015), and six studies undertook corroborative investigations (pH/impedance and endoscopy) (Buts 1987; Carroccio 1994; Cucchiara 1984; Cucchiara 1993; Kierkus 2011; Simeone 1997). Of the studies in children aged one year or older, one study included children with symptomatic GORD (Naeimi 2019), and 10 studies undertook corroborative investigations (endoscopy, pH/impedance studies, or both) (Baker 2010; Borrelli 2002; Gilger 2006; Gunesekaran 2003; Haddad 2013; Omari 2006; Tolia 2006; Tolia 2010a; Tolia 2010b; Tsou 2006). Fourteen studies contained suitable summary data for extraction (described below in 'Interventions and comparisons'). Of those 14 studies, two studies had data on both infants and children (Cucchiara 1984; Zohalinezhad 2015); we discuss these in Included studies and Effects of interventions but do not present them in the summary of findings tables.

Interventions and comparisons

Studies in infants

Two studies with summary data assessed proton pump inhibitors (PPIs) versus placebo (Moore 2003 assessed omeprazole, Davidson 2013 assessed esomeprazole); one study with summary data compared a PPI (omeprazole) with another medication (ranitidine) (Azizollahi 2016); and two studies with summary data assessed a PPI given in different doses (Kierkus 2011 assessed pantoprazole, Hussain 2014 assessed rabeprazole). For H_2 antagonists, Azizollahi 2016 compared ranitidine with another medication (omeprazole). There were no studies with summary data that assessed prokinetics or magnesium alginate.

Studies in children

Six studies with summary data assessed a PPI. Two studies compared a PPI with another medication: Pfefferkorn 2006 compared omeprazole to additional ranitidine, and Zohalinezhad 2015 compared omeprazole to quince syrup. Three studies compared different doses of a PPI: Baker 2010 and Tolia 2006 assessed pantoprazole, Haddad 2013 assessed rabeprazole. For H_2 antagonists, as noted above, Azizollahi 2016 compared ranitidine to omeprazole. Two studies assessed quince syrup: as noted above, Zohalinezhad 2015 compared quince syrup to omeprazole, and Naeimi 2019 compared ranitidine plus quince syrup to ranitidine alone.

Outcomes

Studies in infants

Of studies which compared a PPI to placebo, one study with summary data provided data on clinical symptoms (Moore 2003), and three studies provided data on pH/impedance outcomes: Moore 2003 assessed omeprazole, Davidson 2013 assessed esomeprazole, and Kierkus 2011 assessed pantoprazole. One study on a PPI versus another medication (ranitidine) provided summary symptomatic data (Azizollahi 2016). One study on pantoprazole at different doses provided 24-hour pH/impedance outcome data (Kierkus 2011). One study with summary data assessed a PPI given in different doses (rabeprazole) (Hussain 2014). For H_2 antagonists, one study with symptomatic summary data compared ranitidine to another medication (omeprazole: Azizollahi 2016). There were no studies with summary data assessing prokinetics or alginates.

Studies in children

We included six studies assessing a PPI from which we were able to extract summary data, as follows. Pfefferkorn 2006 assessed omeprazole versus additional ranitidine and provided symptoms scores and reflux index data. Zohalinezhad 2015 provided symptom scores in a comparison of omeprazole to quince syrup. Three studies of pantoprazole provided extracted summary data: Baker 2010 and Tolia 2006 provided symptom scores, and endoscopic and histological scores, and Tsou 2006 provided symptom scores. Haddad 2013 studied rabeprazole and provided symptom scores and endoscopic and histological scores.

As stated above, Azizollahi 2016 assessed an H_2 antagonist (additional ranitidine with omeprazole) and provided summary symptomatic data. Two studies provided symptomatic summary data only on quince syrup (Zohalinezhad 2015 compared quince syrup to omeprazole, and Naeimi 2019 compared ranitidine plus quince syrup to ranitidine alone).

Included studies adopted different definitions of adverse events. Studies also varied in terms of reporting of adverse events and patient monitoring, and potential incomplete reporting. We have presented all reported adverse events.

No studies provided long-term data on the number of infants or children failing to respond to medication and requiring fundoplication.

Excluded studies

We excluded 40 studies (42 records) at the full-text screening stage. The primary reasons for exclusion were: ineligible study design (36 studies); ineligible intervention (three studies); ineligible population (one study). Please see Characteristics of excluded studies for further details.

Risk of bias in included studies

We detail our risk of bias assessments by study in Figure 2 and Figure 3. With many of the older studies, it was difficult to clarify methodological issues from the published protocol.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

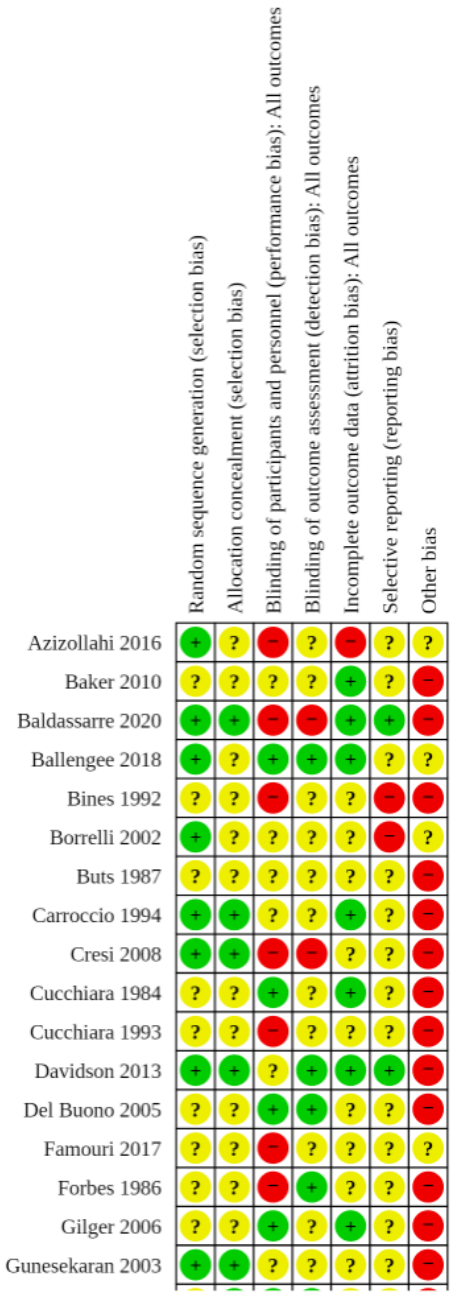


Figure 2. (Continued)

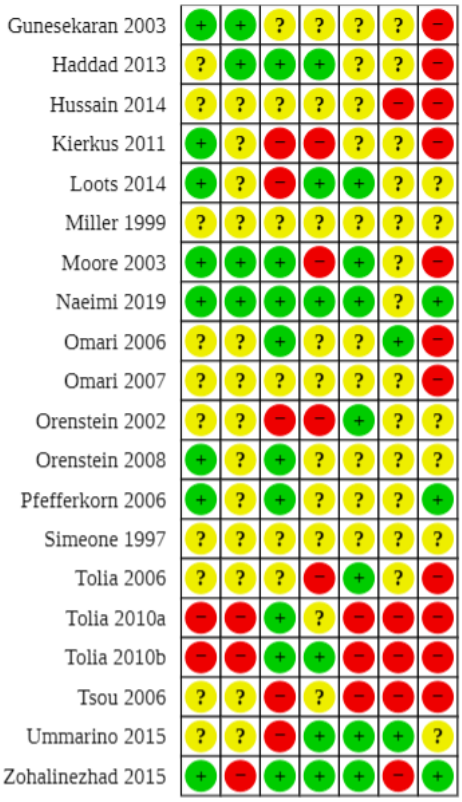
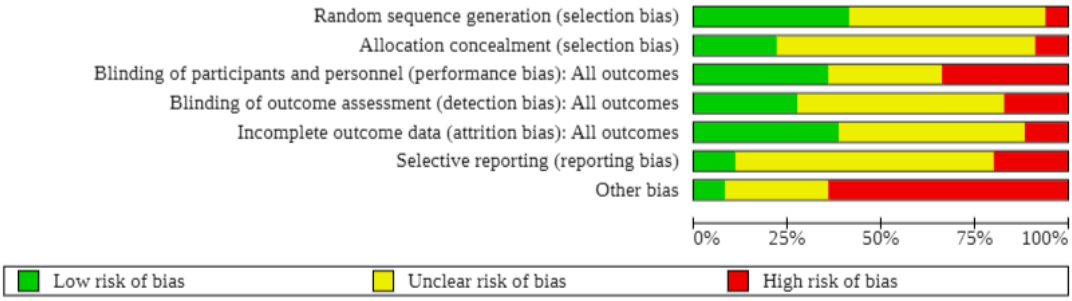


Figure 3. Risk of bias summary: review authors' judgements presented as percentages across all included studies



Random sequence generation (selection bias)

Fifteen studies clearly described an adequate method of random sequence generation, such as blocked randomisation; we assessed these as having a low risk of bias (Azizollahi 2016; Baldassarre 2020; Ballengee 2018; Borrelli 2002; Carroccio 1994; Cresi 2008; Davidson 2013; Gunesekaran 2003; Kierkus 2011; Loots 2014; Moore 2003; Naeimi 2019; Orenstein 2008; Pfefferkorn 2006; Zohalinezhad 2015). Nineteen studies made no reference to or incompletely outlined the method of randomisation used in their trial; we assessed these as having an unclear risk of bias (Baker 2010; Bines 1992; Buts 1987; Cucchiara 1984; Cucchiara 1993; Del Buono 2005; Forbes 1986; Famouri 2017; Gilger 2006; Haddad 2013; Hussain 2014; Miller 1999; Omari 2006; Omari 2007; Orenstein 2002; Simeone 1997; Tolia 2006; Tsou 2006; Ummarino 2015). We judged the remaining two studies to be at high risk of selection bias (Tolia 2010a due to the nature of a post hoc analysis and the risk of bias posed

by the selection of participants with oesophagitis who have not responded satisfactorily to other approved therapy; Tolia 2010b due to the risk of bias posed by the selection of participants for initial endoscopy and then enrolment being performed at the discretion of the investigator).

Allocation

Nine studies specified the method of allocation, such as randomised computer-generated allocation; we assessed these studies as having a low risk of bias in this domain (Azizollahi 2016; Baldassarre 2020; Carroccio 1994; Cresi 2008; Davidson 2013; Gunesekaran 2003; Haddad 2013; Moore 2003; Naeimi 2019). Twenty-four studies made no reference to or incompletely outlined the method of allocation used in their trial; we assessed these as having an unclear risk of bias (Baker 2010; Ballengee 2018; Bines 1992; Borrelli 2002; Buts 1987; Cucchiara 1984; Cucchiara 1993; Del Buono 2005; Forbes 1986; Famouri 2017; Gilger 2006; Hussain 2014; Kierkus 2011; Loots 2014; Miller 1999; Omari 2006; Omari 2007; Orenstein 2002; Orenstein 2008, Pfefferkorn 2006; Simeone 1997; Tolia 2006; Tsou 2006; Ummarino 2015). We judged the remaining three studies to be at high risk of selection bias: Tolia 2010a due to the nature of a post hoc analysis and the risk posed by the enrolment of participants who have not responded satisfactorily to other approved therapy; Tolia 2010b due to the risk of bias of enrolment based on initial endoscopy being performed at the discretion of the investigator; Zohalinezhad 2015 due to the marked difference in baseline symptom score in the omeprazole group, affecting outcomes such as refusal to feed and weight gain.

Blinding

Performance bias

We assessed 13 studies as low risk, with additional detail outlining methodological strategies to ensure equal care between groups and blinding of parents and participants (Ballengee 2018; Cucchiara 1984; Del Buono 2005; Gilger 2006; Haddad 2013; Moore 2003; Naeimi 2019; Omari 2006; Orenstein 2008; Pfefferkorn 2006; Tolia 2010a; Tolia 2010b; Zohalinezhad 2015). Eleven studies had an unclear risk of performance bias, where the blinding between groups was not explained in sufficient detail (Baker 2010; Borrelli 2002; Buts 1987; Carroccio 1994; Davidson 2013; Gunesekaran 2003; Hussain 2014; Miller 1999; Omari 2006; Simeone 1997; Tolia 2006). Hussain 2014 did not specify blinding technique but did use identical placebo and active preparations, we assessed this study as having an unclear risk of bias in this domain. Twelve studies were at high risk of performance bias (Azizollahi 2016; Baldassarre 2020; Bines 1992; Cucchiara 1993; Cresi 2008; Famouri 2017; Forbes 1986; Kierkus 2011; Loots 2014; Orenstein 2002; Tsou 2006; Ummarino 2015). The Azizollahi 2016 study used different preparations (omeprazole capsule versus ranitidine syrup), increasing the risk of bias. Baldassarre 2020, Cresi 2008, Famouri 2017, Kierkus 2011, and Tsou 2006 were open-label, as was the second part of the Bines 1992 study and the first part of the Orenstein 2002 study. There was no detail regarding blinding for Cucchiara 1993, but the participants were on ranitidine twice daily before the trial, and the ranitidine group continued receiving twice-daily dosing, while the omeprazole group received once-daily dosing. Forbes 1986 and Ummarino 2015 had clinician blinding but not parental blinding. In Loots 2014, the medications were double-blind but the children's body positioning was single-blind and parents were aware. This could affect reported symptom control outcomes, which rely heavily on parental reporting and diaries.

Detection bias

We assessed 10 studies as low risk with additional detailing of blinding assessment methods for assessors (Ballengee 2018; Davidson 2013; Del Buono 2005; Forbes 1986; Haddad 2013; Loots 2014; Naeimi 2019; Tolia 2010b; Ummarino 2015; Zohalinezhad 2015). Twenty studies had unclear risk, as they provided insufficient details about assessor blinding to determine risk of bias (Azizollahi 2016; Baker 2010; Bines 1992; Borrelli 2002; Buts 1987; Carroccio 1994; Cucchiara 1984; Cucchiara 1993; Famouri 2017; Gilger 2006; Gunesekaran 2003; Hussain 2014; Miller 1999; Omari 2006; Omari 2007; Orenstein 2008; Pfefferkorn 2006; Simeone 1997; Tolia 2010a; Tsou 2006). We assessed the six remaining studies as high risk (Baldassarre 2020; Cresi 2008; Kierkus 2011; Moore 2003; Orenstein 2002; Tolia 2006). Assessors were aware of the outcome for Baldassarre 2020, Cresi 2008, and Kierkus 2011. Parental diaries and visual analogue scores in Moore 2003 were open to recall bias. In Orenstein 2002, the parents were unblinded to the interventions in part one, affecting the risk of bias for the parental assessment. Tolia 2006 was assessed as high risk as the endoscopic outcomes were not assessed in one group.

Incomplete outcome data

Studies with good completion of outcome data were: Baker 2010; Baldassarre 2020; Ballengee 2018; Carroccio 1994; Cucchiara 1984; Davidson 2013; Gilger 2006; Loots 2014; Moore 2003; Naeimi 2019; Orenstein 2002; Tolia 2006; Ummarino 2015; and Zohalinezhad 2015. We rated these fourteen studies as low risk of bias in this domain. In both Zohalinezhad 2015 and Gilger 2006, only one participant was lost. Loots 2014 lost six of 51 participants. Ballengee 2018 lost two participants (one from each arm of the study) out of 31 and clearly stated the reason for loss (one died and the other developed sepsis). Baldassarre 2020 had no loss of participants after randomisation. In Naeimi 2019, four participants withdrew from the control (ranitidine) arm and one withdrew from the treatment arm (ranitidine and quince syrup).

Eighteen studies did not have enough evidence to determine risk of attrition bias: Bines 1992; Borrelli 2002; Buts 1987; Cresi 2008; Cucchiara 1993; Del Buono 2005; Famouri 2017; Forbes 1986; Gunesekaran 2003; Haddad 2013; Hussain 2014; Kierkus 2011; Miller 1999; Omari 2006; Omari 2007; Orenstein 2008; Pfefferkorn 2006; Simeone 1997. We assessed these as having an unclear risk of bias in this domain.

Four studies showed evidence of significant incomplete outcome data, particularly Azizollahi 2016, Tolia 2010a, Tolia 2010b, and Tsou 2006, sufficient to be considered at high risk of bias in this domain. We obtained further data for Tolia 2010a after direct communication with the authors.

Selective reporting

The risk of bias was low in Baldassarre 2020, Davidson 2013, Omari 2006, Ummarino 2015, and Zohalinezhad 2015.

Twenty-five studies did not have enough evidence to determine risk of reporting bias (Azizollahi 2016; Baker 2010; Ballengee 2018; Buts 1987; Carroccio 1994; Cresi 2008; Cucchiara 1984; Cucchiara 1993; Del Buono 2005; Famouri 2017; Forbes 1986; Gilger 2006; Gunesekaran 2003; Haddad 2013; Kierkus 2011; Loots 2014; Miller 1999; Moore 2003; Naeimi 2019; Omari 2007; Orenstein 2002; Orenstein 2008; Pfefferkorn 2006; Simeone 1997; Tolia 2006).

Reporting bias was evident in: Bines 1992; Borrelli 2002 (excluded severe oesophagitis); Hussain 2014 due to the post hoc analyses; Tolia 2010a; Tsou 2006; Tolia 2010b. We rated these as high risk.

Other potential sources of bias

We identified other sources of bias leading to a judgement of 'high risk' in 23 studies. These included studies with a follow-up of less than two weeks (Baldassarre 2020; Buts 1987; Cresi 2008; Davidson 2013; Del Buono 2005; Gunesekaran 2003; Kierkus 2011; Omari 2006; Omari 2007). In Bines 1992, participants agreeing to an open-label trial may be biased towards those who believed they had an initial benefit from treatment. In Baldassarre 2020, the comparator was a thickened formula. In Carroccio 1994, children received frequent short feeds, positioning advice, and all formula milk was thickened with Medigel 1%. Similarly, in Cucchiara 1984, all infants had thickener added (Nestargel 1%). Davidson 2013 was discontinued prematurely because of poor enrolment: the study estimated needing to recruit 90 participants to achieve 38 neonates in each group to achieve higher than 80% power at the 2-sided alpha level of 0.05 to detect a difference between esomeprazole and placebo in the change in number of symptoms from baseline. In Moore 2003, there was no evidence of reflux oesophagitis seen (erosions or ulcers) at entry endoscopy; loss of vascular pattern or friability was sufficient for inclusion. Moore 2003 included infants with reflux index higher than 5% in 24 hours, only seven infants had endoscopic changes and reflux index higher than 5% in 24 hours, so some of these infants may have had functional reflux.

We assessed the following studies as high risk for other bias as they either had pharmaceutical company support for manuscript-writing, an author was employed by a pharmaceutical company, or both (Baker 2010, Baldassarre 2020; Cucchiara 1993; Davidson 2013; Gilger 2006; Haddad 2013; Hussain 2014; Kierkus 2011; Omari 2007; Tolia 2006; Tolia 2010a; Tolia 2010b; Tsou 2006).

Other sources of bias are diverse, and are discussed in Included studies but were not assessed as providing a significant additional risk of bias.

We considered three studies to be of lower risk due to identified independent funding (Naeimi 2019; Pfefferkorn 2006; Zohalinezhad 2015).

Effects of interventions

See: **Summary of findings 1** Omeprazole compared to placebo for GORD in infants; **Summary of findings 2** Omeprazole compared to ranitidine for GORD in infants; **Summary of findings 3** Esomeprazole compared to placebo for GORD in infants; **Summary of findings 4** Rabeprazole at higher doses (1 mg/kg) compared to rabeprazole at lower doses (0.5 mg/kg) for GORD in children over 1 year of age; **Summary of findings 5** Pantoprazole in higher doses (1.2 mg/kg) compared to pantoprazole at lower doses (0.3 mg/kg) for GORD in children over 1 year of age

We present results below ordered by population (first infants (aged zero to 12 months) then children (aged one to 16 years)), treatment class, comparisons, and outcomes (improvement in clinical symptoms; adverse events; pH-impedance indices; endoscopic findings). Most of the included studies offered an appraisal of improvement in clinical symptoms. However, there was considerable heterogeneity in symptom assessment, such as the use of composite scores as well as individual symptom assessment. Studies in infants commonly assessed number of vomiting episodes, back arching, regurgitation, failure to thrive, feeding difficulties, or abdominal pain/colic. Studies in older children commonly assessed heartburn, epigastric pain, or regurgitation symptoms. Several studies used 24-hour pH/impedance studies, with reflux index and number of reflux episodes the most commonly-used outcomes. The macroscopic appearance of the oesophagus on endoscopy and histological improvement were the most common endoscopic improvement metrics. Most studies described adverse events, and we have summarised these below. We attempted to extract summary statistics from all studies, and where available, we expressed these as the difference in means (i.e. the mean difference, MD) with a 95% confidence interval (CI).

I. Infants

Proton pump inhibitors (PPIs)

Omeprazole

Omeprazole versus placebo

See Summary of findings 1.

Improvement in clinical symptoms

Based on the results of one study (Moore 2003), the evidence is very uncertain about the effect of omeprazole on cry/fuss time compared to placebo (MD -10.0 minutes (min)/24 hours, 95% CI -89.1 to 69.1; 30 infants; very low-certainty evidence; Analysis 1.1).

Adverse events

Although Moore 2003 reported no adverse events in either the omeprazole or placebo groups (30 infants), there was insufficient evidence to extract summary data on adverse events.

pH-impedance indices

The evidence is very uncertain about the effect of omeprazole on reflux index compared to placebo, based on one study assessing reflux index (Moore 2003) (MD -7.0% in 24 hours, 95% CI -4.66 to -9.34; 30 infants; very low-certainty evidence; Analysis 1.2).

Endoscopic findings

No studies were available for this outcome.

Omeprazole versus other treatments: ranitidine

See Summary of findings 2.

Improvement in clinical symptoms

Omeprazole and ranitidine may result in similar symptomatic improvement. Based on evidence from a single study (Azizollahi 2016), omeprazole (0.5 mg/kg/day) provided symptomatic benefit equivalent to ranitidine (2 to 4 mg/kg/day) in 76 infants with troublesome symptoms of GORD. Symptom scores in the omeprazole group improved from 51.93 ± 5.42 to 2.43 ± 1.15, and in the ranitidine group, from 47 ± 5.6 to 2.47 ± 0.58 after two weeks (MD -4.97, 95% CI -2.47 to -7.33; 1 study, 76 infants; very low-certainty evidence; Analysis 2.1). Another study noted improvements in symptom scores in participants treated with omeprazole (Cucchiara 1993). However, Cucchiara 1993 did not report the outcome in sufficient detail to allow extraction of summary statistics and did not differentiate between infants and

children, so we did not include this study in the assessment of evidence certainty.

Adverse events

Cucchiara 1993 noted that, in those randomised to eight weeks of either standard doses of omeprazole (40 mg/day/1.73 m^2 surface area) or higher doses of ranitidine (20 mg/kg/day), one participant sustained a fever and a respiratory infection and was withdrawn. The study did not specify the participant's age or treatment group, so we did not include this result in the assessment of evidence certainty, and there were insufficient data for summary data extraction. Azizollahi 2016 found that, overall, 16 participants withdrew, due to being lost to follow-up, prematurely discontinuing medication, having severe pneumonia, and the mother being unable to complete questionnaires. Azizollahi 2016 did not describe the number of participants with severe pneumonia, so this result was not suitable for inclusion in the summary of findings table.

pH-impedance indices

Although the Cucchiara 1993 study assessed this outcome, trialists did not distinguish between infants and children. We were therefore unable to extract suitable data and did not include this study in our assessment of the evidence certainty.

Endoscopic findings

Although the Cucchiara 1993 study assessed this outcome, trialists did not distinguish between infants and children. We were therefore unable to extract suitable data and did not include this study in our assessment of the evidence certainty.

Omeprazole versus other treatments: quince syrup

Zohalinezhad 2015 used omeprazole as a comparator to assess the efficacy of quince syrup for gastro-oesophageal reflux.

Improvement in clinical symptoms

Although the Zohalinezhad 2015 study assessed this outcome, trialists did not distinguish between infants and children. We were therefore unable to extract suitable data and did not include this study in our assessment of the evidence certainty.

Adverse events

Although the Zohalinezhad 2015 study assessed this outcome, trialists did not distinguish between infants and children. We were therefore unable to extract suitable data and did not include this study in our assessment of the evidence certainty. Zohalinezhad 2015 reported no adverse events in 37 infants and young children (under 60 months of age) in either the quince syrup or omeprazole groups.

pH-impedance indices

No studies were available for this outcome.

Endoscopic findings

Zohalinezhad 2015 did not identify how many participants underwent endoscopy, so we did not include this result in the summary of findings tables and did not assess evidence certainty.

Omeprazole at different doses

No studies were available for this comparison.

Lansoprazole

Lansoprazole versus placebo

Improvement in clinical symptoms

A single study assessing 162 infants (age range: four to 51 weeks) showed no improvement in the lansoprazole group compared to placebo, based on observer assessments and symptom diaries (Orenstein 2008). For participants who went on to take lansoprazole open-label (n = 55), there was no improvement in symptoms, but the trial did not report the outcome in sufficient detail to allow extraction of summary statistics. There was no investigation to confirm GORD in participants, and many of the participants enroled may have had functional reflux. Thus, we were unable to extract summary statistics with which to judge the efficacy of lansoprazole on symptomatic improvement compared to placebo.

Adverse events

The Orenstein 2008 study noted that adverse events were more common in the lansoprazole group (10 participants versus two placebo participants from a total of 162 participants). These included lower respiratory-tract infections (five participants versus one on placebo), diarrhoea (two participants), ileus (one participant), and dehydration (one participant). The trial did not report the outcome in sufficient detail to allow extraction of summary statistics or to estimate the certainty of the evidence. Thus, we were unable to extract summary statistics with which to judge the risk of adverse events.

pH-impedance indices and endoscopic findings

No studies were available for these outcomes.

Lansoprazole versus other treatments or at different doses

No studies were available for these comparisons.

Esomeprazole

Esomeprazole versus placebo

See Summary of findings 3.

Improvement in clinical symptoms

Esomeprazole may provide no symptomatic improvement compared to placebo, based on evidence from a single study. Davidson 2013 compared 52 neonates (premature to one month corrected age) given 0.5 mg/kg esomeprazole or placebo, and noted no improvement compared to placebo in the total number of GORD symptoms (from video monitoring) and GORD-related signs (from cardiorespiratory monitoring) (MD 3.2 episodes fewer, 95% CI 4.6 fewer to 1.8 fewer; 1 study, 52 neonates; very low-certainty evidence; Analysis 3.1).

Adverse events

In the single study comparing esomeprazole to placebo (Davidson 2013), the study did not report the outcome in sufficient detail to allow extraction of summary statistics. We were therefore unable to include this study in our assessment of the evidence certainty.

pH-impedance indices and endoscopic findings

No studies were available for these outcomes.

Esomeprazole versus other treatments: magnesium hydroxide

Improvement in clinical symptoms

A single study was available for this comparison: Loots 2014 compared esomeprazole and antacid (aluminium hydroxide and magnesium hydroxide (Mylanta)) therapy to left lateral positioning (LLP). In this study, 51 infants (aged two weeks to 26 weeks) with symptoms of GOR were randomised to one of four groups: (1) esomeprazole plus LLP; (2) esomeprazole plus head-of-cot elevation; (3) antacid plus LLP; or (4) antacid plus head-of-cot elevation. After two weeks, the esomeprazole groups' symptoms were reported to have improved more than those of the antacid groups, but the trial did not report the outcome in sufficient detail to allow extraction of summary statistics.

Adverse events

Loots 2014 reported five adverse events. Three were not considered serious: urinary tract infection, constipation, and diarrhoea and vomiting (following immunisation). Two of the adverse events were deemed serious: one participant (randomised to esomeprazole plus head elevation) was admitted with rotavirus infection; another (randomised to esomeprazole plus head elevation) was admitted because of reduced oral intake and weight loss. None were thought to be treatment-related. However, the study did not report adverse events in sufficient detail to allow extraction of summary statistics or to assess evidence certainty.

pH-impedance indices

Loots 2014 reported improved reflux index for the esomeprazole groups compared with the antacid groups (although reflux index < 10% in 24 hours in infants is not considered pathological by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)). This study did not report the outcome in sufficient detail to allow extraction of summary statistics or to judge evidence certainty.

Endoscopic findings

No studies were available for this outcome.

Esomeprazole at different doses

Improvement in clinical symptoms

Omari 2007 reported on 50 infants with symptoms of GORD and a reflux index suggestive of acid GOR (> 4% in 24 hours) who were given oral esomeprazole 0.25 mg/kg or 1 mg/kg for eight days. They noted greater symptom improvement in the lower-dose group. However, the trial did not report the outcome in sufficient detail to allow extraction of summary statistics for judging the efficacy of different doses of esomeprazole on symptomatic improvement.

Adverse events

Omari 2007 reported that only one infant with pre-existing colic developed excessive irritability and was withdrawn. However, this study did not report the outcome in sufficient detail to allow extraction of summary statistics for judging the risk of adverse events at different doses.

pH-impedance indices

Omari 2007 reported that reflux index improved in both groups (oral esomeprazole 0.25 mg/kg or 1 mg/kg), with greater improvement seen in the lower-dose group. However, this study did not report the outcome in sufficient detail to allow extraction of summary statistics for assessing the efficacy of esomeprazole on pH-impedance indices.

Endoscopic findings

No studies were available for this outcome.

Rabeprazole

Rabeprazole versus placebo or other treatments

No studies were available for these comparisons.

Rabeprazole at different doses

Improvement in clinical symptoms

The Hussain 2014 study was a five-week, double-blind withdrawal study (following a one- to three-week open-label phase) that compared rabeprazole 5 mg and 10 mg groups to placebo in 268 infants (aged one to 11 months). Only those infants who had improved went on to the double-blind withdrawal phase. Of the 268 randomised infants (placebo: 90; rabeprazole 5 mg: 90; rabeprazole 10 mg: 88), 231 (86%) completed the study. Efficacy endpoints were similarly improved during the open-label phase in all groups, and continued improving during the double-blind withdrawal phase with no difference between the placebo and combined rabeprazole groups. No difference in primary endpoints (I-GERQ scores) were noted. On post hoc analysis outcomes, a reduction in mean regurgitation frequency was seen (−0.79 versus −1.20 times a day), in I-GERQ-Revised scores (−3.6 (−25%) versus −3.9 points (−27%); MD 0.5, 95% CI −1.4 to 2.4), in I-GERQ-Daily Diary scores (−1.87 (−19%) versus −1.85 (−19%); MD 0.5, 95% CI −1.12 to 2.12), indicating equal improvement between the groups. However, given the serious risk of bias inherent in the post hoc nature of the study and given that only infants who had improved went on to the withdrawal phase, we did not include these data in the summary of findings tables.

Adverse events

In the double-blind phase of the study, Hussain 2014 noted equal rates (47%: n = 42) of adverse events between placebo and combined rabeprazole groups (diarrhoea, constipation, flatulence, crying, and rash). Vomiting and worsened GORD was reportedly more common in the placebo group, and eight participants in the rabeprazole groups had elevated gastrin levels noted. However, the study did not report the outcome in sufficient detail to allow extraction of summary adverse events statistics at different doses.

pH-impedance indices

No studies were available for this outcome.

Endoscopic findings

Hussain 2014 performed 12 endoscopies at baseline, but did not repeat them, so we were therefore unable to extract summary data and did not include this study in our assessment of the evidence certainty.

Pantoprazole

Pantoprazole versus placebo or other treatments

No studies were available for these comparisons.

Pantoprazole at different doses

Improvement in clinical symptoms

No studies were available for this outcome.

Adverse events

Kierkus 2011 assessed high-dose (1.2 mg/kg) versus low-dose pantoprazole (0.6 mg/kg) with a 24-hour pH probe performed at baseline and then at day five. One participant developed excessive vomiting (trialists did not explicitly state which group this infant was in), and the participant was withdrawn from the study during the open-label phase (24 infants). There was not enough evidence for pantoprazole at different doses to assess adverse events appropriately.

pH-impedance indices

The evidence is very uncertain about the effect of different doses of pantoprazole on pH-impedance indices, based on the Kierkus 2011 study. Trialists noted improvements in reflux index from baseline in both groups (MD −0.4% in 24 hours (95% CI −0.99 to 0.19)), number of episodes (103.0 (95% CI −3.8 to 209.8)), number of reflux episodes lasting more than five minutes (2.0 (95% CI −0.38 to 4.38)), and duration of the longest reflux episodes (9.0 minutes (95% CI 1.46 to 16.54)). In each group, 50% to 70% of infants had normal reflux indices on enrolment (reflux index < 5% in 24 hours; defined by the authors), but there was no difference between the low-dose and high-dose groups (1 study, 24 infants; very low-certainty evidence). However, the insufficient data at baseline affected our ability to extract summary data, so we have not included this study in the summary of findings tables.

Endoscopic findings

No studies were available for this outcome.

H_2 antagonists

Ranitidine

Ranitidine versus placebo

No studies were available for this comparison

Ranitidine versus other treatments: omeprazole

Improvement in clinical symptoms

Evidence from Azizollahi 2016 indicated that ranitidine was likely to improve clinical symptoms but was not superior to omeprazole. Azizollahi 2016 performed a randomised double-blind trial in 76 infants with troublesome symptoms (diagnosed as GORD) aged between two months and 12 months. Participants had two weeks of standard treatment (smaller, more frequent feeds, hypoallergenic thickened formula), and were then randomised for two weeks to ranitidine (2 to 4 mg/kg/day) or omeprazole (0.5 mg/kg/day). Symptom scores (one of five GORD symptoms (vomiting/regurgitation, irritability/fussing, choking/gagging, arching back, refusal to feed) were assessed weekly for two weeks. In the ranitidine group, symptom scores improved from 47 ± 5.6 to 2.47 ± 0.58 (mean ± SD) compared to the omeprazole group, which improved from a higher mean baseline of 51.93 ± 5.42 to 2.43 ± 1.15 (MD of symptom score change -4.97 (95% CI -2.47 to -7.33). No difference between ranitidine and omeprazole was seen (1 study, 76 infants; very low-certainty evidence). Please see Summary of findings 2.

Adverse events

Azizollahi 2016 found no adverse events (76 infants) but provided insufficient detail. We were therefore unable to extract summary data and did not include this study in our assessment of the evidence certainty regarding adverse events.

pH-impedance indices and endoscopic findings

No studies were available for these outcomes.

Ranitidine versus other treatments: hypoallergenic diet or formula

Improvement in clinical symptoms

There were no suitable summary statistics to assess outcomes. A single study assessed ranitidine (6 mg/kg daily in two divided doses) against a hypoallergenic diet (mothers of breastfed infants were advised to consume only a hypoallergenic diet; formula-fed infants were to feed on hydrolysed protein or amino acid-based formula) in 50 infants aged less than one year with I-GERQ-R scores of more than 7 (Famouri 2017). The study reported that an improvement in vomiting and respiratory symptoms was noted, but improvement in irritability, arching, or feed refusal was not observed. The study did not report the outcome in sufficient detail to allow extraction of summary statistics.

Adverse events

Although a single study noted no adverse events (50 infants) (Famouri 2017), we were unable to extract suitable data and did not include this study in our assessment of the evidence certainty.

pH-impedance indices and endoscopic findings

No studies were available for these outcomes.

Ranitidine at different doses

No studies were available for any outcome.

Cimetidine

Cimetidine versus placebo

No studies were available for any outcome.

Cimetidine versus other treatment: Maalox

Improvement in clinical symptoms

One study compared cimetidine to Maalox over 12 weeks in 33 infants and children (aged two months to 42 months) with a diagnosis of GORD based on symptoms, oesophagitis on endoscopy, and acid reflux on pH probe (Cucchiara 1984). They found that cimetidine and Maalox both provided symptomatic relief (MD 0.29 (95% CI -0.27 to 3.24). However, this study did not report the outcome in sufficient detail to differentiate between infants and children and was not included in the assessment of evidence certainty.

Adverse events

Cucchiara 1984 reported only that two participants on cimetidine had diarrhoea compared to placebo. However, this study did not differentiate between infants and children, so we did not include these data in the assessment of evidence certainty.

pH-impedance indices

Cucchiara 1984 observed that the reflux index was improved in both groups compared to baseline; neither group was superior (MD 0.31% in 24 hours (95% CI −1.45 to 2.1)). However, this study did not report the outcome in sufficient detail to differentiate between infants and children, so we did not include these data in the assessment of evidence certainty.

Endoscopic findings

Cucchiara 1984 found that endoscopic appearances were improved (MD 0.19 (95% CI -2.47 to 2.85)) but the trial did not report the outcome in sufficient detail to differentiate between infants and children and was not included in the assessment of evidence certainty.

Cimetidine at different doses

No studies were available for any outcome.

Famotidine

Famotidine versus placebo

Improvement in clinical symptoms

The single RCT for this comparison, Orenstein 2002, assessed 35 infants (age range 1.3 to 10.5 months) with symptomatic GORD who were given four weeks of famotidine 0.5 mg/kg versus famotidine 1 mg/kg (Phase 1: discussed in 'Famotidine at different doses' comparison below) and then four weeks' double-blind withdrawal comparison of each dose with placebo (Phase 2). Only 8 of 35 participants completed phase 2, giving insufficient data for meaningful comparison. There were no suitable summary statistics to assess improvement outcomes.

Adverse events

Orenstein 2002 noted that only eight of 35 participants completed phase 2 of the study, giving insufficient data for meaningful comparison, so we were therefore unable to extract summary data and did not include this study in our assessment of the evidence certainty. However, in addition to the adverse events reported below, the study report noted that four participants in the famotidine group and four in the placebo group experienced asymptomatic neutropenia which resolved.

pH-impedance indices and endoscopic findings

No studies were available for these outcomes.

Famotidine versus other treatments

No studies were available for any outcome.

Famotidine at different doses

Improvement in clinical symptoms

As described above, a single RCT for this comparison, Orenstein 2002, assessed 35 infants (age range 1.3 to 10.5 months) with symptomatic GORD who were given four weeks of famotidine 0.5 mg/kg versus famotidine 1 mg/kg (Phase 1), followed by four weeks' double-blind withdrawal comparison of each dose with placebo (Phase 2). Twenty-seven participants completed phase 1. In terms of symptom outcomes, a slight improvement in regurgitation frequency/volume and crying time in those infants receiving the reduced dose of famotidine was noted, as well as improved global assessments by parents and physicians. However, the data were not expressed in enough detail to allow extraction of summary symptom or observer statistics. There were no suitable summary statistics to assess outcomes.

Adverse events

Orenstein 2002 observed that 72% of infants receiving famotidine 0.5 mg/kg experienced adverse events and all infants receiving famotidine 1 mg/kg experienced adverse events. However, the data provided did not distinguish between the two groups, so we were unable to extract summary data to assess the certainty of evidence for this outcome. Trialists noted six participants with agitation or irritability (manifested as head-rubbing in two), three participants with somnolence, two participants with anorexia, two with headache, one participant with vomiting, one participant with hiccups, and one participant with candidiasis. Six infants on famotidine experienced new agitation/irritability; two had accompanying head rubbing and all resolved within days of ending therapy (35 infants).

pH-impedance indices and endoscopic findings

No studies were available for these outcomes.

Nizatidine

No studies were available for any comparison.

Prokinetics

Domperidone

Domperidone versus placebo

Improvement in clinical symptoms

Carroccio 1994 assessed symptoms, and noted no difference between domperidone and placebo. The trial did not report the outcome in sufficient detail to allow extraction of summary statistics, and did not differentiate between infants and children over one year of age, so we did not consider this study in assessing the certainty of evidence.

Adverse events

There was insufficient evidence to assess adverse events appropriately for domperidone compared to placebo, based on one study (Cresi 2008). No adverse events were seen (26 neonates).

pH-impedance indices

Two studies were considered. Cresi 2008 randomised 26 neonates to domperidone 0.3 mg/kg or placebo over 24 hours with assessment through a 24-hour oesophageal pH study. Reflux frequency was increased (difference in means between domperidone epochs and placebo: MD -1.26 episodes/hour (95% CI

-2.31 to -0.21), but duration was improved in this brief study (MD 3.5 seconds (95% CI -1.67 to 8.67)). Reflux height (MD -0.03 (95% CI -0.63 to 0.57)) and mean reflux pH (-0.12 (95% CI -0.90 to 0.66)) were no different. As this study only assessed short epochs (8 hours) of data, we have not assessed the certainty of the evidence nor included it in our summary of findings table. Carroccio 1994 also assessed pH indices, and noted no difference between domperidone and placebo. The trial did not report the outcome in sufficient detail to allow extraction of summary statistics, and did not differentiate between infants and children over one year of age, so we did not consider this study in assessing the certainty of the evidence.

Endoscopic findings

No studies were available for this outcome.

Domperidone compared to other treatments

Improvement in clinical symptoms

Carroccio 1994 performed an RCT in 80 participants (one month to 18 months old, with symptoms of reflux) in four groups (domperidone with alginate, domperidone alone, placebo, and domperidone with Maalox, with 20 participants in each group). Trialists assessed symptoms and 24-hour oesophageal pH indices. There were suggested improvement in symptoms in all four groups: it was reported that symptoms were resolved in 16 of 20 participants in the domperidone with Maalox group; in eight of 20 participants in the domperidone with alginate group; in nine of 20 participants in the domperidone alone group; and an improvement in symptoms in seven of 20 participants in the placebo group. However, the trial did not report the outcome in sufficient detail to allow extraction of summary statistics and did not differentiate between infants and children over one year of age, so we did not consider this study in assessing the certainty of the evidence.

Adverse events

No studies were available for this outcome.

pH-impedance indices

Carroccio 1994 assessed 24-hour oesophageal pH indices but did not report the outcome in sufficient detail to allow extraction of summary statistics and did not differentiate between infants and children over one year of age, so we did not consider this study in assessing the certainty of the evidence.

Endoscopic findings

No studies were available for this outcome.

Domperidone at different doses

No studies were available for this comparison.

Erythromycin

Erythromycin versus placebo

Improvement in clinical symptoms

Ballengee 2018 compared erythromycin (50 mg/kg/day) to a visually-indistinguishable placebo in 33 preterm infants with reflux events on pH-impedance monitoring (mean gestational age 27 weeks), and noted no improvement in nurse-reported apnoea/bradycardia and desaturations compared to placebo. However, the trial did not report the outcome in sufficient detail to allow extraction of summary statistics or assessment of evidence certainty.

Adverse events

Whilst Ballengee 2018 reported no increase in apnoeas, bradycardias, and desaturations in the erythromycin group compared to placebo, there were insufficient data for extraction of summary statistics (33 infants) and for judging evidence certainty.

pH-impedance indices

For Ballengee 2018, the primary outcome measure was the total number of reflux events on 24-hour pH-impedance monitoring after one week on erythromycin or placebo. The study found that erythromycin may be inferior to placebo in reducing reflux events, but the trial did not report the outcome in sufficient detail to allow extraction of summary statistics.

Endoscopic findings

No studies were available for this outcome.

Erythromycin versus other treatments or at different doses

No studies were available for these comparisons.

Compound alginate preparations

Sodium alginate plus magnesium alginate versus placebo

Improvement in clinical symptoms

Five studies evaluated sodium alginate plus magnesium alginate (sodium+magnesium alginate; i.e. Gaviscon Infant) (Buts 1987; Carroccio 1994; Del Buono 2005; Forbes 1986; Miller 1999). Miller 1999 and Buts 1987 found symptomatic improvement, but were limited by short follow-up and did not have enough data for extraction of summary statistics. Buts 1987 noted that the number of episodes of regurgitations per day reported by parents was reduced during the trial (20 participants), although summary statistics could not be extracted and the authors did not differentiate between infants and children over one year of age. We did not include these data in the summary of findings tables.

Adverse events

Four studies in sodium+magnesium alginate evaluated adverse events (Buts 1987; Carroccio 1994; Forbes 1986; Miller 1999). Buts 1987 found no adverse events in 20 children but had insufficient data for extraction of summary statistics. Trialists did not differentiate infants from children over one year of age, so we did not assess the certainty of the evidence or include the data in the summary of findings tables. Forbes 1986 noted no adverse events, but these authors also did not differentiate between infants and children, so we did not include the data in the summary of findings tables or assess the certainty of the evidence. Carroccio 1994 also did not report adverse events in sufficient detail to allow extraction of summary statistics and did not differentiate between infants and children, so we did not consider these data in assessing the certainty of the evidence. Miller 1999 noted that 13 participants withdrew due to adverse effects, including diarrhoea and constipation, but with no difference between groups. The trial did not report the outcome in sufficient detail to allow extraction of

summary statistics, and we did not consider these data in assessing the certainty of the evidence.

pH-impedance indices

Two studies assessed this outcome: Del Buono 2005 only noted an improvement in reflux height on manometry, with no other differences compared to placebo, but the trial did not report the outcome in sufficient detail to allow extraction of summary pH statistics. An older formulation of sodium+magnesium alginate (Gaviscon Infant) was evaluated by Forbes 1986, showing no difference in pH indices after 24 hours of treatment, but conclusions were limited by the short-term nature of this study (24 hours). The total number of reflux events per hour were similar between groups (MD −32.0 (95% CI −85.5 to 21.5)) as well as total duration of reflux episodes (MD 22.0 seconds (95% CI −63.6 to 107.1)). As the authors did not differentiate between infants and children over one year of age, we did not include the data in the summary of findings tables or judge the certainty of the evidence.

Endoscopic findings

No data were available for this outcome.

Sodium+magnesium alginate versus other treatments

Improvement in clinical symptoms

No data were available for this outcome. As discussed above, Carroccio 1994 demonstrated no symptomatic benefit in the domperidone and sodium+magnesium alginate group (20 children), compared to placebo or to domperidone, but the trial did not report the outcome in sufficient detail to allow extraction of summary statistics. However, a confounding factor may have been the thickening of all feeds in all groups by Medigel 1%.

Adverse events

As discussed above, Carroccio 1994 did not comment on adverse events, so we did not consider this study in assessing the certainty of the evidence.

pH-impedance indices

Carroccio 1994 performed an RCT in 80 participants (infants aged one month to 18 months old with symptoms of reflux) in four groups, and assessed 24-hour oesophageal pH indices. However, the trial did not report the outcome in sufficient detail to allow extraction of summary statistics and did not differentiate between infants and children over one year of age, so we did not consider this study in assessing the certainty of the evidence.

Endoscopic findings

No studies were available for this outcome.

Sodium+magnesium alginate at different doses

No studies were available for this comparison.

Magnesium (Mg) alginate

Magnesium alginate versus placebo

No studies were available for this comparison

Magnesium alginate versus other treatments

Improvement in clinical symptoms

We identified two studies. Baldassarre 2020 assessed 53 formula-fed infants and 19 breastfed infants (aged three weeks to four months) with IGERQ-R scores above 16, and noted that in formula-fed infants, while both groups improved, no differences in score reduction between magnesium alginate and thickened formula was seen. The breastfed arm did not have a control arm so was not considered. However, the trial included a thickener as a comparator arm, so we have not considered these data in assessing the certainty of evidence. Ummarino 2015 was not included as the trial did not report the outcome in sufficient detail to allow extraction of summary statistics. This study noted magnesium alginate plus simethicone showed improved symptoms compared to thickened formula and lifestyle advice.

Adverse events

We identified two studies. One study noted no adverse events in the magnesium alginate group (75 infants) (Ummarino 2015). Baldassarre 2020 monitored for adverse events and reported that no participants withdrew due to adverse events. However, trialists did not report the presence or absence of adverse events, and so we did not consider this study in assessing evidence certainty.

pH-impedance indices and endoscopic findings

No studies were available for these outcomes.

Magnesium alginate at different doses

No studies were available for this comparison.

II. Children older than one year

Proton pump inhibitors

Omeprazole

Omeprazole versus placebo

No studies were available for this comparison

Omeprazole versus ranitidine

Improvement in clinical symptoms

We assessed two studies (Cucchiara 1993; Pfefferkorn 2006). Pfefferkorn 2006 assessed nocturnal acid breakthrough symptoms after three weeks in 16 participants (aged one to 13 years) with symptomatic GORD with endoscopic/histological changes treated with omeprazole. In the omeprazole group, symptom scores improved from 2.0 ± 0 at baseline, to 0.6 ± 0.4 at week three, to 0.4 ± 0.45 at week 9, to 0.4 ± 0.5 at week 17; difference in means from baseline to week 17: MD -1.6 (95% CI -1.9 to -1.2). The study also reported no additional benefit from adding ranitidine in those with breakthrough symptoms. There was insufficient detail to compare omeprazole plus ranitidine to omeprazole plus placebo for inclusion in a summary of findings table or to assess the certainty of evidence. As discussed above, Cucchiara 1993 noted similar improvements in symptoms in both those randomised to eight weeks of standard doses of omeprazole (40 mg/day/1.73m^2 surface area) and higher doses of ranitidine (20 mg/kg/day). However, we did not consider this evidence further as the trial did not report the outcome in sufficient detail to allow extraction of

summary statistics, and did not differentiate between infants and children so was not considered in the certainty of evidence.

Adverse events

We assessed two studies (Cucchiara 1993; Pfefferkorn 2006). One study noted no adverse events (16 participants) (Pfefferkorn 2006). Cucchiara 1993 noted one participant was withdrawn due to a temperature and a respiratory infection, but it was uncertain which treatment group this participant was from (omeprazole or high-dose ranitidine). We did not consider this evidence further as the trial did not report the outcome in sufficient detail to allow extraction of summary statistics, or differentiate between infants and children so was not considered in the certainty of evidence.

pH-impedance indices

Two studies assessed the impact of omeprazole versus ranitidine on pH-impedance indices. Additional ranitidine may not provide additional benefit. Pfefferkorn 2006 assessed nocturnal acid breakthrough symptoms after three weeks in 16 participants with symptomatic GORD with endoscopic/histological changes (aged one to 13 years) treated with omeprazole. Oesophageal pH studies were performed at baseline, week three, and week 17 on omeprazole. Reflux index improved following initiation of therapy from 14.3 ± 11.5% in 24 hours at baseline to 2.0 ± 2.9% in 24 hours at week three (MD -12.3 (95% CI-18.4 to -6.4)). The reflux index did not change from week three (2.0 ± 2.9% in 24 hours) to week 17 after initiation of ranitidine (5.1 ± 5.1% in 24 hours) (MD 3.1 (95% CI-1.0 to 7.2)). However, as both arms contained omeprazole, we have not included this result in a summary of findings table or assessed the certainty of evidence. Cucchiara 1993 noted improvements in pH indices but was not further considered as the trial did not report the outcome in sufficient detail to allow extraction of summary statistics, and did not differentiate between infants and children so was not considered in the certainty of evidence.

Endoscopic findings

Two studies assessed the impact of omeprazole versus ranitidine on endoscopic findings. Additional ranitidine may not provide additional benefit. Pfefferkorn 2006 assessed endoscopy appearances at baseline and week 17 using Hetzel-Dent scoring (grade 0 to 4). Improvement in endoscopic grade from 3.1 ± 1.4 to 1.6 ± 1.8 occurred in those children receiving omeprazole: MD -1.5 (95% CI-3.1 to 0.1). Improvement in mean histology scores of all participants from baseline (1.8 ± 0.7) to week 17 (0.8 ± 0.9): MD -1.0 (95% CI -1.8 to -0.2) was also seen. However, as both arms contained omeprazole, we have not included this result in a summary of findings table nor assessed the certainty of evidence. Further detail on the effect of ranitidine is discussed below. As discussed above, Cucchiara 1993 noted similar improvements in endoscopic appearances in those randomised to eight weeks of standard doses of omeprazole (40 mg/day/1.73m^2 surface area) or higher doses of ranitidine (20 mg/kg/day). This result was not further considered as the trial did not report the outcome in sufficient detail to allow extraction of summary statistics, and did not differentiate between infants and children so was not considered in the certainty of evidence.

Omeprazole versus quince syrup

Zohalinezhad 2015 was the only included study which investigated this comparison, using omeprazole as a comparator to assess the efficacy of quince syrup.

Improvement in clinical symptoms

Omeprazole may provide symptomatic relief but was not superior to quince syrup, based on one study in 80 children (aged 0 to 18 years) with GORD (Zohalinezhad 2015). Composite Symptom Scores (CSS) improved in both groups (quince syrup versus omeprazole (2 mg/kg/day)). This was seen in infants and young children (aged less than 60 months: discussed above) and 42 children (aged more than 60 months to 18 years) at four and seven weeks compared to baseline. In children aged over five years, at week 7, CSS scores were 37 in the quince group and 43 in the omeprazole group. However, as quince syrup is not clinically prescribable, we have not assessed the certainty of evidence in the summary of findings tables. Please see 'Quince syrup versus other treatments' comparison below for a mean difference (MD).

Adverse events

Zohalinezhad 2015 identified no adverse events in either group (42 children), but the trial did not report the outcome in sufficient detail to allow extraction of summary statistics.

pH-impedance indices

No studies were available for this outcome.

Endoscopic findings

One study was unclear about how many children had had endoscopy (Zohalinezhad 2015), so there were no suitable data for this outcome, and we did not assess evidence certainty.

Omeprazole at different doses

No studies were available for this comparison.

Lansoprazole

Lansoprazole versus placebo

No studies were available for this comparison.

Lansoprazole versus other treatments: alginate

Improvement in clinical symptoms

One study compared lansoprazole plus alginate versus lansoprazole alone in 36 children (age range: 12 months to 12 years) with GORD (based on symptoms, 24-hour pH probe and endoscopy), and reported that symptom scores improved in all groups by week 8 (Borrelli 2002). The trial did not report the outcome in sufficient detail to allow extraction of summary outcome statistics.

Adverse events

One study noted the absence of adverse events (36 children) (Borrelli 2002), but the study did not report the outcome in sufficient detail to allow extraction of summary statistics

pH-impedance indices

Borrelli 2002 compared lansoprazole plus alginate versus lansoprazole alone in 36 children (age range: 12 months to 12 years) with GORD (based on symptoms, 24-hour pH probe and endoscopy). Reflux index improved in all groups by week 8. The trial did not report the outcome in sufficient detail to allow extraction of summary outcome statistics.

Endoscopic findings

Borrelli 2002 compared lansoprazole plus alginate versus lansoprazole alone in 36 children (range 12 months to 12 years) with GORD (based on symptoms, 24-hour pH probe and endoscopy). Endoscopic appearances improved in both groups by week 8. The trial did not report the outcome in sufficient detail to allow extraction of summary outcome statistics.

Lansoprazole at different doses

Improvement in clinical symptoms

One study assessed 63 adolescents (age range: 12 to 17 years) with symptomatic/endoscopic GORD, randomised to lansoprazole 30 mg versus 15 mg (Gunesekaran 2003). After five days of treatment, the symptom diaries and physician assessments in both groups noted improvements in the frequency and severity of heartburn and other symptoms, but the trial did not report the outcomes in sufficient detail to allow extraction of summary statistics.

Adverse events

Gunesekaran 2003 noted that pharyngitis 6% (2/32 in lansoprazole 15 mg) and headache (16% 4/31) were the most commonly-reported adverse events (63 children), but the study did not report adverse events in sufficient detail to allow extraction of summary statistics.

pH-impedance indices and endoscopic findings

No studies were available for these outcomes.

Esomeprazole

Esomeprazole versus placebo or other treatments

No studies were available for these comparisons.

Esomeprazole at different doses

Two studies were considered. Tolia 2010b demonstrated resolution of endoscopically-proven erosive oesophagitis after eight weeks of esomeprazole in 45/109 children aged one to 11 years. Symptoms and safety data were published by the group separately (Gilger 2006), and then a post hoc analysis of some of these children with endoscopically-confirmed GORD (aged 12 months to 36 months old) compared esomeprazole 5 mg or 10 mg daily for eight weeks (Tolia 2010a). The trial did not report the outcome in sufficient detail to allow extraction of summary statistics.

Improvement in clinical symptoms

Two studies were considered. Tolia 2010b reported improvement in reflux symptoms as assessed by physician's global assessment (PGA) and parental diaries, but the trial did not report the outcome in sufficient detail to allow extraction of summary statistics. Subsequently, a post hoc analysis of some of these children with endoscopically-confirmed GORD (aged 12 months to 36 months old) compared esomeprazole 5 mg or 10 mg daily for eight weeks (Gilger 2006). They noted 84.2% had improved symptom scores by the final visit, and no difference was reported between low-dose and high-dose groups. However, the trial did not report the outcome in sufficient detail to allow extraction of summary statistics.

Adverse events

Two studies were considered. Gilger 2006 noted improvement in reflux symptoms as assessed by PGA and parental diaries, but the study did not report the outcome in sufficient detail to allow extraction of summary statistics. Only 9.3% of participants reported 13 adverse events; the most common were diarrhoea (2.8% (3/108)), headache (1.9% (2/108)), and somnolence (1.9% (2/108)). Vomiting in two participants was not judged to be related to treatment. Tolia 2010b did not note any additional adverse events. Again, the study did not report the outcome in sufficient detail to allow extraction of summary statistics

pH-impedance indices

No studies were available for this outcome.

Endoscopic findings

The two available trials did not report the outcome in sufficient detail to allow extraction of summary statistics.

Rabeprazole

Rabeprazole versus placebo or other treatments

No studies were available for these comparisons.

Rabeprazole at different doses

Improvement in clinical symptoms

Rabeprazole at different doses (0.5 mg/kg and 1 mg/kg) may provide similar symptomatic improvement, based on a single study: Haddad 2013 noted a decrease in the mean 'Total GERD Symptoms and Severity' score. The symptom score improved for 0.5 mg/kg and 1 mg/kg dosing in both the low-weight group (< 15 kg) (mean -13.6 ± 13.1) and (-9 ± 11.2): MD 4.6 (95% CI -2.9 to 12.1), and the high-weight group (> 15 kg) (-10.6 ± 11.1) and (-8.3 ± 9.2): MD 2.3 (95% CI -2 to 6.6) by week 12 (1 study, 127 children; very low-certainty evidence; Analysis 4.1). Please see Summary of findings 4.

Adverse events

Rabeprazole at 0.5 mg/kg and 1 mg/kg is likely to give some adverse events, based on a single study: Haddad 2013 noted 95 (84%) children had adverse events, including abdominal pain, nausea, vomiting, bronchopneumonia, gastroenteritis, cough, and choking (1 study, 127 children; very low-certainty evidence).

pH-impedance indices

No studies were available for this outcome.

Endoscopic findings

Rabeprazole at different doses may provide endoscopic and histological improvement, based on a single study: Haddad 2013 found that endoscopic scores in both the low-weight group (0.5 mg/kg mean -1.4 ± 1.1) and 1 mg/kg -1.1 ± 0.7): MD 0.3 (95% CI -0.3 to 0.9) and high-weight group (0.5 mg/kg -1.1 ± 0.7) and (1 mg/kg -1 ± 0.9):

MD 0.1 (95% CI -0.2 to 0.4) improved at week 12 using Hetzel-Dent criteria (1 study, 127 children; very low-certainty evidence; Analysis 4.2). Please see Summary of findings 4. Histological scores (Grades 1 to 5) also improved: MD -0.8 (95% CI -1.06 to -0.53) but this is not reported in the summary of findings table, as discussed in Types of outcome measures.

Pantoprazole

Pantoprazole versus placebo or other treatments

No studies were available for these comparisons.

Pantoprazole at different doses

Pantoprazole may or may not improve symptom scores at 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg pantoprazole in children aged one to five years by week 8 with no difference between 0.3 mg/kg and 1.2 mg/kg dosing (0.3 mg/kg mean −2.4 ± 1.7); 1.2 mg/kg −1.7 ± 1.2): MD 0.7 (95% CI -0.4 to 1.8; 1 study, 60 children; very low-certainty evidence) and may confer some to no increase in the risk of adverse events (very low-certainty evidence).

Improvement in clinical symptoms

Pantoprazole appears to improve symptoms at the different dose-regimens, based on a single study. Baker 2010 looked at 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg pantoprazole in 60 children (aged one to five years) with symptoms of GORD and endoscopic or histological signs of GORD over eight weeks. Symptom scores improved in all dose-regimens from baseline to week 8 (0.3 mg/kg MD −2.4, 95% CI −3.2 to −1.5; 0.6 mg/kg MD −0.6, 95% CI −1.7 to 0.5; 1.2 mg/kg MD −1.7, 95% CI −2.9 to −0.39). Symptom scores improved from baseline to week 8 (0.3 mg/kg mean −2.4 ± 1.7); 1.2 mg/kg −1.7 ± 1.2). There was no difference between 0.3 mg/kg and 1.2 mg/kg dosing: MD 0.7 (95% CI -0.4 to 1.8). Please see Summary of findings 5 and Analysis 5.1. Individual symptoms (abdominal pain, burping, heartburn, pain after eating, difficulty swallowing) improved in all groups after eight weeks (1 study, 60 children; very low-certainty evidence). Two other studies were considered: Tsou 2006 assessed 136 children (aged 12 to 16 years) with symptoms of GORD given either pantoprazole 40 mg (n = 68) or pantoprazole 20 mg (n = 68) over eight weeks. In both groups, composite symptom scores reportedly improved from baseline to end of trial from 177 and 174 by at least 100 points, with improvements in the number of vomiting episodes per day, heartburn symptom score, and epigastric pain score, although the trial did not report the results in sufficient detail to allow independent extraction of summary statistics. Tolia 2006 compared 10 mg, 20 mg, and 40 mg pantoprazole over eight weeks in 53 children (five to 11 years) with symptomatic GORD, and noted symptomatic improvements in all groups treated with pantoprazole, although there was not enough detail to extract summary statistics.

Adverse events

Three studies reported data on adverse events. Tsou 2006 found 82% of 136 children reported an adverse event, mainly headache, and in the high-dose group (40 mg) reported diarrhoea. Five participants had minor derangement of their liver function tests. Tolia 2006, assessing 53 children, noted in the pantoprazole 10 mg group the following: headache (seven participants; 36.8%), rhinitis (five participants; 26.3%), and nausea (three participants; 15.8%); in the pantoprazole 20 mg group, the following: headache (five participants; 27.8%) and rhinitis (three participants each; 16.7%); in the 40 mg group, the following: headache (four participants; 25%). Baker 2010, assessing 60 children aged one to five years, observed no difference between the groups. In the low-dose group, one participant had diarrhoea and nappy rash; in the medium-dose group, one participant had sleep disturbance, one had abdominal pain; in the high-dose group, one participant had rectal bleeding (1 study, 60 participants, very low-certainty evidence). Unfortunately, due to the multiple different dose-regimes, it was only possible to include information for Baker 2010 in the summary of findings table in narrative format.

pH-impedance indices

No studies were available for this outcome.

Endoscopic findings

Two studies reported endoscopy outcomes: there was not enough detail to extract summary statistics. Tolia 2006 had observed that endoscopy appearances showed no improvements in any group, and histologically, in the 10 mg pantoprazole group. In those with non-erosive GORD, 36% improved and no participants with erosive disease were treated within this group. In those receiving pantoprazole 20 mg, of those with non-erosive GORD, 50% of participants improved (n = 9) with 44% unchanged (n = 8). In those with erosive disease, all three were healed at eight weeks. In those treated with pantoprazole 40 mg, of those with non-erosive disease, 68% of participants improved (n = 11) with 25% unchanged (n = 4); 6.2% worsened (n = 1). There was no correlation between composite symptom score changes and endoscopy/biopsy changes. In younger children, endoscopy was performed in four participants with erosive changes (Baker 2010); all four healed, but the trial did not report the outcome in sufficient detail to allow extraction of summary endoscopic statistics. For histology appearances, no scope was performed after treatment in those participants with histological changes only.

H_2 antagonists

Ranitidine

Ranitidine versus placebo

No studies were available for this comparison.

Ranitidine versus other treatments

Improvement in clinical symptoms

Two studies were considered: Cucchiara 1993 (see above), who found similar improvements in symptoms in those randomised to eight weeks of either higher doses of ranitidine (20 mg/kg/day) or standard doses of omeprazole (40 mg/day/1.73 m^2 surface area). The trial did not report the outcome in sufficient detail to allow extraction of summary statistics. Pfefferkorn 2006 noted an improvement in nocturnal acid breakthrough symptoms after three weeks in 18 participants with symptomatic GORD with endoscopic/histological changes (aged one to 13 years) treated with omeprazole, but no additional benefit from additional ranitidine in those with breakthrough symptoms was seen. Symptom scores in both groups reportedly improved from baseline (see omeprazole above), but the trial did not report the outcome in sufficient detail to allow extraction of summary statistics comparing the two groups (symptoms and pH indices) so this study is not reported in the summary of findings table.

Adverse events

Two studies were considered, although one study, Pfefferkorn 2006, noted no adverse events (16 participants). Cucchiara 1993 noted one participant was withdrawn due to a temperature and a respiratory infection, but it was uncertain which treatment group this participant was from (omeprazole or high-dose ranitidine). The trial did not report the outcome in sufficient detail to allow extraction of summary statistics, or differentiate between infants and children, so these data were not considered in the certainty of evidence.

pH-impedance indices

Two studies were considered: Pfefferkorn 2006 assessed nocturnal acid breakthrough symptoms after three weeks in 16 participants with symptomatic GORD with endoscopic/histological changes (aged one to 13 years) treated with omeprazole. The reflux index did not change from week three (2.0 ± 2.9% in 24 hours) to week 17 after initiation of additional ranitidine (5.1 ± 5.1% in 24 hours): MD 3.1 (95% CI-1.0 to 7.2), but direct comparison between omeprazole and ranitidine was not possible. Cucchiara 1993 noted improvements in pH indices but was not further considered as the trial did not report the outcome in sufficient detail to allow extraction of summary statistics, and did not differentiate between infants and children so was not considered in the certainty of evidence.

Endoscopic findings

Two studies were considered: Pfefferkorn 2006 assessed endoscopy appearances at baseline and week 17 using the Hetzel-Dent score (grade 0 to 4), and saw an improvement in grade from 3.1 ± 1.4 to 1.6 ± 1.8: MD -1.5 (95% CI-3.1 to 0.1). An improvement in mean histology scores of all participants from baseline (1.8 ± 0.7) to week 17 (0.8 ± 0.9): MD -1.0 (95% CI -1.8 to -0.2) was also seen, but a direct comparison between omeprazole and ranitidine was not possible as ranitidine was introduced at week 3. As discussed above, Cucchiara 1993 noted similar improvements in endoscopic appearances in both the group randomised to eight weeks of higher doses of ranitidine (20 mg/kg/day) and the group receiving standard doses of omeprazole (40 mg/day/1.73m^2 surface area). This result was not further considered as the trial did not report the outcome in sufficient detail to allow extraction of summary statistics, and the trial did not differentiate between infants and children so was not considered in the certainty of evidence.

Quince syrup and ranitidine versus ranitidine alone

Improvement in clinical symptoms

Ranitidine may provide symptomatic relief but was not superior to quince syrup and ranitidine, based on one study: Naeimi 2019 undertook an outpatient double-blind RCT of ranitidine 8 mg/kg/day plus quince syrup (0.5 mL/kg/day) versus ranitidine alone (8 mg/kg/day) in 96 children aged between one and four years with GORD (diagnosed on clinical symptoms: two of five symptoms (regurgitation or vomiting, poor weight gain for one month, respiratory distress after feeding, feed refusal, and restlessness after feeding)). These symptoms were assessed at two, four, and six weeks with the Global Severity Questionnaire (GSQ-YC). Comparing the total symptom scores showed that ranitidine was effective but that ranitidine plus quince syrup was superior to ranitidine alone: at week 2 (mean ± SD 17.8 ± 2.6 versus 23.4 ± 4.0), week 4 (11.5 ± 2.3 versus 18.8 ± 3.6), and week 6 (12.2 ± 2.3 versus 21.1 ± 4.1): MD at week 6 was 8.9 (95% CI 7.6 to 10.2). In terms of individual symptoms at six weeks, all symptoms were improved in both groups, but there was greater improvement in vomiting (MD 1.3 (95% CI 0.9 to 1.7)), feed refusal (MD 1.9 (95% CI 1.5 to 2.3)), burping/belching (MD 1.8 (95% CI 1.3 to 2.3)), and abdominal pain (MD 1.0 (95% CI 0.5 to 1.5)) in the ranitidine with quince syrup group. No differences in swallowing difficulties (MD 1.7 (95% CI 1.2 to 2.2)) or choking during eating (MD 0.8 (95% CI 0.3 to 1.3)) were seen between the groups. These differences emerged between two and four weeks after starting treatment. As both groups contained ranitidine, we included the certainty of evidence in the quince syrup section.

Adverse events

There was not enough evidence to assess adverse events appropriately for this comparison. However, one study identified no adverse events in either group (96 children) (Naeimi 2019).

pH-impedance indices and endoscopic findings

No studies were available for these outcomes.

Ranitidine at different doses

No studies were available for this comparison.

Cimetidine and Famotidine

No studies were available for any comparisons.

Nizatidine

Nizatidine versus placebo

Improvement in clinical symptoms

Simeone 1997 assessed 26 participants (age range: six months to eight years) with histologic evidence of oesophagitis, randomised to either nizatidine 10 mg/kg twice a day or placebo for eight weeks. Improvement of symptoms was only seen in the nizatidine group, with reductions in abdominal pain (MD 1.5 (95% CI −0.6 to 2.4)), chest pain (MD 0.6 (95% CI −0.50 to 1.70)), regurgitation (MD 1.4 (95% CI 0.5 to 2.3)), and vomiting (MD 1.2 (95% CI 0.15 to 2.3)). However, as the trial included some infants under one year of age, we did not include these data in the summary of findings tables.

Adverse events

Simeone 1997 assessed 26 participants (age range: six months to eight years) randomised to either nizatidine 10 mg/kg twice a day or placebo for eight weeks. A single participant on nizatidine had an urticarial rash, and one participant on placebo was withdrawn due to worsened clinical symptoms. Study authors did not mention the adverse event severity or the ages of the affected participants, so we did not assess the certainty of evidence. No other adverse events were noted.

pH-impedance indices

Simeone 1997 included some infants under one year of age, so we did not include these data in the summary of findings tables. Post-treatment pH measurement showed improved event rates (reflux index, number of episodes pH < 4, number of episodes > 5 minutes, duration of episodes of pH < 4) in the nizatidine group versus placebo, but the trial did not report the outcome in sufficient detail to allow extraction of summary pH statistics.

Endoscopic findings

Simeone 1997 included some infants under one year of age, so we did not include these data in the summary of findings tables. Endoscopy findings included better healing in 69% of participants in the nizatidine group, but the trial did not report the outcome in sufficient detail to allow extraction of summary endoscopy statistics.

Nizatidine versus other treatments or at different doses

No studies were available for these comparisons.

Prokinetics

Domperidone

Domperidone versus placebo

Improvement in clinical symptoms

Bines 1992 assessed the impact of domperidone over four weeks (double-blind) then a further four weeks (open-label) versus placebo in 17 participants (aged five months to 11.3 years). No individual symptom was improved by four weeks. After eight weeks of therapy, 33% of participants treated with domperidone noted an improvement in symptoms. Some improvements were reported after four weeks of little symptom improvement, but as the study included some infants under one year of age, we did not include these data in the summary of findings tables and the trial did not report the outcome in sufficient detail to allow extraction of summary statistics.

Adverse events

Bines 1992 noted no serious adverse events, but six participants had self-limiting diarrhoea (four participants on domperidone, two on placebo). As the study included some infants under one year of age, we did not include these data in the summary of findings tables and the trial did not report the outcome in sufficient detail to allow extraction of summary statistics.

pH-impedance indices

On pH monitoring, Bines 1992 observed there was only an improvement reported in total reflux episodes, with other metrics unchanged. The low number of participants (with some infants under one year of age) and lack of full (24-hour) pH probes limited the applicability of this study. The trial did not report the outcome in sufficient detail to allow extraction of summary statistics.

Endoscopic findings

No studies were available for this outcome.

Domperidone versus other treatments or at different doses

No studies were available for these comparisons.

Quince syrup

Quince syrup versus placebo

No studies were available for this comparison.

Quince syrup versus other treatments: omeprazole

Improvement in clinical symptoms

Quince syrup was as good or better than omeprazole in improving symptoms based on one study (Zohalinezhad 2015). In this study in 80 children (aged 0 to 18 years) with GORD, Composite Symptom Scores (CSS) improved in both the quince syrup and omeprazole (2 mg/kg/day) groups. This was seen in infants and young children (aged less than 60 months: discussed above) and 42 children (aged more than 60 months to 18 years) at four and seven weeks compared to baseline. In children aged over five years, at week 7, CSS scores were 43 in the omeprazole group and 37 in the quince group (MD -6 (95% CI-39.9 to 27)). However, as quince syrup is not a prescribable medicine, we did not include this in the summary of findings tables nor assess the certainty of evidence (please see Methods).

Adverse events

There was not enough evidence to assess adverse events appropriately for quince syrup compared to omeprazole. However, Zohalinezhad 2015 identified no adverse events in either group (42 children).

pH-impedance indices

No studies were available for this outcome.

Endoscopic findings

In Zohalinezhad 2015, it was unclear how many children had had endoscopy, so we did not consider this result in the certainty of evidence.

Quince syrup versus ranitidine

Improvement in clinical symptoms

Quince syrup may provide symptomatic relief in addition to ranitidine, based on one study: Naeimi 2019 undertook an outpatient double-blind RCT of ranitidine (8 mg/kg/day) versus ranitidine 8 mg/kg/day plus quince syrup (0.5 mL/kg/day) in 96 children aged between one and four years with GORD diagnosed on clinical symptoms (two of five symptoms (regurgitation or vomiting, poor weight gain for one month, respiratory distress after feeding, feed refusal, and restlessness after feeding)). These were assessed at two, four, and six weeks with the Global Severity Questionnaire (GSQ-YC). Comparing the total symptom scores showed that ranitidine plus quince syrup was superior to ranitidine alone: at week 2 (mean ± SD 17.8 ± 2.6 versus 23.4 ± 4.0), week 4 (11.5 ± 2.3 versus 18.8 ± 3.6), and week 6 (12.2 ± 2.3 versus 21.1 ± 4.1): MD at week 6 8.9 (95% CI 7.6 to 10.2). In terms of individual symptoms at six weeks, all symptoms were improved in both groups, but there was greater improvement in vomiting (MD 1.3 (95% CI 0.9 to 1.7)), feed refusal (1.9 (95% CI 1.5 to 2.3)), burping/belching (1.8 (95% CI 1.3 to 2.3)), and abdominal pain (1.0 (95% CI 0.5 to 1.5)) in the ranitidine with quince syrup group. No differences in swallowing difficulties (MD 1.7 (95% CI 1.2 to 2.2)) or choking during eating (0.8 (95% CI 0.3 to 1.3)) were seen between the groups. These differences emerged between two and four weeks after starting treatment. However, as quince syrup is not a prescribable medicine, we did not include this result in the summary of findings tables nor assess the certainty of evidence (see above).

Adverse events

There was not enough evidence to assess adverse events appropriately for quince syrup compared to ranitidine alone. However, Naeimi 2019 identified no adverse events in either group (96 children).

pH-impedance indices and endoscopic findings

No studies were available for these outcomes.

Quince syrup at different doses

No studies were available for this comparison.

Compound alginate preparations

Alginate versus placebo

No studies were available for this comparison.

Alginate versus other treatments: lansoprazole

Improvement in clinical symptoms

No suitable data were available for this outcome; one study was considered. Gaviscon liquid was assessed by Borrelli 2002, who, as discussed above, noted improvements in symptoms in children (aged 12 months to 12 years) with erosive oesophagitis given alginate alone, and noted that the greatest improvement in symptoms was seen in children treated with alginate and lansoprazole. The trial did not report the outcome in sufficient detail to allow extraction of summary statistics.

Adverse events

There was not enough evidence to assess adverse events appropriately for alginates compared to lansoprazole. Borrelli 2002 noted no adverse events.

pH-impedance indices

Borrelli 2002 noted improvements in pH indices in children (aged 12 months to 12 years) with erosive oesophagitis given alginate alone, and noted that the greatest improvement was seen in children treated with alginate and lansoprazole. The trial did not report the outcome in sufficient detail to allow extraction of summary statistics.

Endoscopic findings

Borrelli 2002 noted improvements in endoscopic indices in children (aged 12 months to 12 years) with erosive oesophagitis given alginate alone, and noted that the greatest improvement was seen in children treated with alginate and lansoprazole. The trial did not report the outcome in sufficient detail to allow extraction of summary statistics.

Alginate at different doses

No studies were available for this comparison.

Antispasmodics

Baclofen

Baclofen versus placebo

Improvement in clinical symptoms

No studies were available for this outcome.

Adverse events

There was not enough evidence to assess adverse events appropriately for baclofen. Omari 2006 noted no adverse events in the baclofen group in the 48 hours following the trial.

pH-impedance indices

A single study compared baclofen to placebo in a double-blinded RCT in 30 children with resistant GORD (mean age 10.0 ± 0.8 years) (Omari 2006). Children were assessed with manometry/pH for two hours after they were given 0.5 mg/kg baclofen or placebo. The primary outcome (measurement of the incidence of transient lower oesophageal sphincter relaxations (TLESR)) was not a prespecified outcome of this review. The Omari 2006 study assessed pH indices, but did not report the outcome in sufficient detail to allow extraction of summary pH statistics.

Endoscopic findings

No studies were available for this outcome.

Baclofen versus other treatments or at different doses

No studies were available for these comparisons.

III. Other subgroups

We identified no studies assessing the efficacy of drug treatment in children with neurodisability and GORD.

DISCUSSION

We included a total of 36 trials assessing 2251 participants in this review. We were able to extract summary data from 14 RCTs, with the remaining studies having insufficient data for extraction.

Summary of main results

In this review, we cover a wide range of potential treatments for GOR/GORD in a range of population groups. We place the extracted summary data into context with other studies, where available. The Cochrane Gut Group ran the review searches independently to ensure reproducibility.

Overall, the evidence evaluating the role of medications in GORD is of very low certainty. There are several reasons for this, including the heterogeneity of the population, the lack of head-to-head trials, variation in outcome measures, and variability in how well outcome measures (e.g. symptom scores/reflux index/endoscopic appearances) correlate in estimating the severity of GORD. There is also a group of infants and children who have physiological reflux that is problematic but not a pathological disease.

Below, we present outcomes (symptom scores, pH-impedance indices, endoscopic/histological appearances, and adverse events) structured by population (first infants, then children), then by treatment class. We discuss evidence certainty if we were able to extract summary data, and outline our findings below.

I. Infants

Proton pump inhibitors

Please see Summary of findings 1; Summary of findings 2; Summary of findings 3.

For proton pump inhibitor studies with extracted summary data, there is very low-certainty evidence based on single studies that infants with GOR and GORD may or may not benefit from omeprazole and esomeprazole. There is very low-certainty evidence that PPIs improve reflux index and other pH probe markers of GORD, and the correlation between pH probe results and direct symptomatic benefit was very weak in infants. There were no suitable data regarding adverse events or endoscopic metrics in any study in infants. Other studies – from which we could not extract summary statistics – showed mixed efficacy.

Omeprazole

One study (with summary data extracted) compared omeprazole to placebo in infants only. This study noted that crying occurred in both omeprazole-treated and untreated irritable infants, concluding that the cry/fuss time decreased spontaneously with time, and that empirical acid suppression was not indicated in this group. One study (with summary data extracted) comparing omeprazole and ranitidine noted similarly improved GORD symptom scores in infants.

Lansoprazole

No studies provided suitable summary data. Of the studies without summary data, one found no symptomatic difference between lansoprazole and placebo, and of those who went on to take lansoprazole open-label, there was no improvement in symptoms. Many participants may have had physiological reflux, and a risk of adverse events was noted, including lower-respiratory tract infections in infants treated with lansoprazole.

Esomeprazole

One study of neonates showed very low-certainty evidence that esomeprazole was no better than placebo in treating the total number of GORD symptoms (from video monitoring) and GORD-related signs (from cardiorespiratory monitoring). One other study of older infants without summary data reported that infants treated with esomeprazole had improved symptoms and improved reflux index compared to those treated with antacid. For different doses of esomeprazole, one other study without summary data noted improved clinical symptomsin the low-dose group. In terms of adverse events in the same study, one infant (with pre-existing colic) withdrew with irritability. Reflux index was improved in both groups, with greater improvement seen in the lower-dose group.

Pantoprazole

There were no studies assessing symptomatic improvements in infants treated with pantoprazole. However, in terms of pH indices, one study (with summary data extracted) assessing infants only noted improvements in reflux index from baseline in both groups, as well as in number of episodes, number of reflux episodes lasting more than five minutes, and duration of the longest reflux episodes (very low-certainty evidence).

Rabeprazole

There were no studies comparing rabeprazole to placebo or to other drugs. For rabeprazole at different doses, we were unable to extract any summary data. However, a withdrawal study noted no difference in primary symptom scores, and equally high rates of adverse events (diarrhoea, constipation, flatulence, crying, and rash) between groups.

H_2 antagonists

The evidence is very uncertain about the effect of H_2 antagonists on outcome. For H_2 antagonists, based on extracted summary data, there is very low-certainty evidence based on a single study that infants with GORD may or may not have symptomatic benefit from ranitidine. Other studies – from which we could not extract summary statistics – showed mixed efficacy for ranitidine, famotidine, cimetidine, and nizatidine.

Ranitidine

In terms of studies involving infants only, one study with summary data comparing ranitidine to omeprazole showed that the two agents were equivalent in improving symptom scores for infants with symptoms of GORD. For studies without summary data, one study without a control arm reported improved vomiting and respiratory symptoms, but no change in irritability, arching, or feed refusal over two weeks. For adverse events, no summary data were available, but two other studies found no adverse events. One other study assessing both infants and children found similar improvements in symptoms, 24-hour pH and endoscopic indices in those given either standard doses of omeprazole or high doses of ranitidine (20 mg/kg/day) in children refractory to standard-dose ranitidine.

Cimetidine

No studies provided suitable summary data for assessment, so no robust judgement about the certainty of evidence of efficacy or risk of adverse events can be made. One RCT without summary data compared cimetidine to Maalox in infants and young children with GORD, based on symptoms, oesophagitis on endoscopy, and acid reflux on pH probe. This study reported that cimetidine and Maalox provided symptomatic relief, and reflux index and endoscopic appearances were also improved in both groups.

Famotidine

No studies provided suitable summary data for assessment, so no robust judgement about the certainty of evidence of efficacy or risk of adverse events can be made. In terms of studies without summary data,one study noted slight improvement in regurgitation frequency/volume and crying time and improved global assessments by parents and physicians. However, only eight of 35 participants completed phase 2 (double-blind withdrawal versus placebo), giving insufficient data. A high proportion of infants experienced adverse events, including agitation or irritability, somnolence, weight loss, headache, vomiting, hiccups, candidiasis, and asymptomatic neutropenia which resolved.There were no data regarding pH or endoscopic indices.

Nizatidine

No studies provided suitable summary data for assessment, so no robust judgement about the certainty of evidence of efficacy can be made. However, one study of children and infants reported improved symptoms in the nizatidine group and only one participant had an adverse event (urticaria). Post-treatment pH-indices showed improved reflux index, number of episodes of pH less than 4, number of episodes of more than five minutes, and duration of episodes of pH less than 4 in the nizatidine group compared to those given placebos. Endoscopy findings included better healing in a high proportion of participants in the nizatidine group.

Prokinetics

As discussed above, we did not assess metoclopramide here, and there were no studies of prokinetics with suitable summary data, so no robust judgement about the certainty of evidence of efficacy can be made.

Domperidone

No studies provided suitable summary data for assessment. In terms of symptom improvements, there were no studies of infants alone, but two studies involved infants and children older than one year. One found no improvement in symptoms between domperidone and placebo; the other study noted individual symptoms improved after four weeks (double-blind); after a further four weeks (open-label), only a few participants given domperidone noted further symptom improvement. In terms of adverse events, one short study reported no adverse events. Three studies measured pH indices. One very short-term study (8-hour epochs) noted reflux frequency increased in the domperidone group, but duration was improved. In another study, no difference between domperidone and placebo was seen, but the placebo included an added thickener (Medigel 1%). The final study found no difference in reflux index and only improvement in total reflux episodes.

Erythromycin

No studies provided suitable summary data for assessment, so no robust judgement about the certainty of evidence of efficacy or risk of adverse events can be made. One study compared erythromycin in preterm infants over one week to placebo, and found no difference between the two groups in either number of apnoeas/bradycardias and desaturations or reflux events.

Quince syrup

Quince syrup is a traditional Persian medicine. One study compared it to omeprazole, which demonstrated improvement in symptom scores for both the infant groups, and older children from baseline. However, no difference between the treatment groups (quince syrup or omeprazole) was reported. The improvement in symptoms was present at four weeks after initiation of therapy and sustained at the 7-week follow-up. Quince syrup was also compared in combination with ranitidine to ranitidine alone in another study in children. Trialists noted improved global symptom scores, with improvements in vomiting, refusal of eating, burping/belching, and abdominal pain. The evidence for use of quince is limited, with only two studies with relatively small numbers and short follow-up. We did not assess the certainty of the evidence as this medicine is not clinically available.

Compound alginate preparations

No studies provided suitable summary data for assessment, so no robust judgement about the certainty of evidence of efficacy or risk of adverse events can be made.

Sodium+magnesium alginate

There were no summary data available to assess the certainty of evidence for sodium+magnesium alginate (Gaviscon Infant). We identified five studies without summary data; two of these evaluated the current formulation. Both studies noted symptomatic improvement, limited by short follow-up. In terms of pH indices, one study only noted an improvement in reflux height on manometry, with no other differences when compared to placebo in a short-term study. Assessing older preparations of Gaviscon Infant, three studies showed some to no difference in pH indices after 24 hours of treatment with sodium+magnesium alginate.

Magnesium alginate

There were no summary data available to assess the certainty of evidence for magnesium alginate. Of the remaining studies without summary data, one study compared magnesium alginate to thickener. Both groups containing formula-fed infants improved, with no differences in symptom score reduction between magnesium alginate and thickened formula. There was a breastfed study group which was not placebo-controlled. One open-label RCT noted symptom scores were reportedly reduced in the magnesium alginate-plus-simethicone group compared with thickened formula or reassurance groups, although there was some improvement in all groups, with the study limited by relatively small numbers and 8-week follow-up. Whilst there were no summary data, no adverse events were seen in the magnesium alginate group.No studies provided suitable summary data on pH or endoscopic indices for assessment.

Antispasmodics

Baclofen

No studies provided suitable summary data for assessment, so no robust judgement about the certainty of evidence of efficacy or risk of adverse events can be made.

II. Children older than one year of age

Proton pump inhibitors

Please see Summary of findings 4; Summary of findings 5.

In children over one year of age, very low-certainty evidence indicates that PPIs may or may not help GORD outcomes. Single studies with summary data extracted showed PPIs may or may not improve symptom scores, or erosive changes on endoscopy due to GORD, particularly in older children. There were very low-certainty summary data assessing frequency of adverse events, and no robust summary data regarding pH indices in older children. Other studies – from which we could not extract summary statistics – showed efficacy.

Omeprazole

No studies had suitable summary data. Of three other studies, one study comparing omeprazole with high-dose ranitidine noted similar improvements in symptoms, endoscopic findings, and reflux index. No significant adverse events were noted. A second study compared omeprazole to quince syrup in both infants and older children, and found that both treatments provided similar improvements in symptom scores from baseline. We extracted summary data for older children (> 60 months of age) but did not present these in a summary of findings table (very low-certainty evidence). There are insufficient data from RCTs about the long-term safety of omeprazole.

Lansoprazole

No studies provided suitable summary data for assessment, so no robust judgement about the certainty of evidence of efficacy or risk of adverse events can be made. Of the studies without summary

data, one study in children aged one to 12 years, reported symptom scores improving in all groups, with the lansoprazole and alginate group superior to the other two groups. A 24-hour pH study also showed improved reflux index, with the lansoprazole and alginate group superior to the other two groups. Endoscopy appearances were much improved in all three groups. No adverse events were reported. In older children (12- to 17-year-old children), one study of lansoprazole at different doses noted after five days that reflux symptoms were better in both groups. There are insufficient data from RCTs about the long-term safety of lansoprazole.

Esomeprazole

No studies provided suitable summary data for assessment in children, and only studies of esomeprazole at different doses were available. It was not possible to ascertain the certainty of evidence. Of the linked studies without summary data, one studynoted improvement in reflux symptoms, as assessed by physician's global assessment and parental diaries. Reported adverse events included diarrhoea, headache, and somnolence. One other study did not note any additional adverse events. There were no data presented on pH indices. One study noted endoscopic improvement in all groups, with a post hoc analysis of some participants with endoscopically-confirmed GORD (aged 12 months to 36 months) showing improved symptoms but no difference between low-dose and high-dose groups. Repeat endoscopy showed healing in all, confirmed on histology.

Rabeprazole

Please see Summary of findings 4, Analysis 4.1, and Analysis 4.2. One study provided suitable summary data for assessment in children older than one year of age, but only data regarding rabeprazole at different doses were available. Rabeprazole at different doses (0.5 mg/kg and 1 mg/kg) may provide similar symptomatic improvement (very low-certainty evidence). There was an equivalent adverse event profile in both the low- and higher-dose rabeprazole groups. There were no data for pH indices. Rabeprazole at different doses is likely to provide endoscopic and histological improvement,with a minimal clinically useful difference between doses in low-weight and high-weight groups (very low-certainty evidence).

Pantoprazole

Please see Summary of findings 5 and Analysis 5.1. One study of pantoprazole at different doses provided suitable summary data of clinical symptoms for assessment. Pantoprazole appears to improve symptoms at the different dose regimens in one study with summary data (very low-certainty evidence). Two other studies without summary data noted symptomatic improvements in all groups. One study had summary data for adverse events. It noted diarrhoea, nappy (i.e. diaper) rash, sleep disturbance, abdominal pain, and rectal bleeding (one participant each) (very low-certainty evidence). The remaining two studies noted high rates of adverse events (mainly headache). There were no summary data available for pH indices or endoscopic outcomes. Two other studies noted endoscopy outcomes, finding no correlation between symptom scores and endoscopy/biopsy changes.

H_2 antagonists

The evidence is very uncertain about the effect of H_2 antagonists on outcome, due to the absence of summary data. In those studies from which we could not extract summary statistics, the H_2 antagonists ranitidine, cimetidine, and nizatidine showed efficacy in terms of symptom score, pH indices, and endoscopic appearances.

Ranitidine

No studies provided suitable summary data for assessment in children. One study found similar improvements in symptoms, 24-hour pH probe data indices, and endoscopy appearances in those receiving eight weeks of either standard doses of omeprazole or high doses of ranitidine in children who had not responded to standard-dose ranitidine. One other study looked at the addition of ranitidine or placebo, to reduce nocturnal acid breakthrough, in children who had recently started on omeprazole. In this study, symptom scores, pH indices, and endoscopic appearances reportedly improved over 17 weeks, with no difference between ranitidine and placebo groups. There was therefore no additional benefit seen from supplementation of PPI therapy with ranitidine.

Cimetidine

No studies provided suitable summary data for assessment, so no robust judgement about the certainty of evidence of efficacy or risk of adverse events can be made. The only RCT compared cimetidine to Maalox over 12 weeks in infants and young children with a diagnosis of GORD, based on symptoms, oesophagitis on endoscopy, and acid reflux on pH probe. This study reported that cimetidine and Maalox provided symptomatic relief, and that reflux index and endoscopic appearances were also improved in both groups.

Famotidine

No studies provided suitable summary data for assessment, so no robust judgement about the certainty of evidence of efficacy or risk of adverse events can be made.

Nizatidine

No studies provided suitable summary data for assessment, so no robust judgement about the certainty of evidence of efficacy can be made. However, one study reported improved symptoms in the nizatidine group. No summary data could be extracted regarding adverse events, but the study reported only one participant with urticaria. Post-treatment pH indices showed improved reflux index, number of episodes of pH less than 4, number of episodes of more than five minutes, and duration of episodes of pH less than 4 in the nizatidine group compared to placebo. Endoscopy findings included better healing in the majority of participants in the nizatidine group.

Prokinetics

Domperidone

No studies provided suitable summary data for assessment, so no robust judgement about the certainty of evidence of efficacy or risk of adverse events can be made. RCTs evaluating the use of domperidone included two studies involving infants and children older than one year. One study found no difference in improvement in symptoms between domperidone and placebo, but that the thickened feeds (Medigel 1%) could account for improvements in pH outcomes in the placebo group. Symptom improvement remained through six months of follow-up. One shorter-term study noted individual symptoms were improved after four weeks (double-blind). After a further four weeks of domperidone(open-

label) versus placebo, only a low proportion of participants treated with domperidone noted an improvement in symptoms. On pH probe, there was only improvement in total reflux episodes, and some improvement in growth metrics was seen.

Erythromycin

No studies provided suitable summary data for assessment, so no robust judgement about the certainty of evidence of efficacy or risk of adverse events can be made.

Quince syrup

Two studies provided summary symptom data in children older than one year. However, as discussed in the Methods and Results, we have not created a summary of findings table or assessed evidence certainty. One study comparing quince syrup with omeprazole demonstrated improved symptom scores for older children from baseline, with no difference between groups. The improvement in symptoms was present at four weeks after initiation of therapy and sustained at the 7-week follow-up. Quince syrup with ranitidine compared to ranitidine alone showed improved global symptom scores in both groups, with ranitidine and quince syrup superior to ranitidine alone for individual symptoms. There were not enough summary data to appropriately assess evidence certainty for adverse events. However, both studies identified no adverse events.

Antispasmodics

Baclofen

A single study showed improvement in acid reflux and transient lower-oesophageal sphincter relaxations in children treated with baclofen, but this was a short-duration (2-hour) trial (Omari 2006), with no other studies available in this group.

Overall completeness and applicability of evidence

We consider the completeness and applicability of evidence for each class of medication in turn, in infants and children with GORD. Overall, all but two studies were conducted on outpatients across primary and secondary care, where the vast majority of infants and children present with symptoms. The very low-certainty evidence is likely to be applicable to inpatient infants and children diagnosed with GOR and GORD and augment the two neonatal studies, though further studies would confirm this. There were three studies in lower-middle-income settings and 33 in high-income settings, but no studies of infants or children with GORD in low-income settings (see World Bank 2022 for definitions). In terms of outcomes, symptom scores summary data were often available, but adverse events summary data were often lacking. There was evidence of incomplete reporting regarding endoscopic findings and pH indices in three studies. These procedures may discourage recruitment, and are generally only available in tertiary centres.

Proton pump inhibitors

There is incomplete evidence for commonly used PPIs, as the results are based on single studies, with heterogeneity of case definition in infants. There were insufficient data (one study of esomeprazole) involving premature and term neonates and no data on children with neurodisability. There were also insufficient data about the most effective PPI in infants and children, though we presented data on adverse events profiles where available, and included overall messages suggested by studies without summary data for context. Long-term safety needs to be evaluated, and consistency between studies regarding symptom scoring would help meta-analysis.

H_2 antagonists (ranitidine and nizatidine)

With so few RCTs in infants or children, and no appropriate head-to-head comparisons against PPIs, meta-analysis to further investigate the effect of treatment was not possible. Our interpretation of summary data was limited to single studies. No RCTs evaluated the use of H_2 antagonists in physiological reflux. Subgroups of particular importance in which evidence is lacking include neonates and premature babies, as well as children with neurodisability. Evidence of efficacy in resource-limited settings would also be useful to consider.

Prokinetics

For domperidone and erythromycin, there were no studies based on summary data in infants or children. Further studies will substantially alter our understanding of the effect size, either compared to placebo or the other prokinetic agent. There are major limitations in published study design and length of follow-up. Subgroups of particular importance include neonates and children with neurodisability, for which there are no studies in domperidone or erythromycin.

Other agents

The utility of quince syrup in settings outside the single country in which it has been studied needs to be evaluated, as there may be other confounding factors that may affect efficacy in other settings. As quince syrup is not clinically available for prescription, it is difficult to assess how applicable the summary data are.

There were no studies in alginates based on summary data in infants or children over one year of age. Further studies in infants will substantially alter our understanding of the effect size, particularly as the available formulations have evolved over the past three decades.

Further studies to assess whether baclofen has a role in improving GORD in children with neurodisability, who are often prescribed baclofen for concomitant spasticity, would be useful. We have not found enough additional trials in this update to change our assessment of the evidence.

No studies assessed whether children who did not improve with treatment went on to need fundoplication.

Certainty of the evidence

We have included decisions about the certainty of the evidence within the summary of findings tables and considered whether risk of bias affected the certainty of the results enough to merit downgrading the evidence certainty. We appraised the general certainty of all the studies using GRADE criteria. There were insufficient trials for meta-analysis or a funnel plot to investigate reporting (publication) bias. We would have conducted a sensitivity analysis if the exclusion of studies with a high risk of bias was required.

As discussed above, the overall GRADE ratings for the certainty of evidence were all very low as the evidence was mainly based on single studies, with significant methodological concerns about

several studies (as summarised in Risk of bias in included studies, Figure 2, and Figure 3). Only nine studies specified the method of allocation, and 13 studies specified the blinding technique. Fifteen studies had a low risk of attrition bias, but only five studies were found to be at low risk for selective reporting bias. Only three studies had independent funding; pharmaceutical companies provided support for manuscript-writing and funding in several studies. None of the studies assessed in this update has improved the certainty of the evidence, meaning that further studies would add substantially to the evidence base. There was considerable heterogeneity, such as: outcomes analysed by different symptom scores; different participant groups (infants versus children, GOR versus GORD); PPIs in different dosing comparisons, rather than comparing different agents; and different indices (for example, on 24-hour pH/impedance monitoring). Further comparative studies in both infants and children are likely to improve the certainty of evidence.

Potential biases in the review process

The strengths of this review include the incorporation of further papers to reinforce the evidence base and the use of a similar systematic literature search (including handsearching) of multiple databases and relevant reviews, using wide search terms. The last update to the search was on 17 September 2022. Three review authors appraised each study, and a statistician verified the statistical analysis. Questions about newer studies (published from 2018 onward) were addressed by writing to the study authors, but we received no replies. Additional author data would help the robustness of evidence appraisal. There are no conflicts of interest to declare. Potential weaknesses of the review include the absence of sufficient summary data to perform a meta-analysis (and inability to perform a sensitivity analysis to test robustness), the inclusion of studies with few children, the short study duration of most studies, and the degree of outcome heterogeneity affecting the accuracy of conclusions.

Agreements and disagreements with other studies or reviews

This review is broadly consistent with NASPGHAN-ESPGHAN guidelines 2018, and National Institute for Health and Care Excellence (NICE) guidelines (NICE 2019). Other reviews, which include other study designs (such as case-control and cohort studies), draw similar conclusions about the paucity of evidence, and call for further research, particularly into the subgroups discussed above (NICE 2019; Tighe 2009).

We identified no data regarding alerts of concern for specific medications, as discussed in the Description of the intervention section. For example, for ranitidine, we identified no patients experiencing tachyphylaxis in the studies assessed, but this has been identified elsewhere as a concern (Hyman 1985). Additionally, a multicentre observational study noted a nearly seven-fold increased relative risk of necrotising enterocolitis (95% CI 1.7 to 25.0) in ranitidine-treated very low birth weight infants (Terrin 2012), but no studies we analysed identified this complication. Domperidone does not have a Food and Drug Administration (FDA) licence for marketing in the USA, and NICE guidance advises 'do not use' except in specialist paediatric settings (NICE 2019), but no studies we analysed identified this complication. There is a known association between erythromycin and development of pyloric stenosis (Cooper 2002), as well as potential side effects affecting the neonatal microbiome and antimicrobial resistance. NICE guidance advises 'do not use' except in specialist paediatric settings (NICE 2019), but no studies we analysed identified this complication.

AUTHORS' CONCLUSIONS

Implications for practice

Based on studies with summary data, there was no evidence to draw conclusions about the efficacy of medications (proton pump inhibitors (PPIs), H_2 antagonists, alginates, and prokinetics) compared to placebo for infants with gastro-oesophageal reflux (GOR).

For infants with gastro-oesophageal reflux disease (GORD), there was very low-certainty evidence that PPIs (omeprazole and esomeprazole) were effective in improving symptoms, and very low-certainty evidence of absence of symptomatic benefit from PPIs in preterm infants. There were no studies with summary data for prokinetics (such as domperidone), which remain of use only in specialist situations. There were no studies with summary data for alginates. As quince syrup is not clinically available, we did not evaluate the certainty of evidence for this treatment.

In older children with GORD, there was very low-certainty evidence that PPIs (pantoprazole and rabeprazole) may or may not help GORD outcomes, including symptoms and endoscopic/histological metrics. There were no data on pH indices. There was no clear evidence of a possible risk of increased adverse events based on very low-certainty evidence with rabeprazole. There were no studies assessing the use of PPIs in physiological reflux. There was insufficient evidence based on summary data to assess the benefit from H_2 antagonists in providing symptomatic relief. There was no evidence for prokinetics (such as domperidone or erythromycin). As quince syrup is not clinically available, we did not evaluate the certainty of evidence for this treatment. Understanding the applicability to children with GOR of the single low-quality study of baclofen is difficult. It should be noted that the current main clinical use of baclofen is in children with neurodisability receiving baclofen for hypertonia. We identified no studies in children with neurodisability (please see Implications for research).

Implications for research

The burden on primary and secondary care of physiological reflux and GORD is large, and further research is essential to clarify the role of medications in treating GORD. Despite the Pediatric Written Request made by the Food and Drug Administration (FDA) in the USA to improve our knowledge of a class of medications (PPIs) that are widely prescribed, the summary data available remain scarce. Further studies are needed to confirm whether PPIs or H_2 antagonists are superior, and whether individual drugs offer superior efficacy. Our review confirms that the quality and certainty of the evidence would benefit from further studies, especially assessing common medications used to treat GOR (e.g. H_2 antagonists, sodium+magnesium alginate). We would also call for comparisons that include a placebo or a different drug arm, in addition to the current comparisons between same-drug different-dosing. It was also evident that some studies gave participants confounding interventions (e.g. thickened or hydrolysed feeds to infants) that may provide improvements as interventions in their own right. Agreeing on consistent outcome measures and normative values for pH-impedance monitoring and endoscopy

would help research progress in the field. Further studies with longer follow-up periods are needed. Further studies of prokinetics, including quince syrup, are recommended.

We would also highlight the need for randomised controlled trials (RCTs) specifically in children with underlying oesophageal dysmotility (e.g. children with cerebral palsy), who often have difficult and protracted reflux. Most of the trials included in this review excluded this subgroup. These children are often on maximal medical therapies, including prokinetics, for prolonged time periods. Treatment regimens for this group are often extrapolated from other groups of children. Premature babies are often also treated empirically for gastro-oesophageal reflux; for example, as part of managing apnoea. Further RCTs in this age group are also recommended, using consistent outcomes.

Separating industry funding for trials from involvement in manuscript preparation would improve the strength of evidence according to GRADE criteria, when considering future trial design.

Evidence of medication efficacy in low-income countries and over a longer time period would also be useful to consider.

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- Sign-off Editor (final editorial decision): Bob Boyle, Imperial College London, UK
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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Azizollahi 2016

Study characteristics

Azizollahi 2016 *(Continued)*

Methods	Double-blind, single-centre, parallel design outpatient RCT
Participants	76 infants aged between 2 and 12 months with symptoms after standard treatment (smaller, more frequent feeds, hypoallergenic thickened formula) for 2 weeks
Interventions	Omeprazole (0.5 mg/kg/day) versus ranitidine (2 to 4 mg/kg/day)
Outcomes	Symptom scores (1 of 5 GORD symptoms (vomiting/regurgitation, irritability/fussing, choking/gagging, arching back, refusal to feed) assessed weekly for 2 weeks
Notes	No funding declaration given Location: Iran; single centre No potential conflict of interest was reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked random number generation
Allocation concealment (selection bias)	Unclear risk	Patients randomly assigned using randomisation software as above with similar characteristics.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comment on technique, but ranitidine delivered by syrup and omeprazole by capsule
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The report mentions double-blinding but no evidence to judge blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	16 participants excluded: lost to follow-up, pneumonia, prematurely discontinued medications, and mother's inability to complete questionnaire. Remainder (60) completed study.
Selective reporting (reporting bias)	Unclear risk	No evidence to judge risk of selective reporting
Other bias	Unclear risk	Funding source not declared.

Baker 2010

Study characteristics

Methods	Randomised, double-blind, parallel design outpatient study
Participants	60 children (aged 1 to 5 years) with symptoms of GORD and endoscopic or histological signs of GORD at recruitment
Interventions	3 groups: (1) pantoprazole 0.3 mg/kg daily; (2) pantoprazole 0.6 mg/kg daily; (3) pantoprazole 1.2 mg/kg daily delayed-release

Baker 2010 *(Continued)*

Outcomes	Outcomes were assessed in terms of symptoms, endoscopy (in those with erosive changes and side effects). Symptoms were recorded as a validated GOR symptom score (weekly GOR frequency scores: Weekly Gastro-oesophageal Severity Score (WGSS) at baseline and week 8, and individual symptoms (abdominal pain, burping, heartburn, pain after eating, difficulty swallowing) were recorded by parents daily using an eDiary, and endoscopy was performed at week 8 again only in those with erosive changes.
Notes	Followed a Paediatric Written Request (PWR) template, after widespread call from FDA for manufacturers of PPIs for children to carry out RCTs in children. Exclusions: recent acute life-threatening event, eosinophilic oesophagitis, cystic fibrosis, cow's milk protein allergy, *Helicobacter pylori* infection. Location: multicentre, with sites across the USA No potential conflict of interest was reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No comment made re: blinding. Parents recorded symptoms daily on an eDiary
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of assessors not discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data included on symptom score and those participants with erosive oesophagitis who were re-scoped. All participants accounted for, including analysis of those not enroled. Of the 41 participants not included, 17 had normal biopsy. Eosinophilic oesophagitis was noted in 8 participants and withdrawal of consent in 5, *H pylori* positive in 4 and use of prohibited treatments in 3 children. Of those who withdrew: 1 in low-dose group, 4 in medium-dose, 3 in high-dose group.
Selective reporting (reporting bias)	Unclear risk	No comment made
Other bias	High risk	Writing support (Wyeth). Institutional support from drug companies

Baldassarre 2020

Study characteristics

Methods	Multicentre, randomised, cross-over outpatient study
Participants	53 formula-fed infants and 19 breast-fed infants (aged 3 weeks to 4 months) with persisting regurgitation (I-GERQ-R > 16). 72 infants completed the study.

Baldassarre 2020 *(Continued)*

Interventions	Infants with symptoms of reflux (at least 2 episodes of reflux a day and I-GERQ-R scores > 16 at enrolment) had 1 week of behaviour and nutrition advice (e.g. avoid overfeeding, and passive smoking), and feeding support (e.g. on positioning). If symptoms of reflux persisted, formula-fed infants randomly assigned to receive 2 weeks of a magnesium-alginate-based formulation followed by 2 weeks of thickened formula (chosen by parents), or vice-versa, with 1 week washout between groups. Exclusively breastfed infants were followed up for 2 weeks while receiving magnesium alginate as a cohort and are considered separately as not randomised.
Outcomes	GOR symptoms were evaluated through the Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R). Direct cost of treatments was also calculated.
Notes	No funding declaration given Location: Italy Pharmaceutical support (Aurora Biofarma) in providing the study medicine; employed 1 author. The company had no input in the: design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, and approval of the manuscript; and the decision to submit the manuscript for publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated two-treatment allocation sequence nQuery Advisor (v.7.0 software, Statistical Solutions Ltd., Cork, Ireland). Randomisation scheme was performed in blocks of 4 participants
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not undertaken, but participants not aware that I-GERQ-R to be performed at follow-up visits
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors aware of outcome but participants unaware of primary outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up after randomisation, but 16 participants had improved with lifestyle advice and feeding support prior to randomisation.
Selective reporting (reporting bias)	Low risk	No children lost to follow-up
Other bias	High risk	Very short-term follow-up of 2 weeks. Each participant served as their own control. Comparator was thickened formula (choice of the commercial infant thickened formula was left to the parents)

Ballengee 2018

Study characteristics

Methods	Double-blind, placebo-controlled, parallel, single-centre outpatient trial

Ballengee 2018 *(Continued)*

Participants	46 preterm infants under 35 weeks gestation (mean gestational age 27 weeks) with clinical signs of GORD, including only those who had undergone a 24-hour pH-multichannel intraluminal impedence monitoring. 33 infants were randomised after meeting the inclusion criteria.
Interventions	Erythromycin 50 mg/kg/day in divided doses or visually identical 5% dextrose water preparation placebo for 1 week duration. After the 7-day study period, repeat pH-multichannel intraluminal impedence monitoring was performed.
Outcomes	Outcomes assessed as symptoms and reflux events on 24-hour pH study. The primary outcome was changes in the total number of reflux events, with secondary outcomes including changes in the number of acidic and non-acidic events, proximal reflux events, duration of reflux events and nurse-reported apnoea/bradycardia/desaturation.
Notes	The erythromycin dose is standard, as the BNFc 2021 dose is 12.5 mg/kg four times a day. Funding declaration: "All phases of this study were supported through grants obtained from The Gerber Foundation and Thrasher Research Fund." Location: USA No potential conflict of interest was reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block design with stratification by gestational age at birth
Allocation concealment (selection bias)	Unclear risk	No evidence to judge selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Visually indistinguishable placebo; staff blinded to randomisation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome data initially reported by pH probe software independent of assessor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition and all data reported
Selective reporting (reporting bias)	Unclear risk	No evidence to judge risk of selective reporting
Other bias	Unclear risk	There is little normative premature neonate impedance data on which to judge impact. Funding from the Gerber Foundation and Thrasher Research Fund.

Bines 1992

Study characteristics

Bines 1992 *(Continued)*

Methods	Double-blind, placebo-controlled outpatient trial
Participants	17 participants aged 5 months to 11.3 years with pH-probe-confirmed gastro-oesophageal reflux, rated moderate to severe based on symptoms
Interventions	Domperidone (0.6 mg/kg) 30 minutes before meal time or placebo over 4 weeks (double-blind) then a further 4 weeks (open-label)
Outcomes	Outcomes were assessed by symptomatic change (a detailed symptom analysis was not given); 8 to 12 hours oesophageal pH probe (number of episodes pH < 4; longest episode pH < 4 (in minutes)); and adverse events. Growth (weight and height Z scores)and gastric emptying time were reported but were not pre-specified outcomes so are not reported here.
Notes	No funding declaration given Location: USA; single site No potential conflict of interest statement was present

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described by authors
Allocation concealment (selection bias)	Unclear risk	Not described by authors
Blinding of participants and personnel (performance bias) All outcomes	High risk	Part 2 of the trial was open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described by authors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some data not included
Selective reporting (reporting bias)	High risk	Numerous data from outcomes not presented
Other bias	High risk	Participants agreeing to open-label trial likely to be biased towards those who believed they had an initial benefit from treatment. Pharmaceutical support with funding also noted (Janssen)

Borrelli 2002

Study characteristics

Methods	Open-label, parallel-design, single-centre outpatient RCT

Borrelli 2002 *(Continued)*

Participants	36 participants, median age 5.6 years (12 months to 12 years) with diagnosis of GORD based on symptoms, 24-hour pH probe and endoscopy
Interventions	Group A: alginate alone (2 mL/kg/day in divided doses) Group B: lansoprazole 1.5 mg/kg twice daily before meals Group C: lansoprazole and alginate over 8 weeks
Outcomes	Symptoms: reported as symptom score (regurgitation/vomiting, chest pain/irritability, epigastric pain/bloating, nocturnal cough/post-feeding cough) median (range) at baseline, week 4 and week 8. Adverse events were reported. 24-hour pH study (at baseline then week 1) reported using reflux index (% of time oesophageal pH < 4 in 24 hours). Endoscopy appearances: (performed at baseline then week 8) scored using Hetzel-Dent scoring: Grade 0 to 4. Children with grade 3 to 4 oesophagitis on endoscopy were not enroled but given high-dose lansoprazole.
Notes	4 participants lost to follow-up: 1 had upper respiratory tract infection with fever, 2 had poor drug compliance. No list of participants excluded: but infectious diseases, cow's milk protein allergy, neurometabolic conditions, and structural gut abnormalities excluded on investigations as part of workup. No funding declaration given Location: Italy; single site No conflict of interest statement was present.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation sequence
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No comment made
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment made
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No comment made
Selective reporting (reporting bias)	High risk	Children with severe erosive oesophagitis excluded from trial
Other bias	Unclear risk	No comment about funding

Buts 1987

Study characteristics

Buts 1987 *(Continued)*

Methods	Blinded, single-centre, outpatient RCT
Participants	20 infants and children with characteristic symptoms of GOR (vomiting, acid regurgitation related to meals and posture, heartburn, recurrent respiratory tract disorders)
Interventions	Either Gaviscon (10 participants, mean age: 21 months) or a placebo (lactose sachet, 10 participants, mean age: 35 months). 24-hour pH probe at baseline and Day 8; symptom assessment (vomiting and number of episodes of regurgitation within 24 hours) during the time of the recordings were observed by staff.
Outcomes	Symptoms: were recorded as number of episodes of regurgitations per day, and vomiting frequency and volume. No further evaluation of symptoms given 24-hour pH probe was assessed at baseline and day 8. Symptoms including vomiting and number of episodes of regurgitation within 24 hours during the time of the recordings were observed by staff.
Notes	No oesophagitis seen on endoscopy of 14 participants (6 treated with Gaviscon, 8 with placebo). As the study was underpowered (only 10 participants in each group), and data presented as mean (standard error), independent data extraction was not undertaken. No funding declaration given Location: Belgium No conflict of interest statement was present

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind: but no methodological comment made as to blinding technique and who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment made
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only 14 participants endoscoped; none had oesophagitis. Further details on symptom evaluation required
Selective reporting (reporting bias)	Unclear risk	No evidence of selective reporting
Other bias	High risk	No funding/competing interests declaration made. Very short-term follow-up

Carroccio 1994

Study characteristics	
Methods	Double-blind, parallel-group, placebo-controlled, single-centre outpatient RCT
Participants	80 participants (45 male, 35 female: aged 1 to 18 months – median 4.5 months) with symptoms of GORD: 50 had vomiting and slowed growth, 20 had weight loss, 4 had recurrent bronchopneumonia, 5 infants had prolonged crying worse after feeding, 1 had apnoeas
Interventions	Group A: domperidone (0.3 mg/kg/dose) - Gaviscon (0.7 mL/kg/dose) Group B: domperidone (0.3 mg/kg/dose) - Maalox (41 g/1.73m^2/day) Group C: domperidone (0.3 mg/kg/dose) Group D: placebo
Outcomes	Outcomes were measured by symptoms, and 24-hour pH indices (number of episodes pH < 4, duration of episodes of pH < 4, and number of reflux episodes > 5 minutes). Symptom improvement was confirmed on monthly follow-up for 6 months, but a detailed symptom analysis was not given.
Notes	No child had erosions/ulcers on endoscopy prior to treatment. 80 participants divided into small groups limiting power of study. Participants were stratified by age (< 12 months, > 12 months) and reflux index (< 10% in 24 hours, > 10% in 24 hours). All children had their feeds thickened with Medigel 1%, potentially reducing the impact of alginate, and explaining the significant improvement in pH outcomes in placebo group. All participants who were not cured (40 participants) were treated with cisapride/ranitidine (36 participants responded). No funding declaration given Location: Italy No conflict of interest statement was present

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratification and successive block randomisation
Allocation concealment (selection bias)	Low risk	Strata 1: age < 12 months or > 12 months then dependent on results of baseline pH probe (reflux index < 10% in 24 hours or > 10% in 24 hours)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reportedly double-blind (participants, parents, observers) but no comment made as to how parents were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment made as to blinding method
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants also reviewed at 6 months; all those who were cured at 8 weeks remained well. 40 participants with persistent symptoms required cisapride and ranitidine: 36 improved but 4 participants went on to require surgery.
Selective reporting (reporting bias)	Unclear risk	No evidence of selective reporting

Carroccio 1994 *(Continued)*

Other bias	High risk	All children received frequent short feeds, positioning advice, and formula milk was thickened with Medigel 1%. Funding not declared

Cresi 2008

Study characteristics		
Methods	Single-centre, parallel-design RCT over 24 hours in inpatient neonates	
Participants	26 neonates. Mean age (SD): control group 29.5 days (7.4) versus treatment group 24.7 days (13.7)	
Interventions	In treatment group: domperidone 0.3 mg/kg two doses in 24 hours. First epoch: P0 = 8h baseline. Time from 1st dose to 2nd dose (8h) = Second epoch P1. Time from second dose to end of study (8h) = third epoch P2 then compared to control group over 24 hours	
Outcomes	24-hour pH probe and impedance assessing reflux frequency P1 + P2 versus P0 (Mean (SD)); Reflux duration; Reflux height; and Reflux pH.	
Notes	No placebo. No blinding evident. Very short follow-up (24 hours only) No funding declaration given Location: Italy, single centre The authors declared no conflict of interest	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Consecutive recruitment
Allocation concealment (selection bias)	Low risk	Random allocation from odds-on pair from random-number table. Pairing occurred after treatment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding, for participants/parents, operator/analyser or authors
Blinding of outcome assessment (detection bias) All outcomes	High risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant's pH/impedance recording was stopped early: that period was discarded in the analysis. 8% data within pH probes also discarded due to interruptions
Selective reporting (reporting bias)	Unclear risk	No evidence of selective reporting
Other bias	High risk	Very short-term follow-up. No funding issues/conflicts of interest

Cucchiara 1984

Study characteristics	
Methods	Single-centre, single-blinded, parallel-design outpatient RCT
Participants	46 children (29 boys and 17 girls) aged 2 to 58 months (mean 10.3 months) with symptoms of GORD were assessed. Of these, 33 children (20 boys and 13 girls aged 2 to 42 months of age (mean 9 months)) met the criteria for gastro-oesophageal reflux with oesophagitis: with symptoms, oesophagitis on endoscopy, and acid reflux on pH probe.
Interventions	Randomised to either cimetidine 20 mg/kg/day or Maalox 700 mmol/1.73m^2/day, 7 doses a day
Outcomes	Outcomes assessed included symptoms (composite score in brackets): individual symptoms included vomiting/regurgitation (number of episodes a week), anorexia (absent to severe, 0 to 4 points), pneumonia/apnoea (number of episodes in 3 months) > 1:15 points; anaemia (haemoglobin < 7 g/dL = 9 points), weight:height ratio (centiles) < 5th 6 points. 24-hour pH study (reflux index: mean (SD) and number of episodes of gastro-oesophageal reflux), and endoscopy appearances: graded as healed, improved, unchanged/worsened: number (%) at baseline and at 12 weeks
Notes	Exclusions: 13 had an alternative diagnosis including GOR without oesophagitis (5), cows' milk protein intolerance (3), coeliac disease (2), intestinal malrotation (1), and urinary tract infections (2). Of those included, 4 children didn't complete the study: 2 participants in the cimetidine group were excluded (poor drug compliance), and 2 children in the antacid group were excluded (diarrhoea and subsequent reduced antacid intake). No funding declaration given Location: Italy No conflict of interest statement was present

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation technique or allocation not stated
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Observers of pH probe, endoscopy and manometry blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Unclear risk	No evidence of selective reporting

Cucchiara 1984 *(Continued)*

Other bias	High risk	All children had positioning advice, and infants had thickener added (Nestargel 1%). Respiratory complications (e.g. recurrent pneumonia or apnoea) present in 18% of the children studied.

Cucchiara 1993

Study characteristics	
Methods	Single-centre, parallel-design, outpatient RCT
Participants	32 children (aged 6 months to 13.4 years) with GOR based on symptomatology, pH probe and endoscopic findings. All had been unresponsive to an antireflux treatment including combined administration of ranitidine (8 mg/kg/day, given in 2 doses) and cisapride (0 to 8 mg/kg/day, given in 3 doses) for 8 weeks. (Unresponsiveness defined as persistent symptoms and absence of resolution on endoscopy.)
Interventions	8 weeks of either standard doses of omeprazole (40 mg/day/1.73 m^2 surface area) or high doses of ranitidine (20 mg/kg/day)
Outcomes	Improvement was assessed using symptoms, adverse events, 24-hour pH probe data (reflux index: % time oesophageal pH < 4 in 24 hours), and endoscopy. Reflux symptoms were recorded at baseline by parents through a diary card, then weekly through the study. The scoring system was out of 45: vomiting or regurgitation or both (0 to 9 points: 9 if vomiting for more than 5 days in the week); recurrent pneumonia or asthma or both (number of episodes in 6 months: 6 points per episode: maximum of 18 points); anorexia or early satiety (% reduction compared to daily calorie requirement: maximum of 9 points if intake is less than 25% of that expected); pyrosis/chest pain/irritability (number of days/week: maximum of 9 points if affected 7 days a week). pH probe assessment was undertaken at baseline and 8 weeks. Repeat endoscopies were performed within 48 hours of completing the 8-week trial. In terms of histological improvements, healing of oesophagitis was assessed (defined as return to grade 0 or grade 2 of histological score).
Notes	Exclusions were: oesophageal strictures, neurological pathology, and systemic extraintestinal diseases No funding declaration given Location: Italy; single centre No conflict of interest statement was present

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comment made, but the dosing regimes were different between the omeprazole and high-dose ranitidine
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not enough evidence to draw conclusions.

Cucchiara 1993 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7 withdrew: 3 on ranitidine and 4 on omeprazole. 4 of these participants were excluded as a result of noncompliance with the protocol, 2 were lost to follow-up, and 1 was withdrawn because of prolonged fever and upper respiratory infections.
Selective reporting (reporting bias)	Unclear risk	Not enough evidence to comment.
Other bias	High risk	No funding disclosures were made; one author worked for Schering-Plough

Davidson 2013

Study characteristics	
Methods	Multicentre, double-blinded, parallel-design, RCT in neonates in neonatal intensive care units
Participants	52 neonates (premature to 1 month corrected age), with signs and symptoms of GORD
Interventions	0.5 mg/kg esomeprazole once daily for up to 14 days versus placebo
Outcomes	Change from baseline in the total number of GORD symptoms (from video monitoring) and GORD-related signs (from cardiorespiratory monitoring) assessed with simultaneous oesophageal pH/impedance at baseline and 14 days: with cardiorespiratory, and 8-hour video monitoring. Adverse events were recorded. Data readers blinded
Notes	Location: Australia, Germany, UK The study was sponsored by AstraZeneca; it was involved in manuscript-writing, and employed one of the authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation used
Allocation concealment (selection bias)	Low risk	Evidence for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Data readers blinded but unclear if nursing staff were blinded. Identical placebo used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data readers recording outcomes were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant in the esomeprazole group was excluded from the modified ITT analysis because of invalid efficacy measurements, but was included in the safety analysis. 1 participant in the placebo group completed the study, but was lost to follow-up between study completion and the safety follow-up visit.

Davidson 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	No evidence of reporting bias
Other bias	High risk	Very short-term study: the study was discontinued prematurely because of poor enrolment: the study estimated needing to recruit 90 participants to achieve 38 participants in each group to achieve > 80% power at the 2-sided alpha level of 0.05 to detect a difference between esomeprazole and placebo in the change in number of symptoms from baseline. The study was funded by AstraZeneca with support with manuscript writing.

Del Buono 2005

Study characteristics	
Methods	Double-blind, single-centre outpatient RCT
Participants	20 infants (mean age 163.5 days, range 34 to 319 days) exclusively bottle-fed (formula milk or expressed breast milk), with symptoms of GOR (regurgitation > 3 x day any amount or > once/day half the feed); weighing > 2 kg in weight and no signs of infection
Interventions	6 random administrations (3+3) of Gaviscon Infant (625 mg in 225 mL milk) or placebo (mannitol and Solvito N, 625 mg in 225 mL milk) were given (double-blind)
Outcomes	24-hour studies of impedance and dual-channel pH monitoring. pH indices: median number of reflux events/hour, acid reflux events/hour, minimum distal or proximal pH, total acid clearance time per hour (time with pH below 4), and total reflux duration per hour were assessed. No comment on symptoms or adverse events
Notes	Very short-term study. Funding was declared from Reckitt Benckiser Location: UK Conflict of interest declared: Reckitt Benckiser Healthcare (UK) Ltd, the producers of Gaviscon Infant, funded one of the authors

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	Identical preparations given to infants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants/parents reportedly blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded observer interpreted pH data

Del Buono 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No evidence of this
Selective reporting (reporting bias)	Unclear risk	No evidence of this
Other bias	High risk	Very short-term study. Reckitt Benckiser Healthcare (UK) Ltd, the producers of Gaviscon Infant, funded one of the authors (Dr R Del Buono). However, there was no discernable impact on study design.

Famouri 2017

Study characteristics	
Methods	Unblinded, parallel-design, randomised clinical outpatient trial
Participants	50 infants (0 to 12 months old). Mean age of ranitidine group 2.8 months; mean age of hypoallergenic diet group 3.4 months with I-GERQ-R score of > 7
Interventions	Ranitidine 6 mg/kg daily in 2 divided doses versus hypoallergenic diet (in breastfed infants, mothers were advised to eat only hypoallergenic diet and in formula-fed infants, hydrolysed protein or amino-acid based formula)
Outcomes	Symptoms: parental reporting of symptoms of irritability, vomiting, respiratory symptoms, arching and refusal of feeds. I-GERQ at baseline and 2 weeks post intervention. No comment on adverse events
Notes	The authors do not include detailed information regarding attrition in this study. No funding declaration given Location: Iran; single centre. No conflict of interest statement present

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors state only that "participants were randomly allocated"
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	High risk	Parents were not blinded, and no comment made regarding the blinding of personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence of this
Incomplete outcome data (attrition bias)	Unclear risk	This is not made clear by the authors

Famouri 2017 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	No evidence of this
Other bias	Unclear risk	There is no disclosure of interest statement available for this study

Forbes 1986

Study characteristics	
Methods	Single-centre, observer-blinded, parallel-design outpatient RCT
Participants	10 children (mean age 68 months: range 6 to 168 months). All had symptoms of vomiting and water brash at enrolment
Interventions	Gaviscon Infant liquid (antacid plus alginate) 10 mL every 6 hours (for infants) or 20 mL every 6 hours for older children versus placebo 3 times a day. 24-hour pH probe at baseline then consecutively after 24 hours of treatment, so 2 24-hour pH recordings were made.
Outcomes	pH indices: number of reflux episodes, total duration of reflux episodes recorded. No adverse events were reported.
Notes	Observer interpreting pH results was blinded. We did not consider the metoclopramide group (also 10 children): please see Methods and Differences between protocol and review. No standard nursing positions were adopted, and children could move around the bed. No funding declaration given Location: Australia No conflict of interest statement present

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and parents not blinded as placebo administered 3 times daily and Gaviscon liquid 4 times daily for infants and children
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Interpretation of pH data made by blinded observer
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No subgroup analysis of those with endoscopic evidence of oesophagitis

Forbes 1986 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No evidence of this
Other bias	High risk	Very short-term study. No funding declarations

Gilger 2006

Study characteristics	
Methods	Multicentre, randomised, double-blinded (for dose), uncontrolled, parallel-group outpatient study
Participants	109 children aged 1 to 11 years with endoscopically/histologically-confirmed erosive oesophagitis
Interventions	Doses of 5 mg or 10 mg of esomeprazole (8 kg to 20 kg children), 10 mg or 20 mg esomeprazole (> 20 kg children) for 8 weeks
Outcomes	Symptom improvement (assessed by physician's global assessment (PGA) and parental daily diaries at baseline then fortnightly). Adverse events reported regardless of causality
Notes	Endoscopic outcomes published separately (Tolia 2010b) Funding: AstraZeneca Location: USA, Belgium, France, Italy Conflict of interest: study was funded by AstraZeneca with leadership, project management, and editorial assistance

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described by authors
Allocation concealment (selection bias)	Unclear risk	Not described by authors
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents reported outcomes but blinded to dose
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not described by authors
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient safety data not supplied and excluded; otherwise all participants fully accounted for
Selective reporting (reporting bias)	Unclear risk	No evidence of reporting bias
Other bias	High risk	Study funded by AstraZeneca with pharmaceutical writing support noted

Gunesekaran 2003

Study characteristics	
Methods	Phase I, multicentre, parallel-design, double-blind, outpatient RCT
Participants	63 adolescents with symptomatic/endoscopic GORD, or histological changes. Mean age 14.1 years (12 to 17 years)
Interventions	Randomised to 2 arms: 7-day pre-treatment then 5 days of treatment with lansoprazole 15 mg versus 30 mg
Outcomes	In the pre-treatment phase, a physician assessment was followed by 24-hour intragastric pH probe, endoscopy and biopsy, *H pylori* testing, and a symptom diary for one week. After 5 days of treatment, participants underwent physician assessment and analysis of symptom diaries. The pharmacokinetics and intragastric pH monitoring are not considered here, as intragastric pH not an outcome relevant in oesophagitis, and pharmacokinetics are not clinical outcomes being considered within the remits of this review. Severity scores were graded 0 (none) to 3 (severe) for each item. Adverse events recorded: pharyngitis 6% (2/32 in lansoprazole 15 mg) and headache 16% (4/31 in lansoprazole 30 mg) were the most commonly reported adverse events amongst adolescents treated with lansoprazole 15 mg and 30 mg, respectively. 5 participants experienced adverse events considered to be possibly treatment-related. 1 participant with a history of environmental allergies experienced a mild allergic reaction after 3 days of treatment with lansoprazole 15 mg. Amongst those treated with lansoprazole 30 mg, 4 participants each reported 1 occurrence of pain (toothache), diarrhoea, dizziness, and rash.
Notes	Exclusions: systemic disease (e.g. scleroderma)/infection of oesophagus/chronic use of ulcerogenic drugs/use of PPIs. Funding declaration: study supported by a grant from TAP Pharmaceutical Products Inc. Location: USA No conflict of interest statement present

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised in 1:1 fashion to each group
Allocation concealment (selection bias)	Low risk	Difference between treatments concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants/carers blinded. Pathologist examining histological specimens blinded (but not an outcome measure). No discussion of blinding of clinical observers
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No evidence of this

Gunesekaran 2003 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No oesophageal data on pH probe reported
Other bias	High risk	Very short-term follow-up study. However, participants who demonstrated a positive response were offered 3 months of treatment with lansoprazole. Study supported by a grant from TAP Pharmaceuticals.

Haddad 2013

Study characteristics	
Methods	Multicentre, double-blind, parallel-design, outpatient RCT
Participants	127 children aged 1 to 11 years
Interventions	Randomised to rabeprazole 0.5 mg/kg or 1 mg/kg. Children 6 kg to 14 kg received 5 mg if in 0.5 mg/kg group and 10 mg if in 1 mg/kg group. Children > 15 kg received 10 mg if in 0.5 mg/kg group and 20 mg if in 1 mg/kg group. Medications given for 12 weeks
Outcomes	Symptom score: mean 'Total GERD Symptoms and Severity' score, Global Treatment Satisfaction scale by the investigator and Clinical Global Impressions-Improvement scale by the parent/caregiver. Endoscopy/histological healing at baseline and week 12: histological scores (Grades 1-5). Adverse events were reported (as treatment-emergent adverse events).
Notes	At recruitment, 30% of children had already received PPIs: 15% H_2 antagonists, and 2% prokinetics. Funding declared from Janssen Research & Eisai Medical Research Inc. Location: USA, Belgium, Denmark, France, Italy, Poland, Israel, South Africa, and India No conflict of interest statement present

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No comment on randomisation technique
Allocation concealment (selection bias)	Low risk	No difference in baseline characteristics
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Everyone, including the investigator, the contract research organisation, and in-house study personnel, was blinded in the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Everyone, including the investigator, the contract research organisation, and in-house study personnel, was blinded in the study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15% withdrew during study: reasons not given

Haddad 2013 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No evidence to judge risk of selective reporting bias
Other bias	High risk	Janssen provided funding and reviewed the manuscript prior to submission. 4 authors are employees of Janssen Research & Development. This may have affected study design: i.e. same medication, different dose design.

Hussain 2014

Study characteristics	
Methods	Double-blind, multicentre, withdrawal outpatient RCT (following 1- to 3-week open-label phase)
Participants	268 infants (aged 0 to 11 months)
Interventions	Placebo versus rabeprazole 5 mg and 10 mg groups for 5 weeks. Only those children who had improved went on to the double-blind withdrawal phase.
Outcomes	Outcomes were measured by symptom scores (I-GERQ) assessed based on daily diary; endoscopic appearances; and side effects. Weight for height Z-scores also assessed but not reported as not a prespecified outcome. 231 completed first part of study. 108 improved children went into the double-blind withdrawal phase. Post hoc analysis was performed after unblinding the data, based on age subgroups (1 to 4 months; 4 to 8 months; 8 to 12 months): previous acid suppressive treatment–exposed versus treatment-naïve infants; initial I-GERQ-R scores over 23 versus under 23 at entry into the open-label phase; and improvement of the I-GERQ-R score by 10 points versus more than 10 points during the open-label phase. Post hoc analyses were also based on 3 individual questions scored on the I-GERQ-R at entry into the open-label phase. These included frequency of regurgitation more than 3 times a day versus 3 times a day; crying for 1 hour/day versus less than 1 hour a day; and crying during or within 1 hour of feeding always or often versus sometimes, rarely, or never. Endoscopy: only 12 of 268 underwent endoscopy, but the endoscopy was not repeated.
Notes	The study was financially supported by Janssen Research & Development. Multiple authors were employees of Janssen Research and one a consultant to Janssen Research. Location: USA, the Netherlands, South Africa, Belgium, Hungary, Israel, Bulgaria, Italy, Poland Endoscopy: of the 12 of 268 who underwent endoscopy, 10 had signs of GORD on scope Adverse events were recorded: equal percentages (47%) reported adverse events in placebo and combined rabeprazole groups (diarrhoea, constipation, flatulence, crying and rash). 8 participants in rabeprazole groups had elevated gastrin levels.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation technique not specified
Allocation concealment (selection bias)	Unclear risk	Not specified

Hussain 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding technique not specified but identical placebo and rabeprazole preparations used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding technique not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	37 participants didn't complete the study
Selective reporting (reporting bias)	High risk	Post hoc analysis based on age-bands (1 to 4 months, 4 to 8 months, 8 to 12 months), those who had previously had treatment with PPI versus those who were PPI-naïve, those with high I-GERQ scores (< 23) versus lower I-GERQ scores, and analyses of certain I-GERQ questions (crying, frequency of regurgitation, and crying within 1 hour of feeding).
Other bias	High risk	The aim of the lead-in period was to identify those participants who were PPI-responsive: these infants were then more likely to show signs on withdrawal. Pharmaceutical help with funding the study and manuscript preparation (Janssen) was noted, which may have affected study design (post hoc analysis).

Kierkus 2011

Study characteristics	
Methods	Unblinded, single-centre, parallel-design, outpatient RCT
Participants	Study 1: neonates/preterm infants pantoprazole 2.5 mg (approximately 1.2 mg/kg once daily). This study not analysed as not randomised Study 2: 24 participants. Mean age 6.9 months (range 1.3 to 11 months; 1 extremely premature baby) in low-dose treatment group. Mean age 3.6 months (1.1 to 12.1 months; 2 extremely premature babies) in high-dose treatment group.
Interventions	Study 2: randomised to high-dose (1.2 mg/kg) or low-dose pantoprazole (0.6 mg/kg). Mainly pharmacokinetic data but 24-hour pH probe at baseline then day 5. Treatment for 6 weeks
Outcomes	Baseline and steady-state (day 5): pH indices: reflux index (mean ± SD); number of episodes pH < 4; number of episodes lasting more than five minutes; duration of episodes of pH < 4. Related and unrelated adverse events were reported: no serious adverse events after 6 weeks of treatment, although 58% of the 24 participants reported at least 1 adverse event (unrelated).
Notes	Funded by Wyeth, including funding for writing assistance Location: USA, Europe, Australia Conflict of interests disclosed: Wyeth was acquired by Pfizer Inc in October 2009. Multiple authors were employees of Wyeth Research and may have held Wyeth stock. Other investigators or their institutions received compensation from Wyeth Research.
Risk of bias	

Kierkus 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocks of randomised numbers in strict ascending sequential order
Allocation concealment (selection bias)	Unclear risk	At end of trial, infants could continue on same dose or higher dose for 6 weeks
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant excluded in low-dose treatment group: error in pH probe. 2 excluded in high-dose group: 1 pH probe error; 1 at investigator request
Selective reporting (reporting bias)	Unclear risk	No evidence found, although no symptom change reported
Other bias	High risk	Very short-term follow-up. Funded by Wyeth, including funding for writing assistance

Loots 2014

Study characteristics	
Methods	Multicentre, parallel-design, double-blind outpatient RCT
Participants	51 infants aged 2 to 26 weeks with symptomatic GORD
Interventions	Mainly assessing the role of left lateral positioning (LLP), but esomeprazole (PPI) and antacid therapy included. Infants demonstrating a positive GOR symptom association were randomised to 1 of 4 groups: • PPI plus LLP • PPI plus head of cot (i.e. bed) elevated • antacid plus LLP • antacid plus head of cot elevated Cot elevation and antacid were considered "sham" therapies.
Outcomes	Nurse-led symptom observation; using cardiorespiratory and video monitoring, and I-GERQ-R. Also 8-hour pH-impedance (reflux index) at baseline and after 2 weeks.
Notes	Efficacy of positioning not considered in this review. However, the antacid groups did have different pH indices at baseline, and in this age-group, a reflux index of less than 10% in 24 hours was not considered pathological. The study was supported by grants from the National Health and Medical Research Council, the Financial Markets Foundation for Children, the Dutch Digestive Disease Foundation, the Channel 7 Children's

Loots 2014 *(Continued)*

	Research Foundation, and the Women's & Children's Hospital Foundation. Part of the equipment was provided by AstraZeneca. Location: Australia, the Netherlands The authors reported no conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation independently generated by monitor
Allocation concealment (selection bias)	Unclear risk	No evidence to judge risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	Medications were double-blinded. Body positioning was single-blind as parents aware
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 infants withdrew: 3 before starting treatment; 1 poorly compliant; 1 withdrawn by parents at day 9 (did not wish to proceed to head of cot (bed) elevation and antacid) and 1 infant admitted due to poor intake (from 'PPI plus head of cot elevated' group).
Selective reporting (reporting bias)	Unclear risk	No evidence to judge risk of reporting bias
Other bias	Unclear risk	Some equipment provided by AstraZeneca but no influence on study design, or manuscript writing. Additional Sudden Infant Death Syndrome (SIDS) precautions taken, including continuous O_2 saturations monitoring.

Miller 1999

Study characteristics	
Methods	Multicentre, double-blind, placebo-controlled, outpatient RCT
Participants	90 infants with symptoms of GOR at least twice a day for 2 days prior to start of study
Interventions	Sodium alginate (aluminium-free Infant Gaviscon) 312.5 mg/sachet, one to two sachets per feed versus placebo
Outcomes	Improvement in symptoms noted by parents (daily diary) and investigators, at baseline, day 7, and day 14. Symptoms assessed: number of vomiting episodes expressed as median (range) as primary outcome; and assessment of vomiting severity and parental global assessment of improvement at day 14 as secondary outcomes. Infants received up to 4 days additional treatment after day 14.

Miller 1999 *(Continued)*

	No difference in adverse events reported between the 2 groups, but no further details given.
Notes	Exclusions: infants with oesophageal, neuro, cardiac, respiratory, metabolic, hepatic, or renal disease; below 2.5 kg in weight; below 37 weeks' gestation The authors received funding from Parexel International Location: United Kingdom across 25 centres No conflict of interest statement was present

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reportedly double-blind but technique not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Technique not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	From 90 participants: 2 infants in placebo group did not receive treatment = ITT population 88. During study: 20 withdrawals (7 from alginate group; 13 from placebo group; P > 0.2) due to adverse events (alginate: 4; placebo: 7) and lack of efficacy (alginate: 2; placebo: 3). ITT analysis included withdrawals.
Selective reporting (reporting bias)	Unclear risk	No evidence found, but data for Day 7 investigator assessment were not presented
Other bias	Unclear risk	Funded by Reckitt & Colman and Parexel International

Moore 2003

Study characteristics

Methods	Randomised, double-blind, placebo-controlled, cross-over outpatient trial
Participants	30 infants with symptomatic GORD between 3 and 12 months of age (mean 5.4 months) who had previous empirical gastroesophageal reflux treatment, excluding PPI therapy, with either reflux index over 5% in 24 hours OR biopsy evidence of oesophagitis
Interventions	4-week study: omeprazole (2 weeks) then placebo (2 weeks) or vice versa. Infants from 5 kg to 10 kg were given 10 mg daily and > 10 kg were given 10 mg twice daily omeprazole or identical placebo.
Outcomes	Symptoms assessed as crying/fuss time: mean (SD) by Symptom Diary and Visual Analogue Score; sliding scale from 0 to 10 assessing irritability reported by parent over 4 weeks. pH indices assessed as change in reflux index; mean (SD) - % of time spent with oesophageal pH < 4 in 24 hours.

Moore 2003 *(Continued)*

	Authors reported PPI improved reflux index with no effect on crying/fussing compared to placebo. Of note, there was significant reduction in both groups over the 4-week study period compared to baseline. Adverse events were recorded (none noted).
Notes	The study was jointly funded by the J.H. and J.D. Gunn Medical Research Foundation and the Channel 7 Children's Research Foundation. The omeprazole and placebo capsules were supplied free of charge by AstraZeneca. Location: Australia; single-centre study No potential conflict of interest statement was present.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not described by authors but randomisation code used.
Allocation concealment (selection bias)	Low risk	Not described by authors but code broken at end of study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded: parents/infants and observers, code broken at end of study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes expressed as behaviour diary (potential for recall bias) and visual analogue score (potential for parental observer bias).
Incomplete outcome data (attrition bias) All outcomes	Low risk	No table of baseline characteristics. 4 infants dropped out due to significant crying.
Selective reporting (reporting bias)	Unclear risk	No comment made. Only 7 infants had both endoscopic changes and reflux index > 5% in 24 hours.
Other bias	High risk	64 infants evaluated for inclusion. Note NASPGHAN guidance in place at the time considers reflux index > 10% in 24 hours to be pathological in infants. No evidence of reflux oesophagitis seen (erosions or ulcers) at entry endoscopy: loss of vascular pattern or friability enough for inclusion. Some of these infants may have had functional reflux. Independent funding: AstraZeneca only provided the placebo and omeprazole free of charge.

Naeimi 2019

Study characteristics

Methods	Double-blind, parallel-design, single-centre, outpatient RCT
Participants	96 children between 1 and 4 years old with GORD, diagnosed on clinical symptoms: needed 2 of 5 of the following symptoms: (1) regurgitation (or vomiting immediately after feeding); (2) poor weight gain for one month; (3) respiratory distress immediately after feeding; (4) feed refusal; and (5) restlessness up to 3 hours after eating over the preceding month.

Naeimi 2019 *(Continued)*

Interventions	Two groups: ranitidine 8 mg/kg/day versus ranitidine 8 mg/kg/day plus quince syrup (0.5 mL/kg/day). Assessed at 2, 4, and 6 weeks.
Outcomes	Global Severity Questionnaire (GSQ-YC): assessing severity and frequency of vomiting, refusal to eat, difficulty in swallowing, choking during eating, burping/belching, and abdominal or belly pain. Adverse effects of ranitidine or quince syrup were recorded (none noted).
Notes	Significant differences emerged between 2 and 4 weeks after starting the trial. Small sample size and short study duration were other limitations noted, and the authors recommend a larger study to explore the effect of different doses and improve the reliability of the results. The study was funded by a university grant. Location: Iran No conflict of interest statement was present.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation software was used to prepare the randomised list but software not specified.
Allocation concealment (selection bias)	Low risk	The participants in this study were selected randomly and divided into 2 parallel groups. Detailed analyses for differences between groups were undertaken regarding symptom characteristics, age, weight, height, number of siblings, maternal occupation and education, co-existing conditions, atopy, method of birth, and type of feeding (as well as age of weaning). No significant differences identified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants were blinded regarding drug allocation. The research team (a paediatrician and a physician) were also unaware of the participants' allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The research team (a paediatrician and a physician) were unaware of the participants' allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants in the ranitidine group (n = 47) and 1 in the quince syrup plus ranitidine group (n = 49) were excluded due to worsened symptoms or poor compliance.
Selective reporting (reporting bias)	Unclear risk	No evidence of post hoc analyses or changes in end points
Other bias	Low risk	No conflict of interest statement. Funded by a university grant (from Babol University of Medical Sciences, Iran).

Omari 2006

Study characteristics

Methods	Randomised, double-blinded, single-centre, outpatient, placebo-controlled trial

Omari 2006 *(Continued)*

Participants	30 children with resistant GORD. Mean age 10 ± 0.8 years. All children had failed standard therapy (positioning, reassurance, feed thickener, antacids, PPI and H_2 antagonist)
Interventions	Assessed with manometry/pH at baseline for 2 hours after 250 mL of cow's milk and dose of baclofen to ensure tolerability (control period). 0.5 mg/kg baclofen or placebo was then administered. One hour later, 250 mL of milk was given and measurements performed for another 2 hours (test period).
Outcomes	Impedance: transient lower oesophageal sphincter relaxations (TLESR) (median ± CI) versus placebo: during the 2-hour test period compared with the control period. pH: number of acid reflux episodes (pH < 4) detected. Adverse events assessed (1 causing early withdrawal but thought to be unrelated): up to 48 hours following trial.
Notes	Exclusions: previous gastrointestinal surgery, neurological disease, cardiac/respiratory disease, peptic ulcers or cow's milk protein intolerance (CMPI)/lactose intolerance. Significantly higher number of acid reflux episodes and TLESRs at baseline in control group. Very short trial period. Gastric emptying was not evaluated in this review as it was not a prespecified outcome. The study was supported by the Women & Children's Hospital Research Foundation, the J.H. & J.D. Gunn Medical Research Foundation, the Netherlands Organization for Scientific Research and AstraZeneca Location: Australia No conflict of interest statement was available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No evidence provided
Allocation concealment (selection bias)	Unclear risk	No evidence provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents and staff remained blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No evidence provided
Selective reporting (reporting bias)	Low risk	All participants had initially received a test dose to assess tolerability; no data for children who had not tolerated the initial test dose.
Other bias	High risk	Very short-term follow-up. Funded by Women and Children's Research Foundation, the JH & JD Gunn Medical Research Foundation and AstraZeneca R&D.

Omari 2007

Study characteristics	
Methods	Single-centre, randomised, single-blind outpatient study (SH-NEC-0001)
Participants	50 infants with symptoms of GORD (irritability/crying, vomiting, choking/gagging) and reflux index on 24-hour pH probe suggestive of acid GOR (> 4% in 24 hours)
Interventions	Oral esomeprazole 0.25 mg/kg or 1 mg/kg for 8 days
Outcomes	Symptoms were recorded on a symptom chart at baseline and at day 7, based on the I-GERQ. Severity scores were graded 0 (none) to 3 (severe) for each item. A 24-hour pH probe (assessing reflux index) was performed at baseline and on day 7. Adverse events were also monitored through physician assessment.
Notes	Exclusions included a history of upper gastro-intestinal surgery, and congenital drug addiction. Use of any pharmacological antireflux therapy up to 24 hours before, or any PPI up to 72 hours before the first dose of study medication was not permitted. Contemporaneous treatment with medications known to interact with esomeprazole, or to improve symptoms of reflux (e.g. H_2 antagonists) was not permitted. Also republished in full in 2015: other exclusion criteria listed there were: any current/previous clinically significant illness that may interfere with study procedures or with the metabolism of esomeprazole, or that may jeopardise infant safety; any experimental drug or device in the 8-week period before screening; history of surgery of the oesophagus, stomach, duodenum, or jejunum; and congenital drug addiction. Use of any pharmacological antireflux therapy up to 24 hours before, or any PPI up to 72 hours before, the first dose of study medication was not permitted. Treatment with anticholinergics, antineoplastic agents, H_2-receptor antagonists, sucralfate, bismuth-containing compounds, methylxanthines, promotility drugs, macrolide antibiotics, or barbiturates was not permitted. Known hypersensitivity to esomeprazole, substituted benzimidazoles, or any constituents of the esomeprazole formulation also precluded infants from the study. No funding declaration given. Medical writing support was funded by AstraZeneca Location: Australia No conflict of interest statement was present. Further details were supplied by author.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No evidence provided
Allocation concealment (selection bias)	Unclear risk	No evidence provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Staff became aware of which treatment a participant was on based on the weight. Parents remained blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No evidence provided

Omari 2007 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No evidence
Other bias	High risk	Very short-term study. No funding statement but medical writing support by AstraZeneca which may have influenced study design (same medication: different dose comparison) which has less clinical utility.

Orenstein 2002

Study characteristics	
Methods	Eight-week, multicentre, placebo-controlled, two-phase outpatient RCT
Participants	35 infants, mean age 5.5 months (range 1.3 to 10.5 months), male:female 12:14, previous H_2 antagonist therapy in 57%, previous prokinetic use in 37%. All had a clinical diagnosis of GORD.
Interventions	First 4 weeks: observer blind trial of famotidine; second 4 weeks: double-blind withdrawal comparison of each dose with placebo. Phase 1 - famotidine 0.5 mg/kg dose versus famotidine 1 mg/kg dose Phase 2 - each dose category split to continue on dose or receive placebo
Outcomes	Symptoms assessed in terms of improvement in regurgitation frequency, improvement in regurgitation volume, improvement in crying time, and global assessments by parents and physicians. Adverse events were monitored: 6 infants on famotidine experienced new agitation/irritability; 2 of these had accompanying head rubbing. All resolved within days of ending therapy. No breakdown as to which group.
Notes	Exclusion criteria: respiratory complication, previous gastrointestinal surgery, cardiovascular, renal, hepatic, neoplastic or diabetic disease, inability to discontinue previous proton pump inhibitor therapy, sensitivity to famotidine or H_2 antagonists. Study supported by a grant by Merck & Co. Inc. to each of the 3 sites. Location: USA No conflict of interest statement was present

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described by authors
Allocation concealment (selection bias)	Unclear risk	Not described by authors.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Parents unblinded to intervention in part one
Blinding of outcome assessment (detection bias) All outcomes	High risk	Parents unblinded to intervention in part one, with parental assessment a key outcome measure.

Orenstein 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants accounted for, all outcomes clearly defined and reported
Selective reporting (reporting bias)	Unclear risk	No evidence of this, although infants with previous sensitivity to famotidine were excluded.
Other bias	Unclear risk	In selection, infants with previously failed GORD treatment far more likely to be enroled. Study supported by a grant by Merck & Co. Inc. to each of the 3 sites.

Orenstein 2008

Study characteristics	
Methods	Multicentre, double-blind, placebo-controlled outpatient RCT
Participants	162 infants (mean age 16 weeks, range 4 to 51 weeks) with symptoms of GORD – 'crying, fussing or irritability' – within 1 hour after feeding (specifically daily crying noted in diary in > 25% of feeds over 4 days), after 1 week of non-pharmacological treatment.
Interventions	The trial occurred in 3 phases. In the pretreatment phase: small frequent feeds were recommended, as was reduction in smoking, hypoallergenic feeds (or if breastfed, mothers started dairy-free diet), and positioning advice. The treatment phase lasted 4 weeks and infants were randomised to lansoprazole 1:1 (0.2 to 0.3 mg/kg/day in those < 10 weeks old, 1 to 1.5 mg/kg/day in those > 10 weeks old) versus placebo. In the post-treatment phase, investigators could choose to put children on lansoprazole.
Outcomes	Symptom assessment for 30 days following the study was performed. Parent diaries were assessed for symptom scores and individual symptoms (crying/regurgitation/back arching/hoarseness/feed refusal or early stopping/cough or wheeze).
Notes	Takeda Global Research and Development sponsored the clinical trial and data analysis. Location: USA and Poland. 16 centres participated. No potential conflict of interest statement was present. Infants were excluded if PPI taken in previous 30 days or H_2 receptor antagonists within 7 days.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation 1:1 lansoprazole:placebo
Allocation concealment (selection bias)	Unclear risk	No evidence of this
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding reported: randomisation blinded and parents blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Investigators able to find out after 4 weeks who was taking which treatment.

Orenstein 2008 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One participant in lansoprazole group: data missing
Selective reporting (reporting bias)	Unclear risk	No evidence of this
Other bias	Unclear risk	Takeda funded the trial and data analysis but took no part in manuscript preparation

Pfefferkorn 2006

Study characteristics	
Methods	Double-blind, parallel-design, single-centre, outpatient RCT
Participants	18 participants, ages 1 to 13 years (mean 10.3 years) with symptomatic GORD with endoscopic/histological changes
Interventions	Of the 18 participants who received omeprazole (1.4 mg/kg once daily, maximum 60 mg) for the first 3 weeks, 16 (89%) had nocturnal acid breakthrough on pH monitoring and were randomised to ranitidine 4 mg/kg or placebo, whilst continuing omeprazole.
Outcomes	Participants were evaluated for symptoms and adverse events during follow-up at 3, 9 and 17 weeks. Symptoms (heartburn, abdominal pain, vomiting, dysphagia, and ''others'') were recorded (none, same, better, worse) at follow-up. Details of the symptom scoring were not given. At week 17, all participants had repeat 24-hour pH monitoring (reflux index) and endoscopy/histology evaluation using Hetzel-Dent score (grade 0 to 4). Adverse events were monitored: none were seen.
Notes	One participant received esomeprazole 40 mg twice daily; 2 participants in ranitidine group withdrew; 1 participant was lost to follow-up. Location: USA No potential conflict of interest statement was present: funding from Grant-in-Aid from the Riley Childrens' Foundation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Statistician provided a randomisation table
Allocation concealment (selection bias)	Unclear risk	Not clear whether there was block allocation, or how participants were randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Investigators were blinded

Pfefferkorn 2006 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Ranges not included on some data. Two participants in ranitidine group withdrew; 1 was lost to follow-up; 1 participant received esomeprazole 40 mg twice daily.
Selective reporting (reporting bias)	Unclear risk	None
Other bias	Low risk	Funded by a Grant-in-Aid from the Riley Childrens' Foundation.

Simeone 1997

Study characteristics	
Methods	Double-blind, single-centre, parallel-design outpatient RCT
Participants	26 infants and children with histological features of oesophagitis (mild-moderate). 17 boys and 9 girls (median age 1.66 years; range 6 months to 8 years) were recruited.
Interventions	Nizatidine 10 mg/kg twice daily versus placebo for 8 weeks. All participants received positional therapy and dietary manipulation with thickened feeds (dry rice cereal).
Outcomes	Outcomes were assessed in terms of symptoms (symptomatic score assessment by daily diary card kept by parents to record the frequency/severity of GOR symptoms (abdominal pain, chest pain, regurgitation, and vomiting), and physical and symptomatologic physician assessment was performed at baseline and after 4 weeks of therapy); 24-hour pH scores (reflux index, number of episodes pH < 4, no of episodes > 5 minutes, duration of episodes of pH < 4), and endoscopy/histology appearances (healed/improved/unchanged/worse) 48 hours before the end of the therapy at 8 weeks. Adverse events were monitored: 1 participant developed urticaria.
Notes	Children receiving ulcerogenic drugs or with an antireflux agent were excluded from the study. Also excluded were participants with systemic extraintestinal diseases, neurological disorders, or a history of previous surgery. Post-treatment pH-metry was repeated in only 10 participants of the nizatidine group (83.3%) and 9 of the placebo group (75%). No funding declaration given. Location: Italy No potential conflict of interest statement was present.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No comment made
Allocation concealment (selection bias)	Unclear risk	No comment made
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No comment made

Simeone 1997 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment made
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	pH-metry was repeated in 10 participants of the nizatidine group (83.3%) and 9 of the placebo group (75%). Five parents refused re-evaluation.
Selective reporting (reporting bias)	Unclear risk	No evidence of this
Other bias	Unclear risk	No comment made. Funding not stated.

Tolia 2006

Study characteristics	
Methods	Multicentre, double-blind, parallel-design, outpatient RCT
Participants	53 children (5 to 11 years) with symptomatic GORD
Interventions	Comparison of 10, 20, and 40 mg pantoprazole for 8 weeks
Outcomes	Symptom score, endoscopic appearance and histological assessment, adverse events. Overall symptom score assessed using GASP-Q to produce a composite symptom score (CSS). Individual symptoms also assessed (number of vomiting episodes, heartburn, epigastric pain) at week 0 then week 1 then 8. Endoscopy appearances were assessed using Hetzel-Dent scoring. Adverse events were recorded.
Notes	There was no correlation between composite symptom score changes and endoscopy/biopsy changes. Statistically significant increases from baseline were noted in mean values for weight and height at week 8 in the pantoprazole 10 mg and 40 mg dose groups ($P < 0.04$). The participants in the 20 mg group had a significant mean increase in weight at week 8 ($P = 0.023$). Antacid use was reduced in the 20 mg and 40 mg groups at end of treatment. Adverse events noted: pantoprazole 10 mg group: headache (7 participants: 36.8%), rhinitis (5 participants; 26.3%), and nausea (3 participants; 15.8%). Pantoprazole 20 mg group: headache (5 participants; 27.8%), rhinitis (3 participants; 16.7%). Pantoprazole 40 mg group: headache (4 participants; 25%), abdominal pain, asthma, and pharyngitis (3 participants each; 18.8%). No funding declaration given. Location: USA No potential conflict of interest statement was present. Wyeth Research assisted in the preparation of the manuscript.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No comment on randomisation technique
Allocation concealment (selection bias)	Unclear risk	No comment on allocation concealment

Tolia 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded but no comment as to technique. Physician not blinded, but endoscopic findings read by blinded observer. No comment as to how participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No analysis of endoscopy appearances after treatment given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enroled participants accounted for. No evidence of consecutive enrolment, or discussion of those children who refused consent or who were excluded.
Selective reporting (reporting bias)	Unclear risk	No evidence of selective reporting
Other bias	High risk	Wyeth Research involved in the preparation of the manuscript which may have affected study design (same medication, different dosing comparison).

Tolia 2010a

Study characteristics	
Methods	Post hoc analysis of subgroup of multicentre, parallel-design RCT
Participants	Subgroup of 109 participants weighing 8 kg to < 20 kg were randomised 1:1 to receive esomeprazole 5 mg or 10 mg daily.
Interventions	Esomeprazole 10 mg once daily for 8 weeks versus esomeprazole 5 mg once daily
Outcomes	Symptoms were graded as none/mild/moderate/severe (PGA - Physician's Global Assessment symptom score) and by parents telephoning daily to report on the preceding 24 hours' symptoms. Also, the number of vomiting episodes and the use of antacids were assessed. Adverse events were monitored. Endoscopic findings were graded using the Los Angeles (LA) classification for erosive oesophagitis: Grade A is > 1 mucosal break < 5 mm that does not extend between the tops of 2 mucosal folds Grade B is > 1 mucosal break > 5 mm that does not extend between the tops of 2 mucosal folds Grade C is > 1 mucosal break that is continuous between the tops of > 2 mucosal folds but involves < 75% of the circumference of the oesophagus Grade D is > 1 mucosal break that involves > 75% of the circumference of the oesophagus Histology appearances were graded as healed/improved/unchanged.
Notes	Study supported by AstraZeneca LP. Medical writing services provided by Scientific Connexions, Newtown, PA, on behalf of AstraZeneca LP. Multiple authors received grant/research support from, and or were employees of, and or speakers for and or were consultants to AstraZenaca, Wyeth, Johnson and Johnson, TAP, Nutricia, Nestle and GlaxoSmithKline. Location: USA, France, Belgium, and Italy
Risk of bias	

Bias	Authors' judgement	Support for judgement

Tolia 2010a *(Continued)*

Random sequence generation (selection bias)	High risk	See Tolia 2010b: no comment made: higher risk as post hoc analysis and authors also note the potential for selection bias due to enrollment of patients who have not responded satisfactorily to other approved therapy
Allocation concealment (selection bias)	High risk	See Tolia 2010b: no comment made: higher risk as post hoc analysis
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind by dose strata
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comment made
Incomplete outcome data (attrition bias) All outcomes	High risk	Higher risk as post hoc analysis
Selective reporting (reporting bias)	High risk	ITT analysis of all those participants with oesophagitis. Authors wondered about selection bias of those children with oesophagitis (sicker children); 2 children with erosive oesophagitis didn't have follow-up endoscopy
Other bias	High risk	See funding comments: likely influence on study design (same medication: different dose comparison).

Tolia 2010b

Study characteristics	
Methods	Multicentre, double-blinded (for dose), parallel-group, outpatient RCT
Participants	109 children aged 1 to 11 years across Europe and the USA with endoscopically/histologically confirmed erosive oesophagitis
Interventions	Doses of 5 mg or 10 mg of esomeprazole (8 kg to 20 kg children), 10 mg or 20 mg esomeprazole (> 20 kg children) for 8 weeks
Outcomes	Children with erosive oesophagitis underwent an endoscopy after 8 weeks to assess healing of erosions. Outcomes assessed included resolution on endoscopy and side effects. Safety data (adverse events) and symptoms were published by the group separately (Gilger 2006). Endoscopy appearance - presence/absence of erosive oesophagitis
Notes	Baseline symptom characteristics were recorded and mention of record at follow-up, but no follow-up data available, and the trial did not report the outcome in sufficient detail to allow extraction of summary statistics. Baseline histologic appearance recorded and mention of record at follow-up but no follow-up data available. 49 children were excluded: 4 had eosinophilic oesophagitis, 29 had no evidence of reflux oesophagitis on endoscopy, and 16 were excluded for reasons 'not related to endoscopy'. Study funded by AstraZeneca. Location: USA, Belgium, France, Italy

Tolia 2010b *(Continued)*

	Competing interests declared: multiple authors had received grant/research support from AstraZeneca. An author had served as a speaker and a consultant for AP and AstraZeneca and has served as a speaker for Nestle. Another author has received research grants from Wyeth, Johnson & Johnson, and GlaxoSmithKline and has served as a speaker for Takeda and SHS Nutritionals. Three authors were employees of AstraZeneca LP.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described by authors, and initial endoscopy and then enrolment performed at the discretion of the investigator.
Allocation concealment (selection bias)	High risk	Not described by authors
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents reported outcomes but blinded to dose
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endoscopy performed by blinded examiners
Incomplete outcome data (attrition bias) All outcomes	High risk	A high number of participants did not undergo follow-up endoscopic examination (> 50%)
Selective reporting (reporting bias)	High risk	Of 3 potential outcome measures (endoscopic appearance, histologic appearance, and symptoms) only 1 had any follow-up data recorded despite all 3 being recorded at baseline and follow-up measurement described by the authors.
Other bias	High risk	Study funded by AstraZeneca, with pharmaceutical writing support also noted, which may have affected study design (same medication, different dosing comparison).

Tsou 2006

Study characteristics

Methods	Outpatient, multicentre, randomised, double-blind, multidose, parallel-group study
Participants	112 children aged 12 to 16 years with symptomatic GORD
Interventions	Pantoprazole 40 mg (n = 68) versus pantoprazole 20 mg (n = 68)
Outcomes	Improvements were assessed using the GORD Assessment of Symptoms-Pediatric questionnaire (GASP-Q): outcomes expressed as composite symptom score and individual symptom score (vomiting episodes per day, heartburn symptom score, and epigastric pain score), through patient/parent records and physician assessment at baseline and week 8 (Likert score). Side effects also reported.
Notes	In terms of adverse events (expressed as 'treatment-associated adverse events'), a total of 112 participants (82.4%) had a treatment-associated adverse event (AE), as follows: 1 or more treatment-associated AEs = 59 participants (86.8%) in 20 mg group, 53 participants (77.9%) in 40 mg group. No serious

Tsou 2006 *(Continued)*

	AEs/deaths occurred. Commonest treatment-associated AE was headache: 25 participants in 20 mg group; 22 participants in the 40 mg group. The majority were mild. Headache led to early withdrawal of 3 participants in the 40 mg group. 1 participant in the 20 mg group and 7 participants in the 40 mg group reported diarrhoea. Liver function fluctuation in 5 children was noted, and mild uric acid rise in 15 children. The study was supported by Wyeth Research. Wyeth Research were involved in the preparation of the manuscript. Location: USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No evidence provided
Allocation concealment (selection bias)	Unclear risk	No evidence provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No evidence provided as to method of blinding; no true control arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No evidence provided as to blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	159 children screened, and only 139 children entered the study: reasons for the other 20 not given. Otherwise, results analysed on intention-to-treat basis. Good assessment of compliance in teenagers
Selective reporting (reporting bias)	High risk	Children may not have been seen at trial entry by physician, potentially causing recall bias
Other bias	High risk	Final author employed by Wyeth, who funded the research, which may have affected study design (same medication, different dosing comparison).

Ummarino 2015

Study characteristics	
Methods	Single-centre, outpatient, single-blinded, parallel design RCT
Participants	75 infants younger than 1 year old (mean age 5 months, range 1 to 10 months), affected by symptoms of GOR (score > 7/35 on I-GERQ)
Interventions	8 weeks' treatment with magnesium alginate and reassurance, thickened formula feeding (rice-starch) and reassurance, or reassurance (lifestyle changes and reassurance on the condition). Evaluation after 1 (T1) and 2 months (T2).
Outcomes	Parent-reported symptom score (I-GERQ) and individual symptoms (regurgitation, vomiting, and vomiting causing pain). Adverse events were monitored: 1 infant treated with magnesium alginate and simeticone developed constipation.

Ummarino 2015 *(Continued)*

Notes	This study assessed magnesium alginate and simeticone [Gastrotuss] over sodium alginate, given the theoretical advantages of a higher viscosity and lower sodium exposure. Location: Italy, from September 2012 to September 2013 The authors reported no conflicts of interest. There was no funding declaration present.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation confirmed but technique unclear
Allocation concealment (selection bias)	Unclear risk	No information given regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Clinician blinding but no patient blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinician evaluating questionnaire results and follow-ups was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rate of 15% was noted: 2 infants started PPI, 1 infant started Gastrotuss baby therapy, and 5 infants saw a different paediatrician due to persistence of symptoms
Selective reporting (reporting bias)	Low risk	Complete data in enroled infants
Other bias	Unclear risk	No manufacturer support identified

Zohalinezhad 2015

Study characteristics

Methods	Outpatient, single-centre, double-blind, parallel-group RCT
Participants	80 children (0 to 18 years) with GORD
Interventions	Quince syrup versus omeprazole (2 mg/kg/day)
Outcomes	Symptomatic improvement (composite symptom score) based on parental reports assessed at weeks 4 and 7; and adverse events.
Notes	Adequately powered to show a 1-sided significance of 0.05 (80% power) with 32 participants in each group. Unclear how many participants had had endoscopy. Diagnosis of GORD based on 1 month of 2 of 5 symptoms refractory to 'routine' treatments: vomiting immediately after eating, restlessness 1 to 3 hours after feeding, apnoea and respiratory distress after feeding, poor weight gain or refusal to eat. 9 participants declined to participate as they were already on PPIs. No adverse events were noted. Location: Iran

Zohalinezhad 2015 *(Continued)*

	The study was financially supported by Shiraz University of Medical Sciences grants. No potential conflict of interest statement was available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation software used
Allocation concealment (selection bias)	High risk	More children in omeprazole-only group were refusing to eat at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study team (paediatricians, physician administering medications, and statisticians) and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No evidence of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant lost to follow-up or excluded from analysis (due to car accident)
Selective reporting (reporting bias)	High risk	No evidence to judge risk of reporting bias: no conflict of interest statement
Other bias	Low risk	Financial support from Shiraz University

FDA: Food and Drug Administration; **GASP-Q:** GORD Assessment of Symptoms–Pediatric; **GOR:** gastro-oesophageal reflux; **GORD:** gastro-oesophageal reflux disease; **I-GERQ-R:** Infant Gastroesophageal Reflux Questionnaire–Revised; **ITT:** intention-to-treat; **PPI:** proton pump inhibitor; **RCT:** randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Al-Biltagi 2012	Ineligible study design
Ameen 2006	Ineligible study design
Bestebreurtje 2020	Ineligible study design
Bestebreurtje 2017	Ineligible study design
Corvaglia 2010	Ineligible study design
Dhillon 2004	Ineligible study design
Fiedorek 2005	Ineligible study design
Franco 2000	Ineligible study design
Gunesekaran 1993	Ineligible study design

Study	Reason for exclusion
Haddad 2014	Ineligible study design
Hassall 2000	Ineligible study design
Hassall 2012	Ineligible study design
James 2007	Ineligible study design
Kaguelidou 2016	Ineligible study design
Kukulka 2012	Ineligible study design
Kushki 2020	Ineligible study design
Li 2006	Ineligible study design
Loots 2011	Ineligible intervention
Madrazo-de la Garza 2003	Ineligible study design
Martin 2006	Ineligible study design
Nielsen 2004	Ineligible intervention
Omari 2009	Ineligible study design
Orenstein 2005	Ineligible study design
Orsi 2011	Ineligible study design
Pfizer 2021	Ineligible study design
Rabie 2016	Ineligible intervention
Sabahi 2020	Ineligible study design
Salvatore 2006	Ineligible study design
Salvatore 2018	Ineligible study design
Størdal 2005	Ineligible population
Tammara 2011	Ineligible study design
Terrin 2012	Ineligible study design
Tolia 2002	Ineligible study design
Tran 2002	Ineligible study design
Treepongkaruna 2011	Ineligible study design
Ward 2011	Ineligible study design
Winter 2010	Ineligible study design

Study	Reason for exclusion
Winter 2012	Ineligible study design
Zannikos 2011	Ineligible study design
Zhao 2006	Ineligible study design

Characteristics of studies awaiting classification *[ordered by study ID]*

Paknejad 2021

Methods	Double-blind, single-centre, randomised controlled trial
Participants	Children aged 1 to 7 years old, diagnosed with gastroesophageal reflux disease (GERD)
Interventions	Omeprazole and "myrtle fruit syrup" (syrup made from *Myrtus communis* L. fruit) versus control group (omeprazole and placebo syrup) for 8 weeks
Outcomes	GERD symptom questionnaire for young children (GSQ-YC) at baseline, eighth week, and twelfth week (4 weeks after cessation of intervention).
Notes	Awaiting classification

Shahmirzadi 2020

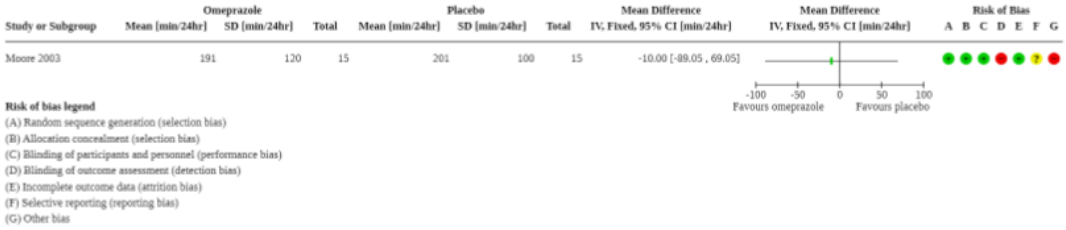
Methods	Single-blinded randomised controlled trial
Participants	Children 6 months to 12 years old with symptomatic gastro-oesophageal reflux disease
Interventions	Control group: omeprazole 1 mg/kg treatment Intervention group: omeprazole plus baclofen 0.25 mg/kg 2 times per day
Outcomes	62 participants in each group: 46 (85.2%) cases in the baclofen treatment group and 32 cases (55.2%) in the non-baclofen treatment group improved (moderate or full remission) at 1 month based on parental reporting.
Notes	No symptom scores. 8 cases in the treatment group with baclofen and 4 cases in the control group were excluded due to lack of follow-up, lack of medication, and incomplete records of participants. No adverse events reported in baclofen group (control group not reported).

DATA AND ANALYSES

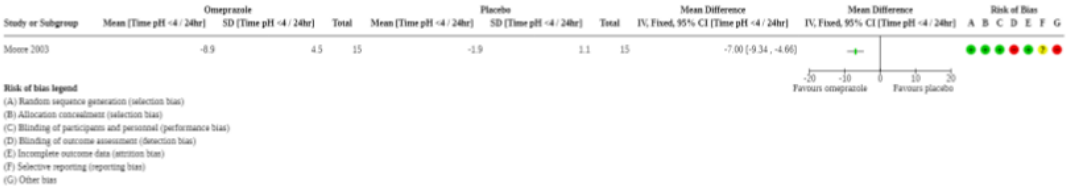
Comparison 1. Omeprazole compared to placebo for infants with GORD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Improvement in cry/fuss time	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2 Improvement in reflux index	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Omeprazole compared to placebo for infants with GORD, Outcome 1: Improvement in cry/fuss time



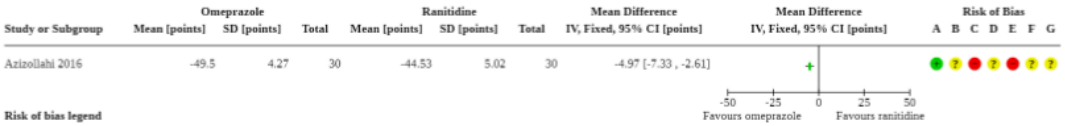
Analysis 1.2. Comparison 1: Omeprazole compared to placebo for infants with GORD, Outcome 2: Improvement in reflux index



Comparison 2. Omeprazole compared to ranitidine for infants with GORD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Improvement in symptom scores (WGSS)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Omeprazole compared to ranitidine for infants with GORD, Outcome 1: Improvement in symptom scores (WGSS)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3. Esomeprazole compared to placebo for infants with GORD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Improvement in number of GORD-related symptoms and signs	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Esomeprazole compared to placebo for infants with GORD, Outcome 1: Improvement in number of GORD-related symptoms and signs

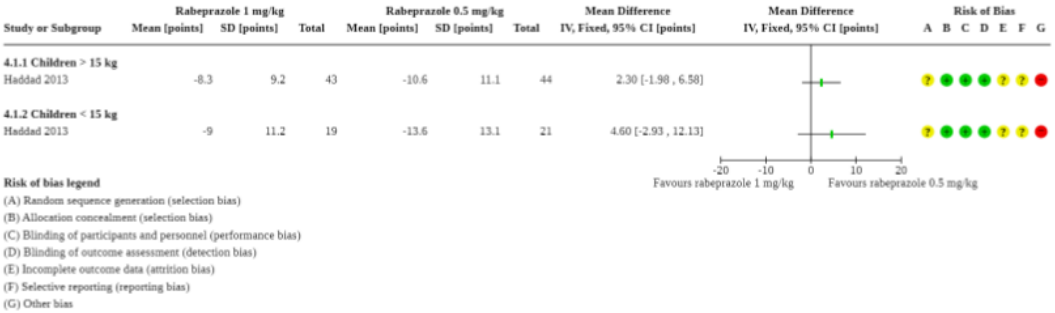
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 4. Rabeprazole at higher doses (1 mg/kg) compared to rabeprazole at lower doses (0.5 mg/kg) for GORD in children older than 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Improvement in symptom score ('Total GERD Symptoms and Severity' score)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1.1 Children > 15 kg	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1.2 Children < 15 kg	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.2 Improvement in endoscopic scores (Hetzel Dent scores)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

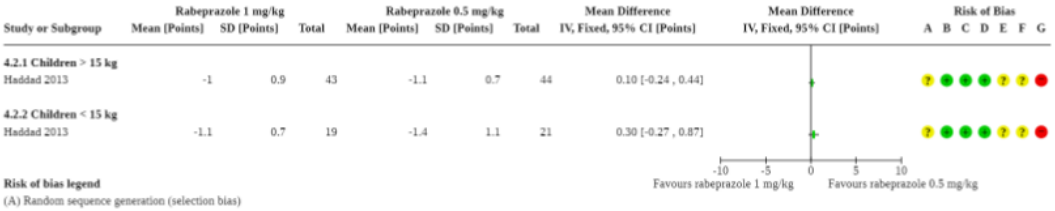
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2.1 Children > 15 kg	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.2.2 Children < 15 kg	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Rabeprazole at higher doses (1 mg/kg) compared to rabeprazole at lower doses (0.5 mg/kg) for GORD in children older than 1 year, Outcome 1: Improvement in symptom score ('Total GERD Symptoms and Severity' score)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.2. Comparison 4: Rabeprazole at higher doses (1 mg/kg) compared to rabeprazole at lower doses (0.5 mg/kg) for GORD in children older than 1 year, Outcome 2: Improvement in endoscopic scores (Hetzel Dent scores)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 5. Pantoprazole in higher doses (1.2 mg/kg) compared to pantoprazole at lower doses (0.3 mg/kg) for GORD in children older than 1 year

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Improvement in symptom scores (WGSS)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5: Pantoprazole in higher doses (1.2 mg/kg) compared to pantoprazole at lower doses (0.3 mg/kg) for GORD in children older than 1 year, Outcome 1: Improvement in symptom scores (WGSS)

APPENDICES

Appendix 1. CENTRAL search strategy (via Ovid Evidence-Based Medicine Reviews Database (EBMR))

1. exp Gastroesophageal Reflux/
2. ((gastroesophag* or gastro-esophag* or gastro-oesophag* or gastric or esophag* or oesophag*) adj3 reflux).tw,kw.
3. (GERD or GORD or NERD or NORD or GER or GOR).tw,kw.
4. (acid adj2 reflux).tw,kw.
5. exp Duodenogastric Reflux/
6. ((duodenogastric or duodeno-gastric or duodenal) adj3 reflux).tw,kw.
7. exp Bile Reflux/
8. (bile adj2 reflux).tw,kw.
9. ((laryngopharyngeal or supraesophag*) adj3 reflux).tw,kw.
10. gastric regurgitation.tw,kw.
11. exp ESOPHAGITIS/
12. (esophagitis or oesophagitis or non-erorisve reflux disease or nonerosive reflux disease).tw,kw.
13. or/1-12
14. exp Proton Pump Inhibitors/
15. proton pump inhibitor*.mp.
16. (PPI or PPIs).tw,kw.
17. (omeprazole or h 16868 or losec or prilosec or rapinex or zegerid).mp.
18. (lansoprazole or lanzoprazole or ag 1749 or agopton or bamalite or lanzor or monolitum or ogast or ogastro or opiren or prevacid or prezal or pro ulco or promeco or takepron or ulpax or zoton).mp.
19. (pantoprazole or by 1023 or protium or protonix or skf-96022).mp.
20. (esomeprazole or nexium).mp.
21. (rabeprazole or aciphex or dexrabeprazole or e 3810 or ly-307640 or pariet).mp.
22. (dexlansoprazole or Kapidex or Dexilant or AGN 20194* or AGN20194* or dexrabeprazole).mp.
23. (tenatoprazole or CAS 113712-98-4 or STU-Na or TAK-390* or TAK390* or TAK-438 or TAK438 or AZD0865 or "AZD 0865").mp.
24. exp Histamine H2 Antagonists/
25. ((histamine or H2 or H-2 or H2R or H 2 R) adj3 (antagonist* or blocker* or blockage* or blockader*)).tw,kw.
26. (H2RA or H2RAs or H2-RA or H2RAs).tw,kw.
27. (antihistaminic* adj2 (H2 or H-2)).tw,kw.
28. (Cimetidine or Tagamet or altramet or biomet or biomet400 or eureceptor or histodil or skf 92334 or skf92334).tw,kw.
29. (ranitidine or zantac or ah 19065 or ah19065 or biotidin or ranisen or ranitidine or sostril or zantic).tw,kw.
30. (Famotidine or Pepcid or mk 208 or mk208 or ym 11170 or ym11170).tw,kw.
31. (Nizatidine or Axid or axid or ly 139037 or ly139037).tw,kw.
32. (Roxatidine or Rotane or Zorpe).tw,kw.
33. (prokinetic* or gastroprokinetic* or gastrokinetic* or gastro-kinetic*).tw,kw.
34. (antiemetic* or anti-emetic).tw,kw.
35. exp Benzamides/
36. (Benzoic Acid Amide or Amides or Phenyl Carboxyamide or Benzamide* or Benzoylamide or benzoates).tw,kw.
37. (Phenylcarboxyamide or Phenylcarboxamide or Benzenecarboxamide or Amid kyseliny benzoove).tw,kw.

38.exp Domperidone/
39.(domperidon* or domidon or Domperi or Domstal or evoxin or gastrocure or motilium or motilium).tw,kw.
40.(motis or nauzelin or Motinorm Costi or Nomit or Brulium or Molax).tw,kw.
41.exp Antiemetics/
42.exp Metoclopramide/
43.(Metoclopramide or cerucal or clopra or gastrese or gastrobid or gastroflux or gastromax or maxolon).tw,kw.
44.(metaclopramide or metozolv or metramid or migravess or mygdalon or octamide or parmid).tw,kw.
45.(primperan or reglan or reliveran or rimetin or Degan or Maxeran or Pylomid or Pramin).tw,kw.
46.exp Cisapride/
47.(Cisapride or alimix or Prepulsid or Propulsid).tw,kw.
48.exp Cholinesterase Inhibitors/
49.(Itopride or ganaton).tw,kw.
50.Mosapride.tw,kw.
51.exp Erythromycin/
52.(erythromycin or aknemycin or emcin or emgel or emycin or eryderm or erygel or erymax).tw,kw.
53.(erymin or eryped or gallimycin or ilosene or ilosone or ilotycin or lauromicina or maracyn).tw,kw.
54.(monomycin or ornacyn or retcin or rommix or romycin or roymicin or staticin or stiemycin or theramycin or tiloryth or wyamycin).tw,kw.
55.(Motilin adj3 (receptor* or agonist*)).tw,kw.
56.((5HT3 or 5HT 3 or 5-HT3 or 5-HT 3) adj3 antagonist*).tw,kw.
57.((5HT or 5-HT or 5-hydroxytryptamine*) adj3 (agonist* or antagonist*)).tw,kw.
58.((5-HT1A or 5HT1A or 5-HT 1A or 5HT 1A) adj3 agonist*).tw,kw.
59.exp Serotonin Antagonists/
60.exp Serotonin 5-HT3 Receptor Antagonists/
61.exp Serotonin 5-HT4 Receptor Agonists/
62.exp Serotonin 5-HT1 Receptor Agonists/
63.(serotonin adj3 receptor adj3 (agonist* or antagonist* or block*)).tw,kw.
64.(tegaserod or Zelnorm or Zelmac).tw,kw.
65.ABT-229.tw,kw.
66.(Tandospirone or Sediel or metanopirone or buspirone).tw,kw.
67.(alosetron or Lotronex).tw,kw.
68.(Acotiamide or YM-443 or Z-338D).tw,kw.
69.(acetylcholinesterase inhibitor* or cholinesterase Inhibitor* or anti-cholinesterase* or anticholinesterase*).tw,kw.
70.((5HT-4 or 5HT4 or 5-HT 4 or 5-HT4) adj3 agonist*).tw,kw.
71.exp Alginates/
72.(Alginates or alginic acid).tw,kw.
73.exp Antacids/
74.(antacid* or alkalinizing agent* or antigastralgic agent*).tw,kw.
75.(aluminum or aldrox or algeldrate or alhydrogel or alugel or amphojel or basalgel or brasivil or dialume or nephrox or pepsamer or rocgel).tw,kw.
76.(calcium carbonate or aragonite or calcite or calcium milk or Chalk or limestone or marble or vaterite).tw,kw.
77.(magnesium or brucite or magnesia).tw,kw.
78.(alexitol sodium or algicon or Almagate or almagel or alubifar or alugastrin or andursil or attapulgite or bicarbonate or carbex or dihydroxyaluminum sodium carbonate or gaviscon or hydrotalcite or magaldrate or Mylanta or novaluzid or rennie or solugastril or titralac or vangatalcite).tw,kw.
79.((gastro* or gastric or stomach) and mucosa* and protect* and (agent* or drug* or medicine* or medication*)).tw,kw.
80.(sucralfate or sulfate or antepsin or carafate or ulcerban or ulcogant or ulsanic).tw,kw.
81.(adopilon or alsucral or sulphate or alusac or andapsin or bisma or dolisec or exinol or hexagastron or inpepsa or iselpin or keal or melicide or musin or neciblok or peptonorm or succosa or sucrabest or sucralbene or sucralfin or sucramal or sulcran or sulcrate or treceptan or ufarene or ulcar or ulcekon or ulcerimin or ulcerlmin or ulcertec orulcogant or ulcyte or ulsaheal or ulsanic or ulsicral or ulsidex forte or unival or urbal or venter).tw,kw.
82.exp bismuth/
83.bismuth*.tw,kw.
84.exp Baclofen/

85.(Baclofen or Antispasmodic*).tw,kw.
86.or/14-85
87.13 and 86
88.exp Adolescent/
89.exp Child/
90.exp Infant/
91.exp Minors/
92.exp Pediatrics/
93.exp Puberty/
94.exp Schools/
95.(baby or babies or child or children or neonatal or pediatric* or paediatric* or peadiatric* or infant* or infancy or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.
96.(postmatur* or prematur* or preterm* or perinat* or boy* or girl* or teen* or minors* or prepubescen* or prepuberty* or pubescen* or puber*).tw,kw.
97.(elementary school* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school* or youth* or young or student* or juvenil* or underage* or (under* adj age*) or under 16).tw,kw.
98.or/88-97
99.87 and 98

Appendix 2. MEDLINE search strategy (via Ovid)

1. exp Gastroesophageal Reflux/
2. ((gastroesophag* or gastro-esophag* or gastro-oesophag* or gastric or esophag* or oesophag*) adj3 reflux).tw,kw.
3. (GERD or GORD or NERD or NORD or GER or GOR).tw,kw.
4. (acid adj2 reflux).tw,kw.
5. exp Duodenogastric Reflux/
6. ((duodenogastric or duodeno-gastric or duodenal) adj3 reflux).tw,kw.
7. exp Bile Reflux/
8. (bile adj2 reflux).tw,kw.
9. ((laryngopharyngeal or supraesophag*) adj3 reflux).tw,kw.
10.gastric regurgitation.tw,kw.
11.exp ESOPHAGITIS/
12.(esophagitis or oesophagitis or non-erorisve reflux disease or nonerosive reflux disease).tw,kw.
13.or/1-12
14.exp Proton Pump Inhibitors/
15.proton pump inhibitor*.mp.
16.(PPI or PPIs).tw,kw.
17.(omeprazole or h 16868 or losec or prilosec or rapinex or zegerid).mp.
18.(lansoprazole or lanzoprazole or ag 1749 or agopton or bamalite or lanzor or monolitum or ogast or ogastro or opiren or prevacid or prezal or pro ulco or promeco or takepron or ulpax or zoton).mp.
19.(pantoprazole or by 1023 or protium or protonix or skf-96022).mp.
20.(esomeprazole or nexium).mp.
21.(rabeprazole or aciphex or dexrabeprazole or e 3810 or ly-307640 or pariet).mp.
22.(dexlansoprazole or Kapidex or Dexilant or AGN 20194* or AGN20194* or dexrabeprazole).mp.
23.(tenatoprazole or CAS 113712-98-4 or STU-Na or TAK-390* or TAK390* or TAK-438 or TAK438 or AZD0865 or "AZD 0865").mp.
24.exp Histamine H2 Antagonists/
25.((histamine or H2 or H-2 or H2R or H 2 R) adj3 (antagonist* or blocker* or blockage* or blockader*)).tw,kw.
26.(H2RA or H2RAs or H2-RA or H2RAs).tw,kw.
27.(antihistaminic* adj2 (H2 or H-2)).tw,kw.
28.(Cimetidine or Tagamet or altramet or biomet or biomet400 or eureceptor or histodil or skf 92334 or skf92334).tw,kw.
29.(ranitidine or zantac or ah 19065 or ah19065 or biotidin or ranisen or ranitidine or sostril or zantic).tw,kw.
30.(Famotidine or Pepcid or mk 208 or mk208 or ym 11170 or ym11170).tw,kw.
31.(Nizatidine or Axid or axid or ly 139037 or ly139037).tw,kw.
32.(Roxatidine or Rotane or Zorpe).tw,kw.

33.(prokinetic* or gastroprokinetic* or gastrokinetic* or gastro-kinetic*).tw,kw.
34.(antiemetic* or anti-emetic).tw,kw.
35.exp Benzamides/
36.(Benzoic Acid Amide or Amides or Phenyl Carboxyamide or Benzamide* or Benzoylamide or benzoates).tw,kw.
37.(Phenylcarboxyamide or Phenylcarboxamide or Benzenecarboxamide or Amid kyseliny benzoove).tw,kw.
38.exp Domperidone/
39.(domperidon* or domidon or Domperi or Domstal or evoxin or gastrocure or motilium or motilium).tw,kw.
40.(motis or nauzelin or Motinorm Costi or Nomit or Brulium or Molax).tw,kw.
41.exp Antiemetics/
42.exp Metoclopramide/
43.(Metoclopramide or cerucal or clopra or gastrese or gastrobid or gastroflux or gastromax or maxolon).tw,kw.
44.(metaclopramide or metozolv or metramid or migravess or mygdalon or octamide or parmid).tw,kw.
45.(primperan or reglan or reliveran or rimetin or Degan or Maxeran or Pylomid or Pramin).tw,kw.
46.exp Cisapride/
47.(Cisapride or alimix or Prepulsid or Propulsid).tw,kw.
48.exp Cholinesterase Inhibitors/
49.(Itopride or ganaton).tw,kw.
50.Mosapride.tw,kw.
51.exp Erythromycin/
52.(erythromycin or aknemycin or emcin or emgel or emycin or eryderm or erygel or erymax).tw,kw.
53.(erymin or eryped or gallimycin or ilosene or ilosone or ilotycin or lauromicina or maracyn).tw,kw.
54.(monomycin or ornacyn or retcin or rommix or romycin or roymicin or staticin or stiemycin or theramycin or tiloryth or wyamycin).tw,kw.
55.(Motilin adj3 (receptor* or agonist*)).tw,kw.
56.((5HT3 or 5HT 3 or 5-HT3 or 5-HT 3) adj3 antagonist*).tw,kw.
57.((5HT or 5-HT or 5-hydroxytryptamine*) adj3 (agonist* or antagonist*)).tw,kw.
58.((5-HT1A or 5HT1A or 5-HT 1A or 5HT 1A) adj3 agonist*).tw,kw.
59.exp Serotonin Antagonists/
60.exp Serotonin 5-HT3 Receptor Antagonists/
61.exp Serotonin 5-HT4 Receptor Agonists/
62.exp Serotonin 5-HT1 Receptor Agonists/
63.(serotonin adj3 receptor adj3 (agonist* or antagonist* or block*)).tw,kw.
64.(tegaserod or Zelnorm or Zelmac).tw,kw.
65.ABT-229.tw,kw.
66.(Tandospirone or Sediel or metanopirone or buspirone).tw,kw.
67.(alosetron or Lotronex).tw,kw.
68.(Acotiamide or YM-443 or Z-338D).tw,kw.
69.(acetylcholinesterase inhibitor* or cholinesterase Inhibitor* or anti-cholinesterase* or anticholinesterase*).tw,kw.
70.((5HT-4 or 5HT4 or 5-HT 4 or 5-HT4) adj3 agonist*).tw,kw.
71.exp Alginates/
72.(Alginates or alginic acid).tw,kw.
73.exp Antacids/
74.(antacid* or alkalinizing agent* or antigastralgic agent*).tw,kw.
75.(aluminum or aldrox or algeldrate or alhydrogel or alugel or amphojel or basalgel or brasivil or dialume or nephrox or pepsamer or rocgel).tw,kw.
76.(calcium carbonate or aragonite or calcite or calcium milk or Chalk or limestone or marble or vaterite).tw,kw.
77.(magnesium or brucite or magnesia).tw,kw.
78.(alexitol sodium or algicon or Almagate or almagel or alubifar or alugastrin or andursil or attapulgite or bicarbonate or carbex or dihydroxyaluminum sodium carbonate or gaviscon or hydrotalcite or magaldrate or Mylanta or novaluzid or rennie or solugastril or titralac or vangatalcite).tw,kw.
79.((gastro* or gastric or stomach) and mucosa* and protect* and (agent* or drug* or medicine* or medication*)).tw,kw.
80.(sucralfate or sulfate or antepsin or carafate or ulcerban or ulcogant or ulsanic).tw,kw.
81.(adopilon or alsucral or sulphate or alusac or andapsin or bisma or dolisec or exinol or hexagastron or inpepsa or iselpin or keal or melicide or musin or neciblok or peptonorm or succosa or sucrabest or sucralbene or sucralfin or sucramal or sulcran or sulcrate or

treceptan or ufarene or ulcar or ulcekon or ulcerimin or ulcerlmin or ulcertec orulcogant or ulcyte or ulsaheal or ulsanic or ulsicral or ulsidex forte or unival or urbal or venter).tw,kw.

82. exp bismuth/
83. bismuth*.tw,kw.
84. exp Baclofen/
85. (Baclofen or Antispasmodic*).tw,kw.
86. or/14-85
87. 13 and 86
88. exp Adolescent/
89. exp Child/
90. exp Infant/
91. exp Minors/
92. exp Pediatrics/
93. exp Puberty/
94. exp Schools/
95. (baby or babies or child or children or neonatal or pediatric* or paediatric* or peadiatric* or infant* or infancy or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.
96. (postmatur* or prematur* or preterm* or perinat* or boy* or girl* or teen* or minors* or prepubescen* or prepuberty* or pubescen* or puber*).tw,kw.
97. (elementary school* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school* or youth* or young or student* or juvenil* or underage* or (under* adj age*) or under 16).tw,kw.
98. or/88-97
99. 87 and 98
100. randomized controlled trial.pt.
101. controlled clinical trial.pt.
102. random*.mp.
103. placebo.ab.
104. drug therapy.fs.
105. trial.ab.
106. groups.ab.
107. or/100-106
108. exp animals/ not humans.sh.
109. 107 not 108
110. 99 and 109

Note: Lines 100-109, Cochrane handbood RCT filter: "Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format". We made the following minor revision: we used "random*" instead of "randomized.ab" or "randomly.ab." to capture word variations such as "randomised, randomization, random".

Appendix 3. Embase search strategy (via Ovid)

1. exp gastroesophageal reflux/
2. ((gastroesophag* or gastro-esophag* or gastro-oesophag* or gastric or esophag* or oesophag*) adj3 reflux).tw,kw.
3. (GERD or GORD or NERD or NORD or GER or GOR).tw,kw.
4. (acid adj2 reflux).tw,kw.
5. exp duodenogastric reflux/
6. ((duodenogastric or duodeno-gastric or duodenal) adj3 reflux).tw,kw.
7. exp bile reflux/
8. (bile adj2 reflux).tw,kw.
9. ((laryngopharyngeal or supraesophag*) adj3 reflux).tw,kw.
10. gastric regurgitation.tw,kw.
11. exp esophagitis/
12. (esophagitis or oesophagitis or non-erorisve reflux disease or nonerosive reflux disease).tw,kw.
13. or/1-12
14. exp proton pump inhibitor/

15.proton pump inhibitor*.mp.
16.(PPI or PPIs).tw,kw.
17.(omeprazole or h 16868 or losec or prilosec or rapinex or zegerid).mp.
18.(lansoprazole or lanzoprazole or ag 1749 or agopton or bamalite or lanzor or monolitum or ogast or ogastro or opiren or prevacid or prezal or pro ulco or promeco or takepron or ulpax or zoton).mp.
19.(pantoprazole or by 1023 or protium or protonix or skf-96022).mp.
20.(esomeprazole or nexium).mp.
21.(rabeprazole or aciphex or dexrabeprazole or e 3810 or ly-307640 or pariet).mp.
22.(dexlansoprazole or Kapidex or Dexilant or AGN 20194* or AGN20194* or dexrabeprazole).mp.
23.(tenatoprazole or CAS 113712-98-4 or STU-Na or TAK-390* or TAK390* or TAK-438 or TAK438 or AZD0865 or "AZD 0865").mp.
24.exp histamine H2 receptor antagonist/
25.((histamine or H2 or H-2 or H2R or H 2 R) adj3 (antagonist* or blocker* or blockage* or blockader*)).tw,kw.
26.(H2RA or H2RAs or H2-RA or H2RAs).tw,kw.
27.(antihistaminic* adj2 (H2 or H-2)).tw,kw.
28.(Cimetidine or Tagamet or altramet or biomet or biomet400 or eureceptor or histodil or skf 92334 or skf92334).tw,kw.
29.(ranitidine or zantac or ah 19065 or ah19065 or biotidin or ranisen or ranitidine or sostril or zantic).tw,kw.
30.(Famotidine or Pepcid or mk 208 or mk208 or ym 11170 or ym11170).tw,kw.
31.(Nizatidine or Axid or axid or ly 139037 or ly139037).tw,kw.
32.(Roxatidine or Rotane or Zorpe).tw,kw.
33.(prokinetic* or gastroprokinetic* or gastrokinetic* or gastro-kinetic*).tw,kw.
34.(antiemetic* or anti-emetic).tw,kw.
35.exp benzamide derivative/
36.(Benzoic Acid Amide or Amides or Phenyl Carboxyamide or Benzamide* or Benzoylamide or benzoates).tw,kw.
37.(Phenylcarboxyamide or Phenylcarboxamide or Benzenecarboxamide or Amid kyseliny benzoove).tw,kw.
38.exp domperidone/
39.(domperidon* or domidon or Domperi or Domstal or evoxin or gastrocure or motilium or motilium).tw,kw.
40.(motis or nauzelin or Motinorm Costi or Nomit or Brulium or Molax).tw,kw.
41.exp antiemetic agent/
42.exp metoclopramide/
43.(Metoclopramide or cerucal or clopra or gastrese or gastrobid or gastroflux or gastromax or maxolon).tw,kw.
44.(metaclopramide or metozolv or metramid or migravess or mygdalon or octamide or parmid).tw,kw.
45.(primperan or reglan or reliveran or rimetin or Degan or Maxeran or Pylomid or Pramin).tw,kw.
46.exp cisapride/
47.(Cisapride or alimix or Prepulsid or Propulsid).tw,kw.
48.exp cholinesterase inhibitor/
49.(Itopride or ganaton).tw,kw.
50.Mosapride.tw,kw.
51.exp erythromycin/
52.(erythromycin or aknemycin or emcin or emgel or emycin or eryderm or erygel or erymax).tw,kw.
53.(erymin or eryped or gallimycin or ilosene or ilosone or ilotycin or lauromicina or maracyn).tw,kw.
54.(monomycin or ornacyn or retcin or rommix or romycin or roymicin or staticin or stiemycin or theramycin or tiloryth or wyamycin).tw,kw.
55.(Motilin adj3 (receptor* or agonist*)).tw,kw.
56.exp motilin receptor agonist/
57.((5HT3 or 5HT 3 or 5-HT3 or 5-HT 3) adj3 antagonist*).tw,kw.
58.((5HT or 5-HT or 5-hydroxytryptamine*) adj3 (agonist* or antagonist*)).tw,kw.
59.((5-HT1A or 5HT1A or 5-HT 1A or 5HT 1A) adj3 agonist*).tw,kw.
60.exp serotonin antagonist/
61.exp serotonin 3 antagonist/
62.exp serotonin 4 agonist/
63.exp serotonin 1 agonist/
64.exp Serotonin 5-HT3 Receptor Antagonists/
65.exp Serotonin 5-HT4 Receptor Agonists/

66.exp Serotonin 5-HT1 Receptor Agonists/
67.(serotonin adj3 receptor adj3 (agonist* or antagonist* or block*)).tw,kw.
68.(tegaserod or Zelnorm or Zelmac).tw,kw.
69.exp tegaserod/
70.ABT-229.tw,kw.
71.exp tandospirone/
72.(Tandospirone or Sediel or metanopirone or buspirone).tw,kw.
73.exp alosetron/
74.(alosetron or Lotronex).tw,kw.
75.exp acotiamide/
76.(Acotiamide or YM-443 or Z-338D).tw,kw.
77.(acetylcholinesterase inhibitor* or cholinesterase Inhibitor* or anti-cholinesterase* or anticholinesterase*).tw,kw.
78.((5HT-4 or 5HT4 or 5-HT 4 or 5-HT4) adj3 agonist*).tw,kw.
79.alginic acid/
80.(Alginates or alginic acid).tw,kw.
81.exp antacid agent/
82.(antacid* or alkalinizing agent* or antigastralgic agent*).tw,kw.
83.(aluminum or aldrox or algeldrate or alhydrogel or alugel or amphojel or basalgel or brasivil or dialume or nephrox or pepsamer or rocgel).tw,kw.
84.(calcium carbonate or aragonite or calcite or calcium milk or Chalk or limestone or marble or vaterite).tw,kw.
85.(magnesium or brucite or magnesia).tw,kw.
86.(alexitol sodium or algicon or Almagate or almagel or alubifar or alugastrin or andursil or attapulgite or bicarbonate or carbex or dihydroxyaluminum sodium carbonate or gaviscon or hydrotalcite or magaldrate or Mylanta or novaluzid or rennie or solugastril or titralac or vangatalcite).tw,kw.
87.exp gastrointestinal mucosa protective agent/
88.((gastro* or gastric or stomach) and mucosa* and protect* and (agent* or drug* or medicine* or medication*)).tw,kw.
89.(sucralfate or sulfate or antepsin or carafate or ulcerban or ulcogant or ulsanic).tw,kw.
90.(adopilon or alsucral or sulphate or alusac or andapsin or bisma or dolisec or exinol or hexagastron or inpepsa or iselpin or keal or melicide or musin or neciblok or peptonorm or succosa or sucrabest or sucralbene or sucralfin or sucramal or sulcran or sulcrate or treceptan or ufarene or ulcar or ulcekon or ulcerimin or ulcerlmin or ulcertec orulcogant or ulcyte or ulsaheal or ulsanic or ulsicral or ulsidex forte or unival or urbal or venter).tw,kw.
91.exp bismuth/
92.bismuth*.tw,kw.
93.exp baclofen/
94.(Baclofen or Antispasmodic*).tw,kw.
95.or/14-94
96.13 and 95
97.exp adolescence/
98.exp adolescent/
99.exp child/
100.exp high school/
101.exp kindergarten/
102.exp middle school/
103.exp newborn/
104.exp nursery school/
105.exp pediatrics/
106.exp primary school/
107.exp puberty/
108.exp school/
109.exp newborn/ or exp pediatrics/
110.(baby or babies or child or children or neonatal or pediatric* or paediatric* or peadiatric* or infant* or infancy or neonat* or newborn* or new born* or kid or kids or adolescen* or preschool or pre-school or toddler*).tw,kw.

111 (postmatur* or prematur* or preterm* or perinat* or boy* or girl* or teen* or minors* or prepubescen* or prepuberty* or pubescen* or puber*).tw,kw.
112 (elementary school* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school* or youth* or young or student* or juvenil* or underage* or (under* adj age*) or under 16).tw,kw.
113 or/97-112
114 96 and 113
115 random:.tw.
116 placebo:.mp.
117 double-blind:.tw.
118 or/115-117
119 exp animal/ not human/
120 118 not 119
121 114 and 120

Note: Lines #115-117, Hedge Best balance of sensitivity and specificity filter for identifying "therapy studies"in Embase. https://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx

Appendix 4. Web of Science search strategy

# 16	#15 AND #14 *Databases=SCI-EXPANDED Timespan=All Years*
# 15	Topic=(single blind*) OR Topic=(double blind*) OR Topic=(clinical trial*) OR Topic=(placebo*) OR Topic=(random*) OR Topic=(controlled clinical trial) OR Topic=(research design) OR Topic=(comparative stud*) OR Topic=(controlled trial) OR Topic=(follow up stud*) OR Topic=(prospective stud*) *Databases=SCI-EXPANDED Timespan=All Years*
# 14	#13 NOT #11 *Databases=SCI-EXPANDED Timespan=All Years*
# 13	#12 AND #1 *Databases=SCI-EXPANDED Timespan=All Years*
# 12	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 *Databases=SCI-EXPANDED Timespan=All Years*
# 11	Topic=(Adult* or Elderly or Middle Aged or Aged) NOT Topic=(infant* or Newborn* or Pediatric* or child* or baby or babies or babe or Adolescent) *Databases=SCI-EXPANDED Timespan=All Years*
# 10	Topic=(Rabeprazole or Esomeprazole or metoclopramide or domperidon* or bethanechol) OR Topic=(Sucralfate) *Databases=SCI-EXPANDED Timespan=All Years*
# 9	Topic=(lansoprazol* or Pantoprazole or omeprazole) *Databases=SCI-EXPANDED Timespan=All Years*
# 8	Topic=(Proton Pump Inhibitor* OR PPI)

(Continued)

	Databases=SCI-EXPANDED Timespan=All Years
# 7	Topic=(Ranitidin*) OR Topic=(Cimetidine) OR Topic=(Famotidine) *Databases=SCI-EXPANDED Timespan=All Years*
# 6	Topic=(H2 antagonist*) *Databases=SCI-EXPANDED Timespan=All Years*
# 5	Topic=(Maalox*) *Databases=SCI-EXPANDED Timespan=All Years*
# 4	Topic=(antacid*) *Databases=SCI-EXPANDED Timespan=All Years*
# 3	Topic=(Gaviscon) *Databases=SCI-EXPANDED Timespan=All Years*
# 2	Topic=(Alginate*) *Databases=SCI-EXPANDED Timespan=All Years*
# 1	Topic=(Gastroesophageal Reflux) OR Topic=(GER or GOR) OR Topic=(GERD or GORD) *Databases=SCI-EXPANDED Timespan=All Years*

WHAT'S NEW

Date	Event	Description
22 August 2023	New citation required and conclusions have changed	Conclusions have been updated regarding the certainty of the evidence
22 August 2023	New search has been performed	Review updated with latest literature search.

HISTORY

Protocol first published: Issue 6, 2010
Review first published: Issue 11, 2014

Date	Event	Description
1 December 2020	New citation required and conclusions have changed	36 (12 new) RCTs are included in this review. Summary data extracted from 14 studies and conclusions updated.

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities

Agree the protocol is still appropriate: Mark Tighe, Mark Beattie,
Confirm the search strategy: Mark Tighe, Mark Beattie
Search for new trials (2 people): Mark Tighe, Iona Liddicoat,
Obtain copies of new trials: Mark Tighe, Iona Liddicoat
Select which trials to include (2 + 1 arbiter) Mark Tighe, Iona Liddicoat +Mark Beattie.
Extract data from trials (2 people) Mark Tighe, Iona Liddicoat
Enter data into RevMan: Mark Tighe, Iona Liddicoat
Carry out the analysis: Mark Tighe, Iona Liddicoat, Edward Andrews, Mark Beattie.
Interpret the analysis Mark Tighe, Nadeem Afzal, Mark Beattie, Iona Liddicoat, Edward Andrews, Andrew Hayen
Update the review Mark Tighe, Iona Liddicoat, Edward Andrews, Nadeem Afzal, Mark Beattie, Andrew Hayen.

DECLARATIONS OF INTEREST

There are no authors' conflicts of interest.

A previous review of the medical treatment of gastro-oesophageal reflux was completed for 'Pediatric Drugs' (publishers: 'Adis') and published in early 2009. However that article is substantially different from the Cochrane review. The Pediatric Drugs article was not funded.

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Internal sources

- Library, University Hospitals Dorset NHS Foundation Trust, UK

  Obtaining manuscripts

External sources

- Cochrane Gut Group, Canada

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between the protocol and the present update:

- Data collection and analysis: we used Review Manager 5.4 and RevMan Web for data collection and analysis, updated from RevMan 5.1.
- Selection of studies: we added reprints of articles to the reference lists of included studies but did not consider them separately if they contained no new data. In the 2014 review, we discarded article reprints. We listed studies that were available only in abstract form, or were only identified in the ISRCTN register, as studies 'awaiting classification'.
- Outcomes: we redesignated the outcome of 'pH/impedance studies' to 'pH/impedance indices' to account for the range of pH measurements described in the available literature.
- Data extraction and management: three review authors (MT, IL, EA) independently extracted study data using a robust data extraction form and checked and entered the data into RevMan 5.4/RevMan Web, with MT, EA, and IL analysing the data and highlighting any discrepancies. In the 2014 review, two review authors extracted and entered study data into RevMan 5.1.
- Measures of treatment effect: we extracted continuous data (e.g. reflux index) for summary data: we used means and standard deviations to derive a standardised mean difference (SMD) with a 95% confidence interval using a fixed-effect model. The latest NASPGHAN/ESPGHAN guidelines do not define normal values for pH-metry and pH-impedance (NASPGHAN-ESPGHAN guidelines 2018). The values of reflux index mentioned in the 2014 review (> 10% in 24 hours in infants and > 4% in 24 hours in children > 12 months) have been modified here with a judgement regarding improvement/non-improvement. Dichotomous data, such as improvement/non-improvement in endoscopic appearance, produced outcome data we presented as risk ratios. In the 2014 review, we used reported data rather than extracting summary data.
- Unit of analysis issues: we considered issues related to multiple observations for the same outcome (e.g. repeated pH-impedance measurements), and consulted the Cochrane Gut group if clarification was required. If we included multi-arm studies, we would analyse multiple intervention groups to prevent arbitrary omission of relevant groups or double-counting of participants. In the 2014 review, there was some overlap in reported data (e.g. according to age criteria); this was corrected in this review.
- Dealing with missing data: we contacted trial authors or sponsors of studies published from 2014 to 2022 to provide missing data, or to seek clarification when we were uncertain about the specifics of a trial pertinent to analysis. In the 2014 review, we contacted study authors of studies published within the previous 10 years (e.g. to 2004).

- Data synthesis: were unable to combine studies meaningfully due to the heterogeneity of studies in terms of outcomes, comparisons, and populations. For continuous measurements, we had planned to use weighted mean differences to pool results from studies using a common measurement scale. Where studies used different measurement scales, we planned to pool standardised mean differences. Instead, we have presented difference in means and 95% confidence intervals for individual studies and summary effects, using the following order: Population > Comparison > Outcome, following updated guidance. Given the individual study differences and heterogeneity in study design, we provided guidance based on individual treatments to give better focus for decision-makers. This differs from the 2014 review.
- Sensitivity analysis: if meta-analysis had been possible, we intended to undertake sensitivity analysis using RevMan Web, to ascertain whether any decisions regarding thresholds influenced result reporting (e.g. choosing age thresholds at 12 months influencing meta-analytic robustness). We planned to integrate the findings into the results and conclusions. This was not considered in the 2014 review. However, a meta-analysis was not possible and sensitivity analysis not required.
- Summary of findings and assessment of the certainty of the evidence: working independently, two authors used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each outcome, and to draw conclusions about evidence certainty within the text of the review. We resolved disagreements through discussion, and involved all review authors involved if the initial two authors could not reach agreement. All authors then reviewed the GRADE considerations in assessing the certainty of evidence and integrated this into the summary of findings tables. The summary of findings tables distinguish results by age (infants, and children aged one to 16 years), then comparison, and the evidence is presented by outcome (symptoms, adverse events, pH-impedance indices, and endoscopic findings), with clear rationales given where evidence was downgraded or upgraded according to GRADE criteria, including if the risk of bias was so great the evidence needed downgrading by two steps.
- Literature search in this update version: we did not search the Cochrane Review Group Specialised Register as it was not updated since the 2014 version and the included RCTs are included in Cochrane CENTRAL, which we did search. We did not search the Centralised Information Service for Complementary Medicine (CISCOM). This database did not yield additional eligible studies for our review in the 2014 version, and it was not available to us for this update. In the 2014 version, we handsearched published abstracts from conference proceedings. For this update, we did not handsearch proceedings from conferences that took place after 2014 because Embase now includes proceedings from these conferences (2000 onwards); these abstracts were searched electronically through our main electronic search. In the 2014 version, we searched the clinical trials register mRCT. In this updated version, we searched the World Health Organization's clinical trials register (ICTPR) and ClinicalTrials.gov (https://clinicaltrials.gov/). We also revisited the search strategies, and added some new terms to reflect the current practice of treatment in the updated search.
- We have used the terms GOR and GORD throughout the review, following NASPGHAN-ESPGHAN guidelines 2018 and NICE 2019 definitions, and we acknowledge that different groups may have used different definitions for these terms in their studies. We have included some narrative where relevant and encourage readers to review the original articles if they wish to ascertain in more detail how other authors distinguish between GOR and GORD.

INDEX TERMS

Medical Subject Headings (MeSH)

Alginates [therapeutic use]; Aluminum Hydroxide [therapeutic use]; Domperidone [therapeutic use]; Drug Combinations; Gastroesophageal Reflux [*drug therapy]; Gastrointestinal Agents [*therapeutic use]; Histamine H2 Antagonists [*therapeutic use]; Magnesium Hydroxide [therapeutic use]; Proton Pump Inhibitors [*therapeutic use]; Randomized Controlled Trials as Topic; Silicic Acid [therapeutic use]; Sodium Bicarbonate [therapeutic use]

MeSH check words

Child; Child, Preschool; Humans; Infant; Infant, Newborn

Article VII: A Service Evaluation Of The Pharmacological Management Of Gastro-Oesophageal Reflux Disease (GORD) In Children With Cerebral Palsy (CP), And Their Communicative Ability

Britton F, Keast J, Tighe MP, 2017. G196(P) A service evaluation of the pharmacological management of gastro-oesophageal reflux disease (GORD) in children with cerebral palsy (CP), and their communicative ability. *Archives of Disease in Childhood*, 102 (Suppl 1), A78
https://doi.org/10.1136/archdischild-2017-313087.193

What does this paper achieve?

Having demonstrated above the absence of evidence in the treatment of GORD in children with neurodisability, I then looked to further understand the issues regarding prevalence and length of treatment, to understand if there were prescribing patterns, and use this to plan further research such as developing an appropriate outcome measure or head-to-head RCTs.

How does it contribute to the evidence-base?

This was the first study to explore the prescribing practices and communicative ability for children with cerebral palsy and GORD. This did not look for the co-existence of H. pylori. It was designed to enable future study design and provides information on how long children were receiving treatment for, the likely combinations, and what proportion of children would be able to converse and articulate symptoms, indicate symptoms in non-verbal ways (IPad, Picture exchange communication) or express pain. As a poster, it received peer feedback at the RCPCH conference (2017) in the British Society of Paediatric Gastroenterology, Hepatology and Nutrition section, and was published in *Archives of Disease in Childhood*. The poster received feedback from a panel of 3 consultant paediatricians and paediatric gastroenterologists and was commended, with no specific concerns raised.

What were the next steps?

This information was built in towards a RfPB bid comparing omeprazole and ranitidine in children with cerebral palsy and GORD. Further feedback highlighted the need to develop a useful outcome measure in this population group.

G196(P) **A SERVICE EVALUATION OF THE PHARMACOLOGICAL MANAGEMENT OF GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) IN CHILDREN WITH CEREBRAL PALSY (CP), AND THEIR COMMUNICATIVE ABILITY**

F Britton, J Keast, M Tighe. *Paediatric Department, Poole General Hospital, Poole, UK*

10.1136/archdischild-2017-313087.193

Aims To gather information to plan a randomised controlled trial (RCT) assessing available medications for GORD in children with CP.

Methods GORD in children with CP causes distress and pain, and may require hospital admission. There are approximately 8000 children with CP aged 5–16 in the UK and half of these children suffer from GORD. Many children with CP remain on drugs for GORD into adulthood with side-effects and cost-implications. These drugs have been assessed in healthy children but little is known about their benefits for children with CP. Further definition of this group is part of a research recommendation of the NICE Guidelines on managing GORD in children.[1] Information from this service evaluation will contribute towards a planned RCT into currently used pharmacological treatments for GORD in children with CP. Understanding the communicative ability of children with significant CP (Gross Motor Functional Classification System level III-V) will help us ascertain how able these children will be to participate in symptom-based questionnaires. Our coding department identified all children within the region with an ICD-10 diagnosis of CP (G80) and GORD (K21), admitted between 01/01/05 and 31/12/15. 54 children were identified with CP and GORD: their records were screened and data collected on the anti-reflux medication prescribed, the length of time on each medication and their communicative ability.

Results The most frequently prescribed anti-reflux medication was omeprazole (70%), with patients remaining on it for an average of 35 months (range 2–120 months). 30% patients had trialled ranitidine: on average for 19 months (4–35 months). Despite the recent MHRA alert of domperidone associated with cardiac side effects[2] 59% of children were on this medication for a comparatively long time: mean 38 months (range 1–104 months). 30% of patients assessed could converse, 41% used communication aids (Ipads or PECS) and a majority (65%) could indicate pain.

Conclusion CP patients remain on a diverse range of anti-reflux medications and understanding the distribution of communicative ability helps effective research in these children, including the choice of outcome assessment tools.

Figure 7.1 : PRISMA diagram of the patients identified with cerebral palsy

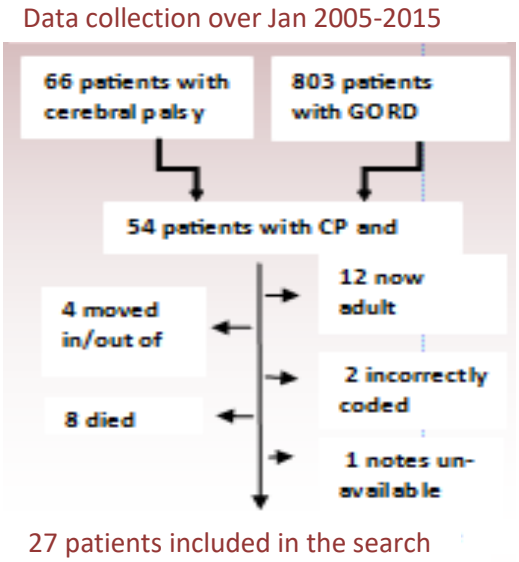
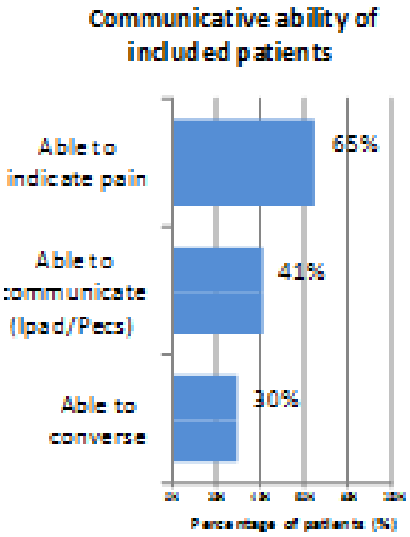


Figure 7.2: Range of communicative abilities (included patients)



A Service Evaluation of the pharmacological management of gastro-oesophageal reflux disease in children with cerebral palsy, and their communicative ability

Britton F[1]; Keast J[1]; Tighe MP[1]

Aim:

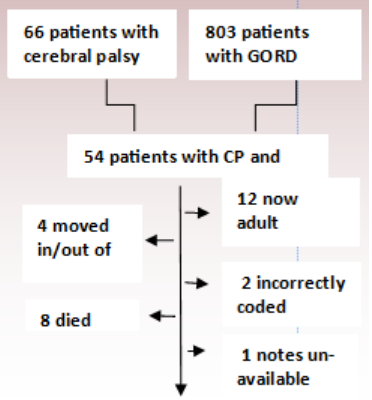
To gather information to plan a randomised controlled trial (RCT) assessing the treatment of GORD in children with significant CP (Gross Motor Functional Classification System (GMFCS) level III-V) .

This service evaluation with consider the currently used pharmacological treatments for GORD in children with CP and also the communicative ability of these children to ascertain how able these children will be to participate in symptom-based questionnaires.

Introduction:

- GORD in children with CP causes distress and pain, and can require hospital admission.
- There are approximately 8000 children with CP aged 5-16 in the UK and half of these children suffer from GORD.
- Many children with CP remain on drugs for GORD into adulthood with side-effects and cost-implications. These drugs have been assessed in healthy children but little is known about their benefits for children with CP. Further definition of this group is part of a research recommendation of the NICE Guidelines on managing GORD in children.[1]

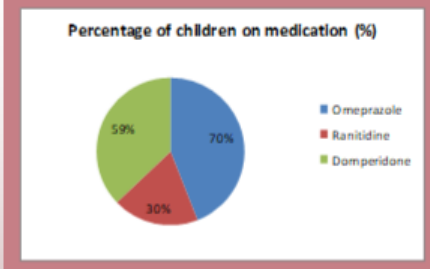
Data collection over time period Jan 2005

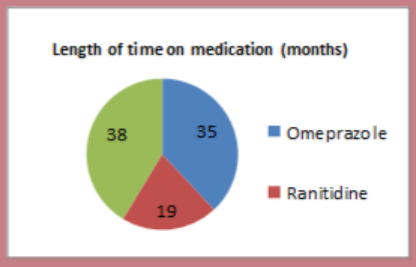


27 patients and included in this service

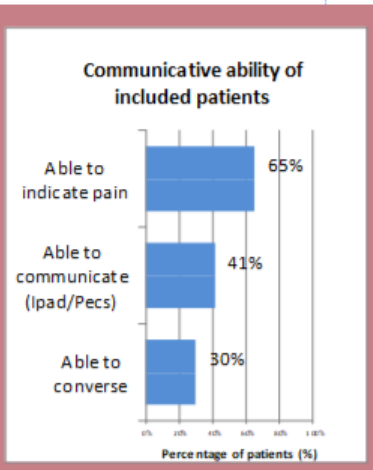
Methods: Data collected from children within the region with an ICD-10 diagnosis of CP (G80) and GORD (K21), admitted between 01/01/05 and 31/12/15.

Results:





- The most frequently prescribed anti-reflux medication was Omeprazole (70%), with patients remaining on it for an average of 35 months (range 2-120months)
- 30% patients had trialed Ranitidine: on average for 19 months (4-35months)
- Despite the recent MHRA alert of Domperidone associated with cardiac side effects[2] ; 59% of children were on Domperidone for a comparatively long time (mean 38 months (1-104 months))



- 30% of patients assessed could converse, 41% used communication aids (Ipads or PECS) and a majority (65%) could indicate pain.

Conclusion: CP patients remain on a diverse range of anti-reflux medications and understanding the distribution of communicative ability helps effective research in these children; including the choice of outcome assessment tools.

References

1. Gastro-oesophageal reflux disease in children and young people: diagnosis and management (NG1): NICE guideline: Published January 2015
2. https://www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects

Poole Hospital NHS
NHS Foundation Trust

Data collection for GORD in children with neurodisability clinical research tool

	1	2	3	2	29	2	32	35	38			51	
Audit ID	On omeprazole ?	How long for (months)?	On ranitidine?	How long for (months)?	On domperidone?	How long for (months)?	Able to converse?	Able to communicate? (e.g.IPAD/PECS)	Able to indicate pain?	Current medication	How long they have been on current medication for	Any other antireflux medications?	
	(Yes, No)		(Yes, No)		(Yes, No)		(Yes, No)	(Yes, No)	(Yes, No)			How long	
1	No	4 months	Yes	33 months	Yes	3 months	No	No	No	Ranitidine	2 years 9 months	No	
2	Yes	15 month	Yes	30 months	Yes	19 months	No	No	No	None	na	No	
3	Yes	18 months	Yes	5 months	Yes	1 month	No	Yes	Yes	Ranitidine and omeprazole	5 months	Yes	lansoprazole 07/12-11/2014
4													Moved to Dorset 05/10, unclear when started omeprazole
5	Yes	9 months	Yes	11 months	Yes	6 months	Yes	Yes	Yes	Omeprazole	9 months	Yes	lansoprazole dec 13 to present.
6	No	na	No	na	Yes	6 months	Yes	Yes	Yes	None	na	No	
7	Yes	55 months	No	na	Yes	5 months	No	No	No	Omeprazole, domperidone	Omeprazole for 4 years 7 months	Yes	Lansoprazole Dec 2011 to March 2012.
8	No	na	Yes	35 months	No	na	No	No	No	Lansoprazole, ranitidine	2 years 11 months	Yes	Lansoprazole since nov 2013 to present
9	Yes	6 months	No	na	Yes	48 months	No	No		Omeprazole	6 months	Yes	domperidone stopped 02/16, gaviscon liquid
10													moved to bristol dec 2014
11	No	na	No	na	No	na	No	No	Yes	Lansoprazole	5 years 1 month	No	lansoprazole since oct 2011 to present
12													died in dec 2015
13	Yes	72 months	No	na	No	na	No	No	No	Omeprazole	6 years	No	
14	Yes	2 months	No	na	Yes	84 months	No	Yes	Yes	None	None	No	lansoprazole
15	Yes	48 months	No	na	Yes	60 months	No	No	No	Omeprazole, domperidone, g	omeprazole 48 months, domperidor	Yes	gaviscon, lansoprazole
16	Yes	7 months	No	na	No	na	Yes	Yes	Yes			No	
17													gaviscon 4 years, died in 2014
18	Yes	24 months	No	na	Yes	24 months	No	No	No	Lansoprazole	51 months	Yes	lansoprazole
19													died in may 2014
20	No	na	No	na	No	na	Yes	Yes	Yes	None	na	Yes	Trial of lansoprazole (2 months), gaviscon 2 months
21													died
22	Yes	120 months	No	na	No	na	No	No	No	Omprazole	10 years	No	
23	Yes	39 months	Yes	16 months	Yes	42 months	No	No	Yes	Lansoprazole, ranitidine, dom	1 year 4 months	No	
24	Yes	105 months	No	na	Yes	104 months	Yes	Yes	No	None	11 months	Yes	Gavison
25	Yes	47 months	No	na	Yes	37 months	Yes	Yes	Yes	None	None	No	
26													died
27	Yes	62 months	No	na	Yes	62 months	No	No	Yes	Lansoprazole	4 years 1 month	No	
28	Yes	3 months	No	na	Yes	97 months	No	No	Yes	Lasoprazole and domperidon	8 years 1 month	Yes	Lansoprazole
29													Died Oct 2009
30													Died Feb 2011
31	Yes	6 months	No	na	No	na	No	Yes	Yes	none	none	No	
32	No	na	No	na	No	na	No	No	Yes	lansoprazole	1 year 2 months	No	
33	Yes	14 months	No	na	No	na	No	No	Yes	Lansoprazole	6 months	Yes	Gaviscon infant

Figure 7.3 Data collection tool

34													Moved to area 05/2008- 09/2013
35	Yes	42 months	Yes	4 months	No	na	No	No	Yes	Omeprazole	3 years 6 months	Yes	Lansoprazole 12/2008-06/2013
36	No	na	No	na	No	na	Yes	Yes	Yes	None	na	No	Had trial of ranitidine no improvement
37													Need old notes
38													Lives in Exeter, one admission in PGH
39													incorrectly coded
40													died
41	No	na	Yes	15 months	Yes	15 months	Yes	Yes	Yes	None	none	Yes	Gaviscon
42													incorectly coded
Yes	19		8		16		8	11	17			13	
No	8		19		11		19	16	9			14	
Total	27		27		27		27	27	26			27	
Percentage	70%		30%		59%		30%	41%	65%			48%	
AVERAGE		35 months		19 months		38 months							

Article VIII: Adaptation of the P-GSQ for children with neurodisability and symptoms of GOR

Mills S, Tuffrey C, Tbaily L, Tighe MP Modification of the Paediatric Gastro-oesophageal Reflux Disease Symptom and Quality of Life Questionnaire (PGSQ) for children with cerebral palsy: a preliminary study. BMJ Paediatrics Open 2024;8:e002256. doi: 10.1136/bmjpo-2023-002256
Published under gold open access: please see publisher page for information.

What does this paper achieve?

Following article VII, as well as VI and V, I successfully bid for £5000 to support this modification of the P-GSQ for children with neurodisability following an RfPB design. As part of the patient-public involvement, we had offered parents example questionnaires such as the P-GSQ, PEDS-QL, KIDSCREEN and the I-GERQ, and families felt the design and shorter nature of the P-GSQ was more suited, given how time-pressured they were in looking after their children. However, families felt that the nature of the questions needed more adaptation, given the significant disabilities their children faced. The P-GSQ has already been validated for use in otherwise well children with GORD (Nelson 2008, Kleinman 2011). Nelson 2008 assessed internal consistency (using Cronbach's alpha), construct validity (by comparing the PGSQ to global symptom questions and the Pediatric Quality of Life subscales) and discriminant validity (by comparing scores between children with and without GORD) in 231 children (aged 2-17years old) and parents. The same group (Kleinman 2011) assessed the responsiveness of the questionnaire subsets to symptom changes for caregivers and adolescents over a 3-week period in 11 clinical sites, and both studies found that the questionnaires correlated well with symptom severity and that the questionnaires were suitable for clinical studies. Following patient-public involvement, we undertook the iterative modification of this symptom questionnaire to develop this symptom outcome measure with 6 parents and benchmarking against the FACES pain score. Cognitive interviews were conducted by the research team with 6 parents/carers of children (aged 3-15) with CP (GMFCS level III-V) who have current or past symptoms of reflux following the work in Article VII. They were asked to interpret the questionnaire using a 'think-aloud technique,' and offer suggestions on alterations to questions. Reasons for changing questions included confusing/difficult to understand questions, differing interpretations of questions and response choices not applying to the patient group.

How does it contribute to the evidence-base?

The P-GSQ questionnaire was modified iteratively following each interview. Overall, parents/carers reported that it was an acceptable expectation to recall information over the past 7 days. They felt the questions were relevant, useful, and related to symptoms that they observe. It

was easy to comprehend with no uncomfortable questions. Some felt it was difficult to comment on questions surrounding school as they were not with their child during the school day. Suggestions for future work included a section specifically focusing on school staff and carers who assist them in the home.

The P-GSQ has now been adapted to improve face validity for families/carers of children with symptoms of GORD and neuro-disability. This outcome questionnaire is now more relevant for this patient population that is quick, acceptable and needs further evaluation and implementation to assess whether it is fit for purpose and will help benchmark any symptom change with treatments or through further studies. As a poster, it received peer feedback at the conference, and was published in a peer-reviewed journal (*Frontline Gastroenterology*) and the article is now published in *BMJ Paediatrics Open*.

What were the next steps?

I am now assessing the acceptability and test-retest reliability with 20 parents in further work. I have recruited 16 of the 20 parents needed to assess this questionnaire. They undertake the test-retest 2 weeks apart, supported by a visual assessment score (FACES scale). I look forward to completing this in 2023 and publishing this in 2024.

BMJ Paediatrics Open

Modification of the Paediatric Gastro-oesophageal Reflux Disease Symptom and Quality of Life Questionnaire (PGSQ) for children with cerebral palsy: a preliminary study

Sarah Mills ,[1] Catherine Tuffrey,[2] Lee Tbaily,[3] Mark Tighe[4]

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjpo-2023-002256).

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ABSTRACT

Objective Gastro-oesophageal reflux disease (GORD) is a common condition affecting children, characterised by the passage of gastric contents into the oesophagus causing pain, vomiting and regurgitation. Children with neurodisability (such as cerebral palsy; CP) are predisposed to more severe GORD due to coexisting gut dysmotility and exclusive/supplementary liquid diet; however, there are no existing tools or outcome measures to assess the severity of GORD in this patient group. For children without CP, the 'Paediatric Gastro-oesophageal Symptom and Quality of Life Questionnaire' (PGSQ) assesses symptoms and response to treatment, but the questions are not suitable for children with significant cognitive impairment. We aimed to adapt the existing PGSQ assessment tool to enable use in evaluating children with CP and GORD.

Patients/interventions Cognitive interviews were conducted by the research team with six parents/carers of children (aged 3–15) with CP (Gross Motor Function Classification System level V) who have current or past symptoms of reflux. They were asked to interpret the questionnaire using a 'think-aloud technique,' and offer suggestions on alterations to questions. Reasons for changing questions included confusing/difficult to understand questions, differing interpretations of questions and response choices not applying to the patient group.

Results The PGSQ was modified iteratively following each interview. Overall, parents/carers reported that it was acceptable to recall information over the past 7 days. In the final version, it was felt the questions were relevant, useful and related to symptoms that they observed. It was easy to comprehend with no uncomfortable questions. Suggestions for future work included a section specifically focusing on the school day answered by school staff and home life answered by carers who assist them in the home.

Conclusions We have adapted the PGSQ to improve relevance and acceptability for families/carers of children with symptoms of GORD and neurodisability. Further work is needed to validate the questionnaire for this patient group.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Gastro-oesophageal reflux disease (GORD) is extremely common in children with cerebral palsy and can be problematic. There are several validated symptom questionnaires for children with GORD without comorbidities.

WHAT THIS STUDY ADDS

⇒ We have adapted the existing Paediatric Gastro-oesophageal Symptom and Quality of Life Questionnaire to improve face validity for families/carers of children with symptoms of GORD and cerebral palsy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This modification will aid in assessing efficacy of pharmacological treatments for GORD in children with cerebral palsy and potentially has significant cost-saving implications if treatments can be initiated/discontinued based on accurate symptom assessment.

INTRODUCTION AND BACKGROUND

Gastro-oesophageal reflux (GOR) is a common problem, characterised by the passage of gastric contents into the oesophagus.[1] GOR affects approximately 50% of infants less than 3 months old[2]; however, most children improve with age, with less than 5% of children with vomiting or regurgitation in infancy continuing to have symptoms after the age of 14 months.[3] In some children, GOR is associated with troublesome symptoms or complications, known as GOR disease (GORD). Children with neurodisability, such as cerebral palsy (CP), are more likely to suffer from GORD, due to coexisting gut dysmotility, exclusive/supplementary liquid diet and other medications (eg, medications for dystonia/epilepsy). Gastrointestinal complications can include oesophagitis

and stricture formation, and extraintestinal sequelae can include secondary anaemia, chronic respiratory disease and faltering growth.[4 5]

It is estimated that there are currently 9000 children across the UK with CP and GORD. Antacids (proton pump inhibitors (PPIs), histamine H2-receptor antagonists (H2RA)) and prokinetics are treatments that are often continued long term in many children without clear evidence of ongoing efficacy. Long-term treatment results in increased workload for parents/carers, treatment costs[6] and potential adverse side effects.[7] This area has been highlighted as a National Institute for Health and Care Excellence (NICE) research recommendation (NG1)[7] as there is a lack of evidence in this patient cohort despite their significantly increased risk of morbidity and mortality due to aspiration and respiratory complications.[8] These children are also more likely to be referred for fundoplication due to failure of medical treatments.[5 9]

Children in this patient group are often empirically treated for GORD without investigations to confirm underlying gastrointestinal pathology.[4] Symptoms may be difficult to distinguish from coexisting dystonia, seizures or pain from other pathologies,[10] and assessment is often affected by communication issues where children have cognitive impairment. Investigations to assess severity of GORD include 24-hour oesophageal pH monitoring and upper gastrointestinal endoscopy. One study found that these investigations in otherwise well children have variable correlations with symptoms and may not accurately predict the degree of improvement with treatment.[11] Frequency and severity of symptoms were shown to vary and were impacted by the types of nutrition consumed, stress, activity levels and intercurrent illnesses. Participants reported that GORD had a major impact on many aspects of the patients' lives, particularly school attendance/performance and participation in extracurricular and social activities. GORD also contributed to general feelings of frustration regarding symptoms, their effect on daily life and the need to take medication.

While assessment tools exist (Paediatric Gastro-oesophageal Symptom and Quality of Life Questionnaire (PGSQ), PEDS-QL GI[12 13]), there are no robust data to help clinicians or researchers understand how well these assessment tools correlate with GORD in children with neurodisability. There is also a lack of understanding of the distributional properties that these tools have in this population and what constitutes a minimal clinically important difference. Establishing a robust outcome measure would allow development of clinical trials, for example, trials assessing efficacy of PPIs versus H2RAs. There are also significant potential cost savings if clinicians could consider initiating or discontinuing anti-reflux medications based on accurate reflux symptom assessment.

Symptom assessments through questionnaires are validated and are currently our most frequently used research tool in assessing improvement in normally developing children. The PGSQ takes on average 7 min to complete in typically developing children and is specific to infants (not assessed in this trial), children or young people (online supplemental appendix 2). The questions are very similar between the age groups, with the phrasing only taking account of the age differences. We aimed to modify the proxy version for parents, as patient and public involvement identified this one as the most likely to be used clinically.

Aims

To adapt the pre-existing PGSQ assessment tool to enable use in evaluating children with CP and GORD. This will allow changes in symptoms resulting from treatments to be measured and support clinical trials evaluating treatment efficacy.

METHODS

We included children with CP (Gross Motor Function Classification System, GMFCS levels III–V) with symptoms of GORD or on treatment for presumed GORD aged between 2 and 16 years. We only excluded children whose parent(s)/guardian(s) were not able to support their participation in the study in the opinion of the investigator (eg, language/communication issues, health, burden). All parents/carers of children meeting the inclusion criteria were approached about participation either during routine clinic appointments or by the paediatric research team.

Prior permission was sought from Takeda Pharmaceutical International (developers of the original PGSQ) to modify the existing questionnaire. Those who were eligible for recruitment were given the opportunity to participate either by phone, in clinic or by letter. Interviews were carried out by members of the research team trained in cognitive interview methods. Prior to the questionnaire, a standardised script was provided detailing the purpose of the study to ensure that all parents/caregivers received the same information. Interviews were recorded and transcribed using Microsoft Teams or WinScribe. Participants were asked to consider understanding, retrieval of information, judgement, response and construct for each question. A copy of the questions is shared in online supplemental appendix 1.

We focused on development and modification of the questionnaire using techniques described by Willis.[14] This involved the participant talking through their thoughts as they read the questions, to ascertain whether each one reflected important and different dimensions of our patient group. Questions were modified based on parent/carer responses. Reasons for alterations included questions reported as not relevant and confusing or difficult to understand. This allowed relevant adjustments to better fit this subgroup of patients considering their communication issues and associated pathologies. Modifications continued until there were no further issues identified or improvements suggested. We only needed six participants using this method. The COnsolidated

criteria for REporting Qualitative research (COREQ) checklist was completed and is available in the appendices. The study was sponsored by University Hospitals Dorset National Health Service (NHS) Foundation Trust.

Patient and public involvement

The public was involved in the design and conduct of this research. Consultation groups were held at two schools for children with profound physical and learning disabilities and complex medical needs (both in Dorset). We outlined our research question to parents of children with CP and they were supportive. One parent was a coapplicant on our funding application to the British Society of Paediatric Gastroenterology, Hepatology and Nutrition. The Children and Clinical Research Group at Southampton NIHR (six children and several parents) reviewed the outcome measures and information sheets and agreed this was an important study. They felt that some of the questions were potentially emotionally challenging so advised that we should administer the questionnaires face to face rather than via the telephone or post. Based on this, participants were given the option to choose to participate in the way which suited them best. On completion of the study, participants will be updated on the results via a study newsletter and dissemination via relevant national charities. In addition to this, consumer members of the NICE Guideline Development Group for GORD in children identified this area as a research priority. Representatives from the NIHR Children Neurosciences Clinical Studies Group provided feedback on the proposed research and felt it addressed an important question.

RESULTS

Patient demographics

A total of six participants were enrolled in the study at one secondary care hospital site (University Hospitals Dorset NHS Foundation Trust). Demographic information is detailed in table 1.

The children were either stable on antireflux medications, discontinuing medications for GORD or starting medications for GORD. This was to help demonstrate how the tool was understood by parents in static circumstances, and when treatments were changing.

Modification pathway

Table 2 demonstrates how the questionnaire evolved with each cognitive interview. The parent/carer narrative is demonstrated along with the changes that were made to the questionnaire based on this feedback. The original and final versions of the questionnaire can be found in online supplemental appendices 2 and 3.

DISCUSSION

This study presents the modification of the pre-existing PGSQ for use in patients with neurodisability (eg, CP and severe learning disability) and GORD.

During the first interview, it was quickly established that questions requiring a response from the child (ie, point to the area where you feel pain) would not be acceptable to parents/carers of children with CP and severe learning disability. Questions regarding physical and social activities were also identified as potentially upsetting to parents/carers, as they highlighted skills that their child may have difficulty with. The most significant modifications, such as the addition or removal of questions and alteration of phrasing, were implemented between version 1 and version 2. Subsequently, parents and carers stated there were no upsetting or distressing questions and that they were mostly representative of their experience of GORD in their child.

One parent felt that they could not answer the questions in the school section because they were not with their child during the school day. They also expressed that their child's school was used to dealing with problems associated with reflux, reducing the impact on schooling activities and therefore would not be an accurate depiction of the severity of their symptoms. They felt that it would be useful for school staff to complete or contribute to this section of the questionnaire.

Some parents felt that they were able to accurately assess their children's symptoms and the frequency at which they were experiencing them, however, could not accurately attribute them to reflux rather than another cause.

Table 1 Patient demographics

Age	Gender	GMFCS level	No of regular medications	Route of feeding	Previous fundoplication?
9 years 7 months	F	V	4	Gastrostomy	No
15 years 11 months	F	V	8	Gastrojejunostomy	No
3 years 3 months	F	V	5	Gastrostomy	No
9 years 7 months	M	V	10	Oral and gastrojejunostomy	No
15 years	M	V	7	Gastrostomy	No
7 years	F	V	5	Gastrostomy	Yes—2016

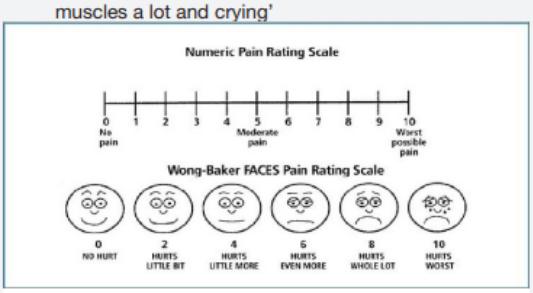
F, female; GMFCS, Gross Motor Function Classification System; M, male.

Table 2 Table following the parent/carer narrative and how this led to the iterative evolution of the PGSQ

Parent/carer narrative	
Interview 1	**Changes made: Version 1 → 2**
► 'They made sense (but) they weren't applicable to my daughters' specific case' (Q1) ► 'It is not possible to do this with a child with complex needs and cerebral palsy; because I can't show exactly, I don't know exactly where the pain is at all' (Q2) ► 'I would find it very difficult, and I don't think it would be accurate at all. I could make something up but that's not what you want' (Q2) ► 'It might be quite upsetting because the child often can't tell you what they do or don't want to do' (Q3) ► 'The wording is in many cases not suitable' (Q3) ► 'You'd need to ask school, because you're not there with your child' (Q4)	► Alteration of language used – Q1: What your child has told you → what you have observed – Q3: Unable to eat what he/she wanted → unable to tolerate usual feed – Q3: Woken up someone in the house → changed sleeping pattern – Q3: Felt frustrated/been in a bad mood/worried/upset → changed behaviour ► Removal of Q2: 'place an X where the child has pain'. ► Removal of upsetting lifestyle questions for example, Q3: missing out on doing things with friends, unable to do physical activities such as ride a bike/swim/play at the playground ► Addition of questions re. additional medications/treatments ► Addition of CP specific questions for example, drawing up legs, increased tone, increased crying/grimacing
Interview 2	**Version 2 → 3**
► 'The wording is easy to understand, not confusing' (Q1) ► '(Q1) is really useful because it makes you feel like symptoms of reflux are being recognised' ► 'I certainly think these questions describe what can happen within the school day with reflux' (Q4)	► Splitting of question r.e. additional medicines/therapies into two separate questions – Extra medications – Extra treatments for example, massage/alternative therapy
Interview 3	**Version 3 → 4**
► 'I think the questions to me is what I've been seeing as his symptoms, so I think that is useful for parents' (Q1) ► 'Yes, I think (the questions) are relevant' (Q1) ► 'It's good to see it put down like this and to actually get the bigger picture of how it's affecting everything' (Overall) ► Reported that the questions are not uncomfortable and easy to read	► Addition of a 'do not know' column to question 2 and 3.
Interview 4	**Version 4 → 5**
► '(the wording) is quite specific, which is good' (Q1) ► 'If he had an undiagnosed reflux problem (the questionnaire) would make me feel like somebody was listening and wanting to help me' (Q1) ► 'I can't think of any symptoms that haven't been covered' (Q1) ► 'The questions are comfortable, describe the symptoms of reflux, no suggestions to change'	► Addition of extra clarification in the introduction 'please include each day that the symptoms were persistent/troubling' to help parents/carers quantify duration – '(I remember) from the last couple of days unless I've had a particularly awful day which would stick in (my) mind'
Interview 5	**Version 5 → 6**
► 'The first set of questions are definitely relevant because they're things that are quantifiable' (Q1) ► 'I've never had to fill in a questionnaire when she's had reflux' ► '(r.e. school) I would be looking at her communications book to see if I could find out the answers' (Q3) ► 'I think the school questions are more directed at children that are in mainstream education rather than special needs schools' (Q3) ► 'Unless you're with your child at school for the whole time you're not going to know the answers' (Q3)	► Formatting of the questionnaire edited to increase visibility of important points of questions for example, making certain words bold ► Changing 'do not know' → 'not relevant/do not know' – 'maybe 'unsure' because sometimes you could be unsure if (their symptoms) are due to reflux symptoms'

Continued

Table 2 Continued

Parent/carer narrative	
Interview 1	**Changes made: Version 1 → 2**
Interview 6	**Version 6 → 7 (final version)**
► 'It's easy to understand and it makes sense' (Q1) ► 'As a parent of a child with cerebral palsy, if they're non-verbal (these are things) you look for anyway. We might not necessarily relate it to reflux, just general discomfort' (Q1) ► 'They are no different to questions you would ask me in a routine consultation' (Q1) ► 'I think these (questions) cover everything' (Q1) ► 'I think it would be hit or miss with different parents because different kids present in different ways. I think it kind of covers enough' (Q2) ► 'School would be more cautious than we are' (Q3) ► Additional suggestion of creating a questionnaire for home carers as well as parents/carers and school staff.	► Addition of visual analogue scale and FACES pain score (see below) – 'She does show discomfort, which is normally she tenses her muscles a lot and crying'  FACES pain/visual analogue scoring system used as part of the questionnaire assessment

PGSQ, Paediatric Gastro-oesophageal Symptom and Quality of Life Questionnaire.

One parent was surprised that some described symptoms, such as bad breath, were signs of reflux; indicating that the questionnaire can help parents/carers identify lesser-known symptoms. This could ultimately assist with medication dosing and treatment plans as parents would be more likely to recognise and report these issues.

Another theme that emerged during the discussion was that the level of children's impairment from neurodisability can differ considerably. A questionnaire of this type may not be suitable for all children; however, we aimed for broad applicability, and parents felt this questionnaire helped. One parent commented that the process had made them feel as if they were being listened to and taken seriously regarding their child's symptoms.

Since there are currently no validated assessment tools in this patient group, this modification could potentially be extremely useful in clinics. A review of our cohort of patients between 2000 and 2015 found that the most common antireflux medication was omeprazole (prescribed in 70% of patients) and that patients remained on this for an average of 35 months.[15] It is widely appreciated that these patients are usually commenced on treatment without investigation to confirm the diagnosis and that it can be difficult to distinguish between GORD and other coexisting pathologies.[4 10] We hope that the modified questionnaire will assist with assessment of severity of symptoms and treatment response so that management can be optimised, improving patient care, costs and quality of life.

There are several limitations of this preliminary study. Due to the iterative process, the finalised questionnaire was only assessed by one parent/carer, though it is being further tested for face validity. In addition to this, the recruits were all locally identified, therefore, it may not be completely representative of other demographics, communities and socioeconomic variations throughout the rest of the UK. The children were all classified as level V using the GMFCS meaning that they have impairments in all areas of motor function,[16] while this is not a surrogate for their ability to process and communicate, the cohort of children did have associated severe intellectual or learning difficulties. The diagnosis of a neurodisability such as CP covers a wide range of patients with a spectrum of communication abilities; therefore, these proxy questions may not be suitable for children who can self-report. Further work could involve development of self-report versions of the PGSQ suitable for this subgroup of children. We should highlight that the wider validation of the original PGSQ no longer applies to our modified version and we intend to further assess the developed tool including feasibility and test–retest reliability in a larger sample. However, the feedback received by parents/carers was that they felt the questionnaire was relevant to their child and the symptoms they observe them to have which are related to GORD.

CONCLUSIONS

We have adapted the existing PGSQ to improve face validity for families/carers of children with symptoms of GORD and neurodisability. More work is needed to ensure that the questionnaire is applicable to as many

children as possible within this patient group. The next phase will involve further assessment of the developed tool including feasibility and test–retest reliability. Future work will be needed to examine construct validity and sensitivity to change.

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Contributors SCM performed qualitative data analysis of the interviews and writing and editing of the paper. MT devised the idea for the project and performed the setup of the study including ethical approval and obtaining grant funding. He was also involved in review and editing of the paper and is the guarantor for this study. CT and LT were involved in development of the research idea and reviewing and editing the paper.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Health Research Authority IRAS ID: 273604. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available on reasonable request. Study began recruitment in 2018. However data could be provided on request.

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Chapter 4: Discussion

GOR and GORD affect over 50% of babies under 3 months, and current prescribing rates for PPIs in infants is approximately 4-4.5% in the US and Ireland, which has increased from 1.5% in 2003 (Illueca 2014). In older children the prevalence of GORD is estimated at 2-4.5% (Okimoto 2015). GOR in infants and children remains an important issue, and this body of work has helped improve the management and treatment of children with GOR/GORD, with appropriate evidence helping the investigation, explanation and prescribing and helping clinicians, patients and families to understand the natural progression of the condition.

This body of work has the strength of using mixed methodologies comprising secondary analysis (Articles I, II and III) and primary data collection (Articles IV-VIII) to provide overlapping data and develop the knowledge-base in the area of GOR/GORD in infants and children. Firstly, considering the evidence-base for the management of GOR in infants and children using the most robust tools available: initially using CEBM levels of evidence, and grades of recommendations then Cochrane criteria, and NICE processes (to formulate NG1 and QS112), with the support of statisticians, health economists and lay representatives. The guidance and recommendations have also had the benefit of 10-12 years of being used in the field and have helped other clinicians in their research. The reviews have also helped to disseminate and highlight the utility of testing (such as pH/impedance monitoring) and management strategies for diagnosed GOR in infants. This work also lays the groundwork for identifying further challenges such as managing reflux in children with cerebral palsy, and developing an outcome measure (the modified P-GSQ) for further testing and validation.

Comparison of different approaches of the systematic reviews:

This thesis highlights three different ways of assessing available evidence. Article I uses Oxford CEBM criteria to appraise all trials assessing pharmacological treatments of GOR/GORD in children, and allows for some downgrading of evidence certainty if there are concerns about methods. Articles IV and VI use Cochrane methodology (only including RCTs) and GRADE criteria to assess the certainty of evidence, and NICE use GRADE criteria as well as health economic data and patient/public involvement in the Guideline Development Group to generate robust conclusions. This allows the downgrading or upgrading of the certainty of evidence for each risk of bias domain, so large RCTs with three or more serious concerns using GRADE criteria would be downgraded to very-low quality evidence. While article I draws on a wider evidence-base, the number of industry-funded trials and cohort studies affected the certainty of evidence, and confidence in the recommendations. Article

IV, and subsequently VI focused on RCTs, though due to heterogeneity of the data, meta-analysis was not possible, and industry-funded influence was lessened by separation extraction of data, and use of GRADE criteria. Article VI was rearranged to focus on Population>Intervention>Outcome to try to produce a clearer message, and the use of MECIR aimed to make the paper more robust. As an author, the Cochrane editorial guidance on phrasing had significantly changed between article IV and VI, with set MECIR phrases such as 'X may or may not offer greater benefit than Y' that I felt may leave clinicians and parents uncertain how to proceed, although the quantification of the certainty of evidence and utility of recommendations was more accurately conveyed. Evaluation of NICE compared to Cochrane processes for systematic reviews has been undertaken, with one review finding that NICE provides greater methodology checklists (7): systematic review and meta-analysis, RCT, cohort study, case-control study, economic evaluation, qualitative study, and prognostic study; and recommends QUADAS-2 tool for diagnostic testing. However, they also found that 'The Cochrane Collaboration's tool for assessing risk of bias is the best available tool for assessing RCTs' (Zeng 2015). NICE has also undertaken surveillance of Cochrane reviews to identify low-value interventions to improve healthcare efficiencies (Garner 2013). It should be emphasized that the rigorous process of systematic reviews has significant clinical utility in improving guideline quality, with another recent review finding that over 50% of clinical guidelines assessed did not utilise a systematic review in generating recommendations for care (Lunny 2021). Each process (Oxford CEBM/Cochrane/NICE) should be strengthened by additional supports such as PRISMA diagrams and prospective registration through PROSPERO. Overall, appraisal and utilisation of the evidence in a clinical context was best done through the NICE process; though resource-heavy, the consideration of the certainty of evidence using GRADE criteria improves clinical care, with a robust process of deriving recommendations that clinicians (including nurses and allied health professionals across primary, secondary and tertiary care), patients/parents and commissioners agreed on, leading to Quality Standards that are implemented across healthcare settings. Research recommendations also lead to the next generation of research studies in GOR/GORD in children.

For infants, this body of work has confirmed that there is a high proportion of diagnosed GOR. In older children, GORD rather than diagnosed GOR is more likely, and treatment is more likely to be effective. Using different techniques regarding evidence synthesis (Articles I, II, III, IV, VI), the analysis of evidence using initially Oxford CEBM criteria, then Cochrane RevMan, then GRADE highlighted which treatments were likely to be effective, and how investigations such as pH studies and now pH/impedance monitoring (Article II, IV) can be best used to answer specific clinical questions, and how some investigations (such as barium swallows: Article V) may only be useful in

very limited indications, saving children unnecessary radiation. In Article III, the robust Cochrane methodology led to a clear analysis of benefit, with independently extracted data, and a detailed assessment of risk of bias and downgrading of recommendations based on the strength of evidence. Articles IV and V have been useful nationally to improve the care of children with GOR, and specifically the audit tool, and evaluation helped improve the identification of children with conditions other than GOR, and improve services' awareness of the potential for other conditions to mimic GOR. NICE express their strength of recommendations with phrasing from 'Do not use' when there is moderate or high-quality evidence of absence of efficacy, or harm, through to 'Consider' when the certainty of evidence is weak or very weak, or 'Offer' when the certainty of evidence is moderate or high-quality. In Article VI: as outlined above, the changes in methodology, independent data extraction and the inclusion of MECIR criteria and robust summary of finding tables, as well as a stronger focus on the quality of evidence using GRADE helped this review be more systematic. A change from p values to standardised mean difference and 95% confidence intervals help the reader better understand the significance of the findings. Those studies in which summary data could not be extracted were not considered further regarding the certainty of evidence. The body of work also highlighted specific high-risk groups, such as children with neurodisability, and sought to establish their communication needs and current range of medication therapy and modify a symptom questionnaire in Articles VII and VIII to help further research in these children.

The findings of articles I, III, IV, V and VI agreed in many areas, though the focus on RCTs through the Cochrane and NICE processes, and evolution towards using GRADE criteria has provided a better quantification of risk of bias regarding study findings, and through extraction of original data, a more robust estimation of the size of effect and strength of evidence. This foundation then led to articles VII and VIII and the iterative redesign of the symptom questionnaire will be of use in future studies for this patient group. Specific areas including the patient group, investigations and treatment efficacy are considered below, as well as further work in children with neurodisability.

Regarding the patient group: Overall Article I, III, IV and VI found that the evidence base of efficacy of pharmacological therapies for infants is mixed, with mostly low- and very-low quality certainty of evidence, reflecting the lived experience of many families, where many babies continue to have persistent symptoms and distress and find significant improvement between the ages of 1-2 years old. In terms of pharmacological strategies, a clear distinction should be drawn between the treatment of infants with diagnosed GOR and those with gastro-oesophageal reflux disease (those with sequelae of GOR, or failure to thrive). In the subgroup of infants with diagnosed GOR, the main problem appears to be caused by the milk bolus, although acid reflux undoubtedly occurs. Underlying transient gut dysmotility, with dysfunction of the lower oesophageal sphincter, a short

oesophagus, high volumes of liquid feeds and a significant proportion of time lying flat are important predisposing factors that improve with time. However, the certainty of evidence is stronger regarding PPIs and H2 antagonists in children with GORD, although this certainty was lessened in Article VI.

Regarding investigations: Article I noted that differentiating GOR from GORD based on observer-reported symptoms alone appeared to be problematic, and the need to understand the pros and cons of a gold-standard investigation (24hr pH-probe monitoring) was identified. Article II observed that 24-hour pH-impedance monitoring has been identified as safe, reproducible, and particularly useful when a patient has a symptom of concern (e.g. posturing or distress) that is contemporaneously linked to an episode of reflux. Article III and VI highlighted that the evidence also highlights significant discrepancies between reported symptom severity scores and endoscopic/histological findings, which are potentially affected by the numbers of children with distressing symptoms but diagnosed GOR. Article VI additionally observed that a high proportion of infants have physiological GOR, with very low-certainty evidence about symptom improvements, changes in pH/impedance indices and no summary data for endoscopic changes. Article V confirmed the utility of the NICE audit tool for GORD for clinicians evaluating their service, and improved our service in Dorset, as although there were good assessments and documentation of red flags for causes other than GORD: recommendations for change included checking head circumference routinely and routine urine dips. This was the first published audit using the NICE audit tool for GORD, and first assessment of how a moderate-sized DGH looks for red-flags in GORD.

In terms of efficacy of medications: for infants: Article I found that Gaviscon Infant® (sachets) are safe and can improve symptoms of GOR (Grade D). For GORD ranitidine (Grade B) and omeprazole and probably lansoprazole (Grade B) are safe and effective medications, which should provide symptomatic relief, and endoscopic and histological healing of oesophagitis. There is less evidence to support the use of domperidone, and metoclopramide has an adverse side-effect profile. More evidence is needed before other H2-receptor antagonists/PPIs or other anti-reflux medications can be recommended. Article III considered that the certainty of evidence for efficacy of Gaviscon Infant® in symptomatic relief of GOR was moderate, but these are short-term studies with small numbers of participants, and evidence for strategies such as reassurance, positioning and use of thickened formula milk in appropriate volumes and frequencies is summarised within the article. For infants with evidence of GORD on investigation (endoscopic changes or abnormal reflux index on pH/impedance probe), evidence of benefit from any medical treatment is weak. Further studies are needed to confirm whether PPIs or H_2 antagonists are superior in the group, and whether individual drugs offer superior efficacy. Weak evidence has been found for acid suppression (PPIs/H2-receptor

antagonists), with consequent decreased gastric enzyme activity, allowing for healing of oesophagitis, and symptomatic improvement. As a result of the factors previously discussed, I was unable to comment as to whether H_2 antagonists are superior to PPIs, but no evidence supports concurrent use. No consistent evidence for prokinetics (such as domperidone) has been found. It is currently difficult to justify continuing prescriptions of domperidone in infants for whom no benefit from empirical use has been reported. The current MHRA alert recommends restricting empirical prescriptions to two weeks and avoiding them in children with co-existing cardiac disease and in those receiving treatment with CYP3A4 inhibitors (EMA 2014), which has led to a marked reduction in prescribing frequency. Article IV (NICE guidance) conclusions included 'Do not offer acid-suppressing drugs, such as proton pump inhibitors (PPIs) or H2 receptor antagonists (H2RAs), to treat overt regurgitation in infants and children occurring as an isolated symptom. Consider a 4-week trial of a PPI or H2RA for infants who have overt regurgitation with 1 or more [additional symptoms]: Offer PPI or H2RA treatment to infants with endoscopy-proven reflux oesophagitis; and (with a few caveats) do not offer metoclopramide, domperidone or erythromycin to treat GOR or GORD. Article VI noted that medications may provide additional benefit (based on very low-certainty evidence), for infants whose symptoms remain bothersome despite non-medical interventions or parental reassurance. If a medication is required, there is no clear evidence based on summary data for omeprazole, esomeprazole (in neonates), H_2 antagonists and alginates for symptom improvements (very low-certainty evidence); and further studies with longer follow-ups are needed.

There was low-quality evidence of absence of efficacy from prokinetics in neonates, infants and children, and no evidence regarding treatment efficacy in children with neurodisability.

Premature babies are often also treated empirically for gastro-oesophageal reflux, for example, causing apnoea; and further RCTs in this age group, using consistent outcomes, were also recommended in articles I, III, IV and VI.

In older children, Article I considered that acid suppression is the mainstay of treatment, and the largest evidence-base supports the initial use of H2-receptor antagonists or PPIs (Grade B). Significant issues with study design were identified, but limited adjustment for risk of bias was allowable using CEBM methodology. In article III PPIs (including omeprazole and lansoprazole) had moderate quality evidence for reducing symptoms and improving erosive oesophagitis, with some evidence for H2 antagonists such as ranitidine and famotidine. Article III noted that among older children with GORD, moderate evidence of benefit from PPIs has been found, along with weak evidence of benefit from H_2 antagonists, in providing symptomatic relief and in improving endoscopic/histological appearances and pH/impedance indices. No consistent evidence has been found for prokinetics (such as domperidone). It is currently difficult to justify prescriptions for

domperidone among children for whom no benefit from empirical use is apparent. The current MHRA alert recommends restricting empirical prescriptions to two weeks and avoiding them in children with co-existing cardiac disease and in those receiving treatment with CYP3A4 inhibitors (EMA 2014). Article IV recommended: Consider a 4-week trial of a PPI or H2RA for children who are unable to tell you about their symptoms (for example those with a neurodisability affecting expressive communication) who have overt regurgitation with 1 or more [additional symptoms] OR for children and young people with persistent heartburn, retrosternal or epigastric pain: Offer PPI or H2RA treatment to children and young people with endoscopy-proven reflux oesophagitis; and (with a few exceptions) do not offer metoclopramide, domperidone or erythromycin to treat GOR or GORD. In Article VI, following the independent extraction of summary data, in children, there was very low-certainty evidence regarding the impact of PPIs (pantoprazole and rabeprazole) on symptom scores, with insufficient summary data to make conclusions regarding other medications. No robust data exists for H_2 antagonists, domperidone or erythromycin.

For children with neurodisability: the specific challenges and paucity of evidence was highlighted in Articles I, III, IV and VI. The need for RCTs into children with underlying oesophageal dysmotility (e.g. children with cerebral palsy) was highlighted, then progressed in articles VII and VIII. These children often have difficult and protracted reflux, as most of these trials specifically excluded this subgroup. They often receive maximal medical therapies, including prokinetics, given for prolonged time periods, and treatment regimens for these groups are often extrapolated from those for other groups of children. In article VII in children with cerebral palsy and GORD, the most frequently prescribed anti-reflux medication was omeprazole (70%), with patients remaining on it for an average of 35 months (range 2 months–10 years). 30% patients had trialled ranitidine: on average for 19 months (4–35 months). Despite the recent MHRA alert of domperidone associated with cardiac side effects, and NICE guidance stating ‘Do not Use’: 59% of children were on domperidone for a comparatively long time: mean 38 months (range 1–104 months), potentially exposing them to risk.

In terms of improving outcome assessment in children with neurodisability, article VII built on the research recommendation of article IV, and assessed communicative ability in children with cerebral palsy; 30% of patients assessed could converse, 41% used communication aids (IPads or PECS (Picture Exchange Communication System)) and a majority (65%) could indicate pain. This helped establish the communication level of children with cerebral palsy and the likely proportions on anti-reflux medication and confirmed that many children are on these medications, often in combination, for many years, including medications with potentially significant side-effects, such as domperidone, that has the potential for therapeutic benefit given the underlying gut dysmotility.

In article VIII, I aimed to adapt the existing P-GSQ proxy assessment tool to enable use in evaluating children with CP and GORD. Cognitive interviews were conducted with 6 parents/carers of children (aged 3-15) with CP (GMFCS level III-V) who have current or past symptoms of reflux. They were asked to interpret the questionnaire using a 'think-aloud technique'. The P-GSQ questionnaire was modified iteratively following each interview. Overall, parents/carers felt the questions were relevant, useful, and related to symptoms that they observe. It was easy to comprehend with no uncomfortable questions. Some felt it was difficult to comment on questions surrounding school as they were not with their child during the school day. Suggestions for future work included a section specifically focusing on school staff and carers who assist them in the home. This will aid in assessing efficacy of pharmacological treatments for GORD in children with cerebral palsy and potentially have significant cost saving implications if treatments can be initiated/discontinued based on accurate symptom assessment.

Strengths and Limitations:

This body of work assessing this common and distressing problem is useful for clinicians caring for infants and children in primary care (health visitors, GPs and nurse practitioners and school nurses) especially when considered with the review of reflux in infancy (Tighe 2010) and learning module (Tighe Pulse 2014), and the patient information within NG1. Clinicians in secondary care (such as paediatricians and neonatologists) are also finding this body of work useful, and this work has been cited internationally (NASPGHAN-ESPGHAN 2018).

Limitations of the existing evidence-base are summarised within articles I, II, III, IV, VI and VIII. Although a lot of the recommendations are similar to the existing published work, this thesis considers the recommendations together across the mixed methodologies and highlights the paucity of evidence in other areas of clinical care, such as neonates and children with other health conditions, and in economically deprived healthcare settings. Follow-ups were often short and studies of infants studied mixed populations: some of whom may have had diagnosed GOR, and some having GORD, and the reviews also describe how the definitions of GOR vs GORD have shifted over the 10-12 years encompassed by the publications in this thesis. The issue of pharmaceutical support for studies has also been commented upon. The thesis didn't comment on areas of clinical overlap such as other gut disorders, food allergy or co-existing Helicobacter pylori infection.

Limitations of this thesis include the absence of children involved in developing the literature reviews, and the drift in definitions of GOR/GORD over time as the body of work evolved. Article VI did evaluate three publications treating children with GORD in resource-limited countries

but further evidence from different communities, especially given the different approaches within communities in managing distressed infants with functional gut symptoms using non-pharmacological techniques may improve prescribing practices. Further gaps have been identified, and are being addressed in future work, for example, testing the modified P-GSQ through further validation, and considering an RCT comparing the most commonly-prescribed PPI (omeprazole) to ta commonly-prescribed H2 antagonist (famotidine or nizatidine), though this thesis lays solid foundations towards this aim (NHS Business Services Authority prescribing data (2014.

What are the implications of this body of work?

This body of work has helped to define the existing evidence-base and assign a level of quality to the evidence through the systematic review (using CEBM criteria) then Cochrane reviews, to make evidence-based recommendations for care and treatment, so that clinicians are better able to work out the benefits of treatment and risk of side-effects and complications. Article II formed the basis of a new clinical service offered to UHD paediatric patients, which has now been running for over 10 years. The knowledge gained, and establishment of expected normal values, helped to underpin Articles III and VI and the clinical utility of pH-impedance monitoring in children with CP is explored in Article VIII.

The review of reflux in infancy (Tighe 2010) helps set into context how many babies have 'normal' crying, and so treating these infants for presumed reflux may have little benefit in the absence of symptoms and has implications in terms of cost and potential side-effects. Through Articles IV and V, the care of infants and children has been improved, with appropriate reduction in testing (e.g. reduced barium swallows), and medications (e.g. less domperidone/metoclopramide/ erythromycin), and Article V enables better assessment of the quality of assessment for GORD, so that children with other conditions are identified earlier. The development of a suitable symptom-based outcome assessment in Article VII improves care of children with cerebral palsy, with their more problematic symptoms and greater implications for their health, such as longer empirical treatment, frequent hospitalisation and increased frequency of surgical intervention.

Further work commentary is contained within the articles, however following this body of work, further work includes validating the modified P-GSQ outcome measure and considering a randomised controlled trial to ascertain if there is an effective medication/combination of medications in children with cerebral palsy. Although ranitidine has been discontinued due to manufacturing issues, there is evolving evidence that PPIs including omeprazole may cause

osteoporosis in adults, which may be accentuated in children with cerebral palsy, who are often non-weightbearing and have gracile bones with poor levels of mineralisation.

Chapter 5: Conclusions

This expanded literature base has helped clinicians to better understand the treatment options and reasonably counsel their patients accordingly. The clinical bottom-line for infants is that as 95% of babies grow out of their GORD by the age of 1 year-2 years (Martin 2002), managing expectations and considering early weaning may improve parental understanding of the likely timing of symptomatic improvement and avoid rapid escalation of medical treatments and over-investigation in the absence of red flags. The introduction of proton pump inhibitors can improve comfort levels in some babies with GORD and may take up to 1 month for healing of mucosal inflammation (and relief of discomfort). The clinical bottom-line for older children is that their symptoms are likely to be more troublesome, more likely to lead to longer-term issues, and proton pump inhibitors are much more effective. This combination of a mainly evidence-based medical model, taking account of important psychosocial factors, helps clinicians appropriately tailor management approach and explanations.

Other medications such as domperidone and erythromycin have evidence of absence of effect, and the number of prescriptions of these medications has significantly reduced since Articles III, IV, and VI. In terms of investigations, 24-hour pH-impedance monitoring has a specific role in ascertaining whether GOR is contemporaneously linked with symptoms, and barium swallow is not useful in quantifying GOR severity. Introduction of better patient information has helped families, and the quality standards and audit tool has helped earlier identification of babies with other conditions, as well as benchmarking standards of care.

Overall Recommendations from this body of work:

1) Validate the P-GSQ in children with GORD and neurodisability.
2) Consider a head-to-head trial of omeprazole vs famotidine in children with CP and GORD using the validated symptom questionnaire.

Guideline summary

Guideline development group membership, NCC-WCH staff and acknowledgements

Table 1: Guideline development group members

Name	Role
Ieuan Davies (Chair)	Consultant Paediatric Gastroenterologist, University Hospital of Wales, Cardiff
Karen Blythe	Advanced Paediatric Nurse Practitioner, Countess of Chester Hospital NHS Foundation Trust
Sarah Currell	Paediatric Dietician, Poole Hospital NHS Foundation Trust
Charlie Fairhurst	Consultant in Paediatric Neurodisability, Evelina London Children's Hospital
Rebecca Harmston	Patient and carer member
Bruce Jaffray	Paediatric Surgeon, The Great North Children's Hospital, Newcastle upon Tyne
Eleanor Jeans	Patient and carer member
Dianne Jones	Health Visitor, Cheshire and Wirral Partnership Trust (West), Chester
John Martin	GP Principal, Taunton, Somerset
Tom McAnea	GP Principal, London
Russell Peek	Consultant Paediatrician, Gloucestershire Hospital NHS Foundation Trust
Mike Thomson	Consultant Paediatric Gastroenterologist, Sheffield Children's Hospital NHS Foundation Trust
Mark Tighe	Consultant Paediatrician, Poole Hospital NHS Foundation Trust

Table 2: Expert adviser to the group

Name	Role
Rowena McArtney	Senior Information Pharmacist, Welsh Medicines Information Centre, University Hospital of Wales, Cardiff

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

Name	Role
David Bevan (until December 2013)	Project Manager
Shona Burman-Roy (from August 2014)	Team Leader
Jiri Chard (until August 2014)	Team Leader
Kate Coles (from January 2014)	Project Manager
Hannah Rose Douglas (until April 2014)	Health Economist
Maryam Gholitabar (from November 2014)	Research Associate
Yelan Guo (October 2013 – February 2014)	Research Associate

Name	Role
Paul Jacklin (from September 2014)	Health Economist
Setor Kunutsor (October – November 2014)	Research Associate
Rosalind Lai (until October 2014)	Information Scientist
Paul Mitchell (June 2014 – August 2014)	Health Economist
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Appendix 1b) Quality Standard QS112: GORD in children

Specialist committee members:

Karen Blythe: Paediatric Nurse
Dr Charlie Fairhurst: Consultant Community Paediatrician
Rebecca Harmston: Patient/ carer member
Dianne Jones: Health Visitor
Dr. Samantha Ross: General Practitioner
Dr Mike Thomson: Consultant Paediatric Gastroenterologist
Dr Mark Tighe Paediatric Consultant

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