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

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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_2 antagonists** 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

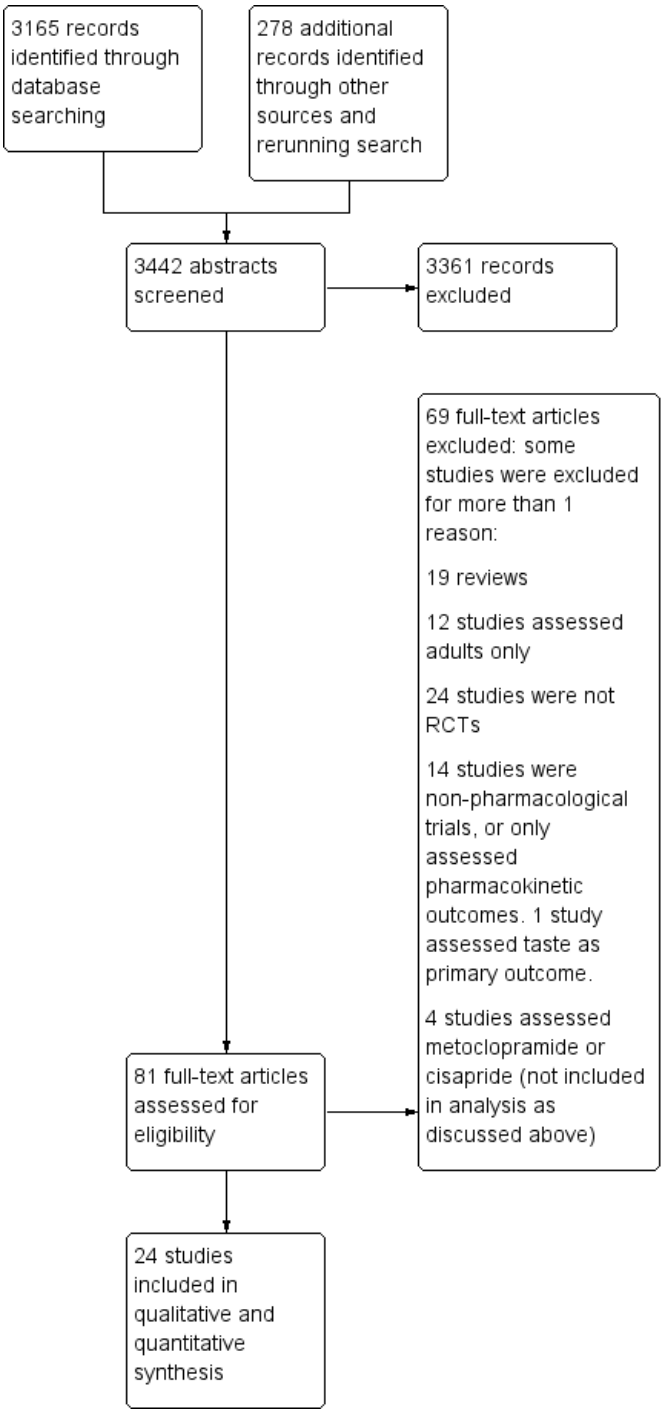
Results of the search

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 base-

line, 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. En-

doscopy 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.

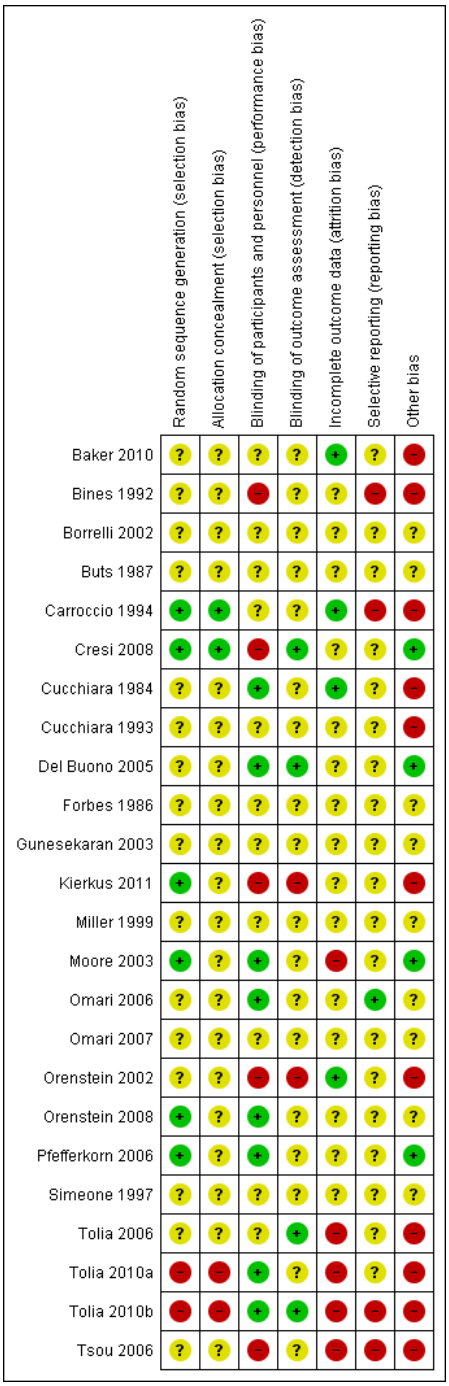
Excluded studies

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.



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 m² 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 H2 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 H2 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 H2 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. H2 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 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

Baker 2010 (*Continued*)

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
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

Bines 1992 (*Continued*)

	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% 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described by study authors

Bines 1992 (*Continued*)

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) *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)

Borrelli 2002 (*Continued*)

	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

Buts 1987 (*Continued*)

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
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

Carroccio 1994 (*Continued*)

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
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**

Cresi 2008 (*Continued*)

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)

Cucchiara 1984 (*Continued*)

	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
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)

Cucchiara 1993 (*Continued*)

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**
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

Cucchiara 1993 (*Continued*)

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**
Random sequence generation (selection bias)	Unclear risk	No comment made

Del Buono 2005 (*Continued*)

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

Forbes 1986 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No comment made
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

Gunesekaran 2003 (*Continued*)

	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

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)

Kierkus 2011 (*Continued*)

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)
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) *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	

Miller 1999 (*Continued*)

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 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

Moore 2003 (*Continued*)

	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) **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

Moore 2003 (*Continued*)

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 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 CMPI/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

Omari 2006 (*Continued*)

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
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**

Omari 2007 (*Continued*)

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
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) All outcomes	High risk	Parents unblinded to intervention in part 1
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
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

Orenstein 2008 (*Continued*)

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 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

Pfefferkorn 2006 (*Continued*)

	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

Simeone 1997 (*Continued*)

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), 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

Simeone 1997 (*Continued*)

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
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%)

Tolia 2006 (*Continued*)

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) All outcomes	High risk	All enrolled participants accounted for. No evidence of consecutive enrolment and no discussion of children who refused consent or who were excluded
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
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 en-

Tolia 2010a (*Continued*)

		doscopy
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) 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**

Tolia 2010b (*Continued*)

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
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.

Tsou 2006 (*Continued*)

	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

(*Continued*)

Grill 1985	Discounted as not an RCT
Gunesekaran 1993	Discounted as not an RCT
Hassall 2000	Discounted as not an RCT
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

(*Continued*)

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 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

(*Continued*)

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.

DATA AND ANALYSES

This review has no analyses.

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**
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 ef-	83 children (3 studies)	⊕⊕◯◯ **Low**	

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

			fect when ranitidine was added to PPI. Cimetidine (33 infants and children) also had very weak evidence for efficacy in delivering symptom relief			
		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 In-	110 infants (2 studies)	⊕⊕◯◯ **Low**	Gaviscon Infant ® has changed to become alu-

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

			fant® 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			minium-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 neurodisabilities	No RCT evidence was identified				
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 omepra-	748 children (12 studies)	⊕⊕◯◯ **Low**	82% of participants taking pantoprazole in one study had an adverse event (mainly headache and diarrhoea)

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

			zole, lansoprazole and esomeprazole than for pantoprazole			
		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	109 children (4 studies)	⊕⊕◯◯ **Low**	

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

			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			
	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)	59 infants and children (2 studies)	⊕◯◯◯ **Very low**	

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

			improved symptoms of GORD			
	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	59 infants and children	⊕⊕◯◯ **Low**	

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

			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)	(2 studies)		
	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

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	110 participants (2 studies)	⊕⊕◯◯ **Low**	Gaviscon Infant® has changed to become aluminium-free, and

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

		showed weak evidence of symptomatic improvement (90 participants). 1 study of 20 children showed no symptomatic improvement			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 hydroxy-carbonate 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 hydroxy-carbonate 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*

(*Continued*)

# 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

Last assessed as up-to-date: 1 June 2014.

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