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[Intervention Protocol]

Interventions for preventing upper gastrointestinal bleeding in people admitted to intensive care units

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the risk/benefit profile of interventions used to prevent upper gastrointestinal bleeding in people admitted to level 2 and level 3 intensive care units*

* Level 2 intensive care units: patients requiring detailed observation or intervention including support for a single failing organ system or postoperative care, and those stepping down from higher levels of care.

Level 3 intensive care units: patients requiring advanced respiratory support alone or basic respiratory support together with support for at least two organ systems.

These levels include all sick patients requiring support for organ failure/dysfunction in intensive care units (Goldhil 2002).

BACKGROUND

Description of the condition

Upper gastrointestinal bleeding due to stress ulcers is a major contributor to increased morbidity and mortality in people admitted to intensive care units (ICUs). Stress ulceration refers to gastrointestinal mucosal injury related to the stress of being critically ill. The injury may vary from diffuse superficial ulcers to deep, haemorrhaging lesions (Neligan 2006). The incidence of bleeding related to stress ulcers in critically ill people on mechanical ventilators ranges from less than 1% to 6% of patients admitted to ICU (Ben-Menachem 1994; Cook 1994a; Kantorova 2004; Schuster 1984; Zandstra 1994). A more recent study using a new tool (HEmorrhage MEasurement Tool - HEME) to assess gastrointestinal bleed in ICU patients observed that 5.2% of those with stress ulcers had major bleeds (Arnold 2007). ICU patients with

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major bleeding as a result of stress ulceration might have mortality rates approaching 48.5% to 65% (Cook 1995; Guillamondegui 2008; Peterson 1994; Zuckerman 1988). In the past few decades, however, with improved standards of care the incidence of stress-induced gastrointestinal bleeding in ICUs has decreased and not all critically ill patients need prophylaxis (Penner 2005).
Gastric bleeding can be diagnosed from a drop in blood pressure necessitating blood transfusion and a rapid heart rate (haemodynamic instability), 'coffee ground' aspiration, vomiting of blood (haematemesis) or passage of dark stools (melena) (Dorland 1995).

Bleeding from stress ulcers

Bleeding from stress ulcers may be trivial or profuse. Trivial bleeds may be detected only through laboratory tests while profuse bleeding results in overt manifestations. Cook et al defined a clinically important bleed as overt bleeding plus one of four features reflecting haemodynamic instability and blood loss. These are as follows.

1. Either a drop in systolic or diastolic blood pressure within 24 hours after upper gastrointestinal bleeding of 20 mm Hg or more; or
2. postural decrease in systolic blood pressure of 10 mg Hg and accelerated pulse rate of 20 beats per minute; or evidence of significant blood loss (this may be difficult to demonstrate in intubated patients).
3. Either a drop in haemoglobin concentration of at least 2 g per decilitre needing two units of packed cell transfusion within 24 hours of the bleed; or
4. failure of a rise in haemoglobin concentration in (g per decilitre) of at least the number of units of blood transfused minus two (Cook 1998a).

Risk factors

Prophylaxis is often recommended for patients with major risk factors. These are:

- patients who have a coagulopathy (a disorder of blood coagulation); and
- patients who require mechanical ventilation for more than 48 hours.

In addition, patients who have at least two or more of the following risk factors for stress ulcers are also often recommended prophylaxis (AHSP 1999; Pfeffer 2007):

- ICU stay longer than one week;
- sepsis or hypotension;
- hepatic or renal failure;
- history of peptic ulcer disease;
- use of high-dose steroids (> 250 mg/day of hydrocortisone or equivalent);
- burns over > 35% of total body surface area;
- immediately after organ transplantation;
- head trauma with Glasgow Coma Scale < 10;
- multiple trauma; or
- occult bleeding for six days or more.

Pathophysiology of stress ulcers

The aetiology and pathophysiology of stress ulcers in ICU patients appear to be multifactorial. Normally the splanchnic microcirculation and the gastric mucosa protect the mucosal epithelium from gastric acids, wherein bicarbonate ions secreted by the mucosa neutralise hydrogen ions. Reduced blood flow due to splanchnic hypoperfusion in critically ill patients, with the resultant ischaemia and impaired cell oxygenation, releases nitric oxide (by increased levels of enzyme nitric oxide synthase) and oxygen free radicals, and reduces prostaglandin synthesis. These mechanisms result in inflammation and cell death. Reperfusion hyperaemia due to elevated nitric oxide levels contributes to further cell death. Slowed upper gastric mobility and the reduced secretion of bicarbonate by the gastric mucosa with the resultant prolonged exposure of the damaged mucosa to gastric acids, as well as a decrease in mucosal repair mechanisms, also contribute to ulceration (Dorland 1995; Spirt 2006).

Consequences of stress ulcers

Major bleeding can be life-threatening and result in death. Minor bleeds can result in an increased need for transfusion and its attendant risks. It is therefore necessary to evaluate strategies that decrease the incidence of ulcer bleeds.

Complications of stress-ulcer prophylaxis: ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is a common complication in mechanically-ventilated patients. The reported incidence of VAP varies from 1% to 28% (Chastre 2002; Rahbar 2006). A systematic review of observational studies and randomised trials revealed that the incidence of VAP ranged from 10% to 20% in people undergoing mechanical ventilation for more than 48 hours (Safdar 2005).

Risk factors for VAP

The risk of VAP increases with the duration of mechanical ventilation continuing over 48 hours but the risk is additionally elevated in people with contributory medical conditions. Additional sources of infection from endotracheal tubes or ventilator circuits and other feeding tubes, or from improper measures to prevent nosocomial infection in ICU staff, increase the risk of VAP (Augustyn 2007; CDC 2003; Masterton 2008).
The disadvantage of stress ulcer prophylaxis is that many of the interventions used for the suppression of gastric acid raise the pH of gastric contents, alter gastric flora and promote tracheo-bronchial colonisation and the gastric colonisation of pathogenic bacteria -

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the aspiration of which causes nosocomial pneumonia or ventilator-associated pneumonia (VAP) (Atherton 1978; Cook 1998b; Craven 1986). In addition to increasing mortality in critically ill patients this can prolong length of hospital stay and increase costs (Safdar 2005). The elevated risk of developing VAP associated with stress ulcer prophylaxis may therefore offset the potential benefits of such therapy.

Diagnosis of VAP

The criteria used to establish the diagnosis of VAP vary. Traditionally clinical features (fever, cough and purulent sputum) coupled with radiological evidence of pneumonia (new lung infiltrates or progression of infiltrates), and elevated white blood cell count, in a patient on mechanical ventilation provide suggestive evidence. Confirmatory cultures from sputum or aspirates from the trachea or pleural fluid in such individuals increase the sensitivity of the diagnosis of bacterial causes of pneumonia. However, these traditional methods are not specific in VAP and blood cultures are reported to have low sensitivity. Standardised techniques used in clinical research studies have included quantitative culture of specimens obtained from endotracheal aspirates, using protected specimen brush (PSB) specimens after bronchoalveolar lavage or via blind catheterisation (non-bronchoscopic protected bronchoalveolar lavage or protected specimen brush specimens). These techniques have improved the sensitivity and specificity of the diagnosis of VAP (CDC 2003; Masterton 2008).

Commonly used criteria to diagnose VAP include the clinical pulmonary infection score (CPIS) that has evolved from the original four criteria (fever, leucocytosis, positive sputum culture and worsening chest X-ray changes) to six criteria (plus increased oxygen requirement and semi-quantitative cultures of tracheal aspirates with or without Gram stain). The added criteria in the CPIS help in selecting, modifying and monitoring therapy, though diagnostic accuracy is similar to the traditional criteria (Masterton 2008).

VAP mortality

Individuals who contract VAP are already critically ill, therefore the death rate from ventilator-associated pneumonia is high. Reported mortality rates range from 24% to 76%, with higher mortality attributed to specific situations (such as underlying disease and organ failure) or types of causative organisms(such as *Pseudomonas* or *Acinetobacter*) (CDC 2003; Chastre 2002). Mortality is doubled in critically ill patients with VAP when compared to those without VAP (Safdar 2005).

It is considered prognostically important to distinguish early-onset and late-onset VAP. The Working Party on Hospital Acquired Pneumonia of the British Society of Antimicrobial Chemotherapy defined the former as occurring during the first four days and the latter as occurring five or more days after starting patients on mechanical ventilation. Early-onset VAP is usually less severe and carries a better prognosis than late-onset VAP (Chastre 2002; Masterton 2008).

Description of the intervention

There are several drugs that are used in the treatment and prevention of gastric ulcers such as those that block histamine 2 receptors (H2 blockers) (ranitidine, cimetidine, famotidine etc.); proton pump inhibitors(esomeprazole, rabeprazole, omeprazole, lansoprazole etc.); prostaglandin analogues (misoprostol); anticholinergics (pirenzepine, propantheline etc.); antacids (sodium bicarbonate, magnesium hydroxide etc.); ulcer protectives (sucralfate, bismuth etc.); and other interventions such as enteric nutrition and early extubation.

How the intervention might work

The interventions used in stress ulcer prophylaxis differ with respect to their mechanism of action, additional protective effects on the gastric endothelium and effects on increasing gastric luminal pH and resultant potential to increase gastric bacterial colonisation, and their side effect profile (Mutlu 2001).

Antacids neutralise gastric acid in a dose-dependent manner and raise the gastric pH. They have other beneficial cytoprotective effects but may cause an increase in magnesium and diarrhoea (magnesium-based antacids), or reduce phosphates and cause constipation (aluminium-based antacids). Nursing costs are also increased due to the need to administer them at frequent intervals (often hourly).

H2 receptor blockers are believed to inhibit gastric acid secretion by blocking histamine receptors but have no additional cytoprotective effects and can cause thrombocytopaenia, interstitial nephritis and confusion (especially in the elderly). Rapid intravenous infusions can cause bradycardia and hypotension and there are many P-450 mediated drug interactions and effects (particularly with cimetidine).

Proton pump inhibitors (PPIs) act by inhibiting the final stage of gastric acid production but have no additional cytoprotective effects on the gastric mucosa and also have P-450 mediated effects. However, it has been found that PPIs may be associated with an increased risk of *Clostridium difficile* diarrhoea (Cunningham 2003; Mutlu 2001).

Prostaglandin analogues inhibit acid secretion and promote mucus and bicarbonate secretion that makes gastric contents alkaline but can cause diarrhoea and abdominal pain. However, they need to be administered four times daily.

Ulcer protective agents, such as sucralfate and colloidal bismuth subcitrate, create a barrier between the gastric acid and the gastric mucosa by coating it. They have additional cytoprotective effects and do not effectively alter gastric pH, but may cause constipation

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and interfere with the absorption of certain antibacterial agents such as tetracyclines and quinolones (Mutlu 2001).

Enteral nutrition helps to maintain gut integrity, modulate stress and the systemic immune response, and attenuate disease severity. Enteral nutrition might also reduce bacterial translocation and infective complications by maintaining the structural integrity of the gut. In addition, enteral nutrition is considered an effective means of stress ulcer prophylaxis, though it may raise gastric pH and theoretically increase rates of nosocomial infections or neutralise the effects of ulcer protective agents (Hinds 1999; McClave 2009) .

Why it is important to do this review

ICU patients are at risk of developing stress ulcers. A proportion will develop clinically important bleeding; the mortality rate in such patients is high (48.5% to 65%). Several randomised controlled trials (RCTs), non-randomised trials and cohort studies have studied the role of different stress ulcer prophylactic drugs and strategies for the prevention of stress ulcers and thereby gastric bleed. Stress ulcer prophylaxis is, however, a risk factor for the development of VAP. Thus the benefits of stress ulcer prophylaxis need to be balanced against this risk.

Previous systematic reviews and meta-analyses were either narrowed to comparisons of two interventions, were inconclusive or generated conflicting results (Cook 1994b; Cook 1996; Cook 1995b; Messori 2000). Commonly used proton pump inhibitors were not included in these systematic reviews.

The effectiveness of oral decontamination with antiseptics and antibiotics in preventing the incidence of VAP was confirmed in a Cochrane Review (Chan 2007). Another Cochrane Review concluded that suctioning with either closed or open tracheal suction systems did not have an effect on the risk of ventilator-associated pneumonia or mortality (Subirana 2007).

Guidelines for the management of hospital-acquired pneumonia in the UK have been produced by the working party on hospital-acquired pneumonia of the British Society for Antimicrobial Chemotherapy (Masterton 2008). They considered the results of a systematic review (Collard 2003) and narrative synthesis of seven meta-analyses (Cook 1991; Cook 1995; Cook 1996; Messori 2000; Tryba 1991; Tryba 1991b; Tryba 1995). This produced discordant results but overall suggested a reduced risk of developing VAP when given sucralfate compared to H2 receptor antagonists (though not when compared to placebo), and evidence from one trial of an increased risk of clinically significant bleeding when sucralfate was given to prevent upper gastrointestinal bleeds compared to H2 receptor antagonists. They recommended that stress ulcer prophylaxis be avoided in people on mechanical ventilation in order to preserve gastric function and reduce VAP. If stress ulcer prophylaxis is indicated then the advantage of sucralfate in reducing the incidence of VAP needs to be balanced by its increased risk of resulting clinically significant upper GI bleeding (Masterton 2008).

Proton pump inhibitors (PPIs) are used increasingly for stress ulcer prophylaxis. An observational study found that pantoprazole was associated with a higher risk of VAP compared to ranitidine (Miano 2009). However, a recent meta-analysis found no strong evidence to suggest any difference between PPIs and H2 blockers with respect to stress ulcer prophylaxis, VAP and mortality among people admitted to ICUs (Lin 2010). Yet another meta-analysis demonstrated that PPIs were more effective than H2 blockers in the prevention of clinically important bleeding due to stress ulcers but there was no difference in the incidence of VAP between the two groups (Pongprasobchai 2009). A trial comparing omeprazole, famotidine and sucralfate could not find any marked difference between them in stress ulcer prophylaxis, though it reported a low incidence of stress ulcer bleeds in high-risk surgical ICU patients. The study also claimed that routine prophylaxis might actually increase the risk of developing VAP (Kantorova 2004).

The Centres for Disease Control in its latest guidelines for the prevention of hospital acquired pneumonia made no recommendations for the preferential use of sucralfate, H2-antagonists or antacids for the prophylaxis of stress ulcer bleeding in patients receiving mechanically-assisted ventilation (CDC 2003).

Clinicians seeking a definitive answer to a) whether routine prophylaxis is indicated for intubated patients on ventilators and b) what is the best intervention do not have adequate guidance at present (Penner 2005).

This Cochrane Review will first address the question of whether stress ulcer prophylaxis is indicated in critically ill people in ICUs on ventilators in terms of reducing the risk of bleeding without increasing the risk of other complications(particularly VAP). We will then seek evidence to suggest which prophylactic agent or agents should be used and in what situations. We aim to provide definitive guidance to inform clinical care, policy and practice guidelines.

OBJECTIVES

To evaluate the risk/benefit profile of interventions used to prevent upper gastrointestinal bleeding in people admitted to level 2 and level 3 intensive care units*

* Level 2 intensive care units: patients requiring detailed observation or intervention including support for a single failing organ system or postoperative care, and those stepping down from higher levels of care.

Level 3 intensive care units: patients requiring advanced respiratory support alone or basic respiratory support together with support for at least two organ systems.

These levels include all sick patients requiring support for organ failure/dysfunction in intensive care units (Goldhil 2002).

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METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

People (any age and gender) admitted to level 2 or level 3 intensive care units for more than 48 hours.
We will excluded trials where participants were admitted to ICUs primarily for the management of gastrointestinal bleeding.

Types of interventions

We will compare the following interventions administered by any route and at any dose.

Drugs that reduce gastric acid secretion

1. H2 receptor antagonists: ranitidine, cimetidine, famotidine, roxatidine, nizatidine, loxatidine.
2. Proton pump inhibitors: esomeprazole, rabeprazole, omeprazole, lansoprazole, pantoprazole.
3. Prostaglandin analogues: misoprostol, enprostol, rioprostil.
4. Anticholinergics: pirenzepine, propantheline, oxyphenonium, doxepin, trimipramine.

Drugs that neutralise gastric acid (antacids)

1. Systemic: sodium bicarbonate, sodium citrate.
2. Non-systemic: magnesium hydroxide, magnesium trisilicate, aluminium hydroxide gel, magaldrate, calcium carbonate.

Ulcer protectives

1. Sucralfate.
2. Colloidal bismuth subcitrate.

Ulcer healing drugs

Carbenoxolone sodium, deglycyrrhizinated liquorice.

Others

1. Enteral nutrition.
2. Any other intervention used to reduce upper gastrointestinal bleeding.
3. Combinations of interventions, e.g. omeprazole-bicarbonate combinations.
4. No prophylaxis.
5. Placebo.

Types of outcome measures

Primary outcomes

Clinically important gastrointestinal bleeding

For the purposes of this review, we will use the definition used by trial authors to define clinically important bleeding. We will record the details of the definition used.

Secondary outcomes

Ventilator-associated pneumonia (VAP)
VAP is defined as pneumonia contracted in a hospital (nosocomial) by a patient on mechanical ventilatory support (by endotracheal tube or tracheostomy) for more than 48 hours (Masterton 2008; Mayhall 2001). The criteria used for the diagnosis of VAP used for the review will be those used by the trial authors. VAP will be subgrouped as early-onset and late-onset, with pneumonia developing before or after five days of mechanical ventilation used to define subgroups.

Mortality

1. All-cause mortality in ICU.
2. All-cause mortality in hospital.

Duration of ICU stay

Duration of intubation

Blood transfusion

1. Number of participants requiring transfusion of more than 2 units of blood.
2. Number of units of blood transfused.

Adverse events of interventions

1. Serious adverse events leading to discontinuation of treatment, prolongation of ICU stay or disability.
2. Any other adverse events (e.g. thrombocytopaenia related to H2 blockers, any other adverse events).

Search methods for identification of studies

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We will attempt to identify all relevant randomised controlled trials (RCTs) and quasi-randomised trials (where allocation to intervention can be predicted) for inclusion, regardless of language or publication status (published, unpublished, in press and in progress). We will exclude non-randomised trials and observational studies.

Electronic searches

We will search the following databases using the search terms listed in Appendix 1 (with appropriate database-specific modifications): the Cochrane Upper Gastrointestinal and Pancreatic Disease Group Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library*; MEDLINE; EMBASE and LILACS.

Searching other resources

We will search reference lists of all articles retrieved by the search and of those from systematic reviews and meta-analyses listed in the background to identify relevant trials. In addition, we will make an effort to search all available conference proceedings for relevant RCTs from the World Federation of Societies of Intensive and Critical Medicine (http://www.world-critical-care.org/), the World Gastroenterology Organisation (http://www.worldgastroenterology.org/about-wgo.html) websites, and from The Digestive Disease Week 1997 May 11 to 14; Washington DC to acquire relevant RCTs. We will contact the individual researchers working in this field, organisations and pharmaceutical companies to identify unpublished and ongoing trials, and provide this information in a table along with the dates when this was done.

We will also search the WHO International Clinical Trials Registry Platform's search portal (http://apps.who.int/trialsearch/) for ongoing clinical trials.

Data collection and analysis

Selection of studies

Two sets of authors (ATG and RK, PT and JPB) will independently screen all citations and abstracts identified by the search strategy to identify potentially eligible studies. We will obtain and assess full reports of potentially eligible studiesfor inclusion in the review based on the inclusion and exclusion criteria. If eligibility is unclear due to inadequate or unclear information, we will attempt to contact trial authors for clarification. In case the trial is published in a different language we will seek help from the Cochrane Upper Gastrointestinal and Pancreatic Disease Group editorial office and our other contacts with the translation process. We will resolve any disagreements through discussion. We will scrutinise each trial report to ensure that multiple publications from the same trial are included only once and all such reports will be linked to the original trial report in the reference list of included studies. We will exclude studies that do not meet the criteria and document the reason for exclusion.

Data extraction and management

The pairs of authors will independently extract data from the trials using pre-tested data extraction forms. We will extract data (where available) on:

Baseline characteristics

The type of ICU care (level 2 or 3); inclusion and exclusion criteria for the participants; reasons for admission to ICU; underlying medical conditions; presence of and severity of organ dysfunction and health status as recorded in trial reports; proportion of participants at admission with coagulopathy, pneumonia, previous gastrointestinal bleed (overt or covert), or diagnosis of oesophageal, duodenal or gastric ulcers or erosions.

Interventions

Details of interventions given (dose, route, duration); additional interventions used in each arm (e.g. enteral feeds, antibiotics); total number randomised.

Outcomes

Definitions or criteria used for the diagnosis of clinically significant upper gastrointestinal bleeding (and source of bleeding), pneumonia (and types of pathogens and sensitivity patterns, if available) and VAP; numbers experiencing each outcome; time to onset of each outcome; and number of dropouts and withdrawals with reasons. For every outcome, we will extract the number analysed and the number randomised in each treatment group to allow for the assessment of losses to follow up. We will resolve any disagreements about data extraction by referring to the trial report and by discussion. Where data are insufficient or missing, we will make attempts to contact the trial authors.

For continuous outcomes, we will extract the arithmetic mean values, standard deviations and the number of participants in whom the outcome was assessed in each of the trial arms. We will note whether the numbers assessed in the trial were the number of participants that completed the trial or the number randomised. If medians have been reported we will extract ranges or interquartile ranges.

Assessment of risk of bias in included studies

The pairs of authors will independently assess the risk of bias in each included study. Disagreements, if any, will be resolved by referring to the trial report, correspondence with the authors of the

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report and through discussions. We will assess each study on the domains of sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective reporting; and other sources of bias and assign a judgement regarding the freedom from the risk of bias as 'yes, 'no' or 'unclear', using guidelines in Higgins 2008 to make these judgements. We will record this information for each included trial in 'Risk of bias' tables in RevMan 5 (Review Manager 2008) and summarise the risk of bias for each study in a summary 'Risk of bias' figure and graph.

Measures of treatment effect

We will first compare interventions to prevent upper gastrointestinal bleeding in people admitted to intensive care units versus placebo or no intervention and then compare specific interventions or combinations of interventions grouped under drug classes. When outcomes are dichotomous we will use risk ratios and when outcomes are continuous we will use the mean difference, with respective 95% confidence intervals.

Unit of analysis issues

If included trials are randomised by clusters of ICUs and if the results have been adjusted for clustering, we will combine the adjusted measures of effects. If results have not adjusted for clustering, we will attempt to adjust the results by multiplying the standard errors of the estimates by the square root of the design effect where the design effect is calculated as D_{Eff} = 1 + (M - 1) ICC, where M is the average cluster size and ICC is the intra-cluster coefficient. If this is not possible, we will not combine them in a meta-analysis, but will present the results in an additional table.

If outcomes are reported both at baseline and at a follow up or at trial endpoints, we will extract both the mean change from baseline and the standard deviation of this mean for each treatment group, as well as the same for endpoint data. We will use endpoint data preferentially but will combine endpoint and change scores for outcomes from trials for each comparison if endpoint data are not available.

If count data are reported in trials, we will extract the total number of events in each group and the total amount of person-time at risk in each group. We will also record the total number of participants in each group. If this information is not available, we will attempt to extract alternative summary statistics such as rate ratios and confidence intervals, if available. If count data are presented as dichotomous outcomes, we will extract the number of participants in each intervention group and the number of participants in each intervention group who experienced at least one event. If count data are presented as continuous outcomes or as a time-to-event outcomes, we will attempt to extract the same information as outlined for continuous and time-to-event outcomes.

If time-to-event outcomes are reported, we will extract the estimates of the log hazard ratio and its standard error. If standard errors are not available we will extract alternative statistics such as confidence intervals or P values.

Dealing with missing data

We will attempt to obtain missing data from trial authors. Where possible, we will extract data to allow an intention-to-treat analysis in which all randomised participants are analysed in the groups to which they were originally assigned. If there is discrepancy in the number randomised and the numbers analysed in each treatment group, we will calculate the percentage loss to follow up in each group and report this information. If dropouts exceed 10% for any trial, we will assign the worse outcome to those lost to follow up for dichotomous outcomes and assess the impact of this in sensitivity analyses with the results of completers.

For continuous data that are missing standard deviations we will either calculate these from other available data such as standard errors, or will impute them using the methods suggested in Higgins 2008. We will not make any assumptions about loss to follow up for continuous data and will analyse results for those who complete the trial.

Assessment of heterogeneity

We will assess heterogeneity between the trials by visual examination of the forest plot to check for overlapping confidence intervals, using the Chi^2 test for homogeneity with a 10% level of significance, and the I^2 statistic. We will use an I^2 statistic value of less than 25% to denote low heterogeneity, 50% or greater significant heterogeneity and 75% or greater substantial heterogeneity.

Assessment of reporting biases

Apart from assessing the risk of selective outcome reporting considered under Assessment of risk of bias in included studies, we will assess the likelihood of potential publication bias using funnel plots, provided that there are at least 10 trials.

Data synthesis

We will synthesise dichotomous data using pooled and weighted risk ratios. We will combine continuous data summarised by arithmetic means and standard deviations using the weighted mean difference. If continuous data are summarised using geometric means, we will combine them on the log scale using the generic inverse variance method and report them on the natural scale. We will compare count data using rate ratios when the total number of events in each group and the total amount of person-time at risk in each group are available, or by relative risks or weighted mean difference if data are presented in dichotomous or continuous forms respectively. We will combine hazard ratios from survival data on the log scale using the inverse variance method and present them on the natural scale.

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Subgroup analysis and investigation of heterogeneity

We will use a fixed-effect model when there is no heterogeneity. Where heterogeneity is significant (I^2 statistic 50% or greater) we will combine the trials using a random-effects model. If severe heterogeneity is present (I^2 statistic >= 75%) and cannot be explained by differences across the trials in terms of clinical or methodological features or by subgroup analyses (see below), we will not combine the trials in a meta-analysis but will present the results in a forest plot. We will stratify the analysis by the type of study, i.e. individual versus cluster-randomised trials.

If data permit, we will carry out the following subgroup analyses for each comparison.

1. Presence or absence of bleeding disorders (e.g. coagulopathies, defined as thrombocyte count < 50/nl, partial thromboplastin time (PTT) > 2 times the upper limit of the normal range, international normalised ratio (INR) > 1.5).
2. Pneumonia at the time of ICU admission.
3. Adults (> 16 to 18 years to 65 to 70 years) versus older adults (> 65 to 70 years) versus children and adolescents.
4. Use of co-interventions that may affect outcomes (e.g. enteral feeds, prophylactic antibiotics and other measures used for selective decontamination for the digestive tract (SDD)).

For the outcome of VAP, we will further subgroup data by the development of early-onset VAP (within four days on ventilation) or late-onset VAP (five or more days on ventilation), or as unclear (if this subgrouping is not possible from information in the report or by contacting trial authors).

Sensitivity analysis

We will conduct sensitivity analyses to investigate the robustness of the results for the primary outcomes by evaluating outcomes in trials with low risk of bias versus those with high risk or unclear risk of bias. We will also undertake sensitivity analyses if trials report dropout rates of 10% or greater, to ascertain differences in outcomes of intention-to-treat (ITT) analysis and analysis of completers. We will also assess the robustness of the results to the use of published and validated criteria to diagnose clinically important bleeding and VAP.

Summarising results

We will import data for the following outcomes from Review Manager 2008 into GRADEprofiler (GRADEpro 2008) and use this to construct 'Summary of findings' (SoF) tables and to guide the conclusions of this review: clinically important gastrointestinal bleeding; ventilator-associated pneumonia; mortality; duration of ICU stay; number of participants requiring transfusion of more than two units of blood; and serious adverse events.

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* *Indicates the major publication for the study*

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APPENDICES

Appendix 1. CENTRAL search strategy

1. (stomach or antrum or antral or pyloric or pylorus or gastri$ or epigastr$ or duodenal or duodenum or gastro-duodenal or gastroduodenal or oeso*ag* or esp*ag* or "upper GI" or UGI).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
2. (h*emorrhag$ or bleed$ or re-bleed$ or rebleed$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3. 1 and 2
4. exp Gastrointestinal Hemorrhage/
5. (gastr$ adj3 mucosal adj3 injur$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. exp injury/ and exp gastric mucosa/
7. or/3-6
8. (stress adj3 ulcer$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
9. (h*emorrhag$ or bleed$ or re-bleed$ or rebleed$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
10. (ulcer$ or lesion$).mp.
11. exp Peptic Ulcer/
12. 9 and (10 or 11)
13. 8 or 12
14. h*ematemesis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
15. (melena or melaena).mp.
16. (coffee adj1 ground).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
17. or/14-16
18. 7 or 13 or 17
19. exp Intensive Care/ or exp Critical Illness/ or exp Critical care/ or exp Intensive care units/ or exp Monitoring, Physiologic/
20. exp Enteral nutrition/
21. (Nasogastric adj2 (intubat* or tube*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
22. exp Intubation, Gastrointestinal/
23. exp Feeding Apparatus/ or exp Nutritional Support/ or exp Enteric Feeding/ or exp Tube Feeding/
24. nasoduodenal tube*.mp.
25. force feeding$.mp.
26. or/19-25
27. exp Histamine H2 Antagonists/
28. H2 receptor Antagonist*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
29. H2 blocker*.mp.
30. (ranitidine or azanplus or biotidin or pylorid or raciran or raniberl or ranisen or ranitidin or rantec or sostril or taladine or tritec or wal-zan or zantac).mp.
31. (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.
32. (famotidine or fluxid or leader acid reducer or mylanta or pepcid).mp.
33. (roxatidine or Roxit).mp.
34. (Nizatidine or axid or zinga).mp.
35. exp proton pump inhibitors/
36. (omeprazole or losec or nexium or prilosec or rapinex or zegerid).mp.

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37. (Esomeprazole or Sompraz or Zoleri or Nexium or Lucen or Esopral or Axagon or Nexiam).mp.
38. (Rabeprazole or aciphex or dexrabeprazole or pariet or rablet).mp.
39. (pantoprazole or protium or protonix).mp.
40. (lansoprazole or agopton or bamalite or lanzoprazole 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.
41. prostaglandins e, synthetic/
42. (misoprostol or cytotec or glefos).mp.
43. enprostil.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
44. rioprostil.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
45. Cholinergic Antagonists/
46. (Pirenzepine or Gastrozepin or Bisvanil or Gasteril or Leblon or Pirenzepin or Pirenzepina or Pirenzepine Gastrozepin or Pirenzepinum or Tabe or Ulcosan).mp.
47. (Propantheline or Pro-Banthine).mp.
48. (Oxyphenonium or Antrenyl or Argicillin or Methacin or Methocidin or Methocidine or Methocidinum or Metocidina or Hydroxymethylgramicidin or Oxiphenonum).mp.
49. (Doxepin or adapin or apodoxepin or aponal or deptran or desidox or doneurin or doxepia or doxepinbiomo or espadox or mareen or prudoxin or quitaxon or silenor or sinequan or xepin or zonalon).mp.
50. (Trimipramine or rhotrimine or stangyl or surmontil).mp.
51. exp antacids/
52. (sodium bicarbonate or baking soda or bicarb or bicarbonate of soda or carbonic acid monosodium salt or citrocarbonate or monosodium carbonate or neut or neutra caine or soda bic or sodium acid carbonate or sodium hydrogen carbonate).mp.
53. (sodium citrate or 2-hydroxypropanetricarboxylic acid or albright's solution or bicitra or citra or citrate or citric acid or cystemme or cystoleve or cytra-2 or liqui-dualcitra or oracit or shohl's solution or uralyt).mp.
54. (magnesium hydroxide or antacids magnesium oh or brucite or magnesium hydrate or mil-par or milk of magnesia).mp.
55. (aluminium hydroxide gel or aldrox or algeldrate or alhydrogel or aloh-gel or alternagel or alu-cap or alu-tab or alugel or aluminium hydroxide mixture bp or aluminium hydroxide oral suspension bp or aluminum hydroxide or aluminum hydroxide gel or amphojel or andursil or basalgel or brasivil or brimos or dialume or hydrated alumina or pepsamer or rocgel).mp.
56. (magnesium trisilicate or sepiolite or Alenic Alka or Gaviscon or Genaton).mp.
57. (Magaldrate or Gadral or Magaltop or Magralibi or Riopan).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
58. (calcium carbonate or alka-mints or alkets or alkums or amilac or amitone or antacid extra strength or aragonite or cacit or caco or cal oys or cal-gest or calcarb or calceos or calci mix or calcichew or calcidrink or calcitab or calcite or calcium antacid or calcium concentrate or calcium liquid softgel or calcium milk or calcium oyster or calcium-based antacid or calmicid or caltrate or caltro or chalk or chewable calcium or chooz or dicarbosil or equilet or extra strength mylanta calci tabs or limestone or maalox antacid barrier or maalox children or maalox quick dissolve or marble or milk of calcium or mor-cal or mylanta child or nephro calci or o-calcium or oscal or oscal or oysco or oyst cal or oyster calcium or oyster shell or pepto-bismol children or rolaids calcium rich or rolaids sodium free or rolaids softchews or super calcium or surpass or titralac or tums or ultra mylanta calci tabs or uni-cal or uni-mint or vaterite).mp.
59. (sucralfate or aluminum sucrose sulfate or antepsin or carafate or ulcerban or ulcogant or ulsanic or xactdose).mp.
60. (colloidal bismuth subcitrate or bi-citrate or biselic or bismofarma or bismuth citrate or bismuth subcitrate or bismuth tripotassium dicitrate or bissubcit or de-nol or de-noltab or gastrodenol or sucrato or tripotassium dicitratobismuthate or ventrisol-polfa).mp.
61. (carbenoxolone sodium or bioplex or bioral or carbenoxalone or carbosan or disodium enoxolone or duogastrone or pharmaxolon or sanodin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
62. Deglycyrrhizinised Liquorice.mp.
63. or/27-62
64. 18 and 26 and 63

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Appendix 2. MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10
12. (stomach or antrum or antral or pyloric or pylorus or gastri$ or epigastr$ or duodenal or duodenum or gastro-duodenal or gastroduodenal or oeso*ag* or esp*ag* or "upper GI" or UGI).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
13. (h*emorrhag$ or bleed$ or re-bleed$ or rebleed$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
14. 12 and 13
15. exp Gastrointestinal Hemorrhage/
16. (gastr$ adj3 mucosal adj3 injur$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
17. exp injury/ and exp gastric mucosa/
18. or/14-17
19. (stress adj3 ulcer$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
20. (h*emorrhag$ or bleed$ or re-bleed$ or rebleed$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
21. (ulcer$ or lesion$).mp.
22. exp Peptic Ulcer/
23. 20 and (21 or 22)
24. 19 or 23
25. h*ematemesis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
26. (melena or melaena).mp.
27. (coffee adj1 ground).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
28. or/25-27
29. 18 or 24 or 28
30. exp Intensive Care/ or exp Critical Illness/ or exp Critical care/ or exp Intensive care units/ or exp Monitoring, Physiologic/
31. exp Enteral nutrition/
32. (Nasogastric adj2 (intubat* or tube*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
33. exp Intubation, Gastrointestinal/
34. exp Feeding Apparatus/ or exp Nutritional Support/ or exp Enteric Feeding/ or exp Tube Feeding/
35. nasoduodenal tube*.mp.
36. force feeding$.mp.
37. or/30-36
38. exp Histamine H2 Antagonists/
39. H2 receptor Antagonist*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
40. H2 blocker*.mp.

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41. (ranitidine or azanplus or biotidin or pylorid or raciran or raniberl or ranisen or ranitidin or rantec or sostril or taladine or tritec or wal-zan or zantac).mp.
42. (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.
43. (famotidine or fluxid or leader acid reducer or mylanta or pepcid).mp.
44. (roxatidine or Roxit).mp.
45. (Nizatidine or axid or zinga).mp.
46. exp proton pump inhibitors/
47. (omeprazole or losec or nexium or prilosec or rapinex or zegerid).mp.
48. (Esomeprazole or Sompraz or Zoleri or Nexium or Lucen or Esopral or Axagon or Nexiam).mp.
49. (Rabeprazole or aciphex or dexrabeprazole or pariet or rablet).mp.
50. (pantoprazole or protium or protonix).mp.
51. (lansoprazole or agopton or bamalite or lanzoprazole 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.
52. prostaglandins e, synthetic/
53. (misoprostol or cytotec or glefos).mp.
54. enprostil.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
55. rioprostil.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
56. Cholinergic Antagonists/
57. (Pirenzepine or Gastrozepin or Bisvanil or Gasteril or Leblon or Pirenzepin or Pirenzepina or Pirenzepine Gastrozepin or Pirenzepinum or Tabe or Ulcosan).mp.
58. (Propantheline or Pro-Banthine).mp.
59. (Oxyphenonium or Antrenyl or Argicillin or Methacin or Methocidin or Methocidine or Methocidinum or Metocidina or Hydroxymethylgramicidin or Oxiphenonum).mp.
60. (Doxepin or adapin or apodoxepin or aponal or deptran or desidox or doneurin or doxepia or doxepinbiomo or espadox or mareen or prudoxin or quitaxon or silenor or sinequan or xepin or zonalon).mp.
61. (Trimipramine or rhotrimine or stangyl or surmontil).mp.
62. exp antacids/
63. (sodium bicarbonate or baking soda or bicarb or bicarbonate of soda or carbonic acid monosodium salt or citrocarbonate or monosodium carbonate or neut or neutra caine or soda bic or sodium acid carbonate or sodium hydrogen carbonate).mp.
64. (sodium citrate or 2-hydroxypropanetricarboxylic acid or albright's solution or bicitra or citra or citrate or citric acid or cystemme or cystoleve or cytra-2 or liqui-dualcitra or oracit or shohl's solution or uralyt).mp.
65. (magnesium hydroxide or antacids magnesium oh or brucite or magnesium hydrate or mil-par or milk of magnesia).mp.
66. (aluminium hydroxide gel or aldrox or algeldrate or alhydrogel or aloh-gel or alternagel or alu-cap or alu-tab or alugel or aluminium hydroxide mixture bp or aluminium hydroxide oral suspension bp or aluminum hydroxide or aluminum hydroxide gel or amphojel or andursil or basalgel or brasivil or brimos or dialume or hydrated alumina or pepsamer or rocgel).mp.
67. (magnesium trisilicate or sepiolite or Alenic Alka or Gaviscon or Genaton).mp.
68. (Magaldrate or Gadral or Magaltop or Magralibi or Riopan).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
69. (calcium carbonate or alka-mints or alkets or alkums or amilac or amitone or antacid extra strength or aragonite or cacit or caco or cal oys or cal-gest or calcarb or calceos or calci mix or calcichew or calcidrink or calcitab or calcite or calcium antacid or calcium concentrate or calcium liquid softgel or calcium milk or calcium oyster or calcium-based antacid or calmicid or caltrate or caltro or chalk or chewable calcium or chooz or dicarbosil or equilet or extra strength mylanta calci tabs or limestone or maalox antacid barrier or maalox children or maalox quick dissolve or marble or milk of calcium or mor-cal or mylanta child or nephro calci or o-calcium or oscal or oscal or oysco or oyst cal or oyster calcium or oyster shell or pepto-bismol children or rolaids calcium rich or rolaids sodium free or rolaids softchews or super calcium or surpass or titralac or tums or ultra mylanta calci tabs or uni-cal or uni-mint or vaterite).mp.
70. (sucralfate or aluminum sucrose sulfate or antepsin or carafate or ulcerban or ulcogant or ulsanic or xactdose).mp.
71. (colloidal bismuth subcitrate or bi-citrate or biselic or bismofarma or bismuth citrate or bismuth subcitrate or bismuth tripotassium dicitrate or bissubcit or de-nol or de-noltab or gastrodenol or sucrato or tripotassium dicitratobismuthate or ventrisol-polfa).mp.

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72. (carbenoxolone sodium or bioplex or bioral or carbenoxalone or carbosan or disodium enoxolone or duogastrone or pharmaxolon or sanodin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
73. Deglycyrrhizinised Liquorice.mp.
74. or/38-73
75. 29 and 37 and 74
76. 11 and 75

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$.tw.
19. Prospective study/
20. or/1-19
21. Case study/
22. Case report.tw.
23. Abstract report/ or letter/
24. or/21-23
25. 20 not 24
26. (stomach or antrum or antral or pyloric or pylorus or gastri$ or epigastr$ or duodenal or duodenum or gastro-duodenal or gastroduodenal or oeso*ag* or esp*ag* or "upper GI" or UGI).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
27. (h*emorrhag$ or bleed$ or re-bleed$ or rebleed$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
28. 26 and 27
29. gastrointestinal hemorrhage/ or duodenum bleeding/ or peptic ulcer bleeding/ or stomach hemorrhage/ or upper gastrointestinal bleeding/
30. (gastr$ adj3 mucosal adj3 injur$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
31. or/28-30
32. (stress adj3 ulcer$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
33. (h*emorrhag$ or bleed$ or re-bleed$ or rebleed$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
34. (ulcer$ or lesion$).mp.
35. exp Peptic Ulcer/

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36. 33 and (34 or 35)
37. 32 or 36
38. h*ematemesis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
39. (melena or melaena).mp.
40. (coffee adj1 ground).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
41. or/38-40
42. 31 or 37 or 41
43. intensive care/ or exp artificial feeding/ or artificial ventilation/ or exp Critical Illness/ or exp Intensive care units/ or patient monitoring/
44. (Nasogastric adj2 (intubat* or tube*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
45. exp digestive tract intubation/
46. exp Feeding Apparatus/ or exp Nutritional Support/
47. nasoduodenal tube*.mp.
48. force feeding$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
49. or/43-48
50. exp histamine H2 receptor antagonist/
51. H2 receptor Antagonist*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
52. H2 blocker*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
53. (ranitidine or azanplus or biotidin or pylorid or raciran or raniberl or ranisen or ranitidin or rantec or sostril or taladine or tritec or wal-zan or zantac).mp.
54. (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.
55. (famotidine or fluxid or leader acid reducer or mylanta or pepcid).mp.
56. (roxatidine or Roxit).mp.
57. (Nizatidine or axid or zinga).mp.
58. exp proton pump inhibitors/
59. (omeprazole or losec or nexium or prilosec or rapinex or zegerid).mp.
60. (Esomeprazole or Sompraz or Zoleri or Nexium or Lucen or Esopral or Axagon or Nexiam).mp.
61. (Rabeprazole or aciphex or dexrabeprazole or pariet or rablet).mp.
62. (pantoprazole or protium or protonix).mp.
63. (lansoprazole or agopton or bamalite or lanzoprazole 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.
64. prostaglandin E/
65. (misoprostol or cytotec or glefos).mp.
66. enprostil.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
67. rioprostil.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
68. cholinergic receptor blocking agent/
69. (Pirenzepine or Gastrozepin or Bisvanil or Gasteril or Leblon or Pirenzepin or Pirenzepina or Pirenzepine Gastrozepin or Pirenzepinum or Tabe or Ulcosan).mp.
70. (Propantheline or Pro-Banthine).mp.
71. (Oxyphenonium or Antrenyl or Argicillin or Methacin or Methocidin or Methocidine or Methocidinum or Metocidina or Hydroxymethylgramicidin or Oxiphenonum).mp.
72. (Doxepin or adapin or apodoxepin or aponal or deptran or desidox or doneurin or doxepia or doxepinbiomo or espadox or mareen or prudoxin or quitaxon or silenor or sinequan or xepin or zonalon).mp.
73. (Trimipramine or rhotrimine or stangyl or surmontil).mp.

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74. antacid agent/
75. (sodium bicarbonate or baking soda or bicarb or bicarbonate of soda or carbonic acid monosodium salt or citrocarbonate or monosodium carbonate or neut or neutra caine or soda bic or sodium acid carbonate or sodium hydrogen carbonate).mp.
76. (sodium citrate or 2-hydroxypropanetricarboxylic acid or albright's solution or bicitra or citra or citrate or citric acid or cystemme or cystoleve or cytra-2 or liqui-dualcitra or oracit or shohl's solution or uralyt).mp.
77. (magnesium hydroxide or antacids magnesium oh or brucite or magnesium hydrate or mil-par or milk of magnesia).mp.
78. (aluminium hydroxide gel or aldrox or algeldrate or alhydrogel or aloh-gel or alternagel or alu-cap or alu-tab or alugel or aluminium hydroxide mixture bp or aluminium hydroxide oral suspension bp or aluminum hydroxide or aluminum hydroxide gel or amphojel or andursil or basalgel or brasivil or brimos or dialume or hydrated alumina or pepsamer or rocgel).mp.
79. (magnesium trisilicate or sepiolite or Alenic Alka or Gaviscon or Genaton).mp.
80. (Magaldrate or Gadral or Magaltop or Magralibi or Riopan).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
81. (calcium carbonate or alka-mints or alkets or alkums or amilac or amitone or antacid extra strength or aragonite or cacit or caco or cal oys or cal-gest or calcarb or calceos or calci mix or calcichew or calcidrink or calcitab or calcite or calcium antacid or calcium concentrate or calcium liquid softgel or calcium milk or calcium oyster or calcium-based antacid or calmicid or caltrate or caltro or chalk or chewable calcium or chooz or dicarbosil or equilet or extra strength mylanta calci tabs or limestone or maalox antacid barrier or maalox children or maalox quick dissolve or marble or milk of calcium or mor-cal or mylanta child or nephro calci or o-calcium or os-cal or oscal or oysco or oyst cal or oyster calcium or oyster shell or pepto-bismol children or rolaids calcium rich or rolaids sodium free or rolaids softchews or super calcium or surpass or titralac or tums or ultra mylanta calci tabs or uni-cal or uni-mint or vaterite).mp.
82. (sucralfate or aluminum sucrose sulfate or antepsin or carafate or ulcerban or ulcogant or ulsanic or xactdose).mp.
83. (colloidal bismuth subcitrate or bi-citrate or biselic or bismofarma or bismuth citrate or bismuth subcitrate or bismuth tripotassium dicitrate or bissubcit or de-nol or de-noltab or gastrodenol or sucrato or tripotassium dicitratobismuthate or ventrisol-polfa).mp.
84. (carbenoxolone sodium or bioplex or bioral or carbenoxalone or carbosan or disodium enoxolone or duogastrone or pharmaxolon or sanodin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
85. Deglycyrrhizinised Liquorice.mp.
86. or/50-85
87. 42 and 49 and 86
88. 25 and 87

Appendix 4. LILACS search strategy

Descriptors in Health Sciences (DeCS) were used to account for Portuguese, Spanish and English terms in LILACS.
(E02.760.190.400 or N02.278.388.493 or E02.760.190) [DeCS Category] and (C06.405.227 or C06.405.227.400 or A12.459.764 or C06.405.227.700) [DeCS Category]

CONTRIBUTIONS OF AUTHORS

Aneesh Thomas George: Developing and drafting the initial version of the protocol, searching for additional references and approving the final version of the protocol.

Prathap Tharyan: Initiating the review, searching for additional references, developing the protocol, training co-authors in the methods of the review and writing the final version of protocol.

JV Peter: Conceptualisation of the review topic, developing the protocol, providing citations and full-text articles for the background, refining the review, approving the final version.

Richard Kirubakaran: Developing the protocol and approving the final version of the protocol.

Jabez Paul Barnabas: Locating and retrieving full-text articles, approving the final version of the protocol.

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