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

Toews I, George AT, Peter JV, Kirubakaran R, Fontes LES, Ezekiel JPB, Meerpohl JJ

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[Intervention Review]

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

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ABSTRACT

Background

Upper gastrointestinal (GI) bleeding due to stress ulcers contributes to increased morbidity and mortality in people admitted to intensive care units (ICUs). Stress ulceration refers to GI mucosal injury related to the stress of being critically ill. ICU patients with major bleeding as a result of stress ulceration might have mortality rates approaching 48.5% to 65%. However, the incidence of stress-induced GI bleeding in ICUs has decreased, and not all critically ill patients need prophylaxis. Stress ulcer prophylaxis can result in adverse events such as ventilator-associated pneumonia; therefore, it is necessary to evaluate strategies that safely decrease the incidence of GI bleeding.

Objectives

To assess the effect and risk-benefit profile of interventions for preventing upper GI bleeding in people admitted to ICUs.

Search methods

We searched the following databases up to 23 August 2017, using relevant search terms: MEDLINE; Embase; the Cochrane Central Register of Controlled Trials; Latin American Caribbean Health Sciences Literature; and the Cochrane Upper Gastrointestinal and Pancreatic Disease Group Specialised Register, as published in the Cochrane Library (2017, Issue 8). We searched the reference lists of all included studies and those from relevant systematic reviews and meta-analyses to identify additional studies. We also searched the World Health Organization International Clinical Trials Registry Platform search portal and contacted individual researchers working in this field, as well as organisations and pharmaceutical companies, to identify unpublished and ongoing studies.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs with participants of any age and gender admitted to ICUs for longer than 48 hours. We excluded studies in which participants were admitted to ICUs primarily for the management of GI bleeding and studies that compared different doses, routes, and regimens of one drug in the same class because we were not interested in intraclass effects of drugs.

Data collection and analysis

We used standard methodological procedures as recommended by Cochrane.

Main results

We identified 2292 unique records. We included 129 records reporting on 121 studies, including 12 ongoing studies and two studies awaiting classification.

We judged the overall risk of bias of two studies as low. Selection bias was the most relevant risk of bias domain across the included studies, with 78 studies not clearly reporting the method used for random sequence generation. Reporting bias was the domain with least risk of bias, with 12 studies not reporting all outcomes that researchers intended to investigate.

Any intervention versus placebo or no prophylaxis

In comparison with placebo, any intervention seems to have a beneficial effect on the occurrence of upper GI bleeding (risk ratio (RR) 0.47, 95% confidence interval (CI) 0.39 to 0.57; moderate certainty of evidence). The use of any intervention reduced the risk of upper GI bleeding by 10% (95% CI -12.0% to -7%). The effect estimate of any intervention versus placebo or no prophylaxis with respect to the occurrence of nosocomial pneumonia, all-cause mortality in the ICU, duration of ICU stay, duration of intubation (all with low certainty of evidence), the number of participants requiring blood transfusions (moderate certainty of evidence), and the units of blood transfused was consistent with benefits and harms. None of the included studies explicitly reported on serious adverse events.

Individual interventions versus placebo or no prophylaxis

In comparison with placebo or no prophylaxis, antacids, H2 receptor antagonists, and sucralfate were effective in preventing upper GI bleeding in ICU patients. Researchers found that with H2 receptor antagonists compared with placebo or no prophylaxis, 11% less developed upper GI bleeding (95% CI -0.16 to -0.06; RR 0.50, 95% CI 0.36 to 0.70; 24 studies; 2149 participants; moderate certainty of evidence). Of ICU patients taking antacids versus placebo or no prophylaxis, 9% less developed upper GI bleeding (95% CI -0.17 to -0.00; RR 0.49, 95% CI 0.25 to 0.99; eight studies; 774 participants; low certainty of evidence). Among ICU patients taking sucralfate versus placebo or no prophylaxis, 5% less had upper GI bleeding (95% CI -0.10 to -0.01; RR 0.53, 95% CI 0.32 to 0.88; seven studies; 598 participants; moderate certainty of evidence). The remaining interventions including proton pump inhibitors did not show a significant effect in preventing upper GI bleeding in ICU patients when compared with placebo or no prophylaxis.

Regarding the occurrence of nosocomial pneumonia, the effects of H2 receptor antagonists (RR 1.12, 95% CI 0.85 to 1.48; eight studies; 945 participants; low certainty of evidence) and of sucralfate (RR 1.33, 95% CI 0.86 to 2.04; four studies; 450 participants; low certainty of evidence) were consistent with benefits and harms when compared with placebo or no prophylaxis. None of the studies comparing antacids versus placebo or no prophylaxis provided data regarding nosocomial pneumonia.

H2 receptor antagonists versus proton pump inhibitors

H2 receptor antagonists and proton pump inhibitors are most commonly used in practice to prevent upper GI bleeding in ICU patients. Proton pump inhibitors significantly more often prevented upper GI bleeding in ICU patients compared with H2 receptor antagonists (RR 2.90, 95% CI 1.83 to 4.58; 18 studies; 1636 participants; low certainty of evidence). When taking H2 receptor antagonists, 4.8% more patients might experience upper GI bleeding (95% CI 2.1% to 9%). Nosocomial pneumonia occurred in similar proportions of participants taking H2 receptor antagonists and participants taking proton pump inhibitors (RR 1.02, 95% CI 0.77 to 1.35; 10 studies; 1256 participants; low certainty of evidence).

Authors' conclusions

This review shows that antacids, sucralfate, and H2 receptor antagonists might be more effective in preventing upper GI bleeding in ICU patients compared with placebo or no prophylaxis. The effect estimates of any treatment versus no prophylaxis on nosocomial pneumonia were consistent with benefits and harms. Evidence of low certainty suggests that proton pump inhibitors might be more effective than H2 receptor antagonists. Therefore, patient-relevant benefits and especially harms of H2 receptor antagonists compared with proton pump inhibitors need to be assessed by larger, high-quality RCTs to confirm the results of previously conducted, smaller, and older studies.

PLAIN LANGUAGE SUMMARY

Interventions for preventing upper gastrointestinal bleeding in people on intensive care units

Review question

We reviewed the evidence about benefits and harms of interventions to prevent clinically important upper gastrointestinal (GI) bleeding in patients who were admitted to the intensive care unit (ICU).

Background

Stress ulcers are seen as superficial damage in the mucous lining of the stomach or intestines that can occur as the result of shock, sepsis, or trauma. Depending on the severity of the damage, afflicted areas may become sore and may start to bleed to varying degrees. Upper GI bleeding due to stress ulcers is a major contributor to increased severity of illness and death among people admitted to ICUs. However,

standards of care have improved, and the incidence of upper GI bleeding in ICUs has decreased. Thus, not all critically ill patients need preventive treatment.

Stress ulcer prophylaxis can result in negative effects such as ventilator-associated pneumonia (VAP). VAP is a lung infection caused by bacteria in people who are being mechanically ventilated. VAP usually manifests as fever, cough, and purulent sputum. The risk for VAP is increased in patients with severe illness, increased length of hospital stay, or use of stress ulcer prophylaxis. Hence, it is necessary to evaluate strategies that safely decrease the incidence of upper GI bleeding.

Study characteristics

The evidence is current to August 2017. We included 106 studies with a total of 15,027 critically ill participants of any age and any gender.

Key results

Relevant effects were found for the following drugs: H2 receptor antagonists, antacids, sucralfate, and proton pump inhibitors.

H2 receptor antagonists inhibit gastric acid secretion by blocking histamine receptors but can cause a small number of blood platelets (thrombocytopenia), inflammation of the kidney (interstitial nephritis), and confusion. Antacids neutralise stomach acid but may cause diarrhoea or constipation. Proton pump inhibitors inhibit the final stage of gastric acid production, and it has been found that they may be associated with increased risk of *Clostridium difficile* diarrhoea. Ulcer protective agents, such as sucralfate, create a barrier between the gastric acid and the gastric mucosa by coating it. They may, however, cause constipation and interfere with the absorption of certain antibacterial agents.

In comparison with placebo or no preventive treatment, H2 receptor antagonists, antacids, and sucralfate might be effective in preventing clinically important upper GI bleeding in ICU patients. Hospital-acquired pneumonia was most likely to occur in ICU patients taking either H2 receptor antagonists or sucralfate when compared with patients given placebo or no preventive treatment.

Evidence of low certainty suggests that proton pump inhibitors were more effective than H2 receptor antagonists in preventing upper GI bleeding in ICU patients. With proton pump inhibitors, 25 of 1000 people were likely to develop upper GI bleeding, and with H2 receptor antagonists, 73 of 1000 people (95% confidence interval 46 to 115 people) were likely to develop upper GI bleeding. The effect of H2 receptor antagonists versus proton pump inhibitors with respect to the risk for developing hospital-acquired pneumonia was consistent with benefits and harms.

Quality of the evidence

Our certainty in the evidence ranged from low to moderate. For effects of different interventions compared with placebo or no prophylaxis, the certainty of evidence was moderate (H2 receptor antagonists) or low (antacids and sucralfate). For effects of H2 receptor antagonists compared with placebo or no preventive treatment on risk of hospital-acquired pneumonia, the certainty of evidence was low. For effects of H2 receptor antagonists compared with proton pump inhibitors on hospital-acquired pneumonia, the certainty of evidence was also low.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Interventions compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Any intervention compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Patient or population: people admitted to intensive care units

Setting: ICU

Intervention: any intervention

Comparison: placebo or no prophylaxis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no prophylaxis	Risk with Interventions				
Clinically important upper GI bleeding	Study population		RR 0.47 (0.39 to 0.57)	3207 (30 RCTs)	⊕⊕⊕⊖ MODERATE ^a	
Follow-up: 15 days [†]	188 per 1000	88 per 1000 (73 to 107)				
Nosocomial pneumonia	Study population		RR 1.15 (0.90 to 1.48)	1331 (9 RCTs)	⊕⊕⊖⊖ LOW ^{b,c}	
Follow-up: 48 hours after extubation [‡]	143 per 1000	164 per 1000 (129 to 211)				
All-cause mortality in ICU	Study population		RR 1.10 (0.90 to 1.34)	2159 (19 RCTs)	⊕⊕⊖⊖ LOW ^{b,d}	
Follow-up: 4 weeks [§]	152 per 1000	168 per 1000 (137 to 204)				
Duration of ICU stay	Mean duration of ICU stay ranged from 8.6 to 11.1 days		-	447 (2 RCTs)	⊕⊕⊖⊖ LOW ^{b,e}	
Follow-up: not reported	MD 0.24 days higher (1.13 days lower to 1.61 higher days)					
Number of participants requiring blood transfusion	Study population		RR 0.63 (0.41 to 0.97)	981 (9 RCTs)	⊕⊕⊕⊖ MODERATE ^f	
Follow-up: 48 hours after discharge [‡]	96 per 1000	60 per 1000 (39 to 93)				
Serious adverse events	Not reported					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

‡Duration of follow-up reported in one study.

†Duration of follow-up reported in four studies.

§Duration of follow-up reported in five studies.

CI: confidence interval; GI: gastrointestinal; ICU: intensive care unit; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by one level for risk of bias because of high risk of selection bias in one study, high risk of performance bias in nine studies, high risk of detection bias in five studies, high risk of attrition bias in four studies, high risk of reporting bias in five studies, and high risk of other biases in four studies.

^bDowngraded by one level for imprecision because effect estimate and 95% CI were compatible with benefit and harm.

^cDowngraded by one level for risk of bias because of high risk of performance bias in three studies, high risk of detection bias in one study, and high risk of attrition bias in two studies.

^dDowngraded by one level for risk of bias because of high risk of performance bias in seven studies and high risk of attrition bias in two studies.

^eDowngraded by one level for risk of bias because of high risk of performance bias in one study.

^fDowngraded by one level for risk of bias because of high risk of selection bias in one study, high risk of performance bias in two studies, high risk of attrition bias in one study, high risk of reporting bias in one study, and high risk of other biases in one study.

Summary of findings 2. H2 receptor antagonists compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units

H2 receptor antagonists compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Patient or population: people admitted to intensive care units

Setting: ICU

Intervention: H2 receptor antagonists

Comparison: placebo or no prophylaxis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no prophylaxis	Risk with H2 receptor antagonists				
Clinically important upper GI bleeding	Study population		RR 0.50 (0.36 to 0.70)	2149 (24 RCTs)	⊕⊕⊕⊖ MODERATE^a	

Follow-up: 15 days/weeks [†]	182 per 1000	91 per 1000 (65 to 127)			
Nosocomial pneumonia	Study population		RR 1.12 (0.85 to 1.48)	945 (8 RCTs)	⊕⊕⊕⊖ LOW ^{b,c}
Follow-up: 48 hours after extubation [‡]	146 per 1000	164 per 1000 (124 to 216)			
All-cause mortality in ICU	Study population		RR 1.12 (0.88 to 1.42)	1428 (14 RCTs)	⊕⊕⊕⊖ LOW ^{b,d}
Follow-up: 4 weeks [§]	145 per 1000	162 per 1000 (127 to 205)			
Duration of ICU stay	Mean duration of ICU stay ranged from 8.6 to 11.1 days	MD 0.73 days higher (0.92 days lower to 2.38 days higher)	-	230 (2 RCTs)	⊕⊕⊕⊖ LOW ^{b,e}
Follow-up: not reported					
Number of participants requiring blood transfusions	Study population		RR 0.58 (0.36 to 0.95)	655 (7 RCTs)	⊕⊕⊕⊖ MODERATE ^f
Follow-up: 48 hours after extubation	112 per 1000	65 per 1000 (40 to 107)			
Serious adverse events	Not reported				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

[†]Duration of follow-up reported in four studies.

[‡]Duration of follow-up reported in two studies.

[§]Duration of follow-up reported in five studies.

^{||}Duration of follow-up reported in one study.

CI: confidence interval; GI: gastrointestinal; ICU: intensive care unit; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by one level for risk of bias because of high risk of selection bias in one study, high risk of performance bias in eight studies, high risk of attrition bias in two studies, high risk of reporting bias in four studies, and high risk of other biases in three studies.

^bDowngraded by one level for imprecision because 95% CI was compatible with benefit and harm.

^cDowngraded by one level for risk of bias because of high risk performance bias in three studies and high risk of attrition bias in one study.

^dDowngraded by one level for risk of bias because of high risk of performance bias in three studies and high risk of attrition bias in one study.

^eDowngraded by one level for risk of bias because of high risk of performance bias in one study.

^fDowngraded by one level for risk of bias because of high risk of selection bias in one study, high risk of performance bias in two studies, high risk of attrition bias in one study, and high risk of other biases in one study.

Summary of findings 3. Proton pump inhibitors compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Proton pump inhibitors compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Patient or population: people admitted to intensive care units

Setting: ICU

Intervention: proton pump inhibitors

Comparison: placebo or no prophylaxis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no prophylaxis	Risk with proton pump inhibitors				
Clinically important upper GI bleeding	Study population		RR 0.63 (0.18 to 2.22)	237 (3 RCTs)	⊕⊕○○ LOW ^{a,b}	
Follow-up: not reported	49 per 1000	31 per 1000 (9 to 108)				
Nosocomial pneumonia	Study population		RR 1.24 (0.77 to 1.98)	227 (2 RCTs)	⊕⊕○○ LOW ^{a,c}	
Follow-up: not reported	188 per 1000	233 per 1000 (145 to 372)				
All-cause mortality in ICU	Study population		RR 1.09 (0.60 to 1.99)	258 (3 RCTs)	⊕⊕○○ LOW ^{a,c}	
Follow-up: not reported	134 per 1000	146 per 1000 (80 to 266)				
Duration of ICU stay	Mean duration of ICU stay ranged from 8.6 to 11.1 days		-	227 (2 RCTs)	⊕⊕○○ LOW ^{a,c}	
Follow-up: not reported	MD 0.03 days lower (1.63 days lower to 1.58 days higher)					
Number of participants requiring blood transfusion	Not reported					

Serious adverse events

Not reported

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; GI: gastrointestinal; ICU: intensive care unit; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by one level for imprecision because 95% CI was compatible with benefit and harm.

^bDowngraded by one level for risk of bias because of high risk of performance bias in one study and high risk of attrition bias in one study.

^cDowngraded by one level for risk of bias because of high risk of performance bias in one study.

Summary of findings 4. Antacids compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Antacids compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Patient or population: people admitted to intensive care units

Setting: ICU

Intervention: antacids

Comparison: placebo or no prophylaxis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no prophylaxis	Risk with antacids				
Clinically important upper GI bleeding	Study population		RR 0.49 (0.25 to 0.99)	774 (8 RCTs)	⊕⊕⊕⊖ LOW ^{a,b}	
Follow-up: not reported	170 per 1000	83 per 1000 (43 to 168)				
Nosocomial pneumonia	Not reported					
All-cause mortality in ICU	Study population		RR 1.01 (0.53 to 1.96)	300 (2 RCTs)	⊕⊕⊕⊖ LOW ^{c,d}	
Follow-up: not reported						

	161 per 1000	163 per 1000 (85 to 316)			
Duration of ICU stay	Not reported				
Number of participants requiring blood transfusions	Study population		RR 0.94 (0.30 to 2.96)	226 (2 RCTs)	⊕⊕⊕⊕ LOW ^{c,e}
Follow-up: not reported	45 per 1000	43 per 1000 (14 to 135)			
Serious adverse events	Not reported				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; GI: gastrointestinal; ICU: intensive care unit; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by one level for inconsistency because of moderate heterogeneity; $I^2 = 56\%$.

^bDowngraded by one level for risk of bias because of high risk of performance bias in five studies, high risk of detection bias in one study, high risk of reporting bias in two studies, and high risk of other biases in one study.

^cDowngraded by one level for imprecision because 95% CI was compatible with benefit and harm.

^dDowngraded by one level for risk of bias because of high risk of performance bias in two studies.

^eDowngraded by one level for risk of bias because of high risk of performance bias in one study.

Summary of findings 5. Sucralfate compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Sucralfate compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Patient or population: people admitted to intensive care units

Setting: ICU

Intervention: sucralfate

Comparison: placebo or no prophylaxis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no prophylaxis	Risk with sucralfate				
Clinically important upper GI bleeding	Study population		RR 0.53 (0.32 to 0.88)	598 (7 RCTs)	⊕⊕⊕⊖ MODERATE ^a	
Follow-up: 15 days [†]	108 per 1000	57 per 1000 (35 to 95)				
Nosocomial pneumonia	Study population		RR 1.33 (0.86 to 2.04)	450 (4 RCTs)	⊕⊕⊖⊖ LOW ^{b,c}	
Follow-up: not reported	122 per 1000	163 per 1000 (105 to 249)				
All-cause mortality in ICU	Study population		RR 0.97 (0.66 to 1.43)	500 (5 RCTs)	⊕⊕⊖⊖ LOW ^{b,d}	
Follow-up: 15 days [†]	165 per 1000	160 per 1000 (109 to 236)				
Duration of ICU stay	Mean duration of ICU stay ranged from 8.6 to 11.1 days		-	224 (2 RCTs)	⊕⊕⊖⊖ LOW ^{b,e}	
Follow-up: not reported	MD 0.02 days lower (1.70 days lower to 1.65 days higher)					
Number of participants requiring blood transfusion	Study population		RR 0.60 (0.15 to 2.44)	200 (1 RCT)	⊕⊕⊖⊖ LOW ^{b,e}	
Follow-up: not reported	50 per 1000	30 per 1000 (8 to 122)				
Serious adverse events	Not reported					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

[†]Duration of follow-up reported in only one study.

CI: confidence interval; GI: gastrointestinal; ICU: intensive care unit; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by one level for risk of bias because of high risk of performance bias in five studies, high risk of reporting bias in one study, and high risk of other biases in one study.
^bDowngraded by one level for imprecision because 95% CI was compatible with benefit and harm.
^cDowngraded by one level for risk of bias because of high risk of performance bias in two studies.
^dDowngraded by one level for risk of bias because of high risk of performance bias in three studies.
^eDowngraded by one level for risk of bias because of high risk of performance bias in one study.

Summary of findings 6. H2 receptor antagonists compared with proton pump inhibitors for preventing upper gastrointestinal bleeding in people admitted to intensive care units

H2 receptor antagonists compared with proton pump inhibitors for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Patient or population: people admitted to intensive care units

Setting: ICU

Intervention: H2 receptor antagonists

Comparison: proton pump inhibitors

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with proton pump inhibitors	Risk with H2 receptor antagonists				
Clinically important upper GI bleeding	Study population		RR 2.90 (1.83 to 4.58)	1636 (13 RCTs)	⊕⊕⊕⊖ LOW ^{a,b}	
Follow-up: not reported	25 per 1000	73 per 1000 (46 to 115)				
Nosocomial pneumonia	Study population		RR 1.02 (0.77 to 1.35)	1256 (10 RCTs)	⊕⊕⊕⊖ LOW ^{c,d}	
Follow-up: 30 days [†]	123 per 1000	126 per 1000 (95 to 166)				
All-cause mortality in ICU	Study population		RR 0.96 (0.78 to 1.19)	1564 (12 RCTs)	⊕⊕⊕⊖ LOW ^{c,e}	
Follow-up: 30 days [†]	158 per 1000	152 per 1000 (124 to 189)				
Duration of ICU stay	Mean duration of ICU stay ranged from 7.7 to 23.6 days		-	482 (5 RCTs)	⊕⊕⊕⊖ LOW ^{c,f}	
Follow-up: not reported	MD 0.14 days higher (1.14 days lower to 1.41 days higher)					
Number of participants requiring blood transfusion	Study population		RR 1.98 (0.75 to 5.21)	575 (3 RCTs)	⊕⊕⊕⊖ MODERATE ^c	
Follow-up: not reported	17 per 1000	35 per 1000				

(13 to 91)

Serious adverse events

Not reported

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

†Duration of follow-up reported in only one study.

CI: confidence interval; GI: gastrointestinal; ICU: intensive care unit; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by one level for inconsistency because of substantial heterogeneity; $I^2 = 59\%$.

^bDowngraded by one level for risk of bias because of high risk of selection bias in one study, high risk of performance bias in five studies, high risk of detection bias in two studies, and high risk of other biases in one study.

^cDowngraded by one level for imprecision because 95% CI was compatible with benefit and harm.

^dDowngraded by one level for risk of bias because of high risk of performance bias in four studies, high risk of detection bias in two studies, and high risk of other biases in one study.

^eDowngraded by one level for risk of bias because of high risk of performance bias in five studies, high risk of attrition bias in one study, and high risk of other biases in one study.

^fDowngraded by one level for risk of bias because of high risk of performance bias in three studies, high risk of attrition bias in one study, and high risk of other biases in one study.

Summary of findings 7. H2 receptor antagonists compared with antacids for preventing upper gastrointestinal bleeding in people admitted to intensive care units

H2 receptor antagonists compared with antacids for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Patient or population: people admitted to intensive care units

Setting: ICU

Intervention: H2 receptor antagonists

Comparison: antacids

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with antacids	Risk with H2 receptor antagonists				
Clinically important upper GI bleeding	Study population		RR 0.96 (0.67 to 1.36)	1700 (16 RCTs)	⊕⊕⊕⊖ LOW ^{a,b}	
Follow-up: 25 days [†]	86 per 1000	82 per 1000				

	(57 to 117)				
Nosocomial pneumonia	Study population		RR 1.05 (0.81 to 1.36)	581 (4 RCTs)	⊕⊕⊕⊕ LOW ^{a,c}
Follow-up: 25 days [†]	280 per 1000	294 per 1000 (227 to 381)			
All-cause mortality in ICU	Study population		RR 1.01 (0.66 to 1.55)	1321 (11 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,d,e}
Follow-up: 25 days [§]	163 per 1000	165 per 1000 (108 to 253)			
Duration of ICU stay	Not reported				
Number of participants requiring blood transfusion	Study population		RR 2.49 (1.35 to 4.62)	744 (6 RCTs)	⊕⊕⊕⊕ MODERATE ^f
Follow-up: not reported	30 per 1000	75 per 1000 (41 to 139)			
Serious adverse events	Not reported				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

[†]Duration of follow-up reported in two studies.

[‡]Duration of follow-up reported in one study.

[§]Duration of follow-up reported in three studies.

CI: confidence interval; GI: gastrointestinal; ICU: intensive care unit; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by one level for imprecision because 95% CI was compatible with benefit and harm.

^bDowngraded by one level for risk of bias because of high risk of selection bias in two studies, high risk of performance bias in 12 studies, high risk of detection bias in two studies, and high risk of reporting bias in two studies.

^cDowngraded by one level for risk of bias because of high risk of selection bias in one study, high risk of performance bias in four studies, high risk of detection bias in one study, and high risk of reporting bias in one study.

^dDowngraded by one level for inconsistency because of moderate heterogeneity; $I^2 = 53\%$.

^eDowngraded by one level for risk of bias because of high risk of selection bias in two studies, high risk of performance bias in nine studies, and high risk of reporting bias in one study.

^fDowngraded by one level for risk of bias because of high risk of selection bias in one study and high risk of performance bias in four studies.

Summary of findings 8. H2 receptor antagonists compared with sucralfate for preventing upper gastrointestinal bleeding in people admitted to intensive care units

H2 receptor antagonists compared with sucralfate for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Patient or population: people admitted to intensive care units

Setting: ICU

Intervention: H2 receptor antagonists

Comparison: sucralfate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sucralfate	Risk with H2 receptor antagonists				
Clinically important upper GI bleeding	Study population		RR 1.10 (0.87 to 1.41)	3316 (24 RCTs)	⊕⊕⊕⊕ LOW ^{a,b}	
Follow-up: 15 days [†]	66 per 1000	73 per 1000 (58 to 93)				
Nosocomial pneumonia	Study population		RR 1.22 (1.07 to 1.40)	3041 (17 RCTs)	⊕⊕⊕⊕ MODERATE ^c	
Follow-up: 25 days [‡]	189 per 1000	230 per 1000 (202 to 264)				
All-cause mortality in ICU	Study population		RR 1.09 (0.95 to 1.24)	3178 (21 RCTs)	⊕⊕⊕⊕ LOW ^{a,d}	
Follow-up: 25 days [§]	204 per 1000	222 per 1000 (194 to 253)				
Duration of ICU stay	Mean duration of ICU stay ranged from 7.9 to 13.7 days		-	1791 (6 RCTs)	⊕⊕⊕⊕ VERY LOW ^{a,e,f}	
Follow-up: 2 weeks	MD 0.01 days higher (1.92 days lower to 1.95 days higher)					
Number of participants requiring blood transfusion	Study population		RR 1.25 (0.70 to 2.23)	1095 (9 RCTs)	⊕⊕⊕⊕ LOW ^{a,g}	
Follow-up: until death or discharge	35 per 1000	43 per 1000 (24 to 77)				

Serious adverse events

Not reported

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

†Duration of follow-up reported in five studies.

‡Duration of follow-up reported in three studies.

§Duration of follow-up reported in six studies.

||Duration of follow-up reported in one study.

CI: confidence interval; GI: gastrointestinal; ICU: intensive care unit; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by one level for imprecision because 95% CI was compatible with benefit and harm.

^bDowngraded by one level for risk of bias because of high risk of selection bias in one study, high risk of performance bias in 20 studies, high risk of detection bias in two studies, high risk of attrition bias in two studies, high risk of reporting bias in four studies, and high risk of other biases in two studies.

^cDowngraded by one level for risk of bias because of high risk of selection bias in two studies, high risk of performance bias in 12 studies, high risk of detection bias in one study, high risk of attrition bias in one study, and high risk of reporting bias in two studies.

^dDowngraded by one level for risk of bias because of high risk of selection bias in two studies, high risk of performance bias in 16 studies, high risk of detection bias in one study, high risk of attrition bias in two studies, high risk of reporting bias in three studies, and high risk of other biases in one study.

^eDowngraded by one level for inconsistency because of considerable heterogeneity; $I^2 = 82\%$.

^fDowngraded by one level for risk of bias because of high risk of performance bias in four studies and high risk of attrition bias in one study.

^gDowngraded by one level for risk of bias because of high risk of performance bias in eight studies, high risk of attrition bias in one study, high risk of reporting bias in one study, and high risk of other biases in one study.

Summary of findings 9. Antacids compared with sucralfate for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Antacids compared with sucralfate for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Patient or population: people admitted to intensive care units

Setting: ICU

Intervention: antacids

Comparison: sucralfate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sucralfate	Risk with antacids				
Clinically important upper GI bleeding	Study population		RR 1.00 (0.72 to 1.39)	1772 (16 RCTs)	⊕⊕⊕⊖ LOW ^{a,b}	
Follow-up: 21 days [†]	66 per 1000	66 per 1000 (47 to 91)				
Nosocomial pneumonia	Study population		RR 1.04 (0.84 to 1.30)	996 (7 RCTs)	⊕⊕⊕⊖ LOW ^{a,c}	
Follow-up: 25 days [‡]	232 per 1000	242 per 1000 (195 to 302)				
All-cause mortality in ICU	Study population		RR 1.15 (0.93 to 1.40)	1249 (11 RCTs)	⊕⊕⊕⊖ LOW ^{a,d}	
Follow-up: 25 days [†]	206 per 1000	237 per 1000 (192 to 289)				
Duration of ICU stay	Mean duration of ICU stay ranged from 10.4 to 16.8 days		-	227 (2 RCTs)	⊕⊕⊕⊖ LOW ^{a,e}	
Follow-up: not reported	MD 2.5 days lower (6.61 days lower to 1.61 days higher)					
Number of participants requiring blood transfusion	Study population		RR 0.73 (0.40 to 1.34)	667 (6 RCTs)	⊕⊕⊕⊖ LOW ^{a,f}	
Follow-up: until discharge or onset of GI bleeding [§]	52 per 1000	38 per 1000 (21 to 69)				
Serious adverse events	Not reported					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

[†]Duration of follow-up reported in four studies.

[‡]Duration of follow-up reported in two studies.

[§]Duration of follow-up reported in one study.

CI: confidence interval; GI: gastrointestinal; ICU: intensive care unit; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^aDowngraded by one level for imprecision because 95% CI was compatible with benefit and harm.

^bDowngraded by one level for risk of bias because of high risk of selection bias in three studies, high risk of performance bias in 12 studies, high risk of detection bias in one study, high risk of attrition bias in one study, high risk of reporting bias in two studies, and high risk of other biases in two studies.

^cDowngraded by one level for risk of bias because of high risk of performance bias in four studies, high risk of detection bias in one study, high risk of reporting bias in one study, and high risk of other biases in one study.

^dDowngraded by one level for risk of bias because of high risk of selection bias in three studies, high risk of performance bias in eight studies, high risk of attrition bias in one study, high risk of reporting bias in one study, and high risk of other biases in one study.

^eDowngraded by one level for risk of bias because of high risk of attrition bias in one study.

^fDowngraded by one level for risk of bias because of high risk of selection bias in one study, high risk of performance bias in six studies, and high risk of other biases in one study.

BACKGROUND

A glossary of the medical terms used in this review can be found in [Appendix 1](#).

Description of the condition

Upper gastrointestinal (GI) 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 GI mucosal injury related to the stress of being critically ill. The injury may vary from diffuse superficial ulcers to deep, bleeding 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 ([Alhazzani 2013](#); [Bardou 2015](#); [Krag 2015](#)). A study using the HEmorrhage MEasurement Tool (HEME) to assess GI bleeding in ICU patients observed that 5.2% of those with stress ulcers had major bleeds ([Arnold 2007](#)). ICU patients with major bleeding as a result of stress ulceration had mortality rates approaching 40% to 50% ([Bardou 2015](#)). Over the past few decades, however, with improved standards of care, the incidence of stress-induced GI bleeding in ICUs and related mortality has decreased ([Krag 2015](#)). Hence, 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, and profuse bleeding results in overt manifestations. [Cook 1998a](#) defined a clinically important bleed as overt bleeding with one of four features reflecting haemodynamic instability and blood loss. These include the following.

- Drop in systolic or diastolic blood pressure (blood pressure during heart contractions or between two heartbeats) of 20 mmHg or more within 24 hours after upper GI bleeding.
- Postural decrease in systolic blood pressure of 10 mmHg and accelerated pulse rate of 20 beats per minute; or evidence of significant blood loss (this may be difficult to demonstrate in intubated patients).
- A drop in haemoglobin concentration of at least 2 g/dL needing two units of packed cell transfusion within 24 hours of the bleed.
- Failure of a rise in haemoglobin concentration (in g/dL) of at least the number of units of blood transfused minus two.

Risk factors

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

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

In addition, prophylaxis is often recommended for patients who have two or more of the following risk factors for stress ulcers ([AHP 1999](#); [Pfeffer 2007](#)).

- ICU stay longer than one week.
- Sepsis or abnormally low blood pressure (hypotension).
- Failure of the liver or kidneys.
- History of peptic ulcer disease.
- Use of high-dose steroids (> 250 mg/d of hydrocortisone or equivalent).
- Burns over > 35% of total body surface area.
- Immediately after organ transplantation.
- Head trauma with Glasgow Coma Scale score < 10.
- Multiple trauma.
- Occult bleeding for six days or longer.

Pathophysiology of stress ulcers

The aetiology - cause or set of causes for a disease - and pathophysiology of stress ulcers in ICU patients appear to be multifactorial. Normally, the splanchnic microcirculation and the gastric mucosa protect the mucosal epithelium - the tissue lining the outer surface of organs - 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 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 reduced secretion of bicarbonate by the gastric mucosa with 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 upper GI bleeding

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

Complications of stress ulcer prophylaxis: ventilator-associated pneumonia

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

Risk factors for ventilator-associated pneumonia

The risk of ventilator-associated pneumonia 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 tubes passing the trachea (endotracheal) or ventilator circuits and other feeding tubes, or from improper measures to prevent nosocomial infection in ICU staff, increase the risk of ventilator-associated pneumonia ([Augustyn 2007](#); [CDC 2003](#); [Masterton 2008](#)).

The disadvantage of stress ulcer prophylaxis is that many of the interventions used for suppression of gastric acid raise the pH of gastric contents, alter gastric flora, and promote tracheobronchial colonisation and gastric colonisation of pathogenic bacteria - the aspiration of which causes nosocomial pneumonia or ventilator-associated pneumonia (Atherton 1978; Cook 1998b; Craven 1986). In addition to increasing mortality in critically ill patients, the aforementioned effects can prolong length of hospital stay and increase costs (Safdar 2005). The elevated risk of developing ventilator-associated pneumonia associated with stress ulcer prophylaxis may therefore offset the potential benefits of such therapy.

Diagnosis of ventilator-associated pneumonia

The criteria used to establish the diagnosis of ventilator-associated pneumonia vary. Traditionally, clinical features (fever, cough, and purulent sputum) combined with radiological evidence for 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 ventilator-associated pneumonia, 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 and use of protected specimen brush (PSB) specimens after bronchoalveolar lavage - a medical procedure to examine the lungs for lung disease - 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 ventilator-associated pneumonia (CDC 2003; Masterton 2008).

Criteria commonly used to diagnose ventilator-associated pneumonia include the clinical pulmonary infection score (CPIS), which 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). Criteria added to the CPIS help practitioners in selecting, modifying, and monitoring therapy, although their diagnostic accuracy is similar to that of traditional criteria (Masterton 2008).

Mortality from ventilator-associated pneumonia

Individuals who contract ventilator-associated pneumonia 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 ventilator-associated pneumonia when compared with those without ventilator-associated pneumonia (Safdar 2005).

It is considered prognostically important to distinguish early-onset from late-onset ventilator-associated pneumonia. 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 the start of mechanical ventilation. Early-

onset ventilator-associated pneumonia is usually less severe and carries a better prognosis than late-onset ventilator-associated pneumonia (Chastre 2002; Masterton 2008).

Description of the intervention

Several pharmacological interventions are used for treatment and prevention of gastric ulcers, such as those that block histamine-2 receptors (H2 receptor antagonists) (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.), and ulcer protectives (sucralfate, bismuth, etc.). Non-pharmacological interventions such as enteral nutrition and early removal of tubes can also be used.

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 mucosa, and effects on increasing gastric luminal pH and resultant potential to increase gastric bacterial colonisation, as well as 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 may reduce phosphates and cause constipation (aluminium-based antacids). Nursing costs are also increased owing to the need to administer antacids at frequent intervals (often hourly).

H2 receptor antagonists are believed to inhibit gastric acid secretion by blocking histamine receptors but have no additional cytoprotective effects and can cause thrombocytopenia, interstitial nephritis, and confusion (especially in the elderly). Rapid intravenous infusions can cause bradycardia - a slow heart rate - and abnormally low blood pressure (hypotension), and many cytochrome P-450-mediated drug interactions and effects may occur (particularly with cimetidine).

Proton pump inhibitors act by inhibiting the final stage of gastric acid production but provide no additional cytoprotective effects on the gastric mucosa and do confer cytochrome P-450-mediated effects. However, it has been found that proton pump inhibitors may be associated with increased risk of *Clostridium difficile* diarrhoea (Arriola 2016; Cunningham 2003; Kwok 2012; Mutlu 2001). Yet, randomised controlled trials (RCTs) have reported very few data on this adverse event (Alhazzani 2017).

Prostaglandin analogues inhibit acid secretion and promote mucus and bicarbonate secretion that makes gastric contents alkaline, meaning that the pH is greater than 7, but they 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 gastric acid and the gastric mucosa by coating the mucosa. These agents have additional cytoprotective effects and do not effectively alter gastric pH, but they may cause constipation and may interfere with the absorption of certain antibacterial agents, such as tetracyclines and quinolones (Mutlu 2001).

Enteral nutrition may be delivered orally or through a feeding tube and 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 providing stress ulcer prophylaxis, although it may raise gastric pH and theoretically increase rates of nosocomial infection 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 of these patients will develop clinically important bleeding, and the mortality rate in such patients is high (48.5% to 65%). Several RCTs, non-randomised studies, and cohort studies have studied the role of different stress ulcer prophylactic drugs and strategies for prevention of stress ulcers and thereby upper GI bleeding. Stress ulcer prophylaxis is, however, a risk factor for the development of ventilator-associated pneumonia. Thus the benefits of stress ulcer prophylaxis need to be balanced against this risk.

Previous systematic reviews and meta-analyses were narrowed to comparisons of two interventions, were inconclusive, or generated conflicting results (Cook 1994b; Cook 1995b; Cook 1996; Lin 2010; Messori 2000). These systematic reviews did not include commonly used proton pump inhibitors. Several more recent systematic reviews investigated the risk-benefit profile of bleeding prophylaxis in ICU patients (Alquraini 2017; Alshamsi 2016; Krag 2014; Pilkington 2012). They most often investigated the effects of a single drug class versus another drug class.

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

A guideline for stress ulcer prophylaxis in the intensive care unit provided by the Danish Society of Anesthesiology and Intensive Care Medicine recommended, first, that stress ulcer prophylaxis should not be used as a routine measure in all critically ill patients and, second, that proton pump inhibitors should be used over H2 receptor antagonists (Rorbaek Madsen 2014).

A guideline from 1999 released by the American Society of Health-System Pharmacists recommended that antacids, H2 receptor antagonists, or sucralfate should be administered to prevent stress ulcers in adults (Armstrong 1999). An updated version of the guideline is expected in 2018. The Eastern Association for the Surgery of Trauma released a guideline in 2008 that recommended use of H2 receptor antagonists, cytoprotective agents, and some proton pump inhibitors as prophylactic treatment against stress ulcers and recommended against use of antacids (Guillamondegui 2008).

Still, a review of current evidence on different pharmacological and non-pharmacological interventions for prophylaxis of upper GI bleeding comparing them versus no active treatment or other active treatments is needed to provide a comprehensive and systematic overview of the research evidence and the benefits and harms of bleeding prophylaxis in patients admitted to the ICU.

OBJECTIVES

To assess the effect and the risk-benefit profile of interventions used to prevent upper GI bleeding in people admitted to level two and level three ICUs. These levels include all sick patients requiring support for organ failure/dysfunction in the ICU (Goldhil 2002).

- Level two ICUs are for patients requiring detailed observation or intervention including support for a single failing organ system or postoperative care and patients stepping down from higher levels of care.
- Level three ICUs are for patients requiring advanced respiratory support alone or basic respiratory support together with support for at least two organ systems.

METHODS

Criteria for considering studies for this review

Types of studies

We followed methods as described in the review protocol (George 2010). We included randomised controlled trials (RCTs) and quasi-randomised controlled studies.

Types of participants

People (any age and gender) admitted to level two or level three ICUs for longer than 48 hours. We excluded studies in which participants were admitted to the ICU primarily for management of upper GI bleeding.

Types of interventions

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

Drugs that reduce gastric acid secretion

- H2 receptor antagonists: ranitidine, cimetidine, famotidine, roxatidine, nizatidine, loxatidine, etc.
- Proton pump inhibitors: esomeprazole, rabeprazole, omeprazole, lansoprazole, pantoprazole, dexlansoprazole, etc.
- Prostaglandin analogues: misoprostol, enprostil, rioprostil, etc.
- Anticholinergics: pirenzepine, propantheline, oxyphenonium, doxepin, trimipramine, etc.
- Potassium-competitive acid blockers

Drugs that neutralise gastric acid (antacids)

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

Ulcer protectives

- Sucralfate
- Colloidal bismuth subcitrate

Ulcer healing drugs

- Carbenoxolone sodium, deglycyrrhizinated liquorice

Others

- Enteral and parenteral nutrition
- Any other intervention used to reduce upper GI bleeding
- Combinations of interventions (e.g. omeprazole-bicarbonate combinations)
- No prophylaxis
- Placebo

We compared each class of drugs versus placebo or no prophylaxis (e.g. H2 receptor antagonists vs placebo or no prophylaxis), and we compared all classes of drugs against one another (e.g. H2 receptor antagonists vs proton pump inhibitors). We did not compare different drugs within a single class versus one another (e.g. ranitidine vs cimetidine) because this type of comparison did not fall within the focus of this review.

Types of outcome measures

Primary outcomes

Clinically important GI bleeding

- For the purposes of this review, we used the definition used by study authors to define clinically important upper GI bleeding. We recorded details of the definition used

Secondary outcomes

Nosocomial pneumonia

- Nosocomial pneumonia including ventilator-associated pneumonia is defined as pneumonia contracted in a hospital (nosocomial) by a patient on mechanical ventilatory support (by endotracheal tube or tracheostomy) for longer than 48 hours (Masterton 2008; Mayhall 2001)
- Criteria used in the review for the diagnosis of ventilator-associated pneumonia will be those used by study authors. This outcome also includes incidence of nosocomial pneumonia because definitions used varied across study reports

Mortality

- All-cause mortality in ICU
- All-cause mortality in hospital

Duration of ICU stay

Duration of intubation

- This also includes duration of mechanical ventilation because definitions varied across study reports.

Blood transfusion

- Number of participants requiring transfusion
- Number of units of blood transfused

Adverse events of interventions

- Serious adverse events leading to discontinuation of treatment, prolongation of ICU stay, or disability
- Any other adverse event (e.g. thrombocytopenia related to H2 receptor antagonists, any other adverse event).

Search methods for identification of studies

We attempted to identify all relevant RCTs and quasi-randomised studies (in which allocation to interventions was attempted but could be predicted) for inclusion, regardless of date or language of publication or publication status (published, unpublished, or in press) We also looked for ongoing studies.

We excluded non-randomised studies.

Electronic searches

With the help of the Cochrane Information Specialist, we searched the following databases up to 23 August 2017, using the search terms listed in [Appendix 2](#): MEDLINE; Embase; the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (2017, Issue 8); the Cochrane Upper Gastrointestinal and Pancreatic Disease Group Specialised Register; and Latin American Caribbean Health Sciences Literature (LILACS).

Searching other resources

We searched the reference lists of all included studies and of relevant systematic reviews and meta-analyses to identify relevant studies. We also searched the World Health Organization (WHO) International Clinical Trials Registry Platform search portal (<http://apps.who.int/trialsearch/>) for ongoing clinical studies up to 23 August 2017. In addition, we searched all available conference proceedings until 2012 for relevant RCTs from the World Federation of Societies of Intensive and Critical Medicine (<http://www.world-critical-care.org/>) and the World Gastroenterology Organisation (<http://www.worldgastroenterology.org/about-wgo.html>) websites. We contacted individual researchers working in this field, as well as organisations and pharmaceutical companies, to identify unpublished and ongoing studies.

Data collection and analysis

Selection of studies

Two review authors from a pool of four (ATG, IT, LEF, and RK) independently screened each citation and abstract yielded by the search strategy to identify potentially eligible studies. Two review authors from a pool of four (IT, LEF, PT, and JVP) independently checked the list of excluded studies to verify the appropriateness of reasons for their exclusion. We obtained and assessed full reports of potentially eligible studies for inclusion in the review based on the inclusion and exclusion criteria. If eligibility was unclear because information was inadequate or unclear, we attempted to contact study authors for clarification. Two review authors (IT, JJM) arranged for abstracts of articles written in non-English languages to be translated for assessment against inclusion. We resolved disagreements through discussion and scrutinised each

study report to ensure that RCTs with multiple publications were included only once by linking additional reports to the original study report included in the reference list of included studies. We documented reasons for exclusion of studies in the [Characteristics of excluded studies](#) tables.

Data extraction and management

Two review authors from a pool of four (IT, LEF, ATG, and RK) independently extracted data from studies using pre-tested data extraction forms. We resolved disagreements related to data extraction by referring to the study report and by having discussions. When available, we extracted data on the following.

Population characteristics

Type of ICU care (level two or three); inclusion and exclusion criteria for participants, as well as their age and gender and the number of participants randomised to each group and included in the study overall.

Interventions

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

Outcomes

Definitions or criteria used for the diagnosis of clinically significant upper GI bleeding (and the source of bleeding), pneumonia (and types of pathogens and sensitivity patterns, if available) and ventilator-associated pneumonia; number of participants experiencing each outcome; and numbers of dropouts and withdrawals with reasons. When data were insufficient or missing, we attempted to contact the study authors.

For continuous outcomes, we extracted arithmetic mean values, standard deviations, and number of participants in each study arm for whom the outcome was assessed. We noted whether numbers assessed in the study were the numbers of participants who completed the study or the numbers randomised. If medians were reported, we attempted to extract ranges or interquartile ranges.

Assessment of risk of bias in included studies

Two review authors from a pool of six (IT, LEF, ATG, RK, PT, and JVP) independently assessed the risk of bias of each included study. We resolved disagreements by referring to the study report, by corresponding with the authors of the report, and by having discussions. We assessed 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. We judged the risk of bias as 'high', 'low', or 'unclear', using guidelines ([Higgins 2011](#)) to make these judgements. We recorded this information for each included study in a 'Risk of bias' table in [Review Manager \(RevMan\) 5.2](#) and summarised the risk of bias for each study in a summary figure and graph. We classified a study's overall risk of bias as high if the study had high risk of bias in any domain. Likewise, we classified the risk of bias as unclear if the study had no high risk of bias and had unclear risk of bias in any domain. Last, we classified a study's overall risk of bias as low if the study had low risk of bias in all domains.

We judged all included studies as being at low risk for detection bias for objectively determined outcomes of 'clinically important GI bleeding' and 'nosocomial pneumonia' if detected through a clear definition mentioned in the study, or if blinding of outcome assessors was clearly described. For other outcomes of interest, we judged the studies as having low risk of detection bias if these outcomes were mainly objective in nature. We judged studies as having unclear risk of detection bias on an outcome basis if they did not address upper GI bleeding or nosocomial pneumonia.

We classified studies that did not include a placebo arm and used different modes of administering study interventions as having high risk of performance bias, as it would not have been possible to blind study personnel and participants.

Measures of treatment effect

We used risk ratios for dichotomous outcomes and mean differences for continuous outcomes, with their respective 95% confidence intervals.

Unit of analysis issues

When outcomes were reported both at baseline and at follow-up or at study endpoints, we used endpoint data preferentially over scores of the mean change from baseline because the standard deviation of this mean change for each treatment group often was not reported. Had only change scores been available from any study, we would have combined endpoint and change scores.

If studies had reported count data, we would have extracted the total number of events in each group, the total extent of person-time at risk in each group, and the total number of participants in each group. If this information had not been available, we would have attempted to extract alternative summary statistics such as rate ratios and confidence intervals, if available. If count data had been presented as dichotomous outcomes, we would have extracted 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 were presented as continuous outcomes or as time-to-event outcomes, we would have attempted to extract the same information as outlined for continuous and time-to-event outcomes.

In case we would have identified any cluster-randomised studies, and if their results had been adjusted for clustering, we would have combined the adjusted measures of effects. If results were not adjusted for clustering, we would have attempted to adjust the results by multiplying standard errors of the estimates by the square root of the design effect when the design effect was calculated as $DEff = 1 + (M - 1) ICC$, where M is the average cluster size and ICC is the intracluster coefficient. If this was not possible, we would not have combined them in a meta-analysis but would have presented these results in an additional table.

Dealing with missing data

We attempted to obtain missing data from study authors. When possible, we extracted data to allow an intention-to-treat analysis in which all randomised participants would be analysed in the groups to which they were originally assigned. Our primary analysis was a complete case analysis. If we noted a discrepancy in the numbers randomised and the numbers analysed for each treatment group, we calculated the percentage lost to follow-up

in each group and reported this information. If dropouts exceeded 10% for any study, we assigned the worst outcome to those lost to follow-up for dichotomous outcomes and assessed the impact of this by performing sensitivity analyses.

For continuous data that were missing standard deviations, we calculated these from other available data such as standard errors, or we imputed them using the methods suggested in [Deeks 2011](#). We did not make any assumptions about loss to follow-up for continuous data, and we will analyse results for those who complete the study.

Assessment of heterogeneity

We assessed heterogeneity between studies by visually examining the forest plot to check for overlapping confidence intervals and by using the χ^2 test for homogeneity with a 10% level of significance and the I^2 statistic. Although we acknowledge that this cutoff is arbitrary, we interpreted I^2 values from 0% to 40% as possibly not important, from 30% to 60% as moderate heterogeneity, from 50% to 90% as substantial heterogeneity, and from 75% to 100% as considerable heterogeneity, depending on whether inconsistency in results was due to differences in the direction of effect estimates between studies rather than to differences in the magnitude of effect estimates favouring an intervention, as well as the strength of evidence for heterogeneity seen in the P value for the χ^2 test for heterogeneity ([Deeks 2011](#)).

Assessment of reporting biases

Apart from assessing the risk of selective outcome reporting considered under [Assessment of risk of bias in included studies](#), we assessed the likelihood of potential publication bias by using funnel plots, provided that at least 10 studies were included in a meta-analysis.

Data synthesis

We first compared interventions used to prevent upper GI bleeding versus placebo or no intervention in people admitted to intensive care units. We stratified analyses according to drug class of the active intervention used versus placebo or no treatment. We included three-armed studies in these comparisons by splitting the comparison arm in two, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). We then compared specific interventions or combinations of interventions grouped under drug classes. For three-armed studies, we considered only the two relevant arms in comparisons of drug classes.

We synthesised comparable data using the Mantel-Haenszel method to derive pooled, weighted risk ratios in fixed-effect meta-analyses. We combined continuous data summarised by arithmetic means and standard deviations using the weighted mean difference. We used the random-effects model for data synthesis when we identified heterogeneity as significant (see above) and found that it could not be explained by subgroup analyses (see below).

Had continuous data been summarised using geometric means, we would have combined them on the log scale using the generic inverse variance method and would have reported them on the natural scale. We would have compared count data using rate ratios when the total number of events in each group and the

total extent of person-time at risk in each group were available, or by using relative risks or weighted mean differences when data were presented in dichotomous or continuous form, respectively. We would have combined hazard ratios from survival data on the log scale by using the inverse variance method and would have presented them on the natural scale.

Subgroup analysis and investigation of heterogeneity

If data permitted, we intended to carry out the following subgroup analyses for each comparison.

- 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).
- Pneumonia at the time of ICU admission.
- Adults (≥ 18 years to 65 years) versus older adults (≥ 65 years) versus children and adolescents (< 18 years).
- Use of co-interventions that may affect outcomes (e.g. enteral feeds, prophylactic antibiotics, other measures used for selective decontamination of the digestive tract (SDD)).

For the outcome of nosocomial pneumonia, we planned to further subgroup data by development of early-onset nosocomial pneumonia (within four days on ventilation) or late-onset nosocomial pneumonia (five or more days on ventilation), or by rating data as unclear (if this subgrouping is not possible by using information in the report or by contacting study authors). We identified no studies within the same comparison that distinguished between early and late onset of pneumonia and determined that a subgroup analysis was not feasible.

Sensitivity analysis

We conducted sensitivity analyses to investigate robustness of results for the primary outcome by evaluating outcomes in studies with low risk of bias versus outcomes in studies with high or unclear risk of bias. We also undertook sensitivity analyses if studies reported dropout rates of 10% or greater, to ascertain differences in outcomes of intention-to-treat (ITT) analysis and analysis of completers. We assessed robustness of results using published and validated criteria to diagnose clinically important bleeding and nosocomial pneumonia.

Summarising results

We imported data for the following outcomes from [Review Manager \(RevMan\) 5.2](#) into the Guideline Development Tool ([GRADEpro 2015](#)) and used this information to construct 'Summary of findings' (SoF) tables and to guide the conclusions of this review. We considered the following outcomes as critically important or important for clinical decisions for inclusion in these summary tables.

- Clinically important upper GI bleeding.
- Nosocomial pneumonia.
- All-cause mortality in ICU.
- Duration of ICU stay.
- Number of participants requiring blood transfusions.
- Serious adverse events.

RESULTS

Description of studies

See [Characteristics of included studies](#), [Characteristics of excluded studies](#), [Characteristics of ongoing studies](#), and [Characteristics of studies awaiting classification](#).

Results of the search

We retrieved 2802 records through database searching between July 2010 and August 2017. We identified 43 additional records

from other sources, which included review of our personal files and records, correspondence with experts in the field, and review of bibliographies of review articles. After resolving duplicates, the final list included 2292 records. After discarding reports that clearly were not relevant, we identified 199 records as potentially eligible for inclusion. In the end, we included in the review 129 records reporting on 121 studies, of which 12 were ongoing studies and two were awaiting classification. We excluded 71 records. The process of study selection is described in [Figure 1](#).

Figure 1. PRISMA flow chart of included studies.

Included studies

We have described in the [Characteristics of included studies](#) tables the 107 completed studies that met the inclusion criteria for this review and have summarised them below. All studies took place in an ICU setting and included critically ill adults or children or both.

Participants, interventions, and comparisons

The 107 studies randomised a total of 15,057 participants to 27 comparisons involving 14 different treatment modalities. Most studies specifically mentioned that they randomised individuals who had no history of GI haemorrhage or peptic ulcer or gastritis or were not undergoing treatments for any of these conditions. The included studies included participants admitted to intensive care units, although the level of ICU into which participants were admitted was not clearly mentioned. Neither was a duration of ICU admission ≥ 48 hours - a necessary inclusion criterion across studies. Among the included studies were five exclusively paediatric studies ([Behrens 1994](#); [Kuusela 1997](#); [Lacroix 1986](#); [Lopez-Herce 1992](#); [Yildizdas 2002](#)); six quasi-randomised studies ([Borrero 1984](#); [Borrero 1985](#); [Borrero 1986](#); [Brophy 2010](#); [Martin 1980](#); [Weigelt 1981](#)); and seven studies reported as conference abstracts only ([Fink 2003](#); [Fogas 2013](#); [Larson 1989](#); [Luk 1982](#); [Phillips 1998](#); [Selvanderan 2016](#); [Wee 2013](#)).

Interventions versus placebo or no prophylaxis

We included a total of 32 studies involving 2151 individuals in any interventional arm (H2 receptor antagonists, antacids, sucralfate, proton pump inhibitors, prostaglandin analogues, or anticholinergics) ($n = 1249$) or in the placebo or no prophylaxis arms ($n = 902$).

H2 receptor antagonists versus placebo or no prophylaxis

We included a total of 26 studies involving 2210 individuals in the H2 receptor antagonist (ranitidine, cimetidine, or famotidine) arm ($n = 1123$) or in the placebo or no prophylaxis arm ($n = 1087$) ([Apte 1992](#); [Basso 1981](#); [Ben-Menachem 1994](#); [Burgess 1995](#); [Chan 1995](#); [Darloug 2003](#); [Friedman 1982](#); [Groll 1986](#); [Halloran 1980](#); [Hanisch 1998](#); [Kantorova 2004](#); [Karlstadt 1990](#); [Kaushal 2000](#); [Lacroix 1986](#); [Larson 1989](#); [Lopez-Herce 1992](#); [Luk 1982](#); [Martin 1993](#); [Metz 1993](#); [Peura 1985](#); [Powell 1993](#); [Reusser 1990](#); [Rohde 1980](#); [van den Berg 1985](#); [Yildizdas 2002](#); [Zinner 1981](#)). Enteral feeding/nasogastric feeding/parenteral feeding was administered to many participants in the following studies: [Apte 1992](#); [Ben-Menachem 1994](#); [Darloug 2003](#); [Halloran 1980](#); [Kantorova 2004](#); [Karlstadt 1990](#); [Martin 1993](#); [Peura 1985](#); and [van den Berg 1985](#).

Proton pump inhibitors versus placebo or no prophylaxis

We included a total of five studies randomising 482 individuals to a proton pump inhibitor (omeprazole or pantoprazole) ($n = 141$) or to placebo or no prophylaxis ($n = 133$) ([Ali 2016](#); [Kantorova 2004](#); [Powell 1993](#); [Selvanderan 2016](#); [Yildizdas 2002](#)). Enteral feeds were administered alone in [Kantorova 2004](#). [Selvanderan 2016](#) did not report how many participants were randomised to each arm, so we were unable to add a total of 214 participants to the total numbers of participants in respective study arms.

Proton pump inhibitors plus sucralfate versus no prophylaxis

One study randomised 80 participants to receive proton pump inhibitors (omeprazole or lansoprazole) plus sucralfate ($n = 40$)

or no prophylaxis ($n = 40$). Participants who did not receive prophylaxis did receive enteral nutrition ([Fang 2014](#)).

Prostaglandin analogues versus placebo or no prophylaxis

One study randomised 58 individuals to receive either a prostaglandin analogue ($n = 29$) or placebo ($n = 29$) ([van Essen 1985](#)).

Anticholinergics versus placebo or no prophylaxis

A total of two studies involving 131 individuals who received an anticholinergic ($n = 59$) or a placebo or no prophylaxis ($n = 72$) were included in the analysis ([Hanisch 1998](#); [Krakamp 1989](#)). Ranitidine was administered to both arms in one study ([Krakamp 1989](#)).

Antacids versus placebo or no prophylaxis

A total of eight studies involving a total of 774 individuals in the antacid arm ($n = 386$) or placebo or no prophylaxis arm ($n = 388$) were included in the analysis ([Basso 1981](#); [Friedman 1982](#); [Hastings 1978](#); [Lopez-Herce 1992](#); [Luk 1982](#); [Maddougall 1977](#); [Pinilla 1985](#); [Zinner 1981](#)).

Sucralfate versus placebo or no prophylaxis

A total of seven studies involving a total of 598 individuals in the sucralfate arm ($n = 302$) and in the placebo or no prophylaxis arm ($n = 296$) were included in the analysis ([Ben-Menachem 1994](#); [Darloug 2003](#); [Eddleston 1994](#); [Kantorova 2004](#); [Kaushal 2000](#); [Lopez-Herce 1992](#); [Yildizdas 2002](#)). Enteral feeds/nasogastric feeding/parenteral feeds were administered to many participants in the following studies: [Ben-Menachem 1994](#) and [Kantorova 2004](#).

Interventions compared with one another

H2 receptor antagonists versus proton pump inhibitors

We included a total of 20 studies involving 2370 individuals given H2 receptor antagonists (ranitidine, cimetidine, or famotidine) ($n = 1037$) or proton pump inhibitors (esomeprazole, omeprazole, rabeprazole, or pantoprazole) ($n = 1333$) ([De Azevedo 2000](#); [Bashar 2013](#); [Brophy 2010](#); [Conrad 2005](#); [Fink 2003](#); [Fogas 2013](#); [Hata 2005](#); [Kantorova 2004](#); [Lee 2014](#); [Levy 1997](#); [Maasoumi 2016](#); [Ng 2012](#); [Phillips 1998](#); [Powell 1993](#); [Solouki 2009](#); [Somberg 2008](#); [Tabeeffar 2012](#); [Terzi 2009](#); [Wee 2013](#); [Yildizdas 2002](#)). Enteral feeds/nasogastric feeding/parenteral feeds were administered to many participants in the following studies: [Brophy 2010](#), [Conrad 2005](#), [Kantorova 2004](#), [Solouki 2009](#), and [Somberg 2008](#). [Somberg 2008](#) randomised participants to four different intermittent dosing regimens of pantoprazole. These arms were combined to form a common interventional arm versus the H2 receptor antagonist, as the review did not aim to investigate efficacy of the same drug based on dose or mode of administration. [Fogas 2013](#) did not report details on the H2 receptor antagonist and proton pump inhibitor used. One study did not report any outcomes of relevance for this review ([Tabeeffar 2012](#)).

H2 receptor antagonists versus antacids

We included a total of 18 studies involving 1795 individuals in H2 receptor antagonist (ranitidine, cimetidine, or famotidine) ($n = 957$) or antacid interventional arms ($n = 835$) ([Basso 1981](#); [Cannon 1987](#); [Friedman 1982](#); [Kingsley 1985](#); [Lamothe 1991](#); [Lopez-Herce 1992](#); [Luk 1982](#); [Martin 1980](#); [Noseworthy 1987](#); [Poleski 1986](#); [Priebe 1980](#); [Prod'hom 1994](#); [Simms 1991](#); [Stothert 1980](#); [Thomason 1996](#); [Tryba 1985](#); [Weigelt 1981](#); [Zinner 1981](#)). [Tryba 1985](#) administered 50 mg

of pirenzepine daily to all randomised participants. Enteral feeds were administered to many participants (Cannon 1987; Simms 1991; Tryba 1985). Lamothe 1991 included four arms (ranitidine, cimetidine, famotidine, and antacids); H2 receptor antagonists were combined to form a common interventional arm versus antacids, as the review did not aim to investigate intraclass efficacy among included interventions.

H2 receptor antagonists versus sucralfate

We included a total of 26 studies involving 3352 individuals given H2 receptor antagonists (ranitidine, cimetidine, or famotidine) (n = 1772) or sucralfate (n = 1647) (Ben-Menachem 1994; Cannon 1987; Cook 1998; Darlong 2003; De Azevedo 2000; Eddleston 1991; Fabian 1993; Kantorova 2004; Kappstein 1991; Kaushal 2000; Laggner 1988; Laggner 1989; Lopez-Herce 1992; Maier 1994; Mustafa 1994; Ortiz 1998; Pickworth 1993; Prakash 2008; Prod'hom 1994; Ruiz-Santana 1991; Ryan 1993; Simms 1991; Stoehr 2006; Thomason 1996; Tryba 1985; Yildizdas 2002). Tryba 1985 administered 50 mg of pirenzepine daily to all randomised participants. Enteral feeds/nasogastric feeding/parenteral feeds were administered to many participants in the following studies: Ben-Menachem 1994, Cannon 1987, Cook 1998, Kantorova 2004, Mustafa 1994, Prod'hom 1994, Ruiz-Santana 1991, Simms 1991, and Tryba 1985. Two studies randomised participants to more than one arm of H2 receptor antagonists (cimetidine bolus and continuous infusion) (Fabian 1993; Ortiz 1998). These arms were combined to form a common interventional arm versus sucralfate, as the review did not aim to investigate efficacy of the same drug based on dose or mode of administration.

H2 receptor antagonists versus anticholinergics

A total of four studies involved 599 individuals given H2 receptor antagonists (ranitidine or famotidine) (n = 307) or anticholinergics (n = 292) (Barandun 1985; Behrens 1994; Hanisch 1998; Tryba 1988). Parenteral nutrition was given at the time of endoscopy to participants in the second study alone.

H2 receptor antagonists versus prostaglandin analogues

One study randomised 127 individuals to receive H2 receptor antagonists (cimetidine) (n = 64) or a prostaglandin analogue (misoprostol) (n = 63) (Martin 1992).

H2 receptor antagonists versus teprenone

One study randomised 140 individuals to receive ranitidine (n = 70) or teprenone (n = 70) (Hata 2005).

H2 receptor antagonist + antacids versus sucralfate

A total of three studies involving 281 individuals in an interventional arm that combined H2 receptor antagonists with antacids (n = 144) or in the sucralfate arm (n = 137) were included in the analysis (Cioffi 1994; Driks 1987; Sirvent 1994). Enteral feeding/parenteral nutrition was administered in Cioffi 1994 and Sirvent 1994. Conventional therapy with antacids, H2 receptor antagonists (cimetidine or ranitidine), or both was administered in Driks 1987; cimetidine was given in the first study and ranitidine in the third study.

Proton pump inhibitors versus teprenone

Hata 2005 randomised 140 individuals to receive rabeprazole (n = 70) or teprenone (n = 70).

Proton pump inhibitors plus naloxone versus naloxone

He 2017 randomised 120 participants to receive pantoprazole plus naloxone (n = 60) or naloxone alone (n = 60).

Proton pump inhibitors versus other medication

Lin 2016 randomised 120 individuals to receive lansoprazole (n = 60) or another medication not further specified (n = 60).

Antacids versus prostaglandin analogues

Skillman 1984 and Zinner 1989, which included 417 individuals in the antacid arm (n = 206) or the prostaglandin analogue arm (n = 211), were included in the analysis.

Antacids versus sucralfate

We included a total of 16 studies involving 1772 individuals given antacids (n = 884) or sucralfate (n = 888) (Bonten 1995; Borrero 1984; Borrero 1985; Borrero 1986; Bresalier 1987; Cannon 1987; Ephgrave 1998; Israsena 1987; Kitler 1990; Lopez-Herce 1992; Mahul 1992; Prod'hom 1994; Simms 1991; Thomason 1996; Tryba 1987; Tryba 1985). Tryba 1985 administered 50 mg of pirenzepine daily to all randomised participants. Enteral feeds/nasogastric feeding/parenteral feeds were administered to many participants in the following studies: Bonten 1995, Cannon 1987, Ephgrave 1998, Mahul 1992, Prod'hom 1994, Simms 1991, and Tryba 1985.

Antacids versus bioflavonoids

Kitler 1990 randomised 198 individuals to receive an antacid (n = 113) or a bioflavonoid ('Maciadanol') (n = 85).

Sucralfate versus proton pump inhibitors

We included a total of four studies involving a total of 424 individuals given sucralfate (n = 205) and a proton pump inhibitor (omeprazole, pantoprazole) (n = 219) (De Azevedo 2000; Kantorova 2004; Khorvash 2014; Yildizdas 2002). Enteral feeds/nasogastric feeding/parenteral feeds were administered to many participants in one study (Kantorova 2004).

Sucralfate versus bioflavonoids

Kitler 1990 randomised 198 individuals to receive sucralfate (n = 113) or a bioflavonoid ('Maciadanol') (n = 85).

Non-pharmacological interventions

Total parenteral nutrition versus any other interventions plus total parenteral nutrition

Ruiz-Santana 1991 randomised 73 individuals to receive total parenteral nutrition (n = 30), total parenteral nutrition plus ranitidine (n = 24), or total parenteral nutrition plus sucralfate (n = 19).

Bowel stimulation protocol versus no prophylaxis

Wang 2015 randomised 100 individuals to receive treatment through a bowel stimulation protocol including abdominal massage, rectal digital stimulation, and enema (n = 50) or no prophylaxis (n = 50).

Nasogastric nutrition versus nasogastric nutrition

Davies 2012 randomised 180 individuals to nasogastric (n = 91) or nasogastric nutrition (n = 89).

Enteral plus parenteral nutrition versus other nutrition regimens

Fan 2016 randomised 120 evenly to receive enteral plus parenteral nutrition or enteral nutrition alone or parenteral nutrition alone.

Funding sources

Most study reports that included information about funding sources mentioned that researchers had received funding from pharmaceutical companies that were involved in production of the tested interventions (23 studies). A total of 17 studies reported institutional funding from, for example, the hospitals involved in the study. Sixty studies provided no information about funding.

Excluded studies

We excluded 71 records from the review mainly for these reasons: 30 studies assessed the efficacy of drugs within the same class, 15 studies were not RCTs, participants in 15 studies were not admitted to the ICU or had an indication that did not fit our inclusion criteria, six studies assessed no health outcomes that were of relevance for the review, and five studies did not take place in an ICU setting. We

have mentioned the reasons for exclusion more elaborately under [Characteristics of excluded studies](#).

Ongoing studies

We retrieved 12 ongoing studies that might be relevant to this review and will be included in the next update.

Studies awaiting classification

We were unable to obtain the full text of two studies and classified them as studies awaiting classification (Labattut 1992; Morris 2001).

We retrieved from study registries 12 studies that were ongoing or finished with no publication identified (ACTRN12616000481471; EUCTR2015-000318-24-DK; EudraCT 2007-006102-19; IRCT201104134578N2; ISRCTN12845429; Krag 2016; NCT00590928; NCT00702871; NCT02157376; NCT02290327; NCT02718261; NCT03098537).

Risk of bias in included studies

Assessments regarding risk of bias for all included studies are depicted in [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding (detection bias): Clinically important upper GI bleeding	Blinding (detection bias): Nosocomial pneumonia	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ali 2016	?	?	?	+	?	+	-	+	?
Apte 1992	?	?	-	+	+	+	+	+	+
Barandun 1985	?	?	+	?	?	+	-	?	+
Bashar 2013	+	?	+	?	+	+	+	+	+
Basso 1981	?	?	-	+	?	?	?	?	?
Behrens 1994	?	?	?	?	?	?	+	+	?
Ben-Menachem 1994	+	+	-	+	+	+	+	+	+
Bonten 1995	?	?	+	?	+	+	+	+	+
Borrero 1984	-	-	-	+	?	?	+	+	+
Borrero 1985	-	-	-	+	?	+	+	+	+
Borrero 1986	-	-	-	+	?	?	+	+	+
Bresalier 1987	?	?	-	+	?	?	+	?	-
Brophy 2010	-	-	-	+	?	+	+	+	+
Burgess 1995	+	?	+	+	?	?	+	+	+
Cannon 1987	+	?	-	+	?	?	+	+	+
Chan 1995	?	?	+	+	?	?	+	-	+
Cioffi 1994	?	?	-	+	+	?	+	+	+
Conrad 2005	?	?	+	+	+	+	+	+	?
Cook 1998	+	+	+	+	+	+	+	+	+

Figure 3. (Continued)

Cook 1998	+	+	+	+	+	+	+	+	+
Darlong 2003	?	?	-	+	?	+	+	+	-
Davies 2012	+	+	-	+	+	+	+	+	+
De Azevedo 2000	?	?	?	?	?	+	+	+	+
Driks 1987	?	?	-	+	+	+	+	+	+
Eddleston 1991	+	?	-	+	+	+	+	+	+
Eddleston 1994	+	?	?	+	+	+	+	+	+
Ephgrave 1998	+	+	+	+	+	+	+	+	+
Fabian 1993	+	?	-	+	+	+	-	+	+
Fan 2016	-	?	?	?	?	?	?	+	+
Fang 2014	+	?	?	?	?	?	+	+	+
Fink 2003	?	?	-	+	?	+	?	+	+
Fogas 2013	?	?	+	-	+	?	?	+	?
Friedman 1982	?	?	+	+	?	+	+	+	+
Groll 1986	?	?	+	+	?	+	?	+	+
Halloran 1980	?	+	+	+	?	+	+	+	+
Hanisch 1998	+	+	+	+	+	+	-	+	+
Hastings 1978	+	?	-	-	?	+	+	+	+
Hata 2005	?	?	?	-	?	+	+	+	+
He 2017	?	?	?	-	?	?	?	+	?
Israsena 1987	+	?	?	?	+	?	-	+	+
Kantorova 2004	+	+	?	+	+	+	+	+	+
Kappstein 1991	-	?	+	+	+	-	+	+	+
Karlstadt 1990	?	?	?	+	-	?	+	+	+
Kaushal 2000	?	?	-	+	?	+	+	+	+
Khorvash 2014	-	-	+	?	+	?	-	?	+
Kingsley 1985	?	?	?	+	?	+	+	+	+
Kitler 1990	+	?	-	+	?	+	?	+	+
Krakamp 1989	?	?	+	+	-	+	+	+	+
Kuusela 1997	+	+	+	+	?	+	+	+	+
Lacroix 1986	-	?	+	+	?	?	+	+	-

Figure 3. (Continued)

Lacroix 1986	+	?	+	+	?	?	+	+	+
Laggner 1988	?	?	-	+	?	+	+	-	+
Laggner 1989	?	?	-	-	+	+	+	+	+
Lamothe 1991	?	?	?	+	?	?	?	?	+
Larson 1989	?	?	+	+	?	+	+	+	-
Lee 2014	?	?	+	+	+	?	+	+	+
Lew 1997	?	?	-	+	-	+	+	+	-
Lin 2016	-	?	?	+	+	?	+	+	+
Lopez-Herce 1992	?	?	-	+	-	+	+	-	+
Luk 1982	?	?	+	+	?	+	+	+	+
Maasoumi 2016	?	?	-	?	?	?	+	?	?
Macdougall 1977	?	?	-	+	?	+	+	-	-
Mahul 1992	?	?	?	?	+	+	+	+	-
Maier 1994	?	?	-	+	+	+	+	+	+
Martin 1980	-	-	-	+	?	+	+	+	+
Martin 1992	?	?	+	+	?	+	+	+	+
Martin 1993	?	+	+	+	+	+	+	+	+
Metz 1993	+	?	+	+	+	+	+	+	+
Mustafa 1994	?	?	-	?	+	+	+	+	+
Ng 2012	+	+	+	+	?	+	+	+	+
Noseworthy 1987	+	+	-	-	?	+	+	+	+
Ortiz 1998	+	?	-	+	?	+	+	-	-
Pan 2004	?	?	+	-	?	+	+	+	+
Peura 1985	?	?	+	+	?	+	+	+	+
Phillips 1998	?	?	-	-	-	+	?	+	+
Pickworth 1993	-	?	+	+	+	?	+	+	+
Pinilla 1985	?	?	?	+	?	?	?	?	+
Poleski 1986	?	?	-	+	?	+	+	+	+
Powell 1993	?	?	+	-	?	+	+	+	+
Prakash 2008	+	?	-	+	+	+	?	+	+
Priebe 1980	+	?	-	+	?	?	+	+	+

Figure 3. (Continued)

Priebe 1980	+	?	-	+	?	?	+	+	+
Prod'hom 1994	+	+	-	+	+	+	+	+	+
Reusser 1980	?	?	-	+	?	+	+	+	+
Rohde 1980	+	?	?	+	?	+	-	-	+
Ruiz-Santana 1991	?	?	-	+	?	+	-	+	?
Ryan 1993	+	?	-	+	+	+	+	+	+
Selvanderan 2015	?	?	+	+	?	?	?	+	?
Selvanderan 2016	?	?	+	+	?	?	?	+	?
Simms 1991	?	?	-	-	-	+	+	+	+
Sirvent 1994	?	?	-	?	+	+	+	-	+
Skillman 1984	+	?	-	+	?	+	+	+	+
Solouki 2009	+	?	-	+	+	+	+	+	+
Somberg 2008	+	+	?	+	+	+	+	+	+
Stoehr 2006	?	?	?	?	?	?	+	+	+
Stothert 1980	+	?	+	+	?	+	+	+	+
Tabeefar 2012	+	?	+	?	?	+	+	+	+
Terzi 2009	?	?	-	+	?	+	-	+	+
Thomason 1996	+	?	-	+	+	+	+	-	+
Tryba 1985	?	?	-	+	?	+	+	+	+
Tryba 1987	?	?	-	+	+	+	+	+	+
Tryba 1988	?	?	-	+	+	?	+	+	+
van den Berg 1985	?	?	+	+	?	+	+	-	+
van Essen 1985	?	?	+	+	?	+	+	+	+
Wang 2015	?	?	?	+	?	?	+	+	?
Wee 2013	?	?	+	?	?	?	?	?	?
Weigelt 1981	-	-	-	+	?	+	+	+	+
Yildizdas 2002	+	?	-	?	+	+	+	+	+
Zinner 1981	?	?	-	+	?	+	+	+	+
Zinner 1989	?	?	+	+	?	+	+	-	+

Allocation

A total of 33 studies clearly mentioned the method employed for generating a random sequence (Bashar 2013; Ben-Menachem 1994; Burgess 1995; Cannon 1987; Cook 1998; Davies 2012; Eddleston

1991; Eddleston 1994; Ephgrave 1998; Fabian 1993; Fang 2014; Hanisch 1998; Hastings 1978; Israsena 1987; Kantorova 2004; Kitler 1990; Kuusela 1997; Metz 1993; Ng 2012; Noseworthy 1987; Ortiz 1998; Prakash 2008; Priebe 1980; Prod'hom 1994; Rohde 1980;

Ryan 1993; Skillman 1984; Solouki 2009; Somberg 2008; Stothert 1980; Tabeeifar 2012; Thomason 1996; Yildizdas 2002). Thirteen studies mentioned the method employed to conceal the allocation, ensuring that they were clearly free from any selection bias (Ben-Menachem 1994; Cook 1998; Davies 2012; Ephgrave 1998; Halloran 1980; Hanisch 1998; Kantorova 2004; Kuusela 1997; Martin 1993; Ng 2012; Noseworthy 1987; Prod'hom 1994; Somberg 2008).

Seven studies were quasi-randomised studies and therefore were judged to have higher risk of selection bias compared with the other studies, which had unclear risk for the domains of 'sequence generation' and 'allocation concealment' (Borrero 1984; Borrero 1985; Borrero 1986; Brophy 2010; Martin 1980; Pickworth 1993; Weigelt 1981).

Blinding

Performance bias

Thirty-seven studies clearly mentioned the methods employed for blinding participants and personnel across all outcomes, and so review authors judged their risk of performance bias as low (Barandun 1985; Bashar 2013; Bonten 1995; Burgess 1995; Chan 1995; Conrad 2005; Cook 1998; Ephgrave 1998; Fogas 2013; Friedman 1982; Groll 1986; Halloran 1980; Hanisch 1998; Kappstein 1991; Khorvash 2014; Krakamp 1989; Kuusela 1997; Lacroix 1986; Larson 1989; Lee 2014; Luk 1982; Martin 1992; Martin 1993; Metz 1993; Ng 2012; Pan 2004; Peura 1985; Pickworth 1993; Powell 1993; Selvanderan 2015; Selvanderan 2016; Stothert 1980; Tabeeifar 2012; van den Berg 1985; van Essen 1985; Wee 2013; Zinner 1989).

Detection bias

Eighty studies reported that researchers used a clear definition for detection of upper GI bleeding, and review authors judged these studies as having low risk of detection bias for this outcome (Ali 2016; Apte 1992; Basso 1981; Ben-Menachem 1994; Borrero 1984; Borrero 1985; Borrero 1986; Bresalier 1987; Brophy 2010; Burgess 1995; Cannon 1987; Chan 1995; Cioffi 1994; Conrad 2005; Cook 1998; Darlong 2003; Davies 2012; Driks 1987; Eddleston 1991; Eddleston 1994; Ephgrave 1998; Fabian 1993; Fink 2003; Friedman 1982; Groll 1986; Halloran 1980; Hanisch 1998; Kantorova 2004; Kappstein 1991; Karlstadt 1990; Kaushal 2000; Kingsley 1985; Kitler 1990; Krakamp 1989; Kuusela 1997; Lacroix 1986; Laggner 1988; Lamothe 1991; Larson 1989; Lee 2014; Levy 1997; Lin 2016; Lopez-Herce 1992; Luk 1982; Macdougall 1977; Maier 1994; Martin 1980; Martin 1992; Martin 1993; Metz 1993; Ng 2012; Ortiz 1998; Peura 1985; Pickworth 1993; Pinilla 1985; Poleski 1986; Prakash 2008; Priebe 1980; Prod'hom 1994; Reusser 1990; Rohde 1980; Ruiz-Santana 1991; Ryan 1993; Selvanderan 2015; Selvanderan 2016; Skillman 1984; Solouki 2009; Somberg 2008; Stothert 1980; Terzi 2009; Thomason 1996; Tryba 1985; Tryba 1987; Tryba 1988; van den Berg 1985; van Essen 1985; Wang 2015; Weigelt 1981; Zinner 1989). Thirty-eight studies reported that researchers used a clear definition for detection of nosocomial pneumonia, and review authors judged their risk of detection bias as low (Apte 1992; Bashar 2013; Ben-Menachem 1994; Bonten 1995; Cioffi 1994; Conrad 2005; Cook 1998; Davies 2012; Driks 1987; Eddleston 1991; Eddleston 1994; Ephgrave 1998; Fabian 1993; Fogas 2013; Hanisch 1998; Israsena 1987; Kantorova 2004; Kappstein 1991; Khorvash 2014; Laggner 1989; Lee 2014; Lin 2016; Mahul 1992; Maier 1994; Martin 1993; Metz 1993; Mustafa 1994; Pickworth 1993; Prakash 2008; Prod'hom 1994; Ryan 1993; Sirvent 1994; Solouki 2009; Somberg 2008; Thomason 1996; Tryba 1987; Tryba 1988; Yildizdas 2002).

Incomplete outcome data

High risk of attrition bias was suspected in eight studies (Barandun 1985; Fabian 1993; Hanisch 1998; Israsena 1987; Khorvash 2014; Rohde 1980; Ruiz-Santana 1991; Terzi 2009). Although two studies conducted per-protocol analyses for outcomes of interest and excluded participants, reports show an imbalance between interventional arms with respect to final numbers of participants (Fabian 1993; Ruiz-Santana 1991). Therefore, review authors judged the likelihood of attrition bias as high. Only one strata of the study was available for analysis (Rohde 1980), and 16% of participants were not accounted for in two studies, respectively (Barandun 1985; Terzi 2009).

Fourteen studies, which reported that researchers conducted a per-protocol analysis for outcomes of interest and excluded participants, showed no imbalance between interventional arms with respect to final numbers of participants (Bresalier 1987; Hanisch 1998; Kantorova 2004; Lopez-Herce 1992; Poleski 1986; Prod'hom 1994; Reusser 1990; Skillman 1984; Stothert 1980; Thomason 1996; van den Berg 1985; van Essen 1985; Yildizdas 2002; Zinner 1989). Therefore review authors judged the likelihood of bias due to attrition as low.

The following studies were unclear on the numbers of participants initially randomised to the interventional arms: Fink 2003, Groll 1986, Kitler 1990, Phillips 1998, and Prakash 2008. Therefore review authors determined that they had unclear risk of attrition bias.

Selective reporting

All studies analysed and reported intended outcomes except the following.

- Barandun 1985 and Laggner 1988 were unclear on reporting of adverse events of interventions.
- Ortiz 1998 and Chan 1995 showed selective or unclear reporting on secondary outcomes of interest.
- Rohde 1980 reported outcomes for only one strata of the study (participants with polytrauma); all other strata were excluded from analysis.
- Thomason 1996 conducted an intention-to-treat analysis for the outcomes of pneumonia and all-cause mortality only.
- Sirvent 1994, van den Berg 1985, Lopez-Herce 1992, and Macdougall 1977 did not report all-cause mortality separately for each intervention arm.
- Zinner 1989 was unclear on the total number of participants in each arm when reporting adverse events due to interventions.
- Chan 1995 reported more outcomes than initially proposed in the Methods section.

We evaluated risk of reporting bias for clinical upper GI bleeding for the following comparisons: any intervention versus no prophylaxis or placebo, H2 receptor antagonists versus no prophylaxis or placebo, H2 receptor antagonists versus proton pump inhibitors, H2 receptor antagonists versus antacids, H2 receptor antagonists versus sucralfate, and antacids versus sucralfate. These were the only comparisons that involved at least 10 studies. Visual inspection of funnel plots revealed no evidence of reporting bias (Figure 4; Figure 5; Figure 6; Figure 7; Figure 8; Figure 9).

Figure 4. Funnel plot of comparison: 1 Interventions versus placebo or no prophylaxis, outcome: 1.1 Clinically important upper GI bleeding.

Figure 5. Funnel plot of comparison: 2 H2 receptor antagonists versus placebo or no prophylaxis, outcome: 2.1 Clinically important upper GI bleeding.

Figure 6. Funnel plot of comparison: 9 H2 receptor antagonists versus proton pump inhibitors, outcome: 9.1 Clinically important upper GI bleeding.

Figure 7. Funnel plot of comparison: 10 H2 receptor antagonists versus antacids, outcome: 10.1 Clinically important upper GI bleeding.

Figure 8. Funnel plot of comparison: 11 H2 receptor antagonists versus sucralfate, outcome: 11.1 Clinically important upper GI bleeding.

Figure 9. Funnel plot of comparison: 19 Antacids versus sucralfate, outcome: 19.1 Clinically important upper GI bleeding.

Other potential sources of bias

Review authors classified 20 studies as having unclear or high risk of bias, as reports were unclear on the baseline characteristics of randomised participants (Ali 2016; Basso 1981; Behrens 1994; Bresalier 1987; Conrad 2005; Darlong 2003; Fogas 2013; He 2017; Lacroix 1986; Larson 1989; Levy 1997; Maasoumi 2016; Macdougall 1977; Mahul 1992; Ortiz 1998; Ruiz-Santana 1991; Selvanderan 2015; Selvanderan 2016; Wang 2015; Wee 2013). Three studies were published only as conference abstracts and did not report enough data for assessment of other biases (Fogas 2013; Selvanderan 2016; Wee 2013). These reasons are elaborately described in the risk of bias tables for these respective studies.

Effects of interventions

See: **Summary of findings for the main comparison** Interventions compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units; **Summary of findings 2** H2 receptor antagonists compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units; **Summary of findings 3** Proton pump inhibitors compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units; **Summary of findings 4** Antacids compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive

care units; **Summary of findings 5** Sucralfate compared with placebo or no prophylaxis for preventing upper gastrointestinal bleeding in people admitted to intensive care units; **Summary of findings 6** H2 receptor antagonists compared with proton pump inhibitors for preventing upper gastrointestinal bleeding in people admitted to intensive care units; **Summary of findings 7** H2 receptor antagonists compared with antacids for preventing upper gastrointestinal bleeding in people admitted to intensive care units; **Summary of findings 8** H2 receptor antagonists compared with sucralfate for preventing upper gastrointestinal bleeding in people admitted to intensive care units; **Summary of findings 9** Antacids compared with sucralfate for preventing upper gastrointestinal bleeding in people admitted to intensive care units

Interventions versus placebo or no prophylaxis

For this comparison, data on eight of our pre-defined outcomes were available.

Clinically important upper GI bleeding

Clinically important upper GI bleeding was analysed (Analysis 1.1) for the comparison of any intervention (H2 receptor antagonists, proton pump inhibitors, prostaglandin analogues, anticholinergics, and sucralfate) versus placebo or no prophylaxis. We identified 31 studies that contributed data to this outcome, which we categorised according to drug class. There seems to be a beneficial

effect of any intervention versus placebo or no prophylaxis on the occurrence of clinically important upper GI bleeding (risk ratio (RR) 0.47, 95% confidence interval (CI) 0.39 to 0.57; moderate certainty of evidence). We have elaborately mentioned further results below under each respective comparison.

Nosocomial pneumonia

Nosocomial pneumonia (which included ventilator-associated pneumonia) was analysed ([Analysis 1.2](#)) for the comparison of any interventions (H2 receptor antagonists, proton pump inhibitors, anticholinergics, and sucralfate vs placebo or no prophylaxis). We identified nine studies that contributed data to this outcome and categorised these data according to drug class. With respect to the occurrence of differences in nosocomial pneumonia between study groups (RR 1.15, 95% CI 0.90 to 1.48; low certainty of evidence), the use of any intervention versus no intervention or prophylaxis was consistent with benefits and harms. We have elaborately mentioned these results below under each respective comparison.

All-cause mortality in ICU

All-cause mortality in the ICU was analysed ([Analysis 1.3](#)) for the comparison of any interventions (H2 receptor antagonists, proton pump inhibitors, prostaglandin analogues, anticholinergics, antacids, and sucralfate vs placebo or no prophylaxis). We identified 18 studies that contributed data to this outcome and organised the data from these studies according to drug class. With respect to all-cause mortality in the ICU, the effect estimate of any intervention versus no intervention or prophylaxis was consistent with benefit and harm (RR 1.10, 95% CI 0.90 to 1.34; low certainty of evidence). We have elaborately mentioned these results below under each respective comparison.

All-cause mortality in hospital

All-cause mortality in the hospital was analysed ([Analysis 1.4](#)) for the comparison of any interventions (H2 receptor antagonists, proton pump inhibitors, antacids, and sucralfate vs placebo or no prophylaxis). We identified five studies that contributed data to this outcome and categorised the data from these studies according to drug class. The effect estimate of any intervention versus no intervention or prophylaxis was consistent with benefits and harms with respect to all-cause mortality in the hospital (RR 1.15, 95% CI 0.85 to 1.55). We have elaborately mentioned these results below under each respective comparison.

Duration of ICU stay

Duration of ICU stay was analysed ([Analysis 1.5](#)) for the comparison of any interventions (H2 receptor antagonists, proton pump inhibitors, and sucralfate vs placebo or no prophylaxis). We identified two studies that contributed data to this outcome and categorised the data from these studies according to drug class. The effect estimate of any intervention versus no intervention or prophylaxis was consistent with benefits and harms with respect to duration of ICU stay (mean difference (MD) 0.24 days, 95% CI -1.13 to 1.61; low certainty of evidence). We have elaborately mentioned these results below under each respective comparison.

Duration of intubation

Duration of intubation was analysed ([Analysis 1.6](#)) for the comparison of any interventions (H2 receptor antagonists, proton pump inhibitors, and sucralfate vs placebo or no prophylaxis). We

identified two studies that contributed data to this outcome and categorised the data from these studies according to drug class. The effect estimate of any intervention versus no intervention or prophylaxis was consistent with benefits and harms with respect to duration of intubation (MD 0.87 days, 95% CI -0.58 to 2.31; low certainty of evidence). We have elaborately mentioned these results below under each respective comparison.

Number of participants requiring blood transfusions

The number of participants requiring blood transfusions was analysed ([Analysis 1.7](#)) for the comparison of any interventions (H2 receptor antagonists, antacids, and sucralfate vs placebo or no prophylaxis). We identified nine studies that contributed data to this outcome and categorised the data from these studies according to drug class. Data seem to show a reduction in the number of participants in the intervention group requiring blood transfusion (RR 0.63, 95% CI 0.41 to 0.97; moderate certainty of evidence). We have elaborately mentioned these results below under each respective comparison.

Units of blood transfused

The number of units of blood transfused was analysed ([Analysis 1.8](#)) for the comparison of any interventions (H2 receptor antagonists and sucralfate vs placebo or no prophylaxis). We identified two studies that contributed data to this outcome and categorised the data from these studies according to drug class. The effect estimate of any intervention versus no intervention or prophylaxis was consistent with benefits and harms with respect to the number of units of blood transfused (MD 0.09 units, 95% CI -0.99 to 1.17). We have elaborately mentioned these results below under each respective comparison.

H2 receptor antagonists versus placebo or no prophylaxis

For this comparison, data on nine of our pre-defined outcomes were available.

Clinically important upper GI bleeding

We identified 24 studies relevant to this outcome (N = 2149) and stratified data into six groups according to drug class members of H2 receptor antagonists. For this outcome, we found evidence suggesting that H2 receptor antagonists reduced the risk of clinically important upper GI bleeding compared with placebo or no prophylaxis (8.3% vs 17.7%; RR 0.50, 95% CI 0.36 to 0.70; [Analysis 2.1](#)). We judged the certainty of the evidence as moderate. This outcome had moderate levels of heterogeneity ($\text{Chi}^2 = 38.78$, $\text{df} = 23.0$ ($P = 0.02$), $I^2 = 40\%$).

Cimetidine versus placebo

We found 10 studies that were relevant to this comparison (N = 772). For this comparison, the effect was consistent with benefits and harms (RR 0.53, 95% CI 0.28 to 1.02). For this outcome, heterogeneity was substantial ($\text{Chi}^2 = 22.25$, $\text{df} = 9.0$ ($P = 0.008$), $I^2 = 60\%$; [Analysis 2.1](#)).

Famotidine versus placebo

For this comparison, we identified a single relevant study (N = 146). The effect was consistent with benefits and harms (RR 2.11, 95% CI 0.20 to 22.79; [Analysis 2.1](#)).

Ranitidine versus placebo

We found five relevant studies for this comparison (N = 446). Evidence suggested a beneficial effect of H2 receptor antagonists compared with placebo within this comparison (RR 0.36, 95% CI 0.17 to 0.77; [Analysis 2.1](#)).

Cimetidine versus no prophylaxis

For this comparison, we identified three relevant studies (N = 516). In this subgroup, the effect was consistent with benefits and harms (RR 0.59, 95% CI 0.23 to 1.48). For this comparison, heterogeneity was moderate ($\chi^2 = 3.53$, df = 2.0 (P = 0.17), $I^2 = 43\%$) ([Analysis 2.1](#)).

Famotidine versus no prophylaxis

We identified a single study for this comparison (N = 50). We found evidence of benefit of H2 receptor antagonists compared with no prophylaxis (RR 0.30, 95% CI 0.09 to 0.96; [Analysis 2.1](#)).

Ranitidine versus no prophylaxis

We found four studies that were relevant to this comparison (N = 219). The effect of H2 receptor antagonists versus no prophylaxis was consistent with benefits and harms (RR 0.51, 95% CI 0.26 to 1.00; [Analysis 2.1](#)). One study with 19 participants in the ranitidine group and 21 participants in the no prophylaxis group reported no events of clinically important upper GI bleeding ([Reusser 1990](#)).

Nosocomial pneumonia

We identified eight studies that were relevant to this outcome (N = 945) and divided the data into five subcategories in accordance with our protocol. The effect of H2 receptor antagonists versus no prophylaxis on nosocomial pneumonia was consistent with benefits and harms (15.8% vs 14.6%; RR 1.12, 95% CI 0.85 to 1.48; [Analysis 2.2](#)). We judged the certainty of this evidence as low.

Cimetidine versus placebo

We identified two relevant studies for this comparison (N = 204). The effect of cimetidine versus placebo on nosocomial pneumonia was consistent with benefits and harms (RR 0.34, 95% CI 0.06 to 2.00). This comparison showed moderate heterogeneity ($\chi^2 = 1.59$, df = 1.0 (P = 0.21), $I^2 = 37\%$; [Analysis 2.2](#)).

Famotidine versus placebo

We included a single study for this comparison (N = 146). The effect of famotidine versus placebo was consistent with benefits and harms (RR 1.48, 95% CI 0.49 to 4.45; [Analysis 2.2](#)).

Ranitidine versus placebo

We found two studies that were relevant to this comparison (N = 277). The effect was consistent with benefits and harms (RR 0.79, 95% CI 0.47 to 1.31; [Analysis 2.2](#)).

Cimetidine versus no prophylaxis

We included a single study in this comparison (N = 200). The effect was consistent with benefits and harms (RR 2.17, 95% CI 0.86 to 5.47; [Analysis 2.2](#)).

Ranitidine versus no prophylaxis

We found two studies that were relevant to this comparison (N = 118). Within this comparison, the effect was consistent with benefits and harms (RR 1.33, 95% CI 0.93 to 1.90; [Analysis 2.2](#)).

All-cause mortality in ICU

We identified 14 studies that contributed data to this outcome (N = 1428). With respect to all-cause mortality in the ICU, the effect of H2 receptor antagonists versus no prophylaxis on nosocomial pneumonia was consistent with benefits and harms (15.8% vs 14.3%; RR 1.12, 95% CI 0.88 to 1.42; [Analysis 2.3](#)). We judged the certainty of this evidence as low.

Cimetidine versus placebo

We found four studies that were relevant to this comparison (N = 478). Data showed no clear difference between H2 receptor antagonists and placebo (RR 1.05, 95% CI 0.66 to 1.68; [Analysis 2.3](#)).

Famotidine versus placebo

We identified a single study for this comparison (N = 146). Data show no clear difference between H2 receptor antagonists and placebo (RR 1.32, 95% CI 0.55 to 3.16; [Analysis 2.3](#)).

Ranitidine versus placebo

We found two relevant studies for this comparison (N = 148). We found no evidence showing a clear difference between the two groups (RR 0.69, 95% CI 0.31 to 1.54; [Analysis 2.3](#)). One study (N = 21) reported no events of all-cause mortality in both groups on the ICU ([Powell 1993](#)).

Cimetidine versus no prophylaxis

We found two relevant studies for this comparison (N = 400). Data show no clear difference between H2 receptor antagonists and no prophylaxis within this comparison (RR 1.00, 95% CI 0.61 to 1.63). For this outcome, heterogeneity was considerable ($\chi^2 = 5.12$, df = 1.0 (P = 0.02), $I^2 = 80\%$; [Analysis 2.3](#)).

Famotidine versus no prophylaxis

We found one study that was relevant to this comparison (N = 50). For this comparison, we found no evidence showing a clear difference between the two groups (RR 1.25, 95% CI 0.59 to 2.64; [Analysis 2.3](#)).

Ranitidine versus no prophylaxis

We found four studies that were relevant to this comparison (N = 206). Data show no clear difference between H2 receptor antagonists and no prophylaxis (RR 1.58, 95% CI 0.97 to 2.58; [Analysis 2.3](#)).

All-cause mortality in hospital

For this outcome, we found four relevant studies (N = 487). Data seemed to show no difference between H2 receptor antagonists and placebo or no prophylaxis with respect to all-cause mortality in the hospital (18.4% vs 15.7%; RR 1.16, 95% CI 0.79 to 1.70; [Analysis 2.4](#)).

Famotidine versus placebo

We found one study that was relevant to this comparison (N = 146). For this comparison, we found no evidence of a clear difference between the two groups (RR 0.89, 95% CI 0.43 to 1.86; [Analysis 2.4](#)).

Ranitidine versus placebo

We found one study that was relevant to this comparison (N = 101). For this comparison, we did not find evidence of a clear difference between the two groups (RR 0.35, 95% CI 0.01 to 8.47; [Analysis 2.4](#)).

Cimetidine versus no prophylaxis

We identified a single study for this comparison (N = 200). We found no evidence of a clear difference between the two groups (RR 1.47, 95% CI 0.88 to 2.46; [Analysis 2.4](#)).

Ranitidine versus no prophylaxis

We found one study that was relevant to this comparison (N = 40). Data show no clear difference between H2 receptor antagonists and no prophylaxis (RR 0.92, 95% CI 0.33 to 2.53; [Analysis 2.4](#)).

Duration of ICU stay

We identified two studies relevant to this outcome (N = 230). Data seemed to show no difference between H2 receptor antagonists and placebo or no prophylaxis with respect to duration of ICU stay (MD 0.73 days, 95% CI -0.92 to 2.38; [Analysis 2.5](#)). We judged the certainty of this evidence as low.

Famotidine versus placebo

We identified a single study for this comparison (N = 146). We found no evidence of a clear difference between the two groups (MD 1.50 days, 95% CI -1.93 to 4.93; [Analysis 2.5](#)).

Ranitidine versus no prophylaxis

We found one study that was relevant to this comparison (N = 84). We found no evidence of a clear difference between the two groups (MD 0.50 days, 95% CI -1.38 to 2.38; [Analysis 2.5](#)). An additional study reported insufficient data for inclusion in a formal meta-analysis ([Reusser 1990](#)). Researchers randomised 19 participants to the ranitidine arm and 21 to the control arm. The mean duration of ICU stay was 13 days (range 6 to 40 days) in the ranitidine group and 17 days (range 5 to 30 days) in the control group.

Ranitidine versus placebo

We identified two studies that looked at this outcome but did not report enough data to be included in formal meta-analyses (N = 154) ([Hanisch 1998](#); [Reusser 1990](#)). In the included studies, 76 participants received ranitidine and 78 received placebo. The mean duration of ICU stay was 9.7 days (2 to 95) and 12.6 days (2 to 58) in [Hanisch 1998](#), and 13 days (16 to 40) and 17 days (5 to 30) in [Reusser 1990](#).

Cimetidine versus no prophylaxis

We identified one study that did not report sufficient information for inclusion in the meta-analysis (N = 200) ([Ben-Menachem 1994](#)). The duration of ICU stay was 4 days (2 to 9 days) in the cimetidine group (n = 100) and 3 days (2 to 6 days) in the group that received no prophylaxis (n = 100).

Duration of intubation

For this outcome, we found two relevant studies and categorised data into two comparisons (N = 230). Data seemed to show no difference between H2 receptor antagonists and placebo or no prophylaxis with respect to duration of intubation (MD 0.79 days, 95% CI -0.95 to 2.54; [Analysis 2.6](#)). [Apte 1992](#) assessed the duration

of intubation but did not report enough data for inclusion in meta-analyses.

Famotidine versus placebo

We found one study that was relevant to this comparison (N = 146). We found no evidence of a clear difference between the two groups (MD 1.20 days, 95% CI -1.86 to 4.26; [Analysis 2.6](#)).

Ranitidine versus no prophylaxis

We identified a single study for this comparison (N = 84). Data show no clear difference between H2 receptor antagonists and no prophylaxis (MD 0.60 days, 95% CI -1.52 to 2.72; [Analysis 2.6](#)).

Ranitidine versus placebo

We identified two studies that looked at this outcome but did not report enough data for inclusion in formal meta-analyses (N = 148) ([Apte 1992](#); [Hanisch 1998](#)). In the included studies, 73 participants received ranitidine and 75 received placebo. The mean duration of intubation was 8.2 days (2 to 93) and 10.2 days (2 to 55) in [Hanisch 1998](#), and 7.5 days (3 to 28) and 12.5 days (3 to 63) in [Apte 1992](#).

Number of participants requiring blood transfusions

Data seemed to show a beneficial effect of H2 receptor antagonists compared with placebo or no prophylaxis with respect to the number of participants requiring blood transfusions (6.4% vs 11.2%; RR 0.58, 95% CI 0.36 to 0.95; seven studies; 655 participants; [Analysis 2.7](#)). We judged the certainty of this evidence as moderate.

Cimetidine versus placebo

We found three studies that were relevant to this comparison (N = 107). For this outcome, within this comparison, we found evidence suggesting that H2 receptor antagonists were different in their effect compared with placebo (RR 0.39, 95% CI 0.19 to 0.79; [Analysis 2.7](#)). Results favoured cimetidine over placebo.

Ranitidine versus placebo

We identified two relevant studies for this comparison (N = 148). We found no evidence of a clear difference between the two groups (RR 1.05, 95% CI 0.24 to 4.60). This comparison had substantial heterogeneity ($\text{Chi}^2 = 1.89$, $\text{df} = 1.0$ ($P = 0.17$), $I^2 = 47\%$; [Analysis 2.7](#)).

Cimetidine versus no prophylaxis

We found two studies that were relevant to this comparison (N = 400). Data show no clear difference between H2 receptor antagonists and no prophylaxis (RR 0.77, 95% CI 0.35 to 1.71; [Analysis 2.7](#)).

Ranitidine versus no prophylaxis

We found two studies that were relevant to this comparison (N = 74) ([Apte 1992](#); [Reusser 1990](#)). For this outcome, within this comparison, we found no evidence suggesting that H2 receptor antagonists were different in their effects compared with no prophylaxis. Researchers reported no events in either treatment group, and we could not include these studies in the meta-analysis.

Units of blood transfused

For this outcome, we found two relevant studies and categorised data into two comparisons (N = 209). Data seemed to show no difference between H2 receptor antagonists and placebo or no prophylaxis with respect to the number of units of blood transfused

(MD 0.33 units, 95% CI -0.04 to 0.70; [Analysis 2.8](#)). This outcome had considerable heterogeneity ($\text{Chi}^2 = 9.49$, $\text{df} = 1.0$ ($P = 0.0$), $I^2 = 89\%$).

Cimetidine versus placebo

We found one study that was relevant to this comparison ($N = 9$). Evidence suggested a difference between H2 receptor antagonists and placebo (MD -4.35 units, 95% CI -7.35 to -1.35; [Analysis 2.8](#)). One study reported 11 blood transfusions in the cimetidine group ($n = 26$) and 41 in the placebo group ($n = 24$) and reported no standard deviation ([Halloran 1980](#)). Another study reported that the mean volume of blood transfused was 600 mL (0 to 900 mL) in the cimetidine group ($n = 114$) and 550 mL (0 to 1200 mL) in the placebo group ($n = 107$) ([Groll 1986](#)).

Cimetidine versus no prophylaxis

We included a single study in this comparison ($N = 200$). We found evidence suggesting a difference between H2 receptor antagonists and no prophylaxis favouring no prophylaxis (MD 0.40 units, 95% CI 0.03 to 0.77; [Analysis 2.8](#)).

Ranitidine vs placebo

We identified one study that looked at this outcome but did not report enough data for inclusion in formal meta-analyses ([Hanisch 1998](#)). In the included study, 57 participants received ranitidine and 57 received placebo. A mean of two units of blood was transfused in each of the three participants with GI bleeding in the ranitidine group, and 12 units was transfused in the single surviving participant with GI bleeding in the placebo group.

Adverse events of interventions

For this outcome we found eight relevant studies and divided the data into 12 comparisons according to type of adverse event.

Diarrhoea

We found two studies that were relevant to this comparison ($N = 225$). We found no evidence of a clear difference between the two groups (RR 1.30, 95% CI 0.57 to 2.96; [Analysis 2.9](#)).

Thrombocytopenia

We found one study that was relevant to this comparison ($N = 200$). We found no evidence of a clear difference between the two groups (RR 3.0, 95% CI 0.12 to 72.77; [Analysis 2.9](#)).

Hypophosphataemia

We identified a single study in this comparison ($N = 25$). We found no evidence of a clear difference between the two groups (RR 3.75, 95% CI 0.17 to 84.02; [Analysis 2.9](#)).

Mental confusion

We identified five relevant studies for this comparison ($N = 657$). We found evidence that H2 receptor antagonists increased the risk for mental confusion compared with placebo or no prophylaxis (RR 2.01, 95% CI 1.10 to 3.65; [Analysis 2.9](#)).

Nausea and vomiting

We found two studies that were relevant to this comparison ($N = 287$). We found no evidence of a clear difference between the two groups (RR 0.46, 95% CI 0.09 to 2.35; [Analysis 2.9](#)).

Increased creatinine levels

We included a single study in this comparison ($N = 2000$). Evidence showed no clear difference between H2 receptor antagonists and placebo or no prophylaxis (RR 1.04, 95% CI 0.64 to 1.69; [Analysis 2.9](#)).

Erythema (superficial reddening of the skin)

We found one study that was relevant to this comparison ($N = 70$). Data showed no clear difference between H2 receptor antagonists and placebo or no prophylaxis (RR 3.00, 95% CI 0.13 to 71.22; [Analysis 2.9](#)).

Pancreatitis

We found one study that was relevant to this comparison ($N = 39$). We found no evidence of a clear difference between the two groups (RR 0.29, 95% CI 0.01 to 6.66; [Analysis 2.9](#)).

Chest infection

We found one study that was relevant to this comparison ($N = 101$). Data showed no clear difference between H2 receptor antagonists and placebo or no prophylaxis (RR 1.74, 95% CI 0.92 to 3.30; [Analysis 2.9](#)).

Delirium

We found one study that was relevant to this comparison ($N = 39$). Data showed no clear difference between H2 receptor antagonists and placebo or no prophylaxis (RR 2.59, 95% CI 0.11 to 59.93; [Analysis 2.9](#)).

Hallucinations

We included a single study in this comparison ($N = 39$). We found no evidence of a clear difference between the two groups (RR 2.59, 95% CI 0.11 to 59.93; [Analysis 2.9](#)).

Severe bleeding

We included a single study in this comparison ($N = 101$). Data showed no clear difference between H2 receptor antagonists and placebo or no prophylaxis (RR 0.35, 95% CI 0.01 to 8.47; [Analysis 2.9](#)).

Proton pump inhibitors versus placebo or no prophylaxis

For this comparison, data on six of our pre-defined outcomes were available. Omeprazole was administered in all three studies providing data for this comparison. Placebo was administered in two studies as comparator, and in one study no prophylaxis was given as comparator.

Clinically important upper GI bleeding

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 3.1](#)). In the three included studies that contributed data to the analyses, 114 participants received proton pump inhibitors and 123 participants received either placebo or no prophylaxis. The event occurred in 2.6% and 4.9% of participants in the two groups. Data seemed to show no difference between proton pump inhibitors and placebo or no prophylaxis with respect to the occurrence of clinically important upper GI bleeding (RR 0.63, 95% CI 0.18 to 2.22). We judged the certainty of the evidence as low.

We identified two additional studies. [Selvanderan 2016](#) included 214 participants and did not report how many participants were randomised to the two interventions. [Powell 1993](#) included 21 participants in the proton pump inhibitor arm and 10 in the placebo arm. Both trials reported no events of clinically important upper GI bleeding in either group.

Omeprazole versus placebo

We found one relevant study for this comparison (N = 147). We found no evidence of a clear difference between the two groups (RR 1.04, 95% CI 0.07 to 16.34; [Analysis 3.1](#)).

Omeprazole versus no prophylaxis

We identified a single study for this comparison (N = 80). We found no evidence of a clear difference between the two groups (RR 0.74, 95% CI 0.13 to 4.18; [Analysis 3.1](#)).

Pantoprazole versus placebo

We included a single study for this comparison (N = 10). We found no evidence of a clear difference between the two groups (RR 0.28, 95% CI 0.02 to 4.66; [Analysis 3.1](#)).

Nosocomial pneumonia

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 3.2](#)). In the two included studies, 110 participants received proton pump inhibitors and 117 received placebo. Nosocomial pneumonia occurred in 22.8% of the group that received proton pump inhibitors and 18.7% of the group that received placebo or no prophylaxis. Data seemed to show no difference between proton pump inhibitors and placebo or no prophylaxis with respect to the occurrence of nosocomial pneumonia (RR 1.24, 95% CI 0.77 to 1.98). We judged the certainty of the evidence as low.

We identified an additional study that was published as a conference abstract and did not report enough data for formal meta-analysis ([Selvanderan 2016](#)). Researchers randomised a total of 214 participants to receive pantoprazole or placebo. One participant in the placebo group and two in the pantoprazole group developed ventilator-associated complications including pneumonia. Data showed eight and 12 cases of clinician-adjudicated nosocomial pneumonia in pantoprazole and control groups, respectively.

Omeprazole versus placebo

We identified a single study for this comparison (N = 147). Data show no clear difference between proton pump inhibitors and placebo within this comparison (RR 1.67, 95% CI 0.57 to 4.86; [Analysis 3.2](#)).

Omeprazole versus no prophylaxis

We included a single study in this comparison (N = 80). We found no evidence of a clear difference between the two groups. Nosocomial pneumonia occurred in 44.7% and 40.5% of participants in the groups that received omeprazole or no prophylaxis, respectively (RR 1.11, 95% CI 0.66 to 1.84; [Analysis 3.2](#)).

All-cause mortality in ICU

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 3.3](#)). In the three included studies, 131 participants received proton pump inhibitors and 127

received either placebo or no prophylaxis. The event occurred in 13.3% and 13.4% of participants in the two groups. Data seemed to show no difference between proton pump inhibitors and placebo or no prophylaxis with respect to all-cause mortality in the ICU (RR 1.09, 95% CI 0.60 to 1.99). We judged the certainty of this evidence as low.

We identified an additional study that was published as a conference abstract and did not provide enough data for formal meta-analysis ([Selvanderan 2016](#)). Researchers randomised a total of 214 participants to receive pantoprazole or placebo. The study reported an adjusted hazard ratio for mortality with pantoprazole of 1.68 (95% CI 0.97 to 2.90).

Omeprazole versus placebo

We found two relevant studies for this comparison (N = 178). We found no evidence of a clear difference between the two groups (RR 1.20, 95% CI 0.51 to 2.83; [Analysis 3.3](#)).

Omeprazole versus no prophylaxis

We included a single study in this comparison (N = 80). Data show no clear difference between proton pump inhibitors and no prophylaxis within this comparison with respect to all-cause mortality in the ICU (RR 0.98, 95% CI 0.42 to 2.29; [Analysis 3.3](#)).

All-cause mortality in hospital

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 3.4](#)). In the included study, 75 participants received proton pump inhibitors and 75 received placebo. All-cause mortality occurred in 18.7% of the group that received proton pump inhibitors and 17.3% of the group that received placebo. Data seemed to show no difference between proton pump inhibitors and placebo or no prophylaxis with respect to all-cause mortality in hospital (RR 1.08, 95% CI 0.54 to 2.13).

Duration of ICU stay

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 3.5](#)). In the two included studies, 110 participants received proton pump inhibitors and 117 received either placebo or no prophylaxis. Data seemed to show no difference between proton pump inhibitors and placebo or no prophylaxis with respect to length of ICU stay (MD -0.03 days, 95% CI -1.63 to 1.58; two studies; 227 participants; [Analysis 3.5](#)). We judged the certainty of this evidence as low.

Omeprazole versus placebo

We included a single study in this comparison (N = 147). We found no evidence of a clear difference between the two groups (MD -0.90 days, 95% CI -3.96 to 2.16; [Analysis 3.5](#)).

Omeprazole versus no prophylaxis

We included a single study in this comparison (N = 80). Data show no clear difference between proton pump inhibitors and no prophylaxis (MD 0.30 days, 95% CI -1.58 to 2.18; [Analysis 3.5](#)).

Duration of intubation

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 3.6](#)). In the two included studies, 110 participants received sucralfate and 107 received either placebo or no prophylaxis. Data seemed to show no difference

between proton pump inhibitors and placebo or no prophylaxis with respect to duration of intubation (MD 0.36 days, 95% CI -1.43 to 2.15).

Omeprazole versus placebo

We included a single study in this comparison (N = 147). Data show no difference between proton pump inhibitors and placebo with respect to duration of intubation (MD 0.50 days, 95% CI -2.72 to 3.72; [Analysis 3.6](#)).

Omeprazole versus no prophylaxis

We found one study that was relevant to this comparison (N = 800). We found no evidence of a clear difference between the two groups (MD 0.30 days, 95% CI -1.85 to 2.45; [Analysis 3.6](#)).

Pirenzepine versus placebo

We identified one study that looked at this outcome but did not report enough data for inclusion in formal meta-analyses ([Hanisch 1998](#)). In the included study, 44 participants received pirenzepine and 57 received placebo. The mean duration of intubation was 8.2 days (2 to 32) and 10.2 days (2 to 55) in the two groups, respectively.

Adverse events

One study including 214 participants compared pantoprazole versus placebo ([Selvanderan 2015](#)). Researchers tested 30 participants assigned to pantoprazole and 40 assigned to placebo for *Clostridium difficile* infection. One participant in the pantoprazole group was infected with *C. difficile*.

Proton pump inhibitors plus sucralfate versus placebo or no prophylaxis

For this comparison, data on one of our pre-defined outcomes were available. One study compared early and late administration of omeprazole plus lansoprazole plus sucralfate versus no prophylaxis. For this comparison, we included only participants with late start of therapy (48 to 72 hours) to fit the inclusion criteria of this review. We did not include in the analysis the group with early start of therapy (12 to 24 hours). The only outcome measured that was of relevance to this review was the occurrence of clinically important upper GI bleeding.

Clinically important upper GI bleeding

Data seemed to show no difference between proton pump inhibitors plus sucralfate and placebo or no prophylaxis with respect to the occurrence of clinically important upper GI bleeding (20.0% vs 37.5%; RR 0.53, 95% CI 0.26 to 1.12; one study; 80 participants who contributed data to this comparison ([Analysis 4.1](#)). We judged the certainty of this evidence as moderate.

Prostaglandin analogues versus placebo or no prophylaxis

For this comparison, data on two of our pre-defined outcomes were available. Only one study provided data for this comparison. It included 58 people, of whom 29 received prostaglandin analogues and 29 received placebo.

Clinically important upper GI bleeding

Data seemed to show no difference between prostaglandin analogues and placebo with regard to the occurrence of clinically important upper GI bleeding (10.3% in both groups; RR 1.00, 95%

CI 0.22 to 4.55; one study; 58 participants; [Analysis 5.1](#)). We judged the certainty of this evidence as moderate.

All-cause mortality in ICU

Data seemed to show no difference between prostaglandin analogues and placebo with regard to all-cause mortality in the ICU (27.6% and 24.1%; RR 1.14, 95% CI 0.48 to 2.74; one study; 58 participants; [Analysis 5.2](#)). We judged the certainty of this evidence as moderate.

Anticholinergics versus placebo or no prophylaxis

For this comparison, data on three of our pre-defined outcomes were available. Two studies provided data for this comparison. Both studies administered pirenzepine to a total of 59 participants and placebo or placebo plus ranitidine to 72 participants. In [Krakamp 1989](#), ranitidine was the co-intervention given to both arms.

Clinically important upper GI bleeding

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 6.1](#)). In the two studies that contributed data towards this outcome, the event occurred in 10.2% and 9.7% of participants. Data seemed to show no difference between anticholinergics and placebo or no prophylaxis with respect to the occurrence of clinically important upper GI bleeding (RR 0.95, 95% CI 0.36 to 2.51). We judged the certainty of this evidence as low.

Pirenzepine versus placebo

We found one study that was relevant to this comparison (N = 101). We found no evidence of a clear difference between the two groups (RR 1.94, 95% CI 0.34 to 11.13; [Analysis 6.1](#)).that

Pirenzepin plus ranitidine versus placebo plus ranitidine

We found one study that was relevant to this comparison (N = 30). Data show no clear difference between the two groups (RR 0.60, 95% CI 0.17 to 2.07; [Analysis 6.1](#)).

Nosocomial pneumonia

We classified the study on the basis of its intervention and comparison arms (as shown in [Analysis 6.2](#)). In the single included study, 44 participants received anticholinergics and 57 received placebo. The event occurred in 22.7% and 21.1% of participants in both groups. Data seemed to show no difference between anticholinergics and placebo with respect to the occurrence of nosocomial pneumonia (RR 1.08, 95% CI 0.51 to 2.27; one study; 101 participants). We judged the certainty of this evidence as low.

All-cause mortality in ICU

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 6.3](#)). In the two included studies, 59 participants received anticholinergics and 72 received placebo alone or placebo with ranitidine. The event occurred in 25.4% and 20.8% of participants in both groups. Data seemed to show no difference between anticholinergics and placebo with respect to all-cause mortality in the ICU (RR 1.23, 95% CI 0.66 to 2.30). We judged the certainty of this evidence as low.

Pirenzepine versus placebo

We included a single study in this comparison (N = 101). We found no evidence of a clear difference between the two groups (RR 1.30, 95% CI 0.65 to 2.60; [Analysis 6.3](#)).

Pirenzepin plus ranitidine versus placebo plus ranitidine

We found one study that was relevant to this comparison (N = 30). We found no evidence of a clear difference between the two groups (RR 1.0, 95% CI 0.24 to 4.18; [Analysis 6.3](#)).

Duration of ICU stay

We identified one study that looked at this outcome but did not report enough data for inclusion in formal meta-analyses ([Hanisch 1998](#)). In the included study, 44 participants received pirenzepine and 57 received placebo. The mean duration of ICU stay was 9.9 days (2 to 39) and 12.6 days (2 to 58), respectively.

Duration of intubation

We identified one study that looked at this outcome but did not report enough data for inclusion in formal meta-analyses ([Hanisch 1998](#)). In the included study, 44 participants received pirenzepine and 57 received placebo. The mean duration of intubation was 8.0 days (2 to 32) and 10.2 days (2 to 55), respectively.

Units of blood transfused

We identified one study that looked at this outcome but did not report enough data for inclusion in formal meta-analyses ([Hanisch 1998](#)). In the included study, 44 participants received pirenzepine and 57 received placebo. The mean number of units of blood transfused was four units in each of the three patients with GI bleeding in the pirenzepine group and 12 units in the single surviving participant with GI bleeding in the placebo group.

Antacids versus placebo or no prophylaxis

For this comparison, data on five of our pre-defined outcomes were available. Among the eight studies that provided data for this comparison, two studies administered placebo and five studies provided no prophylaxis.

Clinically important upper GI bleeding

Data seemed to show a beneficial effect of antacids compared with placebo or no prophylaxis with respect to the occurrence of clinically important upper GI bleeding. The outcome occurred in 7.2% of the antacids group and in 17.7% of the placebo group (RR 0.49, 95% CI 0.25 to 0.99; eight studies; 774 participants; [Analysis 7.1](#)). We judged the certainty of this evidence as low. This outcome had substantial heterogeneity ($\text{Chi}^2 = 15.92$, $\text{df} = 7.0$ ($P = 0.03$), $I^2 = 56\%$).

Antacids versus placebo

We found two studies that were relevant to this comparison (N = 145). Data show no clear difference between antacids and placebo (RR 2.04, 95% CI 0.72 to 5.79; [Analysis 7.1](#)).

Antacids versus no prophylaxis

We found six studies that were relevant to this comparison (N = 629). For this outcome, within this comparison, we found evidence suggesting that antacids had a beneficial effect compared with no prophylaxis (RR 0.35, 95% CI 0.20 to 0.60; [Analysis 7.1](#)).

All-cause mortality in ICU

Data seemed to show no difference between anticholinergics and no prophylaxis with respect to all-cause mortality in the ICU. The event occurred in 15.9% of the antacids group and in 16.1% of the group that received no prophylaxis (RR 1.01, 95% CI 0.53 to 1.96; two studies; 300 participants; [Analysis 7.2](#)). We judged the certainty of the evidence as low.

All-cause mortality in the hospital

Data seemed to show no difference between anticholinergics and no prophylaxis with respect to all-cause mortality in the hospital. The event occurred in 30.7% of the intervention group and in 21.3% of the control group (RR 1.44, 95% CI 0.79 to 2.64; one study; 126 participants; [Analysis 7.3](#)).

Duration of intubation

We identified one study that did not report enough data for inclusion in formal meta-analysis ([Pinilla 1985](#)). Study participants received either antacids (n = 65) or no specific prophylaxis (n = 61). The mean duration of ventilation in the antacids group was 136.4 hours (range 0 to 360) and in the control group 173.6 hours (range 12 to 552).

Number of participants requiring blood transfusions

Data seemed to show no difference between antacids and no prophylaxis with respect to the number of participants requiring blood transfusion. In the intervention group, 4.3% of participants required blood transfusion, and in the control group, 4.5% required blood transfusion (RR 0.94, 95% CI 0.30 to 2.96; two studies; 226 participants; [Analysis 7.4](#)). We judged the certainty of the evidence as low.

Adverse events of interventions

We identified four studies relevant to this outcome and categorised data according to seven adverse events.

Diarrhoea

We included four relevant studies in this comparison (N = 395). For this outcome, within this comparison, we found evidence suggesting that antacids increased the risk of diarrhoea compared with placebo or no prophylaxis. Diarrhoea occurred in 16.4% of the intervention group and 4.5% of the control group (RR 3.56, 95% CI 1.83 to 6.94; [Analysis 7.5](#)). For this comparison, heterogeneity was moderate ($\text{Chi}^2 = 4.99$, $\text{df} = 3.0$ ($P = 0.17$), $I^2 = 39\%$).

Hypomagnesaemia

We included a single study in this comparison (N = 25). We found no evidence of a clear difference between the two groups (RR 3.75, 95% CI 0.17 to 84.02; [Analysis 7.5](#)). Researchers reported one event in the intervention group and none in the control group.

Hypophosphataemia

We found two studies that were relevant to this comparison (N = 225). For this outcome, we found evidence suggesting that antacids increased the risk of hypophosphataemia compared with placebo or no prophylaxis (16.2% and 2.6%; RR 5.48, 95% CI 1.81 to 16.61; [Analysis 7.5](#)). Data showed 18 events in the intervention group and three in the control group.

Hypermagnesaemia

We included a single study in this comparison (N = 100). Data show no clear difference between antacids and placebo or no prophylaxis (RR 6.73, 95% CI 0.36 to 127.02; [Analysis 7.5](#)). Researchers reported three events in the intervention group and none in the control group.

Nausea and vomiting

We found three studies that were relevant to this subgroup (N = 370). Data show no clear difference between antacids and placebo or no prophylaxis (RR 2.39, 95% CI 0.86 to 6.64; [Analysis 7.5](#)). Researchers reported 11 events in the intervention group and four in the control group.

Mental confusion

We included a single study in this comparison (N = 200). Data show no clear difference between antacids and placebo or no prophylaxis (RR 1.27, 95% CI 0.61 to 2.67; [Analysis 7.5](#)). Fourteen events occurred in the intervention group and 11 in the control group.

Creatinine increase

We found one relevant study (N = 200). We found no evidence of a clear difference between the two groups (RR 1.17, 95% CI 0.73 to 1.87; [Analysis 7.5](#)). The event occurred in 28 and 24 participants in the two groups, respectively.

Sucralfate versus placebo or no prophylaxis

For this comparison, data on nine of our pre-defined outcomes were available. Among the seven studies that provided data for this comparison, placebo was administered in two studies and no prophylaxis was given in five studies.

Clinically important upper GI bleeding

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 8.1](#)). Data seemed to show a beneficial effect of sucralfate compared with placebo or no prophylaxis with respect to the occurrence of clinically important upper GI bleeding. The event occurred in 6.3% of participants in the intervention group and in 10.8% of participants of the control group (RR 0.53, 95% CI 0.32 to 0.88; seven studies; 598 participants; [Analysis 8.1](#)). We judged the certainty of this evidence as moderate.

Sucralfate versus placebo

We identified two relevant studies (N = 170). Data show no clear difference between sucralfate and placebo (RR 1.40, 95% CI 0.30 to 6.62; [Analysis 8.1](#)). For this comparison, heterogeneity was moderate ($\text{Chi}^2 = 1.53$, $\text{df} = 1.0$ ($P = 0.22$), $I^2 = 35\%$).

Sucralfate versus no prophylaxis

We identified five relevant studies for this comparison (N = 428). We found evidence for a beneficial effect of sucralfate compared with no prophylaxis (RR 0.46, 95% CI 0.26 to 0.80; [Analysis 8.1](#)).

Nosocomial pneumonia

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 8.2](#)). We identified four studies relevant to this outcome (N = 450). Data seemed to show no difference between sucralfate and placebo or no prophylaxis with

respect to the occurrence of ventilator-associated pneumonia. The event occurred in 15.9% and 12.2% of the two groups, respectively (RR 1.33, 95% CI 0.86 to 2.04; [Analysis 8.2](#)). We judged the certainty of this evidence as low.

Sucralfate versus placebo

We identified two relevant studies (N = 170). Data show no clear difference between sucralfate and placebo (RR 1.43, 95% CI 0.49 to 4.16; [Analysis 8.2](#)).

Sucralfate versus no prophylaxis

We found two relevant studies (N = 280). We found no evidence of a clear difference between the two groups (RR 1.30, 95% CI 0.82 to 2.07; [Analysis 8.2](#)). This comparison had moderate heterogeneity ($\text{Chi}^2 = 1.51$, $\text{df} = 1.0$ ($P = 0.22$), $I^2 = 34\%$).

All-cause mortality in ICU

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 8.3](#)). Data seemed to show no difference between sucralfate and placebo or no prophylaxis with respect to all-cause mortality in the ICU. The event occurred in 16.3% and 16.5% in the two groups, respectively (RR 0.97, 95% CI 0.66 to 1.43; five studies; 500 participants). We judged the certainty of this evidence as low.

Sucralfate versus placebo

We identified two relevant studies (N = 170). Data show no clear difference between sucralfate and placebo (RR 0.92, 95% CI 0.48 to 1.80; [Analysis 8.3](#)).

Sucralfate versus no prophylaxis

We found three studies that were relevant to this review (N = 330). We found no evidence of a clear difference between the two groups (RR 0.99, 95% CI 0.62 to 1.60; [Analysis 8.3](#)).

All-cause mortality in hospital

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 8.4](#)). Data seemed to show no difference between sucralfate and placebo or no prophylaxis with respect to all-cause mortality in the hospital. The event occurred in 17.8% and 18.3% in the two groups, respectively (RR 0.97, 95% CI 0.62 to 1.52; two studies; 344 participants).

Sucralfate versus placebo

We included a single study in this comparison (N = 144). Data show no clear difference between sucralfate and placebo (RR 1.09, 95% CI 0.54 to 2.18; [Analysis 8.4](#)).

Sucralfate versus no prophylaxis

We included a single study in this comparison (N = 200). We found no evidence of a clear difference between the two groups (RR 0.89, 95% CI 0.49 to 1.62; [Analysis 8.4](#)).

Duration of ICU stay

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 8.5](#)). Data seemed to show no difference between sucralfate and placebo or no prophylaxis with respect to duration of ICU stay (MD -0.02 days, 95% CI -1.70 to 1.65; two studies; 224 participants). We judged the certainty of this evidence as low.

Sucralfate versus placebo

We found one study that was relevant to this comparison (N = 144). We found no evidence of a clear difference between the two groups (MD -0.70 days, 95% CI -4.07 to 2.67; [Analysis 8.5](#)).

Sucralfate versus no prophylaxis

We found one study that was relevant to this comparison (N = 80). We found no evidence of a clear difference between the two groups (MD 0.20 days, 95% CI -1.73 to 2.13; [Analysis 8.5](#)). We identified one study that did not report sufficient information for inclusion in the meta-analysis ([Ben-Menachem 1994](#)). In this study, the duration of ICU stay was 3 days (2 to 8.5 days) in the sucralfate group (n = 100) and 3 days (2 to 6 days) in the group that received no prophylaxis (n = 100).

Duration of intubation

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 8.6](#)). Data seemed to show no difference between sucralfate and placebo or no prophylaxis with respect to duration of intubation (MD 1.42, 95% CI -0.27 to 3.10; two studies; 224 participants).

Sucralfate versus placebo

We included a single study in this comparison (N = 144). Data show no clear difference between sucralfate and placebo (MD 0.80 days, 95% CI -2.20 to 3.80; [Analysis 8.6](#)).

Sucralfate versus no prophylaxis

We found one study that was relevant to this comparison (N = 80). Data show no clear difference between sucralfate and no prophylaxis (MD 1.70 days, 95% CI -0.34 to 3.74; [Analysis 8.6](#)).

Number of participants requiring blood transfusion

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 8.7](#)). Data seemed to show no difference between sucralfate and no prophylaxis with respect to the number of participants requiring blood transfusion. Blood transfusion was required by 3% and 5% of the two groups, respectively (RR 0.60, 95% CI 0.15 to 2.44; one study; 200 participants). We judged the certainty of this evidence as low.

Units of blood transfused

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 8.8](#)). Data seemed to show an unfavourable effect of sucralfate with respect to the number of units of blood transfused (MD 0.80, 95% CI 0.32 to 1.28; one study; 200 participants).

Adverse events of interventions

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 8.9](#)). For this outcome, we found a single study that measured nausea and vomiting as an adverse event. Data seemed to show no difference between sucralfate and placebo or no prophylaxis with respect to the occurrence of adverse events. The sucralfate group included four participants with nausea and vomiting and the placebo group included none (RR 9.00, 95% CI 0.50 to 161.13; one study; 70 participants).

H2 receptor antagonists versus proton pump inhibitors

For this comparison, data on eight of our pre-defined outcomes were available. Among the 18 studies that provided data for this comparison, ranitidine was administered in nine studies, cimetidine in two, and famotidine in six. Two studies combined the pantoprazole arms ([Fink 2003](#); [Somberg 2008](#)), and one study combined the omeprazole arms to form a common interventional arm for comparison with H2 receptor antagonists ([Powell 1993](#)), as the review did not aim to investigate intraclass efficacy among included interventions. [Tabeeifar 2012](#) compared pantoprazole (n = 11) and ranitidine (n = 8), but reported no outcomes that were of relevance for this review.

Clinically important upper GI bleeding

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 9.1](#)). Data seemed to show increased risk of clinically important upper GI bleeding under H2 receptor antagonists when compared with proton pump inhibitors. The event occurred in 6.9% and 1.7% of participants in the two groups, respectively (RR 2.90, 95% CI 1.83 to 4.58; 13 studies; 1636 participants). Five studies with 525 participants reported that no events occurred in either group. We judged the certainty of this evidence as low.

Cimetidine versus omeprazole

We found one study that was relevant to this comparison (N = 359). We found no evidence of a clear difference between the two groups (RR 1.4, 95% CI 0.55 to 3.61; [Analysis 9.1](#)).

Cimetidine versus pantoprazole

We found one study that was relevant to this comparison (N = 202) ([Somberg 2008](#)). We found no evidence of a difference between the two groups, but no events were reported in either group.

Famotidine versus lansoprazole

We included a single study in this comparison (N = 51). We found no evidence of a clear difference between the two groups (RR 3.63, 95% CI 0.15 to 84.98; [Analysis 9.1](#)).

Famotidine versus omeprazole

We included a single study in this comparison (N = 143). Data show no clear difference between famotidine and omeprazole (RR 2.03, 95% CI 0.19 to 21.87; [Analysis 9.1](#)).

Famotidine versus pantoprazole

We found two studies that were relevant to this comparison (N = 159). Data show no clear difference between famotidine and pantoprazole (RR 0.73, 95% CI 0.18 to 3.04). This comparison had substantial heterogeneity ($\chi^2 = 2.44$, df = 1.0 (P = 0.12), $I^2 = 59\%$; [Analysis 9.1](#)).

Famotidine versus esomeprazole

We identified two relevant studies for this comparison (N = 371). For this outcome, we found evidence suggesting that famotidine seemed to increase the risk for upper GI bleeding compared with esomeprazole (RR 7.53, 95% CI 1.39 to 40.85; [Analysis 9.1](#)).

Ranitidine versus omeprazole

Five studies contributed data to this comparison (N = 413). We found evidence of increased risk of GI bleeding with ranitidine compared with omeprazole (RR 4.08, 95% CI 1.99 to 8.36; [Analysis 9.1](#)). [Powell 1993](#) (N = 31) reported no events in either of the two study arms.

Ranitidine versus pantoprazole

We found two studies that were relevant to this comparison (N = 213). We found no evidence of a clear difference between ranitidine and pantoprazole, and no events were reported in either treatment group ([Analysis 9.1](#)).

Ranitidine versus rabeprazole

We found one study that was relevant to this comparison (N = 140). Data show no clear difference between ranitidine and rabeprazole (RR 9.00, 95% CI 0.49 to 164.09; [Analysis 9.1](#)).

H2 receptor antagonists (not defined) versus proton pump inhibitors (not defined)

We included a single study in this comparison (N = 79) ([Fogas 2013](#)). We found no evidence of a clear difference between the two groups, and no events were reported in either treatment group ([Analysis 9.1](#)).

Nosocomial pneumonia

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 9.2](#)). Data seemed to show no difference between H2 receptor antagonists and proton pump inhibitors with respect to the occurrence of nosocomial pneumonia. The event occurred in 13.3% and 12.1% of participants in the two groups, respectively (RR 1.02, 95% CI 0.77 to 1.35; eight studies; 1256 participants). We judged the certainty of this evidence as low.

Cimetidine versus omeprazole

We found one study that was relevant to this comparison (N = 359). Data show no clear difference between cimetidine and omeprazole (RR 0.84, 95% CI 0.45 to 1.54; [Analysis 9.2](#)).

Cimetidine versus pantoprazole

We identified a single study for this comparison (N = 202). Data show no clear difference between cimetidine and pantoprazole (RR 0.89, 95% CI 0.28 to 2.91; [Analysis 9.2](#)).

Famotidine versus esomeprazole

We included a single study in this comparison (N = 60). Data show no clear difference between famotidine and esomeprazole (RR 1.00, 95% CI 0.07 to 15.26; [Analysis 9.2](#)).

Famotidine versus omeprazole

We included a single study in this comparison (N = 143). Data show no clear difference between famotidine and omeprazole (RR 0.89, 95% CI 0.34 to 2.32; [Analysis 9.2](#)).

Ranitidine versus omeprazole

We identified five relevant studies for this comparison (N = 413). Data show no clear difference between ranitidine and omeprazole

(RR 1.19, 95% CI 0.80 to 1.75; [Analysis 9.2](#)). This comparison had moderate heterogeneity ($\text{Chi}^2 = 6.07$, $\text{df} = 4.0$ ($P = 0.19$), $I^2 = 34\%$).

H2 receptor antagonists (not defined) versus proton pump inhibitors (not defined)

We found one study that was relevant to this comparison (N = 79). Data show no clear difference between H2 receptor antagonists and proton pump inhibitors (RR 1.03, 95% CI 0.47 to 2.26; [Analysis 9.2](#)).

All-cause mortality in ICU

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 9.3](#)). Data seemed to show no difference between H2 receptor antagonists and proton pump inhibitors with respect to all-cause mortality in the ICU. The event occurred in 19.3% and 16.3% of participants in the two groups, respectively (RR 0.96, 95% CI 0.78 to 1.19; 12 studies; 1564 participants). We judged the certainty of this evidence as low.

Cimetidine versus omeprazole

We found one study that was relevant to this comparison (N = 359). We found no evidence of a clear difference between the two groups (RR 0.76, 95% CI 0.45 to 1.30; [Analysis 9.3](#)).

Cimetidine versus pantoprazole

We found one study that was relevant to this comparison (N = 202). We found no evidence of a clear difference between the two groups (RR 0.80, 95% CI 0.25 to 2.55; [Analysis 9.3](#)).

Famotidine versus omeprazole

We found one study that was relevant to this comparison (N = 143). We found no evidence of a clear difference between the two groups (RR 1.13, 95% CI 0.49 to 2.61; [Analysis 9.3](#)).

Ranitidine versus omeprazole

We identified five relevant studies for this comparison (N = 387). We found no evidence of a clear difference between the two groups (RR 1.10, 95% CI 0.86 to 1.40; [Analysis 9.3](#)).

Ranitidine versus pantoprazole

We found three studies that were relevant to this comparison (N = 333). Data show no clear difference between the two groups (RR 0.66, 95% CI 0.31 to 1.43; [Analysis 9.3](#)).

Ranitidine versus rabeprazole

We found one study that was relevant to this comparison (N = 140). We found no evidence of a clear difference between the two groups (RR 3.00, 95% CI 0.12 to 72.40; [Analysis 9.3](#)).

All-cause mortality in the hospital

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 9.4](#)). Data seemed to show no difference between H2 receptor antagonists and proton pump inhibitors with respect to all-cause mortality in the hospital. The event occurred in 5.5% and 7.2% of participants, respectively (RR 0.72, 95% CI 0.37 to 1.43; two studies; 454 participants).

Famotidine versus esomeprazole

We found one study that was relevant to this comparison (N = 311). We found no evidence of a clear difference between the two groups (RR 0.37, 95% CI 0.04 to 3.49; [Analysis 9.4](#)).

Famotidine versus omeprazole

We included a single study in this comparison (N = 143). Data show no clear difference between famotidine and omeprazole (RR 0.80, 95% CI 0.39 to 1.63; [Analysis 9.4](#)).

Duration of ICU stay

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 9.5](#)). Data seemed to show no difference between H2 receptor antagonists and proton pump inhibitors with respect to duration of ICU stay (MD 0.14 days, 95% CI -1.14 to 1.41; five studies; 482 participants). We judged the certainty of this evidence as low.

Famotidine versus esomeprazole

We included a single study in this comparison (N = 60). We found no evidence of a clear difference between the two groups (MD -0.30 days, 95% CI -6.51 to 5.91; [Analysis 9.5](#)).

Famotidine versus omeprazole

We found one study that was relevant to this comparison (N = 143). Data show no clear difference between the two groups (MD 2.40 days, 95% CI -0.44 to 5.24; [Analysis 9.5](#)).

Famotidine versus pantoprazole

We included a single study in this comparison (N = 129). We found no evidence that famotidine was clearly different in its effects compared with pantoprazole, for no standard deviation was reported in the study ([Wee 2013](#)).

Ranitidine versus omeprazole

We found three studies that were relevant to this comparison (N = 279). We found no evidence of a clear difference between the two groups (MD -0.44 days, 95% CI -1.90 to 1.02; [Analysis 9.5](#)).

Ranitidine versus pirenzepine

We identified one study that looked at this outcome but did not report enough data for inclusion in formal meta-analyses ([Hanisch 1998](#)). In the included study, 44 participants received pirenzepine and 57 received ranitidine. The mean duration of ICU stay was 9.9 (2 to 39) days and 9.7 (2 to 95) days in the two groups, respectively.

Duration of intubation

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 9.6](#)). We identified six studies relevant to this outcome (N = 671). However, only five studies contributed data to our meta-analysis. We found no difference between H2 receptor antagonists and proton pump inhibitors with respect to duration of intubation (MD -0.35 days, 95% CI -1.48 to 0.78; five studies; 542 participants).

Famotidine versus omeprazole

We included a single study in this comparison (N = 143). We found no evidence of a clear difference between the two groups (MD 0.70 days, 95% CI -2.24 to 3.64; [Analysis 9.6](#)).

Famotidine versus pantoprazole

We found one study that was relevant to this comparison (N = 129). For this outcome, data seemed to show no difference in effect between famotidine (6.3 days; n = 61) and pantoprazole (6.5 days;

n = 68). However, data (no SD/SE) reported were insufficient for inclusion in study meta-analyses ([Analysis 9.6](#)). We identified an additional study that was published as a conference abstract and did not report enough data for formal meta-analysis ([Wee 2013](#)). Researchers included 61 participants in the famotidine group and 68 in the pantoprazole group. The mean duration of intubation was 6.3 days in the famotidine group and 6.5 days in the pantoprazole group.

Ranitidine versus omeprazole

We identified three relevant studies for this comparison (N = 279). We found no evidence of a clear difference between the two groups (MD -0.78 days, 95% CI -2.24 to 0.67; [Analysis 9.6](#)).

Ranitidine versus pantoprazole

We found one study that was relevant for this comparison (N = 120). Data show no clear difference between ranitidine and pantoprazole (MD 0.07 days, 95% CI -2.18 to 2.32; [Analysis 9.6](#)).

Ranitidine versus pirenzepine

We identified one study that looked at this outcome but did not report enough data for inclusion in formal meta-analyses ([Hanisch 1998](#)). In the included study, 44 participants received pirenzepine and 57 received ranitidine. The mean duration of intubation was 8.2 (2 to 32) days and 8.2 (2 to 93) days in the two groups, respectively.

Number of participants requiring blood transfusion

Data seemed to show no difference between H2 receptor antagonists and proton pump inhibitors with respect to the number of participants requiring blood transfusion (3.8% and 1.7%; RR 1.98, 95% CI 0.75 to 5.21; three studies; 575 participants; [Analysis 9.7](#)). We judged the certainty of this evidence as low.

Cimetidine versus omeprazole

We included a single study in this comparison (N = 359). Data show no clear difference between cimetidine and omeprazole (RR 0.98, 95% CI 0.29 to 3.34; [Analysis 9.7](#)).

Ranitidine versus omeprazole

We found one study that was relevant to this comparison (N = 76). We found no evidence of a clear difference between the two groups (RR 5.00, 95% CI 0.25 to 100.80; [Analysis 9.7](#)).

Ranitidine versus rabeprazole

We included a single study in this comparison (N = 140). Data show no clear difference between ranitidine and rabeprazole (RR 9.00, 95% CI 0.49 to 164.09; [Analysis 9.7](#)).

Adverse events of interventions

For this outcome, we found five relevant studies and categorised data according to 12 adverse events.

Pyrexia

We identified a single study that reported on this adverse event (N = 202). Data show no clear difference between H2 receptor antagonists and proton pump inhibitors (RR 0.93, 95% CI 0.05 to 19.03; [Analysis 9.8](#)).

Thrombocytopenia

Two relevant studies reported on this adverse event (N = 253). Data show no clear difference between H2 receptor antagonists and proton pump inhibitors for thrombocytopenia (RR 3.64, 95% CI 0.65 to 20.46; [Analysis 9.8](#)).

Neuroleptic malignant syndrome

We identified a single study that reported on this adverse event (N = 202). We found no evidence of a clear difference between the two groups (RR 1.56, 95% CI 0.06 to 37.42; [Analysis 9.8](#)).

Cholestatic jaundice

We found one study that reported on this adverse event (N = 202). We found no evidence of a clear difference between the two groups (RR 1.56, 95% CI 0.06 to 37.42; [Analysis 9.8](#)).

Abnormal liver function test

A single study reported on this adverse event (N = 202). Data show no clear difference between H2 receptor antagonists and proton pump inhibitors (RR 1.56, 95% CI 0.06 to 37.42; [Analysis 9.8](#)).

Pruritus

We found one study that reported on this adverse event (N = 202). Data show no clear difference between H2 receptor antagonists and proton pump inhibitors (RR 1.56, 95% CI 0.06 to 37.42; [Analysis 9.8](#)).

Phlebitis

A single study reported on this adverse event (N = 202). Data show no clear difference between H2 receptor antagonists and proton pump inhibitors (RR 1.56, 95% CI 0.06 to 37.42; [Analysis 9.8](#)).

Major cardiovascular events

We found a single study that reported on this adverse event (N = 311). We found no evidence of a clear difference between the two groups (RR 0.79, 95% CI 0.26 to 2.43; [Analysis 9.8](#)).

Abdominal distension and vomiting

We included a single study in this comparison (N = 90). We found no evidence of a clear difference between the two groups (RR 1.15, 95% CI 0.62 to 2.14; [Analysis 9.8](#)).

Hypomagnesaemia

We included a single study in this comparison (N = 129). We found no evidence of a clear difference between the two groups (RR 0.43, 95% CI 0.16 to 1.13; [Analysis 9.8](#)).

Nausea and vomiting

We included a single study in this comparison (N = 129). We found no evidence of a clear difference between the two groups (RR 0.48, 95% CI 0.13 to 1.77; [Analysis 9.8](#)).

C difficile-related diarrhoea

We included a single study in this comparison (N = 129). We found no evidence of a clear difference between the two groups (RR 1.11, 95% CI 0.16 to 7.67; [Analysis 9.8](#)).

H2 receptor antagonists versus antacids

For this comparison, data on seven of our pre-defined outcomes were available. Among the 18 studies that provided data for

this comparison, ranitidine was administered in four studies and cimetidine in 13; one study included four arms (ranitidine, cimetidine, famotidine, and antacids) ([Lamothe 1991](#)). H2 receptor antagonists were combined to form a common interventional arm versus antacids, as the review did not aim to investigate intraclass efficacy among included interventions. [Tryba 1985](#) administered pirenzepine as a concomitant medication to both cimetidine and antacid arms.

Clinically important upper GI bleeding

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 10.1](#)). In the 16 included studies, 884 participants received ranitidine, cimetidine, or famotidine, and 816 received antacids. Clinically important upper GI bleeding occurred in 8.4% and 8.6% of participants in both groups. Data seemed to show no difference between the two groups with respect to the occurrence of clinically important upper GI bleeding (RR 0.96, 95% CI 0.67 to 1.36; 16 studies; 1700 participants). We judged the certainty of this evidence as low.

Nosocomial pneumonia

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 10.2](#)). In the four included studies, 288 participants received ranitidine or cimetidine, and 293 received antacids. Nosocomial pneumonia occurred in 29.2% and 28.0% of participants in the two groups, respectively. Data seemed to show no difference between the two groups with respect to the occurrence of the outcome of interest (RR 1.05, 95% CI 0.81 to 1.36). We judged the certainty of this evidence as low.

Cimetidine versus antacids

We identified two relevant studies for this comparison (N = 136). Data show no clear difference between cimetidine and antacids (RR 1.24, 95% CI 0.70 to 2.19; [Analysis 10.2](#)).

Ranitidine versus antacids

We included two relevant studies in this comparison (N = 445). Data show no clear difference between ranitidine and antacids (RR 1.00, 95% CI 0.75 to 1.34; [Analysis 10.2](#)).

All-cause mortality in ICU

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 10.3](#)). In the 11 included studies, 472 participants received cimetidine, 33 received cimetidine plus pirenzepine, and 178 received ranitidine. Overall, 638 participants received antacids. [Tryba 1985](#) administered pirenzepine as a concomitant medication to both cimetidine and antacid arms. All-cause mortality occurred in 16.1% and 16.3% of the participants in both groups. Data seemed to show no difference between the two groups with respect to all-cause mortality (RR 1.01, 95% CI 0.66 to 1.55). We judged the certainty of this evidence as very low.

Cimetidine versus antacids

We found eight studies that were relevant to this comparison (N = 885). We found no evidence of a clear difference between the two groups (RR 1.05, 95% CI 0.69 to 1.59). Heterogeneity was moderate ($\chi^2 = 10.02$, df = 7.0 (P = 0.19), $I^2 = 30\%$; [Analysis 10.3](#)).

Cimetidine plus pirenzepine versus antacid plus pirenzepine

We included a single study in this comparison (N = 66). We found no evidence of a clear difference between the two groups (RR 1.25, 95% CI 0.37 to 4.25; [Analysis 10.3](#)).

Ranitidine versus antacids

We found two studies that were relevant to this comparison (N = 370). We found no evidence of a clear difference between the two groups (RR 1.13, 95% CI 0.14 to 8.97). This comparison had considerable heterogeneity ($\text{Chi}^2 = 6.71$, $\text{df} = 1.0$ ($P = 0.01$), $I^2 = 85\%$; [Analysis 10.3](#)).

All-cause mortality in hospital

We classified the study on the basis of its intervention and comparison arms (as shown in [Analysis 10.4](#)). In the single included study, 80 participants received ranitidine and 81 received antacids. The event occurred in 33.8% and 39.5% of participants in the two groups. Data seemed to show no difference between the two groups with respect to all-cause mortality in the hospital (RR 0.85, 95% CI 0.57 to 1.29).

Duration of intubation

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 10.5](#)). In the three included studies, 64 participants received cimetidine and 57 received antacids. Data seemed to show no difference between the two groups with respect to duration of intubation (MD -0.81 days, 95% CI -3.85 to 2.23).

Number of participants requiring blood transfusions

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 10.6](#)). In the six included studies, 379 participants received cimetidine or ranitidine and 365 received antacids. The event occurred in 8.2% and 3.0% of participants in both groups. Data seemed to show increased risk of blood transfusion in the H2 receptor antagonists arm compared with the antacids arm (RR 2.49, 95% CI 1.35 to 4.62). We judged the certainty of this evidence as moderate.

Cimetidine versus antacids

We found five studies that were relevant to this comparison (N = 583). We found evidence of a difference between cimetidine and antacids (RR 2.47, 95% CI 1.32 to 4.63; [Analysis 10.6](#)). Results favour the antacids arm.

Ranitidine versus antacids

We included a single study in this comparison (N = 161). We found no evidence of a clear difference between the two groups (RR 3.04, 95% CI 0.13 to 73.46; [Analysis 10.6](#)).

Number of units of blood transfused

We identified one study that addressed this outcome but did not report enough data for inclusion in a formal meta-analysis ([Priebe 1980](#)). The study included 38 participants who received cimetidine and 37 who received antacids. Blood transfusions were required only for participants with GI bleeding, all of whom were included in the cimetidine group. It was reported that one participant received two units of blood and three participants received a total of four units of blood.

Adverse events of interventions

We identified 12 studies relevant to this outcome and divided the data into 12 groups according to adverse events.

Diarrhoea

We found seven studies that were relevant to this comparison (N = 863). We found evidence of a difference between H2 receptor antagonists and antacids. Diarrhoea occurred in 2.1% and 10.4% of participants in the two groups, respectively (RR 0.23, 95% CI 0.13 to 0.43; six studies; 777 participants; [Analysis 10.7](#)). Results favour the H2 receptor antagonist arm. This comparison had moderate heterogeneity ($\text{Chi}^2 = 11.3$, $\text{df} = 5.0$ ($P = 0.05$), $I^2 = 56\%$).

Thrombocytopaenia

We found four studies that were relevant to this comparison (N = 452). We found no evidence of a clear difference between the two groups (RR 1.40, 95% CI 0.93 to 2.09; [Analysis 10.7](#)). This comparison had moderate heterogeneity ($\text{Chi}^2 = 5.88$, $\text{df} = 3.0$ ($P = 0.12$), $I^2 = 49\%$).

Nausea and vomiting

We included four relevant studies in this comparison (N = 380). We found no evidence of a clear difference between the two groups (RR 0.46, 95% CI 0.19 to 1.1; [Analysis 10.7](#)).

Hypophosphataemia

We included two relevant studies in this comparison (N = 108). Data show no clear difference between H2 receptor antagonists and antacids (RR 0.24, 95% CI 0.04 to 1.3; [Analysis 10.7](#)).

Hypomagnesaemia

We included a single study in this comparison (N = 22). We found no evidence of a clear difference between the two groups (RR 0.33, 95% CI 0.02 to 7.39; [Analysis 10.7](#)).

Increase in creatinine

We found two studies that were relevant to this comparison (N = 286). Data show no clear difference between H2 receptor antagonists and antacids (RR 0.85, 95% CI 0.56 to 1.28; [Analysis 10.7](#)).

Mental confusion

We found four studies that were relevant to this comparison (N = 476). We found no evidence of a clear difference between the two groups (RR 1.26, 95% CI 0.77 to 2.07; [Analysis 10.7](#)).

Hypermagnesaemia

We included two relevant studies in this comparison (N = 115). Data show no clear difference between H2 receptor antagonists and antacids (RR 0.58, 95% CI 0.17 to 2.03; [Analysis 10.7](#)).

Rash/Erythema

We found two studies that were relevant to this comparison (N = 231). We found no evidence of a clear difference between the two groups (RR 3.02, 95% CI 0.32 to 28.53; [Analysis 10.7](#)).

Alkalosis

Alkalosis is a primary rise in the plasma bicarbonate concentration. We included a single study in this comparison (N = 75). We found

no evidence of a clear difference between the two groups (RR 0.32, 95% CI 0.01 to 7.73; [Analysis 10.7](#)).

Dryness of mouth

We included a single study in this comparison (N = 67). We found no evidence of a clear difference between the two groups (RR 5.15, 95% CI 0.26 to 103.33; [Analysis 10.7](#)).

Leucopaenia

We included a single study in this comparison (N = 161). We found no evidence of a clear difference between the two groups (RR 3.04, 95% CI 0.13 to 73.46; [Analysis 10.7](#)).

H2 receptor antagonists versus sucralfate

For this comparison, data on nine of our pre-defined outcomes were available. Among the 25 studies that provided data for this comparison, ranitidine was administered in 15 studies, cimetidine in seven, and famotidine in two. [Tryba 1985](#) administered pirenzepine as a concomitant medication to both cimetidine and sucralfate arms. Two studies randomised participants to more than one arm of H2 receptor antagonists (cimetidine bolus and continuous infusion) ([Fabian 1993](#); [Ortiz 1998](#)). These arms were combined to form a common interventional arm versus sucralfate, as the review did not aim to investigate efficacy based on dose or mode of administration of the same drug. We included one study that compared ranitidine (n = 15) with sucralfate (n = 15) but did not provide data on any of the outcomes relevant to this review.

Clinically important upper GI bleeding

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 11.1](#)). In the 24 included studies, 1761 participants received ranitidine, cimetidine, or famotidine, and 1638 received sucralfate. Clinically important upper GI bleeding occurred in 7.6% and 6.6% of participants in the two groups, respectively. Data seemed to show no difference between the two groups with respect to the occurrence of clinically important upper GI bleeding (RR 1.10, 95% CI 0.87 to 1.41; 24 studies; 3316 participants). An additional study with 83 participants reported no events of clinically important upper GI bleeding in either treatment group ([Pickworth 1993](#)). We judged the certainty of this evidence as low.

Cimetidine versus sucralfate

We included seven relevant studies in this comparison (N = 873). We found no evidence of a clear difference between the two groups (RR 1.37, 95% CI 0.87 to 2.14; [Analysis 11.1](#)).

Famotidine versus sucralfate

We included two relevant studies in this comparison (N = 190). Data show no clear difference between H2 receptor antagonists and sucralfate (RR 0.62, 95% CI 0.21 to 1.78; [Analysis 11.1](#)).

Ranitidine versus sucralfate

We found 14 studies that were relevant to this comparison (N = 2186). Data show no clear difference between H2 receptor antagonists and sucralfate (RR 1.03, 95% CI 0.76 to 1.39; [Analysis 11.1](#)). An additional study with 83 participants reported no events of clinically important upper GI bleeding in either treatment group ([Pickworth 1993](#)).

Cimetidine plus pirenzepine versus sucralfate plus pirenzepine

We included a single study in this comparison (N = 67). We found no evidence of a clear difference between the two groups (RR 5.15, 95% CI 0.26 to 103.33; [Analysis 11.1](#)).

Nosocomial pneumonia

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 11.2](#)). In the 17 included studies, 1547 participants received ranitidine or cimetidine or famotidine, and 1460 received sucralfate. Nosocomial pneumonia occurred in 23.5% and 18.9% of participants in both groups. Data seemed to show increased risk of nosocomial pneumonia in the H2 receptor antagonist group compared with the sucralfate group (RR 1.22, 95% CI 1.07 to 1.40; 17 studies; 3041 participants). We judged the certainty of the evidence as moderate.

Cimetidine versus sucralfate

We included five relevant studies in this comparison (N = 758). Data show no clear difference between cimetidine and sucralfate (RR 1.13, 95% CI 0.87 to 1.47; [Analysis 11.2](#)).

Famotidine versus sucralfate

We found one study that was relevant to this comparison (N = 140). We found no evidence of a clear difference between the two groups (RR 1.13, 95% CI 0.40 to 3.20; [Analysis 11.2](#)).

Ranitidine versus sucralfate

We found 11 studies that contributed data to this comparison (N = 2143). For this outcome, within this comparison, we found evidence suggesting that ranitidine was clearly different in its effects compared with sucralfate (RR 1.26, 95% CI 1.07 to 1.48; [Analysis 11.2](#)). One study with 70 participants reported no events in either treatment arm ([Lopez-Herce 1992](#)).

All-cause mortality in ICU

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 11.3](#)). In the 21 included studies (N = 3178), 1652 participants received cimetidine, ranitidine, or famotidine, and 1526 received sucralfate. All-cause mortality occurred in 22.0% and 20.4% of participants in both groups. We found no difference between the two groups with respect to all-cause mortality in the ICU (RR 1.09, 95% CI 0.95 to 1.24). We judged the certainty of this evidence as low.

Cimetidine versus sucralfate

We found six studies that were relevant to this comparison (N = 814). Data show no clear difference between H2 receptor antagonists and sucralfate (RR 1.18, 95% CI 0.91 to 1.54; [Analysis 11.3](#)).

Famotidine versus sucralfate

We found two studies that were relevant to this comparison (N = 190). We found no evidence of a clear difference between the two groups (RR 1.23, 95% CI 0.69 to 2.19; [Analysis 11.3](#)).

Ranitidine versus sucralfate

We included 12 relevant studies in this comparison (N = 2107). We found no evidence of a clear difference between the two groups (RR 1.04, 95% CI 0.88 to 1.22; [Analysis 11.3](#)).

Cimetidine plus pirenzepine versus sucralfate plus pirenzepine

We included a single study in this comparison (N = 67). We found no evidence of a clear difference between the two groups (RR 1.29, 95% CI 0.38 to 4.38; [Analysis 11.3](#)).

All-cause mortality in hospital

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 11.4](#)). In the four included studies (N = 717), 366 participants received cimetidine, ranitidine, or famotidine, and 351 received sucralfate. All-cause mortality in the hospital occurred in 22.7% and 20.2% of participants in both groups. Data showed no significant differences between the two groups (RR 1.14, 95% CI 0.86 to 1.50).

Cimetidine versus sucralfate

We found two studies that were relevant to this comparison (N = 413). Data show no clear difference between H2 receptor antagonists and sucralfate (RR 1.28, 95% CI 0.86 to 1.92; [Analysis 11.4](#)). For this comparison, heterogeneity was moderate ($\text{Chi}^2 = 1.9$, $\text{df} = 1.0$ ($P = 0.17$), $I^2 = 47\%$).

Ranitidine versus sucralfate

We included a single study in this comparison (N = 164). We found no evidence of a clear difference between the two groups (RR 1.11, 95% CI 0.71 to 1.74; [Analysis 11.4](#)).

Famotidine versus sucralfate

We included a single study in this comparison (N = 140). Data show no clear difference between H2 receptor antagonists and sucralfate (RR 0.82, 95% CI 0.40 to 1.71; [Analysis 11.4](#)).

Duration of intubation

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 11.5](#)). In the 10 included studies (N = 1751), 864 participants received cimetidine, ranitidine, or famotidine, and 887 received sucralfate. Data seemed to show no difference between the two groups with respect to duration of intubation (MD 0.22 days, 95% CI -1.55 to 2.00). This outcome had considerable heterogeneity ($\text{Chi}^2 = 50.79$, $\text{df} = 9.0$ ($P = 0.0$), $I^2 = 82\%$).

Cimetidine versus sucralfate

We identified two relevant studies for this comparison (N = 97). Data show no clear difference between H2 receptor antagonists and sucralfate (MD 0.58 days, 95% CI -1.71 to 2.87; [Analysis 11.5](#)). We identified an additional study that did not provide enough data for formal meta-analysis ([Kappstein 1991](#)). Of the included participants, 55 received cimetidine and 49 received sucralfate. The mean duration of mechanical ventilation was 5.36 days in the cimetidine group and 5.02 days in the sucralfate group. We identified an additional study that did not report enough data on the duration of intubation for inclusion in a formal meta-analysis ([Ryan 1993](#)). This study included 56 participants in the cimetidine group and 58 in the sucralfate group. The mean duration of intubation was 5.1 days in the cimetidine group and 5.6 days in the sucralfate group.

Famotidine versus sucralfate

We included a single study in this comparison (N = 140). Data show no clear difference between H2 receptor antagonists and sucralfate (MD 0.40 days, 95% CI -2.30 to 3.10; [Analysis 11.5](#)).

Ranitidine versus sucralfate

We included seven relevant studies in this comparison (N = 1514). Data show no clear difference between H2 receptor antagonists and sucralfate (MD 0.15 days, 95% CI -2.12 to 2.43; [Analysis 11.5](#)). For this outcome, heterogeneity was considerable ($\text{Chi}^2 = 45.57$, $\text{df} = 6.0$ ($P = 0.0$), $I^2 = 86\%$). [Cook 1998](#) reported insufficient data for inclusion in our meta-analyses. The median duration of intubation was seven days and eight days, respectively, in the ranitidine group (n = 596) and the sucralfate group (n = 604).

Duration of ICU stay

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 11.6](#)). In the six included studies (N = 1791), 904 participants received ranitidine or famotidine and 887 received sucralfate. Data seemed to show no difference between the two groups with respect to duration of ICU stay (MD 0.01 days, 95% CI -1.92 to 1.95). For this outcome, heterogeneity was considerable ($\text{Chi}^2 = 28.48$, $\text{df} = 5.0$ ($P = 0.0$), $I^2 = 82\%$) and heterogeneity could not be explained by differences among the different subcomparisons. We judged the certainty of this evidence as very low.

Cimetidine versus sucralfate

We found one study that was relevant to this comparison (N = 213). We found no evidence of a clear difference between the two groups (MD 0.0 days, 95% CI -3.05 to 3.05; [Analysis 11.6](#)). Another study with 300 participants did not provide sufficient data for inclusion in our meta-analyses, but data seemed to show no difference between cimetidine (median number of days = 4; n = 100) and sucralfate (median number of days = 3; n = 100) or control (median number of days = 3; n = 100) with respect to duration of ICU stay ([Ben-Menachem 1994](#)).

Famotidine versus sucralfate

We found one study that was relevant to this comparison (N = 140). We found no evidence of a clear difference between the two groups (MD 2.2 days, 95% CI -0.96 to 5.36; [Analysis 11.6](#)).

Ranitidine versus sucralfate

We found four studies that were relevant to this comparison (N = 1438). We found no evidence of a clear difference between the two groups (MD -0.43 days, 95% CI -2.70 to 1.84; [Analysis 11.6](#)). This comparison had considerable heterogeneity ($\text{Chi}^2 = 21.37$, $\text{df} = 3.0$ ($P = 0.0$), $I^2 = 85\%$). [Cook 1998](#) reported insufficient data for inclusion in meta-analyses. The median length of ICU stay in both groups was nine days (n = 596 and 604, respectively).

Number of participants requiring blood transfusion

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 11.7](#)). In the nine included studies (N = 1095), 603 participants received cimetidine or ranitidine and 492 received sucralfate. Blood transfusions were required by 4.5% and 3.5% of participants in the two groups. Data seemed to show no difference between study arms with respect to the number of participants requiring blood transfusion (RR 1.25, 95% CI 0.70 to 2.23). We judged the certainty of this evidence as low.

Cimetidine versus sucralfate

We included five relevant studies in this comparison (N = 732). We found no evidence of a clear difference between the two groups (RR 1.00, 95% CI 0.47 to 2.16; [Analysis 11.7](#)).

Ranitidine versus sucralfate

We found four studies that were relevant to this comparison (N = 363). We found no evidence of a clear difference between the two groups (RR 1.77, 95% CI 0.71 to 4.39; [Analysis 11.7](#)).

Units of blood transfused

We classified the single study that contributed data for this outcome from its intervention and comparison arms (as shown in [Analysis 11.8](#)) ([Ben-Menachem 1994](#)). In the included study (N = 200), 100 participants received cimetidine and 100 received sucralfate. The mean number of units of blood transfused was 1.6 (1.3) and 2.0 (2.0). Data seemed to show no difference between the two groups with respect to the mean number of units of blood transfused (MD -0.40, 95% CI -0.87 to 0.07). An additional study did not provide enough data (no SE or SD reported) for inclusion in formal meta-analysis ([Fabian 1993](#)). This study reported that the mean number of required blood transfusions was 9.0 in the sucralfate group (n = 206) and 10.3 in the cimetidine group (n = 410).

Adverse events of interventions

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 11.9](#)). We identified six studies relevant to this outcome and divided the data from these studies according to eight adverse events.

Thrombocytopaenia

We found two studies that were relevant to this adverse event (N = 240). We found no evidence of a clear difference between the two groups (RR 4.72, 95% CI 0.56 to 39.47; [Analysis 11.9](#)).

Nausea and vomiting

We found two studies that were relevant to this comparison (N = 137). Nausea and vomiting seemed to be reduced in the H2 receptor antagonists arm (RR 0.07, 95% CI 0.01 to 0.54; two studies; 137 participants; [Analysis 11.9](#)).

Hypermagnesaemia

We found one study that was relevant to this adverse event (N = 40). Data show no clear difference between H2 receptor antagonists and sucralfate (RR 2.71, 95% CI 0.31 to 23.93; [Analysis 11.9](#)).

Rash/Erythema

We found two relevant studies for this adverse event (N = 233). We found no evidence of a clear difference between the two groups (RR 3.06, 95% CI 0.32 to 28.87; [Analysis 11.9](#)).

Confusion

We identified three relevant studies for this adverse event (N = 382). We found no evidence of a clear difference between the two groups (RR 4.48, 95% CI 0.77 to 26.0; [Analysis 11.9](#)).

Neutropaenia

We found one study that was relevant to this adverse event (N = 114). We found no evidence of a clear difference between the two groups (RR 5.18, 95% CI 0.25 to 105.47; [Analysis 11.9](#)).

Dryness of mouth

We identified a single study for this adverse event (N = 67). Data show no clear difference between H2 receptor antagonists and sucralfate for this adverse event (RR 5.15, 95% CI 0.26 to 103.33; [Analysis 11.9](#)).

Leucopaenia

We found one study that was relevant to this adverse event (N = 163). We found no evidence of a clear difference between the two groups (RR 3.11, 95% CI 0.13 to 75.26; [Analysis 11.9](#)).

H2 receptor antagonists versus anticholinergics

For this comparison, data on five of our pre-defined outcomes were available. Among the four studies that provided data for this comparison, ranitidine was administered in two studies, cimetidine in one, and famotidine in one.

Clinically important upper GI bleeding

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 12.1](#)). In the three included studies (N = 556), 285 participants received either ranitidine or cimetidine, and 271 received pirenzepine. Clinically important upper GI bleeding occurred in 4.2% and 3.0% of participants in the two groups. Data seemed to show no difference between the two groups with respect to the occurrence of clinically important upper GI bleeding (RR 1.37, 95% CI 0.58 to 3.26). We rated the certainty of this evidence as low.

Cimetidine versus pirenzepine

We included a single study in this comparison (N = 55). Data show no clear difference between H2 receptor antagonists and anticholinergics (RR 1.45, 95% CI 0.26 to 7.99; [Analysis 12.1](#)).

Ranitidine versus pirenzepine

We included two relevant studies in this comparison (N = 501). For this comparison, we found no evidence of a clear difference between the two groups (RR 1.35, 95% CI 0.50 to 3.67; [Analysis 12.1](#)).

Nosocomial pneumonia

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 12.2](#)). In the three included studies (N = 544), 279 participants received ranitidine or famotidine, and 265 received pirenzepine. Nosocomial pneumonia occurred in 6.5% and 5.3% of participants in both groups. Data seemed to show no difference between the two groups with respect to occurrence of the outcome of interest (RR 0.96, 95% CI 0.50 to 1.84). We judged the certainty of this evidence as low.

Famotidine versus pirenzepine

We found one study that was relevant to this comparison (N = 43). Data show no clear difference between H2 receptor antagonists and anticholinergics (RR 0.32, 95% CI 0.01 to 7.42; [Analysis 12.2](#)).

Ranitidine versus pirenzepine

We found two studies that were relevant to this comparison (N = 501). Data show no clear difference between H2 receptor antagonists and anticholinergics (RR 1.03, 95% CI 0.53 to 2.01). This comparison had moderate heterogeneity ($\chi^2 = 1.42$, df = 0.23 (P = 0.11), $I^2 = 30\%$; [Analysis 12.2](#)).

All-cause mortality in ICU

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 12.3](#)). In the two included studies (N = 501), 257 participants received ranitidine and 244 received pirenzepine. All-cause mortality occurred in 5.8% and 6.6% of participants in the two groups. Data seemed to show no difference between the two groups with respect to occurrence of the outcome of interest (RR 0.89, 95% CI 0.21 to 3.87). This outcome had substantial heterogeneity ($\chi^2 = 4.08$, df = 1.0 (P = 0.04), $I^2 = 75\%$). We judged the certainty of this evidence as very low.

Duration of ICU stay

We identified one study that looked at this outcome but did not report sufficient data for inclusion in formal meta-analyses ([Hanisch 1998](#)). In the included study, 57 participants received ranitidine and 44 received pirenzepine. The mean duration of ICU stay was 9.7 days (2 to 95) and 9.9 days (2 to 39), respectively.

Duration of intubation

We identified one study that looked at this outcome but did not report sufficient data for inclusion in formal meta-analyses ([Hanisch 1998](#)). In the included study, 57 participants received ranitidine and 44 received pirenzepine. The mean duration of mechanical ventilation was 8.2 days (2 to 93) and 8.0 days (2 to 32), respectively.

Number of participants requiring blood transfusions

We classified the study on the basis of its intervention and comparison arms (as shown in [Analysis 12.4](#)). In the included study, 57 participants received ranitidine and 44 received pirenzepine. The event occurred in 5.3% and 6.8% of participants in the two groups. Data seemed to show no difference between the two groups with respect to the number of participants requiring blood transfusion (RR 0.77, 95% CI 0.16 to 3.64). We judged the certainty of this evidence as low.

Number of units of blood transfused

We identified one study that looked at this outcome but did not report sufficient data for inclusion in formal meta-analyses ([Hanisch 1998](#)). In the included study, 57 participants received ranitidine and 44 received pirenzepine. The mean number of units of blood transfused was two units for each of the three participants with GI bleeding in the ranitidine group, and four units for each of the four participants with GI bleeding in the pirenzepine group.

Adverse events of interventions

We classified studies on the basis of their intervention and comparison arms and adverse events of interventions (as shown in [Analysis 12.5](#)). Researchers reported no adverse events other than tachycardia and high temperature.

Tachycardia

A single study looked at this adverse event (N = 55). Data show no clear difference between H2 receptor antagonists and anticholinergics for tachycardia (RR 0.11, 95% CI 0.01 to 1.90; [Analysis 12.5](#)).

High temperature

We found one study that looked at this adverse event (N = 43). For this adverse event, we found no evidence of a clear difference between the two groups (RR 0.53, 95% CI 0.21 to 1.32; [Analysis 12.5](#)).

H2 receptor antagonists versus prostaglandin analogues

For this comparison, data on two of our pre-defined outcomes were available. One study provided data for this comparison. Study groups received ranitidine (n = 64) and misoprostol (n = 63), respectively. The only outcomes measured that were relevant for this review were clinically important upper GI bleeding and all-cause mortality in the ICU.

Clinically important upper GI bleeding

We classified this study on the basis of intervention and comparison arms (as shown in [Analysis 13.1](#)). In the single included study, 64 participants received cimetidine and 63 received misoprostol. Clinically important upper GI bleeding occurred in 4.7% and 11.1% of participants in the two groups. Data seemed to show no difference between the two groups with respect to the occurrence of clinically important upper GI bleeding (RR 0.42, 95% CI 0.11 to 1.56). We judged the certainty of this evidence as low.

All-cause mortality in ICU

We classified this study on the basis of intervention and comparison arms (as shown in [Analysis 13.2](#)). In the included study, 64 participants received cimetidine and 63 received misoprostol. All-cause mortality occurred in 39.1% and 30.2% of participants in the two groups. Data seemed to show no difference between the two groups with respect to all-cause mortality (RR 1.30, 95% CI 0.80 to 2.10). We judged the certainty of this evidence as moderate.

H2 receptor antagonists versus teprenone

For this comparison, data on three of our pre-defined outcomes were available. One study provided data for this comparison. Study groups received ranitidine or teprenone, respectively. The only outcomes measured that were relevant for this review were clinically important upper GI bleeding, all-cause mortality in the ICU, and number of participants requiring blood transfusion.

Clinically important upper GI bleeding

We classified this study on the basis of intervention and comparison arms (as shown in [Analysis 14.1](#)). In the included study, 70 participants received ranitidine and 70 received teprenone. Clinically important upper GI bleeding occurred in 5.7% and 5.7% of participants in the two groups. Data seemed to show no difference between the two groups with respect to the occurrence of clinically important upper GI bleeding (RR 1.00, 95% CI 0.26 to 3.84). We judged the certainty of this evidence as low.

All-cause mortality in ICU

We classified this study on the basis of intervention and comparison arms (as shown in [Analysis 14.2](#)). In the included study, 70

participants received ranitidine and 70 received teprenone. All-cause mortality in the ICU occurred in 1.4% and 1.4% of participants in the two groups. Data seemed to show no difference between the two groups with respect to all-cause mortality (RR 1.00, 95% CI 0.06 to 15.67). We judged the certainty of this evidence as moderate.

Number of participants requiring blood transfusions

We classified this study on the basis of intervention and comparison arms (as shown in [Analysis 14.3](#)). In the included study, 70 participants received ranitidine and 70 received teprenone. Blood transfusions were required by 5.7% and 5.7% of participants in both groups. Data seemed to show no difference between the two groups with respect to the number that needed blood transfusion (RR 1.00, 95% CI 0.26 to 3.84). We judged the certainty of this evidence as moderate.

H2 receptor antagonists plus antacids versus sucralfate

For this comparison, data on six of our pre-defined outcomes were available. Among the three studies that provided data for this comparison, cimetidine was administered in [Cioffi 1994](#), ranitidine was administered in [Sirvent 1994](#), and either ranitidine or cimetidine was administered in [Driks 1987](#), along with antacids, and outcomes were compared with those following administration of sucralfate.

Clinically important upper GI bleeding

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 15.1](#)). In the two included studies that contributed data to this outcome, 119 participants received ranitidine or cimetidine plus antacids, and 111 received sucralfate. Clinically important upper GI bleeding occurred in 1.7% and 8.1% of participants in the two groups. Data seemed to show a beneficial effect of H2 receptor antagonists plus antacids compared with sucralfate with respect to the occurrence of upper GI bleeding (RR 0.24, 95% CI 0.06 to 0.95). We judged the certainty of this evidence as moderate.

Cimetidine plus antacids versus sucralfate

We included a single study in this comparison (N = 100). We found no evidence of a clear difference between the two groups (RR 0.14, 95% CI 0.01 to 2.70).

Ranitidine plus antacids versus sucralfate

We included a single study in this comparison (N = 51) ([Sirvent 1994](#)). We found no evidence of a clear difference between the two groups, for no events were reported in either treatment group.

Cimetidine or ranitidine plus antacids versus sucralfate

We included a single study in this comparison (N = 130). We found no evidence of a clear difference between the two groups (RR 0.29, 95% CI 0.06 to 1.41).

Nosocomial pneumonia

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 15.2](#)). In the three included studies, 144 participants received cimetidine or ranitidine plus antacids, and 137 received sucralfate. Nosocomial pneumonia occurred in 25.0% and 24.1% of participants in the two groups. For this outcome, heterogeneity was substantial ($\chi^2 = 6.36$, $df = 2.0$ ($P = 0.04$), $I^2 = 69\%$), and data seemed to show no difference between

the two groups with respect to the occurrence of nosocomial pneumonia (RR 1.09, 95% CI 0.51 to 2.32). We judged the certainty of this evidence as very low.

Cimetidine plus antacids versus sucralfate

We included a single study in this comparison (N = 100). We found no evidence of a clear difference between the two groups (RR 0.53, 95% CI 0.26 to 1.07).

Ranitidine plus antacids versus sucralfate

We included a single study in this comparison (N = 51). We found no evidence of a clear difference between the two groups (RR 1.27, 95% CI 0.64 to 2.53).

Cimetidine or ranitidine plus antacids versus sucralfate

We included a single study in this comparison (N = 130). We found no evidence of a clear difference between the two groups (RR 2.02, 95% CI 0.89 to 4.58).

All-cause mortality in ICU

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 15.3](#)). In the two included studies, 119 participants received cimetidine or ranitidine plus antacids, and 111 received sucralfate. All-cause mortality occurred in 35.3% and 25.2% of participants in the two groups. Data seemed to show no difference between the two groups with respect to all-cause mortality in the ICU (RR 1.38, 95% CI 0.92 to 2.05).

Cimetidine plus antacids versus sucralfate

We included a single study in this comparison (N = 100). We found no evidence of a clear difference between the two groups (RR 1.00, 95% CI 0.46 to 2.19).

Cimetidine or ranitidine plus antacids versus sucralfate

We included a single study in this comparison (N = 130). We found no evidence of a clear difference between the two groups (RR 1.57, 95% CI 0.99 to 2.50).

Duration of ICU stay

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 15.4](#)). In the included study, 69 participants received cimetidine or ranitidine plus antacids, and 61 received sucralfate. Data seemed to show no difference between the two groups with respect to duration of ICU stay (MD 3.60 days, 95% CI -1.11 to 8.31). We judged the certainty of this evidence as low.

Duration of intubation

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 15.5](#)). In the two included studies, 119 participants received cimetidine or ranitidine plus antacids, and 111 received sucralfate. Data seemed to show no difference in duration of intubation for both study groups (MD -1.24 days, 95% CI -13.82 to 11.33). Heterogeneity was substantial for this outcome ($\chi^2 = 4.32$, $df = 1.0$ ($P = 0.04$), $I^2 = 77\%$).

Cimetidine plus antacids versus sucralfate

We included a single study in this comparison (N = 100). We found evidence showing a clear difference between the two groups (MD

-8.80 days, 95% CI -20.11 to -2.51). Results favour the cimetidine plus antacids arm.

Cimetidine or ranitidine plus antacids versus sucralfate

We included a single study in this comparison (N = 130). We found no evidence of a clear difference between the two groups (MD 4.20 days, 95% CI -0.54 to 8.94).

Number of participants requiring blood transfusions

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 15.6](#)). In the included study, 69 participants received cimetidine or ranitidine plus antacids, and 61 received sucralfate. Blood transfusions were required by 0% and 1.6% of participants in both groups. Data seemed to show no difference between the two groups with respect to the number of participants requiring blood transfusion (RR 0.30, 95% CI 0.01 to 7.12). We judged the certainty of this evidence as low.

Proton pump inhibitors versus teprenone

For this comparison, data on two of our pre-defined outcomes were available, and only one study contributed data.

Clinically important upper GI bleeding

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 16.1](#)). In the single included study, 70 participants received proton pump inhibitors and 70 received teprenone. Clinically important upper GI bleeding occurred in 0% and 5.7% of participants in both groups. We found no evidence of a clear difference between the two groups in this comparison (RR 0.11, 95% CI 0.01 to 2.03; [Analysis 16.1](#)). We judged the certainty of this evidence as low.

All-cause mortality in ICU

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 16.2](#)). In the single included study, 70 participants received proton pump inhibitors and 70 received teprenone. All-cause mortality occurred in 0% and 0.7% of participants in both groups. Data show no clear difference between proton pump inhibitors and teprenone (RR 0.33, 95% CI 0.01 to 8.04). We judged the certainty of this evidence as moderate.

Number of participants requiring blood transfusion

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 16.3](#)). In the single included study, 70 participants received proton pump inhibitors and 70 received teprenone. Data show no clear difference between proton pump inhibitors and teprenone with respect to the number of participants requiring blood transfusion (RR 0.11, 95% CI 0.01 to 2.03). We judged the certainty of this evidence as moderate.

Proton pump inhibitors plus naloxone versus naloxone

For this comparison, data on three of our pre-defined outcomes were available. One study contributed data towards this comparison ([He 2017](#)). In the single included study, 60 participants received proton pump inhibitors (pantoprazole) plus naloxone, and 60 received naloxone alone.

Clinically important upper GI bleeding

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 17.1](#)). Clinically important upper GI bleeding occurred in 1.6% and 8.33% of participants of the two groups, respectively. We found no evidence of a clear difference between the two groups in this comparison (RR 0.19, 95% CI 0.02 to 1.65; one study; 120 participants).

All-cause mortality in the hospital

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 17.2](#)). All-cause mortality occurred in 5.0% and 21.7% of participants in the two groups, respectively. Data seemed to show a beneficial effect of pantoprazole plus naloxone on all-cause mortality in the hospital (RR 0.23, 95% CI 0.06 to 0.89; one study; 120 participants).

Adverse events

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 17.3](#)). Gastrointestinal discomfort, the only adverse event reported, occurred in 10.0% and 18.33% of participants in the two groups, respectively. We found no evidence of a clear difference between the two groups for this comparison (RR 0.40, 95% CI 0.14 to 1.14; one study; 120 participants).

Proton pump inhibitors versus other medication (not defined)

For this comparison, data on three of our pre-defined outcomes were available. One study contributed data towards this comparison. In the single included study, 60 participants received proton pump inhibitors (lansoprazole), and 60 received other medication not further specified.

Clinically important upper GI bleeding

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 18.1](#)). Clinically important upper GI bleeding occurred in 0% and 10.0% of participants in the two groups, respectively. We found no evidence of a clear difference between the two groups for this comparison (RR 0.08, 95% CI 0.00 to 1.34).

Nosocomial pneumonia

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 18.2](#)). Nosocomial pneumonia occurred in 6.7% and 10% of participants in the two groups, respectively. We found no evidence of a clear difference between the two groups in this comparison (RR 0.67, 95% CI 0.20 to 2.24).

All-cause mortality in hospital

For this outcome, we found a single study (N = 120). All-cause mortality in the hospital occurred in 10% and 0% of participants in the two groups, respectively. Data seemed to show no clear difference between proton pump inhibitors and other medication (not defined) (RR 5.00, 95% CI 0.25 to 102.00).

Antacids versus sucralfate

For this comparison, data on eight of our pre-defined outcomes were available. Among the 16 studies that provided data for

this comparison, one study administered pirenzepine as a co-intervention in both arms (Tryba 1985).

Clinically important upper GI bleeding

We classified studies on the basis of their intervention and comparison arms (as shown in Analysis 19.1). In the 16 included studies (N = 1772), 890 participants received antacids and 882 received sucralfate. The event occurred in 6.6% of participants in both groups. Data seemed to show no clear differences between the two groups with respect to the occurrence of clinically important upper GI bleeding (RR 1.00, 95% CI 0.72 to 1.39). We judged the certainty of this evidence as low.

Antacids versus sucralfate

We found 15 studies that were relevant to this comparison (N = 1705). We found no evidence of a clear difference between the two groups (RR 0.96, 95% CI 0.69 to 1.35; Analysis 19.1).

Antacid plus pirenzepine versus sucralfate plus pirenzepine

We found one study that was relevant to this comparison (N = 67). Data seemed to show no clear difference between antacids and sucralfate (RR 5.15, 95% CI 0.26 to 103.33; Analysis 19.1).

Nosocomial pneumonia

We classified studies on the basis of their intervention and comparison arms (as shown in Analysis 19.2). In the seven studies that contributed to this outcome, 501 participants received antacids and 495 received sucralfate. The event occurred in 24.4% and 23.2% of participants in the two groups. Data seemed to show no clear difference between the two groups with respect to the occurrence of nosocomial pneumonia (RR 1.04, 95% CI 0.84 to 1.30). We judged the certainty of this evidence as low.

All-cause mortality in ICU

We classified studies on the basis of their intervention and comparison arms (as shown in Analysis 19.3). In the 11 studies that contributed to this outcome (N = 1249), 628 participants received antacids and 621 received sucralfate. The event occurred in 23.9% and 20.6% of participants in the two groups. Data seemed to show no clear difference between the two groups with respect to all-cause mortality in the ICU (RR 1.15, 95% CI 0.93 to 1.40). We judged the certainty of this evidence as low.

Antacid versus sucralfate

We found 10 studies that were relevant to this comparison (N = 1182). Data seemed to show no clear difference between antacids and sucralfate (RR 1.15, 95% CI 0.94 to 1.41; Analysis 19.3).

Antacid plus pirenzepine versus sucralfate plus pirenzepine

We found one study that was relevant to this comparison (N = 67). Data seemed to show no clear difference between antacids plus pirenzepine and sucralfate plus pirenzepine (RR 1.03, 95% CI 0.28 to 3.78; Analysis 19.3).

All-cause mortality in hospital

We classified studies on the basis of their intervention and comparison arms (as shown in Analysis 19.4). In the three studies that contributed to this outcome (N = 450), 227 participants received antacids and 223 received sucralfate. The event occurred in 33.0% and 33.2% of participants in both groups. Data seemed

to show no clear difference between the two groups with respect to all-cause mortality in the hospital (RR 0.98, 95% CI 0.69 to 1.39). This outcome had moderate heterogeneity ($\chi^2 = 3.38$, $df = 2.0$ ($P = 0.18$), $I^2 = 41\%$).

Duration of ICU stay

We classified studies on the basis of their intervention and comparison arms (as shown in Analysis 19.5). In the two studies that contributed to this outcome, 120 participants received antacids and 107 received sucralfate. Data seemed to show no clear difference between the two groups with respect to duration of ICU stay (MD -2.50 days, 95% CI -6.61 to 1.61). We rated the certainty of this evidence as low.

Duration of intubation

We classified studies on the basis of their intervention and comparison arms (as shown in Analysis 19.6). In the four studies that contributed to this outcome (N = 281), 142 participants received antacids and 139 received sucralfate. Data seemed to show no clear difference between the two groups with respect to duration of intubation (standardised mean difference (SMD) -0.18, 95% CI -0.41 to 0.06).

Number of participants requiring blood transfusion

We classified studies on the basis of their intervention and comparison arms (as shown in Analysis 19.7). In the six studies that contributed to this outcome (N = 667), 338 participants received antacids and 329 received sucralfate. The event occurred in 3.6% and 5.2% of participants in the two groups. Data seemed to show no clear difference between the two groups with respect to the number of participants requiring blood transfusion (RR 0.73, 95% CI 0.40 to 1.34). We judged the certainty of this evidence as low.

Adverse events of interventions

We classified studies on the basis of their intervention and comparison arms and adverse events of the intervention (as shown in Analysis 19.8). We identified nine studies that were relevant to this outcome and categorised data into six adverse events as reported in these studies.

Diarrhoea

We identified six relevant studies for this outcome (N = 599). For this outcome, we found evidence suggesting that antacids were clearly different in their effects compared with sucralfate. This event occurred in 11.4% and 0% of the participants in both groups (RR 12.4, 95% CI 3.88 to 39.64; Analysis 19.8). Results favour the sucralfate arm.

Hypermagnesaemia

We found four studies that were relevant to this outcome (N = 317). For this outcome, we found evidence suggesting that antacids were clearly different in their effects compared with sucralfate (RR 4.72, 95% CI 1.24 to 17.95; Analysis 19.8). This event occurred in 6.5% and 0.6% of participants in the two groups. Results favour the sucralfate arm.

Nausea and vomiting

We included three relevant studies for this outcome (N = 223). For the occurrence of nausea and vomiting, we found no evidence of a clear difference between the two groups (RR 0.63, 95% CI 0.28

to 1.41; [Analysis 19.8](#)). This event occurred in 7.0% and 11.9% of participants in the two groups.

Thrombocytopenia

We included a single study that looked at this outcome (N = 38). Data show no clear difference between antacids and sucralfate with respect to the occurrence of thrombocytopenia (RR 5.00, 95% CI 0.26 to 97.70; [Analysis 19.8](#)). This event occurred in 10.5% and 0% of the participants in both groups.

Severe alkalosis

We found one study that was relevant to this outcome (N = 100). Data show no clear difference between antacids and sucralfate (RR 3.00, 95% CI 0.13 to 71.92; [Analysis 19.8](#)). This event occurred in 2.0% and 0% of the participants in both groups.

Allergic reactions

We found one study that was relevant to this outcome (N = 100). For this comparison, we found no evidence of a clear difference between the two groups (RR 0.20, 95% CI 0.01 to 4.06; [Analysis 19.8](#)). Allergic reactions occurred in 0% and 4.0% of participants in the two groups.

Antacids versus prostaglandin analogues

For this comparison, data on three of our pre-defined outcomes were available. Two studies contributed data for this comparison.

Clinically important upper GI bleeding

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 20.1](#)). In the two included studies (N = 329), 162 participants received antacids and 185 participants received prostaglandin analogues. This event occurred in 2.4% and 7.8% of participants in the two groups. Data seemed to show a beneficial effect of antacids compared with prostaglandin analogues on the occurrence of clinically important upper GI bleeding (RR 0.33, 95% CI 0.12 to 0.91). Results favour antacids. We judged the certainty of this evidence as moderate.

All-cause mortality in ICU

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 20.2](#)). In the two studies that contributed to this outcome (N = 417), 206 participants received antacids and 211 received prostaglandin analogues. This event occurred in 6.3% and 7.6% of participants in both groups. Data show no difference between the two groups with respect to all-cause mortality in the ICU (RR 0.84, 95% CI 0.42 to 1.67). We judged the certainty of this evidence as low.

Adverse events of interventions

We classified this study on the basis of its intervention and comparison arms and adverse events of the intervention (as shown in [Analysis 20.3](#)).

Diarrhoea

We found only one study that was relevant to this comparison (N = 368). We found no evidence of a clear difference between the two groups (RR 0.92, 95% CI 0.64 to 1.33; [Analysis 20.3](#)).

Elevated serum bicarbonate

We found one study that was relevant to this comparison (N = 338). We found evidence of a clear difference between antacids and prostaglandin analogues with respect to the occurrence of elevated serum bicarbonate (RR 2.21, 95% CI 1.27 to 3.87; [Analysis 20.3](#)).

Phosphate levels below 2.5 mg/dL

We found one study that was relevant to this outcome (N = 276). We found evidence of a clear difference between antacids and prostaglandin analogues for the occurrence of phosphate levels below 2.5 mg/dL (RR 1.66, 95% CI 1.01 to 2.73; [Analysis 20.3](#)). Results favour prostaglandin analogues.

Antacids versus bioflavonoids

For this comparison, data on two of our pre-defined outcomes were available. Only one study contributed data towards this comparison. In the single included study, 113 participants received antacids and 85 received bioflavonoids.

Clinically important upper GI bleeding

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 21.1](#)). Clinically important upper GI bleeding occurred in 5.3% of participants in the antacid arm and in 8.2% of participants in the bioflavonoid arm. Data show no difference between the two groups with respect to the occurrence of clinically important upper GI bleeding (RR 0.64, 95% CI 0.22 to 1.85; 198 participants; one study). We judged the certainty of this evidence as low.

Number of participants requiring blood transfusion

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 21.2](#)). In the single included study, 113 participants received antacids and 85 received bioflavonoids. This event occurred in 2.4% of participants in the bioflavonoid arm and in no participants in the antacids arm. Data show no difference between the two groups with respect to the number of participants requiring blood transfusion (RR 0.15, 95% CI 0.01 to 3.10; 198 participants; one study). We judged the certainty of this evidence as low.

Sucralfate versus proton pump inhibitors

For this comparison, data on eight of our pre-defined outcomes were available. Three studies contributed data for this comparison.

Clinically important upper GI bleeding

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 22.1](#)). In the three included studies (N = 287), 139 participants received sucralfate and 148 received proton pump inhibitors (omeprazole). Clinically important upper GI bleeding occurred in 5.8% and 2% of participants in both groups. Data showed no difference between the two groups with respect to the occurrence of clinically important upper GI bleeding (RR 2.58, 95% CI 0.77 to 8.63). We judged the certainty of this evidence as low.

Ventilator-associated pneumonia

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 22.2](#)). In the four studies that contributed to this outcome (N = 424), 210

participants received sucralfate and 214 received proton pump inhibitors. Nosocomial pneumonia occurred in 16.6% and 25.2% of participants in the two groups. Data showed no difference between the two groups with respect to the occurrence of nosocomial pneumonia (RR 0.67, 95% CI 0.41 to 1.09). We judged the certainty of this evidence as low.

Sucralfate versus omeprazole

We found three studies that were relevant to this comparison (N = 287; n = 139 in the sucralfate arm and n = 148 in the proton pump inhibitor arm). We found no evidence of a difference between the two interventions (RR 0.88, 95% CI 0.57 to 1.36).

Sucralfate versus pantoprazole

We found one study that was relevant to this comparison (N = 137). We found evidence of a clear difference between sucralfate and proton pump inhibitors (RR 0.39, 95% CI 0.20 to 0.75). Results favour the sucralfate arm.

All-cause mortality in ICU

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 22.3](#)). In the four studies that contributed to this outcome (N = 424), 205 participants received sucralfate and 219 received proton pump inhibitors (omeprazole). All-cause mortality in the ICU occurred in 15.6% and 14.6% of participants in both groups. Data show no significant differences between the two groups with respect to all-cause mortality in the ICU (RR 1.07, 95% CI 0.68 to 1.68). We judged the certainty of this evidence as low.

Sucralfate versus omeprazole

We included three relevant studies in this comparison (N = 287). Data showed no clear difference between sucralfate and proton pump inhibitors (RR 1.26, 95% CI 0.75 to 2.11; [Analysis 22.3](#)).

Sucralfate versus pantoprazole

We included a single study in this comparison (N = 137). We found no evidence of a clear difference between the two groups (RR 0.65, 95% CI 0.25 to 1.68; [Analysis 22.3](#)).

All-cause mortality in hospital

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 22.4](#)). In the two studies that contributed to this outcome (N = 278), 140 participants received sucralfate and 138 received proton pump inhibitors. This event occurred in 13.5% and 17.4% of participants in the two groups. Data showed no significant difference between the two groups with respect to all-cause mortality in the hospital (RR 0.79, 95% CI 0.46 to 1.37).

Sucralfate versus omeprazole

We included a single study in this comparison (N = 141). Data show no clear difference between sucralfate and proton pump inhibitors (RR 0.97, 95% CI 0.49 to 1.91; [Analysis 22.4](#)).

Sucralfate versus pantoprazole

We included a single study in this comparison (N = 137). Data show no clear difference between sucralfate and proton pump inhibitors (RR 0.56, 95% CI 0.21 to 1.45; [Analysis 22.4](#)).

Duration of ICU stay

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 22.5](#)). In the two studies that contributed to this outcome (N = 217), 107 participants received sucralfate and 110 received proton pump inhibitors. Data seemed to show no difference between the two groups with respect to duration of ICU stay (MD 0.01 days, 95% CI -1.68 to 1.70). We judged the certainty of this evidence as low.

Duration of intubation

We classified studies on the basis of their intervention and comparison arms (as shown in [Analysis 22.6](#)). In the three studies that contributed to this outcome (N = 354), 173 participants received sucralfate and 181 received proton pump inhibitors. Data seemed to show no significant difference between the two groups with respect to duration of intubation (MD -0.16 days, 95% CI -1.61 to 1.28).

Number of participants requiring blood transfusion

We classified this studies on the basis of their intervention and comparison arms (as shown in [Analysis 22.7](#)). In the single study that contributed to this outcome (N = 70), 32 participants received sucralfate and 38 received proton pump inhibitors. Blood transfusions were required by 6.25% and 0% of participants in the two groups, respectively. Data seemed to show differences between the two groups with respect to the number of participants requiring blood transfusion (RR 5.91, 95% CI 0.29 to 118.78). We judged the certainty of this evidence as moderate.

Adverse events of interventions

For this outcome, we found a single study and categorised data according to eight adverse events (N = 1096).

Fever

For this outcome, we found evidence suggesting that sucralfate was clearly different in its effects compared with proton pump inhibitors (RR 0.81, 95% CI 0.70 to 0.94; [Analysis 22.8](#)). Researchers reported 54 and 62 events in both treatment arms, respectively. Results favour the sucralfate arm.

Leucocytosis

For this outcome, we found evidence suggesting that sucralfate was clearly different in its effects compared with proton pump inhibitors (RR 0.66, 95% CI 0.55 to 0.80; [Analysis 22.8](#)). Researchers reported 45 and 63 events in both treatment arms, respectively. Results favour the sucralfate arm.

Sudden purulent sputum

Data show no clear difference between sucralfate and proton pump inhibitors for this outcome (RR 0.85, 95% CI 0.38 to 1.86; [Analysis 22.8](#)). Researchers reported 10 and 11 events in the two treatment arms, respectively.

Sudden cough or aggravation of coughing

We found evidence of a clear difference between sucralfate and proton pump inhibitors within this outcome (RR 0.23, 95% CI 0.07 to 0.79; [Analysis 22.8](#)). Researchers reported 3 and 12 events in the two treatment arms, respectively. Results favour the sucralfate arm.

Dyspnoea (breathing discomfort)

We found evidence of a clear difference between sucralfate and proton pump inhibitors within this outcome (RR 0.68, 95% CI 0.54 to 0.87; [Analysis 22.8](#)). Researchers reported 39 and 53 events in the two treatment arms, respectively. Results favour the sucralfate arm.

Rales or bronchial sounds

We found evidence of a clear difference between sucralfate and proton pump inhibitors for this outcome (RR 0.31, 95% CI 0.19 to 0.51; [Analysis 22.8](#)). Researchers reported 14 and 42 events in the two treatment arms, respectively. Results favour the sucralfate arm.

Aggravation of blood gas exchange

For this comparison, we found no evidence of a clear difference between the two groups (RR 0.76, 95% CI 0.49 to 1.18; [Analysis 22.8](#)). Researchers reported 23 and 28 events in the two treatment arms, respectively.

Change in sputum quality

For this outcome, we found evidence suggesting that sucralfate was clearly different in its effects compared with proton pump inhibitors (RR 0.23, 95% CI 0.13 to 0.40; [Analysis 22.8](#)). Researchers reported 11 and 45 events in the two treatment arms, respectively. Results favour the sucralfate arm.

Sucralfate versus bioflavonoids

For this comparison, data on two of our pre-defined outcomes were available. Only one study contributed data towards this comparison.

Clinically important upper GI bleeding

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 23.1](#)). In the single included study (N = 185), 100 participants received sucralfate and 85 received bioflavonoids. Clinically important upper GI bleeding occurred in 9% of participants in the antacid arm and in 8.2% of participants in the bioflavonoid arm. Data showed no clear difference between the two groups with respect to the occurrence of clinically important upper GI bleeding (RR 1.09, 95% CI 0.43 to 2.81). We judged the certainty of this evidence as low.

Number of participants requiring blood transfusions

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 23.2](#)). In the single included study (N = 185), 100 participants received antacids and 85 received bioflavonoids. Blood transfusions were required by 1% of participants in the sucralfate arm and by 2.4% of participants in the bioflavonoid arm. Data showed no clear difference between the two groups with respect to the number of participants requiring blood transfusion (RR 0.42, 95% CI 0.04 to 4.61). Results did not favour any intervention. We judged the certainty of this evidence as low.

Total parenteral nutrition versus any other intervention plus total parenteral nutrition

For this comparison, data on three of our pre-defined outcomes were available. One study contributed data towards this comparison. In the single included study, 30 participants received total parenteral nutrition, 24 received H2 receptor antagonist plus total parenteral nutrition, and 19 received sucralfate plus total

parenteral nutrition. We compared the effects of total parenteral nutrition versus H2 receptor antagonists plus total parenteral nutrition and total parenteral nutrition versus sucralfate plus total parenteral nutrition separately.

Clinically important upper GI bleeding

For this outcome, we found a single study and categorised data by two comparisons. We judged the certainty of this evidence as low.

Total parenteral nutrition versus H2 receptor antagonists plus total parenteral nutrition alone

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 24.1](#)). This event occurred in 3.3% of participants in the total parenteral nutrition arm and in 4.2% of participants in the H2 receptor antagonist (ranitidine) plus total parenteral nutrition arm. Data showed no significant differences between the two groups with respect to the occurrence of clinically important upper GI bleeding (RR 0.80, 95% CI 0.05 to 12.14; 54 participants; one study).

Total parenteral nutrition versus sucralfate plus total parenteral nutrition

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 24.1](#)). Clinically important upper GI bleeding occurred in 3.3% of participants in the total parenteral nutrition arm and in 10.5% of participants in the sucralfate plus total parenteral nutrition arm. Data seemed to show no difference between the two groups with respect to the occurrence of clinically important upper GI bleeding (RR 0.32, 95% CI 0.03 to 3.26; 49 participants; one study). Results did not favour any intervention.

All-cause mortality in ICU

For this outcome, we found a single study and categorised data by two comparisons. We judged the certainty of this evidence as low.

Total parenteral nutrition versus H2 receptor antagonists plus total parenteral nutrition

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 24.2](#)). All-cause mortality in the ICU occurred in 2.3% of participants in the total parenteral nutrition arm and in 2.1% of participants in the H2 receptor antagonist plus total parenteral nutrition arm. Data seemed to show no difference between the two groups with respect to all-cause mortality in the ICU (RR 1.12, 95% CI 0.41 to 3.09; 54 participants; one study). Results did not favour any intervention.

Total parenteral nutrition versus sucralfate plus total parenteral nutrition

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 24.2](#)). All-cause mortality in the ICU occurred in 23.3% of participants in the total parenteral nutrition arm and in 36.8% of participants in the sucralfate plus total parenteral nutrition arm. Data seemed to show no difference between the two groups with respect to all-cause mortality in the ICU (RR 0.63, 95% CI 0.26 to 1.52; 49 participants; one study). Results did not favour any intervention.

Duration of intubation

For this outcome, we found a single study and categorised data by two comparisons. We judged the certainty of this evidence as low.

Total parenteral nutrition versus H2 receptor antagonists plus total parenteral nutrition

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 24.3](#)). Data seemed to show no difference between the two groups with respect to duration of intubation (MD -2.00 days, 95% CI -9.53 to 5.53; 54 participants; one study).

Total parenteral nutrition versus sucralfate plus total parenteral nutrition

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 24.3](#)). Data seemed to show no difference between the two groups with respect to duration of intubation (MD 3.00, 95% CI -1.50 to 7.50; 49 participants; one study).

Bowel stimulation versus no prophylaxis

One study contributed data towards this comparison. In the single included study, 50 participants received a bowel stimulation protocol and 50 participants received no prophylaxis. This comparison had a single outcome.

Clinically important upper GI bleeding

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 25.1](#)). Clinically important upper GI bleeding occurred in 14.0% and 36.0% of participants in the two groups, respectively. We found evidence of a clear difference between bowel stimulation and no prophylaxis (RR 0.39, 95% CI 0.18 to 0.85). Results favour the bowel stimulation protocol arm.

Nasojejunal nutrition versus nasogastric nutrition

For this comparison, data on four of our pre-defined outcomes were available. One study contributed data towards this comparison. In the single included study, 91 participants received nasojejunal nutrition and 89 received nasogastric nutrition.

Clinically important upper GI bleeding

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 26.1](#)). Clinically important upper GI bleeding occurred in 15.4% and 5.6% of participants in the two groups, respectively. For this outcome, we found evidence suggesting that nasojejunal nutrition was clearly different in its effect compared with nasogastric nutrition (RR 2.74, 95% CI 1.03 to 7.28). Results favour nasogastric nutrition. We judged the certainty of this evidence as moderate.

Nosocomial pneumonia

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 26.2](#)). Nosocomial pneumonia occurred in 19.8% and 21.3% of participants in the two groups. Data seemed to show no difference between nasojejunal nutrition and nasogastric nutrition (RR 0.93, 95% CI 0.52 to 1.65). We judged the certainty of this evidence as low.

All-cause mortality in hospital

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 26.3](#)). All-cause mortality occurred in 14.3% and 13.5% of participants in the two groups. Data seemed to show no clear difference between nasojejunal nutrition and nasogastric nutrition (RR 1.06, 95% CI 0.51 to 2.19).

Duration of ICU stay

This study did not report enough data for inclusion in formal meta-analyses. The median duration of the ICU stay was 11 days and 10 days in the nasogastric group (n = 89) and the nasojejunal group (n = 91), respectively.

Duration of mechanical ventilation

This study did not report enough data for inclusion in formal meta-analyses. The median duration of mechanical ventilation was eight days in both the nasogastric group (n = 89) and the nasojejunal group (n = 91).

Adverse events of interventions

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 26.4](#)). Researchers reported 77 and 76 adverse events, including vomiting, witnessed aspiration, abdominal distension, and diarrhoea, in the two groups, respectively. We found no evidence of a clear difference between the two groups in this comparison (RR 0.99, 95% CI 0.88 to 1.12).

Enteral plus parenteral nutrition versus other nutrition regimens

For this comparison, data on five of our pre-defined outcomes were available. One study contributed data towards this comparison ([Fan 2016](#)). In the single included study with three treatment arms, 40 participants received enteral plus parenteral nutrition and 80 received other nutrition regimens, 40 received enteral nutrition, and 40 received parenteral nutrition.

Nosocomial pneumonia

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 27.1](#)). Nosocomial pneumonia occurred in 27.5% and 35.0% of participants in the two groups, respectively. Data seemed to show no clear difference between enteral plus parenteral nutrition and interventions in the other study groups (RR 0.79, 95% CI 0.44 to 1.40; one study; 120 participants).

All-cause mortality in the hospital

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 27.2](#)). All-cause mortality in the hospital occurred in 10.0% and 36.2% of participants in the two groups, respectively. All-cause mortality seemed to be lower in the group receiving enteral plus parenteral nutrition than in the groups receiving other nutrition regimens (RR 0.20, 95% CI 0.06 to 0.60; one study; 120 participants).

Duration of ICU stay

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 27.3](#)). Duration of ICU stay seemed to be shorter in the study group receiving enteral plus parenteral nutrition compared with groups receiving other

nutrition regimens (MD -5.98 days, 95% CI -8.81 to -3.16; one study; 120 participants).

Duration of intubation

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 27.4](#)). Duration of intubation seemed to be shorter in the study group receiving enteral plus parenteral nutrition compared with the groups receiving other nutrition regimens (MD -7.37 days, 95% CI -9.29 to -5.45; one study; 120 participants).

Adverse events of interventions

We classified this study on the basis of its intervention and comparison arms (as shown in [Analysis 27.5](#) and following).

Occurrence of stress ulcers

Data seemed to show no differences between study groups with respect to the occurrence of stress ulcers (RR 0.69, 95% CI 0.36 to 1.33; one study; 120 participants). Researchers reported nine events in the intervention group and 26 in the control groups.

Diarrhoea

Data seemed to show no difference between study groups with respect to the occurrence of diarrhoea (RR 0.42, 95% CI 0.17 to 1.02; one study; 120 participants). Researchers reported that the event occurred in eight participants in the intervention group and in 30 participants in control groups.

Pyæmia

Data seemed to show no difference between study groups with respect to the occurrence of pyæmia (RR 0.88, 95% CI 0.37 to 2.09; one study; 120 participants). Researchers reported 10 events in the intervention group and 22 events in the control groups.

Intracranial infection

Data seemed to show no difference between study groups with respect to the occurrence of intracranial infection (RR 0.43, 95% CI 0.15 to 1.25; one study; 120 participants). Researchers reported five events in the intervention group and 20 events in the control groups.

Hypoproteinaemia

Data seemed to show a beneficial effect of enteral plus parenteral nutrition on the occurrence of hypoproteinaemia (RR 0.11, 95% CI 0.04 to 0.27; one study; 120 participants). Researchers reported seven events in the intervention group and 54 events in the control groups.

Subgroup analyses

Presence of bleeding disorders

We identified three studies that explicitly reported including patients with bleeding disorders ([Conrad 2005](#); [Kantorova 2004](#); [Martin 1992](#)). Only two studies compared a common intervention and a comparator (H2 receptor antagonists vs proton pump inhibitors). Subgroup analyses provided no evidence of a difference between studies that explicitly included patients with bleeding disorders and those that did not include such patients (test for subgroup differences P value = 0.09). Further, there seemed to be no difference between groups with respect to the occurrence

of nosocomial pneumonia (test for subgroup differences P value = 0.37) and all-cause mortality in the ICU (test for subgroup differences P value = 0.52). Researchers provided no data on other outcomes and comparisons for this subgroup that could be formally included in meta-analysis.

Pneumonia at time of admission

We identified four studies that explicitly reported including participants with pneumonia at the time of ICU admission ([Ben-Menachem 1994](#); [Karlstadt 1990](#); [Martin 1993](#); [Metz 1993](#)). The proportion of participants with pneumonia ranged from 2.33% to 21% in these studies, respectively. All studies compared the effects of H2 receptor antagonists (cimetidine or ranitidine) versus placebo or no prophylaxis. Subgroup analyses provided no evidence of a difference between studies that explicitly included patients with pneumonia at the time of admission and those that did not include such patients (test for subgroup differences P value = 0.28). Data showed no difference between groups with respect to the occurrence of nosocomial pneumonia (test for subgroup differences P value = 0.54) and all-cause mortality in the ICU (test for subgroup differences P value = 0.20). Researchers provided no data on other outcomes and comparisons for this subgroup that could be formally analysed in meta-analysis.

Infants and children

We identified five studies that explicitly reported including only children and adolescents ([Behrens 1994](#); [Kuusela 1997](#); [Lacroix 1986](#); [Lopez-Herce 1992](#); [Yildizdas 2002](#)). All participants in these studies were aged from 0 to 20 years. Two studies compared effects of H2 receptor antagonists versus placebo, and three studies had multiple study arms including H2 receptor antagonists, anticholinergics ([Behrens 1994](#)), antacids ([Lopez-Herce 1992](#)), sucralfate ([Lopez-Herce 1992](#); [Yildizdas 2002](#)), and proton pump inhibitors ([Yildizdas 2002](#)), as well as placebo or no prophylaxis. In infants and adolescents, data showed no difference between H2 receptor antagonists and placebo or no prophylaxis with respect to the occurrence of clinically important upper GI bleeding (test for subgroup differences P value = 0.10), nosocomial pneumonia (test for subgroup differences P value = 0.84), or all-cause mortality in the ICU (test for subgroup differences P value = 0.52); duration of ICU stay (test for subgroup differences P value = 0.62); duration of intubation (test for subgroup differences P value = 0.75); or number of participants requiring blood transfusion (test for subgroup differences P value = 0.37). Researchers provided no data on other outcomes of this comparison for this subgroup that could be formally included in meta-analysis.

We detected no differences between H2 receptor antagonists and sucralfate with respect to the occurrence of clinically important upper GI bleeding in infants (test for subgroup differences P value = 0.61), nosocomial pneumonia (test for subgroup differences P value = 0.75), all-cause mortality in the ICU (test for subgroup differences P value = 0.92), duration of ICU stay (test for subgroup differences P value = 0.84), or duration of intubation (test for subgroup differences P value = 0.90). We found no data on other outcomes in this comparison for this subgroup that could be formally analysed in meta-analysis. Moreover, researchers provided no data on other outcomes and comparisons for this subgroup that could be formally analysed in meta-analysis.

The reporting quality of the included studies did not permit other subgroup analyses. No studies explicitly included only adults over

the age of 65 years. Thus, insufficient data were available for analysis of the effect of bleeding prophylaxis in older adults only. Furthermore, use of co-interventions and the level of detail of reporting about co-interventions varied strongly among studies, so that meaningful subgroup analyses were not possible with respect to differences in effect due to co-interventions.

Sensitivity analyses

Studies with low risk of bias versus studies with unclear or high risk of bias

Only two studies had an overall low risk of bias (Cook 1998; Ephgrave 1998), and one study had low risk of bias, when risk of performance and detection bias was assessed for upper GI bleeding only (Ng 2012).

Cook 1998 compared H2 receptor antagonists (ranitidine) (n = 596) versus sucralfate (n = 604). This study found lower risk of upper GI bleeding with H2 receptor antagonists (RR 0.44, 95% CI 0.21 to 0.92; one study; 1200 participants) compared with studies with unclear and high risk of bias (RR 1.28, 95% CI 0.98 to 1.66; 23 studies; 2199 participants). Data seemed to show no difference between study groups with respect to the occurrence of nosocomial pneumonia in the study with low risk of bias (RR 1.18, 95% CI 0.92 to 1.51; one study; 1200 participants), and studies with unclear or high risk of bias found increased risk of nosocomial pneumonia (RR 1.21, 95% CI 1.02 to 1.43; 14 studies; 1807 participants). The latter result favoured the sucralfate arm. Data show no differences between studies with low risk of bias and studies with unclear or high risk of bias in the comparison of H2 receptor antagonists versus sucralfate with respect to the outcome all-cause mortality in the ICU, duration of intubation, and duration of ICU stay. No studies reported data on other outcomes pre-defined in this review, so that no further sensitivity analyses were possible.

Ephgrave 1998 compared antacids (n = 70) versus sucralfate (n = 70) and reported no differences in effect between the study with low risk of bias and studies with unclear or high risk of bias with respect to the outcomes clinically important upper GI bleeding, nosocomial pneumonia, and all-cause mortality in the ICU. No other outcomes of this comparison were available for sensitivity analysis.

Ng 2012 compared an H2 receptor antagonist (famotidine) (n = 149) versus a proton pump inhibitor (esomeprazole) (n = 164) and reported no differences in effect between the study with low risk of bias and studies with unclear or high risk of bias with respect to the outcomes clinically important upper GI bleeding and all-cause mortality in the hospital. No studies reported data on other outcome pre-defined in this review, so that no further sensitivity analyses were possible.

Studies with attrition greater than 10%

Six studies had an attrition rate greater than 10% (Barandun 1985; Fabian 1993; Hanisch 1998; Israsena 1987; Ruiz-Santana 1991; Terzi 2009).

Barandun 1985 compared H2 receptor antagonists (n = 28) versus anticholinergics (n = 27) and noted no apparent differences in this comparison with respect to the occurrence of clinically important upper GI bleeding when excluding from analysis the study with an attrition rate of 10% or higher. No other outcomes of this comparison were available for sensitivity analysis.

Fabian 1993 compared H2 receptor antagonists (n = 410) versus sucralfate (n = 206) and noted no apparent differences in this comparison with respect to the occurrence of clinically important upper GI bleeding, nosocomial pneumonia, all-cause mortality in the ICU or the hospital, duration of ICU stay, and the number of participants requiring blood transfusions when excluding from analysis the study with an attrition rate of 10% or higher. No other outcomes of this comparison were available for sensitivity analysis.

Hanisch 1998 compared an H2 receptor antagonist (ranitidine) (n = 57) versus an anticholinergic (pirenzepine) (n = 44) or placebo (n = 57) and noted no apparent difference in effect size and direction when excluding the study with an attrition rate of 10% from the comparison of H2 receptor antagonists versus anticholinergics or placebo. Neither did direction or strength of effect change when the study with an attrition rate of 10% was removed from the comparison of anticholinergics and placebo.

Israsena 1987 compared antacids (n = 47) versus sucralfate (n = 40) and noted no apparent difference in effect size and direction when excluding from analysis the study with an attrition rate of 10%.

Ruiz-Santana 1991 was the only study comparing total parenteral nutrition with total parenteral nutrition plus other medications. So, no sensitivity analysis could be performed.

Terzi 2009 compared an H2 receptor antagonist (ranitidine) (n = 10) versus a proton pump inhibitor (pantoprazole) (n = 10) and noted no apparent difference in effect size and direction when excluding from analysis the study with an attrition rate of 10%.

Studies with published and validated criteria to diagnose clinically important upper GI bleeding and nosocomial pneumonia

Lack of detail regarding criteria used to diagnose the primary endpoints of the review did not allow sensitivity analysis.

DISCUSSION

This review includes 107 randomised controlled trials that randomised 15,057 participants admitted to the intensive care unit (ICU) to receive interventions to prevent clinically important upper gastrointestinal (GI) bleeding. The various interventions yielded 27 sets of comparisons.

Summary of main results

Clinically important upper GI bleeding due to stress ulcers is a major contributor to increased morbidity and mortality among patients admitted to ICU. The main objective of this review was to assess whether interventions that are commonly used to prevent upper GI bleeding in patients admitted to the ICU are effective in preventing such bleeding, when used alone or in combination. Interventions most commonly used were H2 receptor antagonists, proton pump inhibitors, anticholinergics, antacids, sucralfate, and prostaglandin analogues. However, one of the most common adverse events associated with using these drugs, as discussed before, consists of raised pH of gastric contents, altered gastric flora, and promotion of tracheobronchial and gastric colonisation with pathogenic bacteria - aspiration of which can cause nosocomial pneumonia or ventilator-associated pneumonia. Some of the included studies investigated ventilator-associated pneumonia as one of the outcomes, whereas other studies looked into this outcome in a

more generic way and addressed it as 'nosocomial pneumonia'. Because ventilator-associated pneumonia is considered a type of nosocomial pneumonia, we included results of studies that looked into either of these outcomes under the common term 'nosocomial pneumonia'.

Effect of any intervention versus placebo or no prophylaxis

In comparison with placebo, research findings suggest a beneficial effect of any prophylactic intervention on the occurrence of clinically important upper GI bleeding (risk ratio (RR) 0.47, 95% confidence interval (CI) 0.39 to 0.57; moderate certainty of evidence). Use of any intervention reduced the risk of clinically important upper GI bleeding by 9% (95% CI -11% to -7%). Data seemed to show no difference between any intervention and placebo or no prophylaxis with respect to the occurrence of any adverse events, including nosocomial pneumonia (low certainty of evidence), all-cause mortality in the ICU (low certainty of evidence) or the hospital, duration of ICU stay (low certainty of evidence), duration of intubation (low certainty of evidence), number of participants requiring blood transfusions (moderate certainty of evidence), and units of blood transfused.

Effects of single drug classes versus placebo or no prophylaxis

Among the different interventions that were compared with placebo or no prophylaxis, researchers found that antacids, H2 receptor antagonists, antacids, and sucralfate seemed to be effective in preventing clinically important upper GI bleeding in ICU patients and produced significant results. Investigators found that H2 receptor antagonists reduced the risk of clinically important upper GI bleeding by 11% (95% CI -0.16 to -0.06) compared with placebo or no prophylaxis (RR 0.50, 95% CI 0.36 to 0.70; moderate certainty of evidence). Antacids reduced the risk of bleeding by 9% (95% CI -0.17 to -0.00) compared with placebo or no prophylaxis. Among ICU patients, sucralfate reduced the risk by 5% (95% CI -0.10 to -0.01) compared with placebo or no prophylaxis (RR 0.53, 95% CI 0.32 to 0.88; low certainty of evidence). Remaining interventions were not found to be significantly associated with lower rates of occurrence of upper GI bleeding in ICU patients when compared with placebo or no prophylaxis. This might be due to lack of sufficiently large randomised controlled trials (RCTs) in these comparisons.

Results of the review indicate that nosocomial pneumonia might occur more often in ICU patients taking H2 receptor antagonists or sucralfate when compared with ICU patients given placebo or no prophylaxis. Data seem to show no difference between H2 receptor antagonists and placebo or no prophylaxis in the occurrence of nosocomial pneumonia (RR 1.12, 95% CI 0.85 to 1.48; low certainty of evidence). Similarly, there seems to be no difference between sucralfate and placebo or no prophylaxis in the occurrence of nosocomial pneumonia (RR 1.33, 95% CI 0.86 to 2.04; low certainty of evidence).

Effects of one drug class versus another drug class

When H2 receptor antagonists were compared with proton pump inhibitors, evidence of low certainty suggested that proton pump inhibitors were significantly more effective in preventing upper GI bleeding in ICU patients (RR 2.90, 95% CI 1.83 to 4.58). Low-certainty evidence also suggested no apparent difference in the incidence of nosocomial pneumonia with H2 receptor antagonists compared with proton pump inhibitors (RR 1.02, 95% CI 0.77 to 1.35).

Results indicated that the usefulness of proton pump inhibitors over H2 receptor antagonists to prevent upper GI bleeding in ICU patients likely outweighs the possible adverse event of nosocomial pneumonia.

Evidence of low certainty suggested that H2 receptor antagonists compared with sucralfate were not significantly different in preventing upper GI bleeding in ICU patients (RR 1.10, 95% CI 0.87 to 1.41). However, evidence of moderate certainty shows that under H2 receptor antagonists, participants had increased risk of nosocomial pneumonia (RR 1.22, 95% CI 1.07 to 1.40). Evidence of low quality suggests that H2 receptor antagonists and antacids were comparable with respect to the outcomes of upper GI bleeding (RR 0.96, 95% CI 0.67 to 1.36) and nosocomial pneumonia in ICU patients (RR 1.05, 95% CI 0.81 to 1.36).

Evidence of moderate certainty showed that when H2 receptor antagonists plus antacids were compared with sucralfate, GI bleeding occurred in fewer participants taking H2 receptor antagonists plus antacid than those taking sucralfate (RR 0.24, 95% CI 0.06 to 0.95). However, use of H2 receptor antagonists plus antacids was comparable with use of sucralfate in the incidence of nosocomial pneumonia (RR 1.09, 95% CI 0.51 to 2.32; very low certainty of evidence).

This review found no other relevant differences between interventions and comparator interventions with regard to the occurrence of clinically important upper GI bleeding and nosocomial pneumonia.

Overall completeness and applicability of evidence

Completeness

We searched multiple sources for relevant randomised controlled studies and included and excluded studies on the basis of inclusion and exclusion criteria. We believe that we have identified all randomised controlled studies relevant to the objectives of this review. Still evidence gaps indicate that further research would be helpful in guiding decision-making. One of these gaps reflects lack of evidence about the effects of bleeding prophylaxis on different population subgroups, including people with pneumonia at the time of ICU admission, as well as the effects of co-interventions such as different feeding regimens, antibiotics, etc., on the effectiveness of bleeding prophylaxis. Furthermore, evidence from RCTs is needed on the effects of proton pump inhibitors on *Clostridium difficile* infection-related diarrhoea. This adverse event has been observed in non-randomised studies but rarely in RCTs. *C. difficile* infection-related diarrhoea was not included as an outcome of this review at the stage of formulating the review protocol. We identified only two studies that reported on this adverse event (Selvanderan 2015; Wee 2013).

Applicability

Upper GI bleeding occurs in ICU patients as the result of stress ulcers, and excessive blood loss further increases mortality and morbidity among ICU patients. The various interventions that are compared in this review are available worldwide and can prevent bleeding from stress ulcers in ICU patients. Furthermore, no compelling evidence suggests that any interventions clearly increase the risk of ventilator-associated pneumonia or nosocomial pneumonia, which might further warrant their usage in ICU patients. Evidence from this review shows that among the different

interventions, antacids, H₂ receptor antagonists, sucralfate, and proton pump inhibitors confer the greatest benefit with respect to the occurrence of clinically important upper GI bleeding. We included studies that investigated the effects of bleeding prophylaxis in a broad spectrum of participants. Populations in these studies included different age groups, both genders, and different reasons for admission, such as burns, trauma, etc. In addition, we included studies that had been conducted in a variety of countries and ICU settings.

Quality of the evidence

We assessed the overall certainty of evidence using the GRADE approach (Schunemann 2008). This approach integrates evaluations regarding study limitations with judgements regarding inconsistency of results, indirectness, or deviations from accepted practice in the way interventions and comparisons were given, as well as populations studied, choice of outcomes, and methods of ascertainment used; imprecision in the estimates in terms of statistical and clinical importance; and the likelihood that publication bias affected the estimates. Overall, the main reasons for downgrading the certainty of evidence were risk of bias in the included studies and imprecision of the overall effect estimate.

Any intervention compared with placebo or no prophylaxis

Certainty of the evidence for any intervention versus placebo or no prophylaxis was moderate for the primary outcome of preventing clinically important upper GI bleeding in ICU patients, meaning that we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (Summary of findings for the main comparison) (Balslem 2011). Certainty of the evidence was judged as low for the outcomes of nosocomial pneumonia, all-cause mortality in the ICU, duration of ICU stay, and duration of intubation. This means that our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. Certainty of evidence for the number of participants requiring blood transfusion was judged as moderate. However, usefulness of the interventions in preventing upper GI bleeding in ICU patients seems to outweigh their adverse effects, such as nosocomial pneumonia, when compared with placebo or no prophylaxis.

H₂ receptor antagonists compared with placebo or no prophylaxis

Certainty of the evidence for H₂ receptor antagonists versus placebo or no prophylaxis was moderate for the primary outcome of preventing clinically important upper GI bleeding in ICU patients (Summary of findings 2). Overall certainty of the evidence was judged as low for the outcomes of nosocomial pneumonia, all-cause mortality in the ICU, duration of ICU stay, and duration of intubation. Certainty for the number of participants requiring blood transfusions was judged as moderate. However, usefulness of the interventions in preventing upper GI bleeding in ICU patients seems to outweigh their adverse effects such as nosocomial pneumonia, when compared with placebo or no prophylaxis.

Antacids compared with placebo or no prophylaxis

Overall certainty of the evidence for antacids versus placebo or no prophylaxis was low for the primary outcome of preventing clinically important upper GI bleeding in ICU patients, as well

as for the outcomes all-cause mortality in the ICU and numbers of participants requiring blood transfusion. None of the included studies reported on nosocomial pneumonia. Given the fact that antacids are no longer the first choice for preventing clinically important upper GI bleeding in ICU patients, further research most probably is not needed for this comparison (Summary of findings 4).

Sucralfate compared with placebo or no prophylaxis

Although evidence suggests that sucralfate might have a protective effect when compared with placebo or no prophylaxis, overall certainty of the evidence was moderate for the outcome of clinically important upper GI bleeding in ICU patients. Overall certainty of the evidence was judged as low for the outcomes of nosocomial pneumonia, all-cause mortality in the ICU, duration of ICU stay, and numbers of participants requiring blood transfusion (Summary of findings 5).

H₂ receptor antagonists compared with proton pump inhibitors

Overall certainty of the evidence for H₂ receptor antagonists versus proton pump inhibitors was low for the primary outcome of preventing clinically important upper GI bleeding in ICU patients, as well as for the outcomes of nosocomial pneumonia, all-cause mortality in the ICU, and duration of ICU stay. Certainty of the evidence for the outcome of number of participants requiring blood transfusion was judged as moderate (Summary of findings 6).

H₂ receptor antagonists compared with antacids

Overall certainty of the evidence for H₂ receptor antagonists versus antacids was low for clinically important upper GI bleeding and nosocomial pneumonia. Certainty was judged as very low for all-cause mortality in the ICU and as moderate for the number of participants requiring blood transfusion. However, antacids are no longer the first line of choice for preventing GI bleeding in ICU patients, and further evidence probably is not needed for this comparison (Summary of findings 7).

H₂ receptor antagonists compared with sucralfate

Overall certainty of the evidence was low for H₂ receptor antagonists versus sucralfate for the outcome clinically important upper GI bleeding in ICU patients. Overall certainty of the evidence was judged as moderate for the outcome of nosocomial pneumonia. Moreover, certainty of the evidence for the outcomes of all-cause mortality in the hospital and number of participants requiring blood transfusion was low, and certainty was very low for the outcome duration of ICU stay (Summary of findings 8). This means that we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Antacids compared with sucralfate

Overall certainty of the evidence for antacids versus sucralfate was low for clinically important upper GI bleeding, nosocomial pneumonia, all-cause mortality in the ICU, duration of ICU stay, and number of participants requiring blood transfusion (Summary of findings 9).

Potential biases in the review process

We used standard methods as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We chose critical and important outcomes for the 'Summary of findings' tables before extracting data from the included studies by using the GRADE approach through discussion.

Given the large numbers of comparisons and outcomes in this review, the review might be prone to false-positive results. Therefore, all results must be interpreted with caution.

Temporal changes in clinical care and response to ICU patients at increased risk for upper GI bleeding could have contributed to heterogeneity and increased the uncertainty of findings. Exploratory sensitivity analyses by year of publication not reported in further detail did not alter the consistency of study results nor the direction of effect. Included trials included participants with different indications at baseline, which is very important to consider when one is interpreting the findings of this review. Furthermore, treatment regimens varied across the included studies.

Because of the small number of included studies, we did not perform the following subgroup analyses: studies that explicitly included only adults over the age of 65 years, and studies that used any co-interventions. Additionally, we could not perform the following sensitivity analyses owing to lack of available data from the included trials: studies with published and validated criteria for diagnosis of clinically important upper GI bleeding and nosocomial pneumonia. Results from subgroup analyses must be interpreted with caution because the number of included studies is relatively small and the power to detect any statistical differences in effect is limited. Information from such subgroup and sensitivity analyses would be relevant for guiding decision-making in practice.

Agreements and disagreements with other studies or reviews

In recent years, several non-Cochrane reviews have investigated the risk-benefit profile of bleeding prophylaxis in ICU patients and their findings have been published (Alhazzani 2017; Alquraini 2017; Alshamsi 2016; Barkun 2012; Krag 2014; Pilkington 2012). The most recent reviews confirmed the beneficial effect of stress ulcer prophylaxis on clinically important upper GI bleeding, as is supported by this Cochrane review.

Alhazzani 2017 conducted a network meta-analysis of randomised controlled studies and found that proton pump inhibitors might be more effective than H2 receptor antagonists but might also increase the risk of ventilator-associated pneumonia. Similar results were yielded when Barkun 2012 conducted a meta-analysis. Review authors concluded that routine stress ulcer prophylaxis is not warranted, and that benefits and harms should be carefully considered in practice.

Alquraini 2017 compared sucralfate versus H2 receptor antagonists in ICU patients for prevention of upper GI bleeding and the incidence of pneumonia. This review found no difference between the two treatments in the occurrence of upper GI bleeding but found a lower incidence of nosocomial pneumonia in the sucralfate arm, which confirms the findings of this review.

Alshamsi 2016 compared proton pump inhibitors and H2 receptor antagonists and, among others, their effects on prevention of upper GI bleeding and nosocomial pneumonia. Results of their review confirm our results that proton pump inhibitors were more effective in preventing upper GI bleeding in critically ill patients when compared with H2 receptor antagonists, and that effects of both interventions on the incidence of pneumonia were similar.

Krag 2014 conducted a systematic review using Cochrane methods and compared the effects of H2 receptor antagonists or proton pump inhibitors versus placebo or no treatment. They reported lower risk of upper GI bleeding in the pooled effect of all studies with treatment versus placebo or no treatment. However, they emphasised that this result was not maintained in an analysis of low risk of bias studies only. Similar to our findings, risk of pneumonia was not significantly different between treatment and no prophylaxis or placebo.

Last, Pilkington 2012 compared H2 receptor antagonists versus proton pump inhibitors and found no difference between the two treatments with respect to the occurrence of upper GI bleeding and pneumonia. These findings cannot be confirmed by our review, possibly because we included newer studies.

Overall, existing and recent systematic reviews confirm the results of this review. However, their scope is limited to reporting the effects of two interventions compared with each other or of one or two interventions compared with placebo or no prophylaxis. Published reviews are of reasonable quality as assessed by Cochrane methods (Alshamsi 2016; Krag 2014), and two reviews used the GRADE approach to assess the certainty of evidence (Alhazzani 2017; Alquraini 2017). Therefore, our review constitutes the most comprehensive and most up-to-date piece of work on this important medical topic.

AUTHORS' CONCLUSIONS

Implications for practice

This review found evidence of moderate certainty to show that tested interventions might be effective in preventing upper GI bleeding in ICU patients compared with placebo or no prophylaxis. Further, sucralfate or H2 receptor antagonists might be effective in preventing upper gastrointestinal bleeding in ICU patients compared with placebo or no prophylaxis. Further, the effect estimate of proton pump inhibitors versus placebo or no prophylaxis is not significant, but it does not preclude potential benefit in preventing upper GI bleeding. Nosocomial pneumonia was slightly more frequent among patients receiving prophylaxis, but this adverse event might be outweighed by the benefits of the interventions. Results regarding the effectiveness of preventing upper GI bleeding must be interpreted with caution because most studies included in the comparison H2 receptor antagonists versus placebo or no prophylaxis were published in the 1980s and 1990s, and only evidence of low certainty (due to inconsistency and risk of bias) suggests that proton pump inhibitors are more effective than H2 receptor antagonists.

Decisions in practice should be based on individual assessments of patient needs and underlying conditions. Recent evidence indicates that prevention of upper GI bleeding with H2 receptor antagonists results in reduced cost and increased survival compared with use of proton pump inhibitors (Hammond 2017;

MacLaren 2014). Still, local context must be considered in selection of treatment.

Implications for research

Our findings reveal low-certainty evidence on assessment of nosocomial pneumonia in ICU patients undergoing prophylaxis for upper GI bleeding. Given that antacids are almost no longer used in practice, further good quality research is needed to assess the risk of nosocomial pneumonia in patients receiving sucralfate, H₂ receptor antagonists, or protons pump inhibitors.

Provided H₂ receptor antagonists and proton pump inhibitors are the drugs used most often, and proton pump inhibitors seem to be more effective in preventing clinically important upper GI bleeding, the effect of proton pump inhibitors on any adverse event including nosocomial pneumonia and mortality must be investigated in meta-analyses or explored by larger, high-quality RCTs conducted to confirm the positive risk-benefit balance. In addition, more research is needed on the effectiveness of different treatments planned on admission to the ICU.

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Cathy Yuan conducted literature searches for the review update in June 2016 and August 2017.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ali 2016

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 10 participants</p> <p>Number analysed: 10 participants</p> <p>Pantoprazole</p> <ul style="list-style-type: none"> Age (years; mean (SD)): - (-) Number of participants (n): 4 Gender (male/female; n): - <p>Placebo</p> <ul style="list-style-type: none"> Age (years, mean (SD)): - (-) Number of participants (n): 6 Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> Receiving > 5 doses of pantoprazole/placebo Being mechanically ventilated <p>Exclusion criteria: -</p> <p>Baseline imbalances: -</p>
Interventions	<p>Pantoprazole</p> <ul style="list-style-type: none"> Dose (total/d): 40 mg Duration of treatment (days): - Route: IV Intervention: IV pantoprazole (40 mg), mean 8.8 (0.3) doses Concomitant medications: mechanical ventilation <p>Placebo</p> <ul style="list-style-type: none"> Dose (total/d): - Duration of treatment (days): - Route: IV Intervention: placebo, mean 10.7 (1.1) doses Concomitant medications: - <p>Adherence to regimen: -</p> <p>Duration of trial: -</p> <p>Duration of follow-up: -</p>
Outcomes	Outcomes sought in review and reported in trial

Ali 2016 (Continued)

- Clinically important GI bleeding

Outcomes sought but not reported in trial

- VAP
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Blood transfusions
- Adverse events of interventions

Outcomes reported in trial but not used in review

- -

Notes	<p>Setting: ICU</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <ul style="list-style-type: none"> • Ethics approval: - <p>Informed consent: -</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: -</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: mentioned only that participants were randomised to treatment. Not enough information on method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: no information about allocation concealment reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: mentioned only that the trial was double-blind. No information about the method of blinding
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	<p>Comment: mentioned that outcome assessment was done blinded to intervention. Presence of 1 or more macroscopic abnormalities (erythema or oedema, erosions, ulcerations, and nasogastric tube lesions) and GI bleeding was assessed, blinded to intervention, at endoscopy by a single experienced gastroenterologist</p> <p>Quote: "assessed, blinded to intervention, at endoscopy by a single experienced gastroenterologist"</p>
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: The outcome was not addressed in this trial
Blinding of outcome assessment (detection bias)	Low risk	Comment: mentioned that outcome assessment was done blinded to intervention

Ali 2016 (Continued)

Adverse reactions of interventions

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Conference abstract reports about 10 participants from a larger prospective trial. Those who received > 5 doses of pantoprazole or placebo (n = 84) were eligible for the endoscopy substudy, but unclear why data from only 10 participants are reported
Selective reporting (reporting bias)	Low risk	Comment: Outcomes reported in Methods section are also reported in Results section
Other bias	Unclear risk	Comment: not enough information reported in conference abstract to assess other biases

Apte 1992

Methods	Open-label parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 34 participants</p> <p>Number analysed: 34 participants</p> <p>Ranitidine</p> <ul style="list-style-type: none"> Age (years; mean (range)): 27 (10 to 55) Number of participants (n): 16 Gender (male/female; n): 12/4 <p>No prophylaxis</p> <ul style="list-style-type: none"> Age (years, mean (range)): 26 (11 to 88) Number of participants (n): 18 Gender (male/female; n): 11/7 <p>Inclusion criteria</p> <ul style="list-style-type: none"> Tracheotomised patients in medical ICU with tetanus <p>Exclusion criteria</p> <ul style="list-style-type: none"> Pneumonia diagnosed before tracheostomy Ranitidine received before randomisation <p>Baseline imbalances: Participants were tracheotomised patients with tetanus. Maximum tetanus severity score was 11 (4 to 16) in the ranitidine group and 10 (6 to 16) in the control group. Groups were similar with respect to age and gender distribution</p>
Interventions	<p>Ranitidine</p> <ul style="list-style-type: none"> Dose (total/d): 200 mg Duration of treatment (days): - Route: IV Intervention: 50 mg IV 6-hourly Concomitant medications: 3 participants whose gastric pH did not increase to > 4 received additional antacids (30 mL 4-hourly), Tetanus was treated with anti-tetanus serum, penicillin, diazepam, and

Apte 1992 (Continued)

neuromuscular blockade with mechanical ventilation when indicated. All participants received intermittent nasogastric feeding (300 to 400 mL 4-hourly)

No prophylaxis

- Dose (total/d): -
- Duration of treatment (days): -
- Route: -
- Intervention: -
- Concomitant medications: Tetanus was treated with anti-tetanus serum, penicillin, diazepam, and neuromuscular blockade with mechanical ventilation when indicated. All participants received intermittent nasogastric feeding (300 to 400 mL 4-hourly)

Adherence to regimen: 34 tracheotomised participants who were admitted to medical ICU with tetanus were randomly assigned to ranitidine or control group within 24 hours of tracheal intubation. Six participants who had pneumonia before tracheostomy or had ranitidine before randomisation were excluded. All remaining participants were studied until 48 hours after extubation

Duration of trial: -

Duration of follow-up: studied daily until 48 hours after tracheal extubation

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Clinically important upper GI bleeding <ul style="list-style-type: none"> ◦ Gross bleed (bright red or altered blood) ◦ Occult bleeding (by benzidine test) • VAP: diagnosed by appearance of new infiltrates on chest radiograph or bronchial breath sounds on examination and positive tracheal culture along with fever (axillary temperature > 38°C), leucocytes (> 13,000 cells/mm³), and purulent sputum (> 25 leucocytes per low-power field) • All-cause mortality in ICU • Duration of intubation (median and range provided) • Number of participants requiring blood transfusion (no participant required this) • Number of units of blood transfused (no participant required this) <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • All-cause mortality in hospital • Duration of ICU stay • Adverse events of interventions <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none"> • Intragastric pH status (with and without enteral nutrition) • Gastric colonisation
Notes	<p>Setting: Medical ICU in Department of Medicine, Department of Microbiology, King Edward Memorial Hospital, Parel, Bombay, India</p> <p>Source of funding: Quote: "Study supported, in part, by a grant from Seth GS medical College and KEM Hospital research Society"; Torrent Pharmaceuticals provided ranitidine</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The study was approved by the institutional ethics committee"</p> <p>Informed consent: Quote: "The study was approved by the institutional ethics committee [with] waived informed consent"</p> <p>Comment: not obtained, as mentioned in the trial report</p>

Apte 1992 (Continued)

Clinical trials registration: -

Sample size calculation: -

Additional notes: Trial included patients with tetanus. Trial reports that gram-negative bacilli were the predominant organisms that caused pneumonia. Participants treated with ranitidine developed pneumonia significantly earlier (median 3 days, range 1 to 5) than participants given control (median 5 days, range 3 to 14 days)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not enough information on method of randomisation reported
Allocation concealment (selection bias)	Unclear risk	Comment: not enough information on method of allocation concealment reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This trial compared an intervention vs no prophylaxis (blinding was not possible)
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: GI bleeding was an objective outcome that was detected as per the definition in the trial protocol
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: Pneumonia was an objective outcome that was detected as per the definition in the trial protocol
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All participants who were randomised were included in analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: This trial was supported in part by a grant from Seth GS Medical College and KEM Hospital Research Society. The role of the sponsor in the conduct and reporting of the trial is unclear. No other form of bias is suspected

Barandun 1985

Methods	Double-blind parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 66 participants</p> <p>Number analysed: 55 participants</p> <p>Pirenzepine</p>

Barandun 1985 (Continued)

- Age (years; mean (SD)):-
- Number of participants (n): 27
- Gender (male/female; n): -

Cimetidine

- Age (years; mean (SD)):-
- Number of participants (n): 28
- Gender (male/female; n): -

Inclusion criteria

- Age > 16 years
- Patients in surgical ICU

Exclusion criteria

- Gastroscopy not possible
- On therapy for ulcer
- Receiving operation of stomach

Baseline imbalances: baseline imbalances comparable, also in terms of severity of injury/trauma

Interventions

Pirenzepine

- Dose (total/d): 40 mg
- Duration of treatment (days): -
- Route: IV
- Intervention: 4 × 10 mg IV
- Concomitant medications: -

Cimetidine

- Dose (total/d): 800 mg
- Duration of treatment (days): -
- Route: IV
- Intervention: 4 × 200 mg IV
- Concomitant medications: -

Adherence to regimen: 11 participants withdrew from the trial. However, no reasons are mentioned in the trial report. Also no mention of which interventional group these 11 participants belonged to

Duration of trial: -

Duration of follow-up: not clearly mentioned, probably until discharge

Outcomes

Outcomes sought in review and reported in trial

- Clinically important upper GI bleeding
- Adverse events of interventions

Outcomes sought but not reported in trial

- VAP
- All-cause mortality in ICU
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Number of participants requiring blood transfusion
- Number of units of blood transfused

Barandun 1985 (Continued)

Outcomes reported in trial but not used in review

- Number of lesions on gastroscopy

Notes	Setting: Surgical ICU, Chur, Switzerland Source of funding: - Conflicts of interest: - Ethics approval: - Informed consent: - Clinical trials registration: - Sample size calculation: -	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not enough information reported on method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: not enough information reported on method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: This appears to be a double-dummy placebo-controlled trial, in which participants from group 1 got a placebo that looks like the intervention in group 2 and vice versa. Thus personnel would have been blinded and likelihood of performance bias is low
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: not enough information reported on the criteria for diagnosis of upper GI bleeding
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: The trial did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: This appears to be a double-dummy placebo-controlled trial, in which participants from group 1 got a placebo that looks like the intervention in group 2 and vice versa. Thus the likelihood of detection bias seems low
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 11 participants withdrew from the trial, but reasons for withdrawal and the group to which they were randomised are not clearly mentioned in the trial report
Selective reporting (reporting bias)	Unclear risk	Comment: All intended outcomes were reported but no clear mention of the number of participants in the cimetidine group who had confusion and high K levels
Other bias	Low risk	Comment: The trial report is unclear on the source of funding. No other sources of bias detected

Bashar 2013

Methods	Double-blind parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 146 participants</p> <p>Number analysed: 120 participants</p> <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 50.63 (20.78) • Number of participants (n): 60 • Gender (male/female; n): 16/44 <p>Pantoprazole</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 43.67 (19.58) • Number of participants (n): 60 • Gender (male/female; n): 18/42 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Intubated patients • Age > 18 years • Acute Physiology and Chronic Health Evaluation score (APACHE II) < 25 <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Pneumonia • GI bleeding upon ICU admission • History of gastrectomy • Anticipated need for tracheal intubation in less than 48 hours • Known sensitivity to the studied medication <p>Baseline imbalances: We found no statistically significant differences between the 2 groups regarding baseline characteristics, such as age, sex, or APACHE II</p>
Interventions	<p>Ranitidine</p> <ul style="list-style-type: none"> • Dose (total/d): 150 mg IV or 300 mg PO • Duration of treatment (days): during NPO time or when oral feeding started • Route: IV or PO • Duration of follow-up (days, mean (SD)): 15.67 (7.11) • Intervention: following admission to the ICU, 50 mg intravenous ranitidine (ranitidine 50 mg, Caspian Tamin Co., Rasht, Iran) was administered 3 times daily to 1 group of participants during NPO time to prevent stress ulcers. Thereafter, the day after oral feeding initiation, 150 mg oral ranitidine tablets (ranitidine 150 mg, Darou Pakhsh, Tehran, Iran) were administered twice daily until the end of the trial • Concomitant medications: GI prophylaxis continued until ICU discharge. Other treatments were similarly administered to both groups according to the ICU protocol <p>Pantoprazole</p> <ul style="list-style-type: none"> • Dose (total/d): 40 mg IV or 40 mg PO • Duration of treatment (days): during NPO time or when oral feeding started • Route: IV or PO • Duration of follow-up (days): 17.58 (7.90) (until discharge) • Intervention: Second group received 40 mg intravenous pantoprazole (Pepticare 40 mg, Ronak Pharmaceutical Co., Saveh, Iran) once daily during NPO time. The day after oral feeding initiation, it was

Bashar 2013 (Continued)

replaced with 40 mg pantoprazole tablets (E.C. Tablet Pantoprazole 40 mg, Osveh, Tehran, Iran) once a day for stress ulcer prophylaxis until the end of the trial

- Concomitant medications: GI prophylaxis was continued until ICU discharge. Other treatments were similarly administered to both groups according to the ICU protocol

Adherence to regimen: -

Duration of trial: July 2011 to July 2012

Duration of follow-up: -

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • All-cause mortality in ICU • Duration of intubation <p>Outcomes sought in review but not reported in trial</p> <ul style="list-style-type: none"> • Clinically important GI bleeding • VAP • All-cause mortality in hospital • Duration of ICU stay • Number of participants requiring blood transfusion • Number of units of blood transfused • Adverse events <p>Outcomes reported, but not used in the review</p> <ul style="list-style-type: none"> • Days until VAP incidence
Notes	<p>Setting: ICU, Iran</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Trial was approved by the Ethics Committee of Hamedan University of Medical Sciences.</p> <p>Informed consent: Written informed consent was obtained from legal guardians of participants</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Conflicts of interest: -</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomised using online random allocation software (www.allocationsoftware.com)"
Allocation concealment (selection bias)	Unclear risk	Comment: not enough information reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients and the attending intensivists responsible for data collection were blinded to the assigned groups"

Bashar 2013 (Continued)

Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: Trial did not address this outcome
Blinding (detection bias) Nosocomial pneumonia	Low risk	Quote: "Patients underwent chest radiography which was repeated at least twice a week" Comment: Objective outcome measurement unlikely to introduce bias
Blinding of outcome as- sessment (detection bias) Adverse reactions of inter- ventions	Low risk	Quote: "The patients and intensivists responsible for data collection were blinded to the assigned groups"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All participants were followed up until discharge
Selective reporting (re- porting bias)	Low risk	Comment: All outcomes listed in the Methods section were reported in the Re- sults section
Other bias	Low risk	Comment: no other sources of bias suspected

Basso 1981

Methods	Single-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 168 participants</p> <p>Number analysed: 168 participants</p> <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): - • Number of participants (n): 60 • Gender (male/female; n): - <p>Antacids (Maalox)</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): - • Number of participants (n): 52 • Gender (male/female; n): - <p>No prophylaxis</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): - • Number of participants (n): 56 • Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Patient admitted to the ICU <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Evidence of gross upper GI bleeding before or during the 12 hours after start of the trial

Basso 1981 (Continued)

- Gastric or oesophageal operations
- Age < 12 years
- Having coagulopathies

Baseline imbalances: Risk categories and risk factors in the 3 groups were comparable

Interventions	<p>Cimetidine</p> <ul style="list-style-type: none"> • Dose (total/d): 800 mg • Duration of treatment (days): min 10 • Route: IV or PO • Intervention: 200 mg every 6 hours IV or orally • Concomitant medications: - <p>Antacids (Maalox)</p> <ul style="list-style-type: none"> • Dose (total/d): 2400 mL • Duration of treatment (days): min 10 • Route: NG tube or PO • Intervention: 10 mL/h by NG tube or orally • Concomitant medications: - <p>No prophylaxis</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days): min 10 • Route: - • Intervention: - • Concomitant medications: - <p>Adherence to regimen: 16 participants died, 6 did not comply with therapy, and 9 were transferred to other institutions. Therefore, 31 participants did not complete 10 days of the trial</p> <p>Duration of trial: March 1978 to April 1979</p> <p>Duration of follow-up: not clearly mentioned in trial report</p>
Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Clinically important GI bleeding diagnosed by clinical signs of haematemesis, melena, blood in NG tube or stool, or change in haematocrit • All-cause mortality in ICU (not reported separately for each arm) • Number of units of blood transfused (not mentioned separately for each arm) <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • VAP • All-cause mortality in hospital • Duration of ICU stay • Duration of intubation • Participants requiring blood transfusion • Adverse events of interventions <p>Outcomes reported but not used in review</p> <ul style="list-style-type: none"> • Nil
Notes	<p>Setting: ICU, University of Rome</p> <p>Source of funding: -</p>

Basso 1981 (Continued)

Ethics approval: -

Informed consent: Quote: "Informed consent was obtained from either the participant or their closest relative"

Clinical trials registration: not provided

Sample size calculation: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was done in a single blind manner, assigning the treatment according to a list of randomised values" Comment: not enough information reported on method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: not enough information reported on method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial and personnel were not blinded
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "The observer assessing the occurrence of gastrointestinal bleeding did not know the type of prophylactic measures the patient was receiving"
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: The trial did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: Unclear whether outcome assessors were blinded for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	Unclear risk	Comment: All-cause mortality in ICU and units of blood transfused were not mentioned separately for each interventional arm. Unclear whether this contributed to reporting bias
Other bias	Unclear risk	Comment: source of funding and baseline characteristics unclear

Behrens 1994

Methods	Open-label randomised controlled trial
Participants	Baseline characteristics Number randomised: 43 participants Number analysed: 43 participants

Behrens 1994 (Continued)

Pirenzepine

- Age (years; mean (SD)): 2.62 (-) overall
- Number of participants (n): 21
- Gender (male/female; n): 24/19 overall

Famotidine

- Age (years; mean (SD)): 2.62 (-) overall
- Number of participants (n): 22
- Gender (male/female; n): 24/19 overall

No prophylaxis

- Age (years; mean (SD)): 2.62 (-) overall
- Number of participants (n): 36
- Gender (male/female; n): 24/19 overall

Inclusion criteria

- Undergoing corrective or palliative surgery for congenital heart disease

Exclusion criteria

- Having operations that usually have a short and uncomplicated postoperative recovery, such as repair of an atrial septal defect, valvotomy for aortic stenosis, or repair of coarctation of the isthmus

Baseline imbalances: There were no differences between groups that did not receive any prophylaxis (not randomised) and the group that did receive prophylaxis (randomised to pirenzepine and famotidine)

Interventions

Pirenzepine

- Dose (total/d): 1 mg/kg bw
- Duration of treatment (days): until participants were fed fully by mouth
- Route: IV
- Intervention: In older participants, 2 doses were given; children who weighed less than 10 kg were given 3 doses. Daily dose was reduced to 0.5 mg/kg if serum creatinine exceeded 3 mg/dL
- Concomitant medications: Full parental nutrition was given at the time of endoscopy. All participants were treated with antibiotics after operation: cefuroxime or cefotiam at the dose of 100 mg/kg bw/d

Famotidine

- Dose (total/d): 1 mg/kg bw
- Duration of treatment (days): until participants were fed fully by mouth
- Route: IV
- Intervention: In older participants, 2 doses were given; children who weighed less than 10 kg were given 3 doses. Daily dose was reduced to 0.5 mg/kg if serum creatinine exceeded 3 mg/dL
- Concomitant medications: Full parenteral nutrition was given at the time of endoscopy. All participants were treated with antibiotics after operation: cefuroxime or cefotiam at the dose of 100 mg/kg/d

No prophylaxis

- Dose (total/d): -
- Duration of treatment (days): until participants were fed fully by mouth
- Route: -
- Intervention: -
- Concomitant medications: Full parenteral nutrition was given at the time of endoscopy. All participants were treated with antibiotics after operation: cefuroxime or cefotiam at the dose of 100 mg/kg/d. Intravenous

Behrens 1994 (Continued)

Adherence to regimen: -

Duration of trial: October 1988 to November 1991

Duration of follow-up: -

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> VAP: diagnosis probably based on microbiological, clinical, and radiological findings Adverse events of interventions <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> Clinically important upper GI bleeding All-cause mortality in ICU All-cause mortality in hospital Duration of ICU stay Duration of intubation Participants requiring blood transfusion Units of blood transfused <p>Outcomes reported in report but not used in review</p> <ul style="list-style-type: none"> Severe inflammation or ulceration of the upper GI tract (no upper GI bleeding reported) Gastric pH values Relationship between GI lesions and underlying diseases Severe inflammation or ulceration of the upper GI tract (through endoscopy)
Notes	<p>Setting: University Children's Hospital, Department of Pediatric Gastroenterology, Erlangen, Germany</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The study was approved by the committee on human research of the University of Erlangen-Nurnberg"</p> <p>Informed consent: -</p> <p>Clinical trial registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: Gastric cultures were positive in 95% of participants with mean gastric pH > 4 and in 80% of participants with mean gastric pH < 4. Five and 4 participants in the 2 groups required mechanical ventilation. <i>Candida</i> sp was the predominant species cultured from gastric and tracheal secretions of participants given pirenzepine and famotidine. In the pirenzepine and famotidine groups, an organism cultured from the stomach was grown from the tracheal secretion, 1 to 4 days later, in 6 and 5 participants, respectively</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not enough information reported on method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: not enough information reported on method of allocation concealment

Behrens 1994 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: unclear on blinding of personnel, although regimens and mode of administration of interventions were similar
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: The physician who performed endoscopy to detect inflammation or ulceration of the upper GI tract was not blinded to the intervention. There is no clear definition of GI bleeding in the trial. Therefore, unclear on the likelihood of performance or detection bias
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: no mention of blinding technicians who cultured gastric secretions for pathogenic bacteria, radiologists who interpreted chest X-rays, or physicians who performed the clinical examination. No clear definition of VAP provided in the trial
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: not enough information reported on blinding of outcome assessors for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were included in the analysis
Selective reporting (reporting bias)	Low risk	Comment: Trial compared participants who received prophylaxis vs participants who did not receive prophylaxis. In the intervention group, participants were randomised to receive either pirenzepine or famotidine. The outcome of interest (VAP) was reported separately for participants who were randomised to 2 different arms (pirenzepine and famotidine)
Other bias	Unclear risk	Comment: source of funding not clearly mentioned in the trial report. Baseline data on randomised groups unclear

Ben-Menachem 1994

Methods	Single-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 304 participants</p> <p>Number analysed: 300 participants</p> <p>Sucralfate</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 60.1 (16.8) Number of participants (n): 100 Gender (male/female; n): 51/49 <p>Cimetidine</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 59 (18.1) Number of participants (n): 100 Gender (male/female; n): 51/49 <p>Control</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 59.6 (18)

Ben-Menachem 1994 (Continued)

- Number of participants (n): 100
- Gender (male/female; n): 51/49

Inclusion criteria

- Age > 18 years
- Admitted to Medical ICU
- Informed consent from participant or legally authorised representative

Exclusion criteria

- Expected stay at ICU of 24 hours or less
- Evidence of gastrointestinal bleeding (haematemesis, vomiting of "coffee grounds", haematochezia, or melena) at time of admission to the ICU
- Treatment with antacids, H₂ receptor antagonists, sucralfate, or omeprazole during the 24 hours before entering the ICU
- Use of non-steroidal anti-inflammatory agents, systemic anticoagulants, or thrombolytic agents during previous 7 days
- Surgery requiring general anaesthesia during previous 2 weeks
- Closed head injury or clinical evidence of increased intracranial pressure
- Grade 4 hepatic encephalopathy
- Oesophageal or gastric surgery in previous year
- History of gastrointestinal bleeding during previous year
- Pregnancy or lactation

Baseline imbalances: Quote: "One hundred patients were randomly assigned to each of the treatments. The groups were similar with regard to age, gender, percentage of participants admitted from the emergency room, severity of illness, admission diagnoses, corticosteroid usage and coagulopathy. Patients often had more than one reason for ICU admission. The mean APACHE II scores for the control, sucralfate, and cimetidine groups were 16.5 ± 6.9 , 16.8 ± 6.9 , and 18.0 ± 8.0 , respectively. Approximately one-third of the patients in each group had APACHE II scores greater than 20.0

Comment: The 3 groups were similar with respect to demographic and other risk factors for stress haemorrhage at the beginning of the trial. The most common diagnosis on admission was pneumonia, which was reported in 89 participants. Bacterial pneumonia (control: 23; sucralfate: 26; cimetidine: 21). Non-bacterial pneumonia was diagnosed (control: 9; sucralfate: 4; cimetidine: 6). Coagulopathy was present in 16, 14, and 21 participants in the 3 randomised groups

Interventions

Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days): -
- Route: nasogastric tube
- Intervention: 1 g of medication orally or as a suspension through the nasogastric tube every 6 hours. Nasogastric tube was clamped for 1 hour after sucralfate administration
- Concomitant medications: 69% of participants received enteral nutrition through a 10-Fr feeding tube. 1% received parenteral nutrition. Corticosteroids were used in all groups

Cimetidine

- Dose (total/d): varies
- Duration of treatment (days): -
- Route: IV
- Intervention: 300 mg intravenous loading dose followed by continuous intravenous infusion according to creatinine clearance: more than 50 mL/min, 900 mg/d; 20 to 50 mL/min, 600 mg/d; and less than 20 mL/min, 300 mg/d. Cimetidine dose was titrated to maintain gastric pH ≥ 4.0 . With 2 consecutive gastric pH values < 4.0 , dose was increased by the following amounts based on creatinine clearance: 300 mg/d, 200 mg/d, and 100 mg/d. Maximum allowable cimetidine doses for participants grouped by renal function were 2400 mg/d, 1600 mg/d, and 800 mg/d

Ben-Menachem 1994 (Continued)

- Concomitant medications: 57% of participants received enteral nutrition through a 10-Fr feeding tube. 7% of cimetidine group received parenteral nutrition. Corticosteroids were used in all groups

No prophylaxis

- Dose (total/d): -
- Duration of treatment (days): -
- Route: -
- Intervention: -
- Concomitant medications: 72% of participants received enteral nutrition through a 10-Fr feeding tube. 1% received parenteral nutrition. Corticosteroids were used in all groups

Adherence to regimen: Although 304 participants were randomised, only 300 (100 in each group) were part of the trial because 1 participant died 2 hours after admission, 3 participants were randomised on 2 different occasions, and second admissions were excluded. Results for only 291 participants were available when the trial was finally reviewed by the second committee. The 8 participants who did not agree to endoscopy might have been excluded from the trial denominator (unclear on the 1 remaining participant)

Duration of trial: 1 February to 25 November 1992

Duration of follow up: until death or discharge from ICU

Outcomes
Outcomes sought in review and reported in trial
Primary outcomes

- Clinically important GI bleeding defined as:
 - Persistent haematemesis (red blood or guaiac-positive 'coffee grounds') that did not clear with 1.5 L saline lavage
 - 3-Point decrease in haematocrit during 24 hours accompanied by red blood or guaiac-positive 'coffee grounds' material that cleared with lavage, or melena, or 3 guaiac-positive stools without evidence of lower gastrointestinal bleed
 - Any unexplained 6-point decrease in haematocrit during a 48-hour period (added as a safety measure because some participants would not receive prophylaxis)

Note: Median time from ICU admission to onset of stress-related haemorrhage was 5 days

- VAP defined as:
 - Chest roentgenogram obtained 72 or more hours after ICU admission that showed a new and persistent infiltrate
 - Fever, leucocytosis, or both
 - Purulent tracheobronchial secretions
 - Gram-stained sputum showing more than 25 polymorphonuclear leucocytes and fewer than 10 squamous epithelial cells per low-power field
 - Recovery of an accepted nosocomial pathogen from sputum culture
- All-cause mortality in ICU
- All-cause mortality in hospital
- Duration of ICU stay
- Number of participants requiring blood transfusion
- Adverse events of interventions&&

Note: Nosocomial pneumonia occurred after a mean of 6.9 ± 7.2 days in the ICU (median 9 days)

Outcomes sought but not reported in trial

- Duration of intubation
- Units of blood transfused

Outcomes reported in trial but not used in review

Ben-Menachem 1994 (Continued)

- Duration of hospital stay

Notes

Setting: Henry Ford Hospital and Health Sciences Center, Detroit, Michigan

Source of funding: Quote: "Grant support: in part from the Henry Ford Hospital Research and Education Funds to Dr. Ben-Menachem and to Dr. Fogel"

Conflicts of interest: -

Ethics approval: Quote: "This protocol was reviewed and approved by the Henry Ford Hospital Institutional Review Board"

Informed consent: Quote: "Informed consent was obtained from the patient or from legally authorized representatives when the patient could not provide consent"

Clinical trials registration: -

Sample size calculation: Quote: "We estimated sample size to provide 80% power to detect a 75% reduction in bleeding rate, that is, a 12% bleeding rate for the control group compared with a 3% rate in either of the two treatment groups. We used an alpha value of 0.05 (two-tailed) adjusted for the comparison of the control group with each of the prophylaxis groups. As a result of these assumptions, 160 patients were needed in each of the three groups"

Additional notes: Mechanical ventilation was used in 65, 72, and 76 participants in the 3 respective groups. Respiratory failure and high dose of corticosteroid were independently associated with increased risk of stress-related haemorrhage. According to the trial report, 43 participants satisfied the criteria for significant GI bleeding (as per the definition), and 19 of these participants did not have stress-related bleeding (as determined by oesophagogastroduodenoscopy). Among them, 12 participants (4 controls, 3 receiving sucralfate, and 5 receiving cimetidine) had a normal result of endoscopy, suggesting that the change in haematocrit was due to fluid shifts. Seven participants bled from causes not due to stress ulceration, and 8 participants did not have endoscopy (5 did not give consent, 1 participant with lymphoma and thrombocytopaenia died of multiple-organ system failure 10 days after the bleeding episode. Three of the 8 participants met criterion 3 of diagnosis

Quote: "Two of 20 patients in the control group with coagulopathy had stress-related haemorrhage. In the cimetidine and sucralfate groups, the incidences were 1 of 22 and 2 of 17, respectively ($P > 0.05$)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was by sealed envelope using the permuted block design" Comment: Method to generate a random sequence is clearly mentioned in the trial report
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was by sealed envelope using the permuted block design" Comment: Method for allocation concealment is clearly mentioned in the trial report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was a single-blind trial, and the mode of drug administration could not have allowed blinding. Therefore, risk of performance bias is high
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "The primary study end point was substantial haemorrhage from stress gastritis. Information regarding hematocrit, haemoccult status of stool and nasogastric aspirate, and volume status [were] presented daily to two investigators who were blinded to therapy"

Ben-Menachem 1994 (Continued)

		Comment: Trial report mentions blinding of outcome assessors for the primary outcome of GI bleed, which was an objective outcome detected as per the definition used in the trial
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: Outcome assessors were not blinded. However, this was an objective outcome that was diagnosed as per the definition used in the trial protocol. Therefore, the likelihood of performance or detection bias is low
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature, so the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Although 304 participants were randomised, only 300 were analysed, as 1 participant died 2 hours after admission, 3 were randomised on 2 different occasions, and second admissions were excluded. Results for only 291 participants were available when the trial was finally reviewed by the second committee. The 8 participants who did not agree to endoscopy might have been excluded from the trial denominator (unclear for the 1 remaining participant). However, intention-to-treat analysis was done with 100 participants in each of the 3 groups. Therefore, there was no attrition bias
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes are reported. A subgroup analysis was desirable for participants who received enteral feeds
Other bias	Low risk	Comment: This trial was supported in part by Henry Ford Hospital Research and Education Funds. The role of the sponsor in the conduct and reporting of this trial is unclear. No other form of bias is suspected

Bonten 1995

Methods	Stratified double-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 141 participants</p> <p>Number analysed: 141 participants</p> <p>Antacids</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 58.6 (18.6) • Number of participants (n): 74 • Gender (male/female; n): 46/28 <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 57.3 (19.4) • Number of participants (n): 67 • Gender (male/female; n): 42/25 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Mechanically ventilated • Expected ICU stay $\geq$ 3 days • Informed consent from participants/family representative <p>Exclusion criteria</p>

Bonten 1995 (Continued)

- Age < 15 years
- Admitted for massive gastric haemorrhage or bleeding oesophageal varices, after oesophageal or gastric surgery, when a nasogastric tube could not be placed
- Receiving H2 antagonists or H + K + ATP-ase inhibitors

Baseline imbalances: Demographic characteristics of both groups, such as age, gender, and severity of illness, which was assessed by the APCHE score, were almost similar. Most participants were given a diagnosis of cardiovascular problems (30 in both groups). Neoplastic disease was more common among participants assigned to the antacid group when compared with the sucralfate group (12 and 5), whereas renal insufficiency and immunodeficiency were more common among participants in the sucralfate group (1 and 6 and 3 and 7, respectively). All other underlying conditions including presence of pneumonia (9 in antacid group and 10 in sucralfate group) on admission were similar between both groups

Interventions

Antacids

- Dose (total/d): 180 mL
- Duration of treatment (days; mean (SD)): 11 (16.8)
- Route: nasogastric tube
- Intervention: 30 mL every 4 hours at 2.00 through 22.00 hours + sucralfate placebo at hours when antacids were administered + 10 mL of sterile water
- Concomitant medications: antibiotics

Sucralfate

- Dose (total/day): 5 g
- Duration of treatment (days; mean (SD)): 13.3 (12.7)
- Route: nasogastric tube
- Intervention: 1 g every 4 hours at 0.00 through 20.00 hours + antacid placebo at the hours that antacids were administered + 10 mL of sterile water
- Concomitant medications: antibiotics

Adherence to regimen: Gastric pH was determined within 24 hours after admission via continuous intragastric monitoring. Participants were stratified into 2 groups according to gastric pH value measured on the first day of admission, which was < 3 (n = 69) or ≥ 3 (n = 72) (continuous intragastric pH in 84 and indicator papers in 57 participants; for 28 in the latter group, continuous pH monitoring was performed later). Participants were later randomised to 2 treatment arms, amongst whom 74 received antacids and 67 received sucralfate

Duration of trial: August 1992 to August 1993

Duration of follow-up: probably until discharge or death

Outcomes

Outcomes sought in review and reported in trial

- Incidence of clinically important GI bleeding; suspicion of gastrointestinal bleeding was endoscopically confirmed and treated according to standard clinical practice. Participant was excluded from the trial from that day onwards
- VAP; in case of clinical suspicion of pneumonia, bronchoscopy with protected specimen brush (PSB) and bronchoalveolar lavage (BAL) was performed. Diagnosis was established when ≥ 3 of the following criteria were established: rectal temperature > 38°C or < 35.5°C; blood leucocytosis ($> 10 \cdot 10^3/\text{mm}^3$); and/or left shift or blood leucopenia ($< 3 \cdot 10^3/\text{mm}^3$); > 10 leucocytes per high-power stain in gamma field of tracheal aspirate; or positive culture from tracheal aspirate, in combination with a new or progressive infiltrate on chest radiograph and the presence of a sample of secretions obtained by BAL (cutoff point $\geq 10^4$ cfu/mL) or protected specimen brush (cutoff point $\geq 10^3$ cfu/mL), positive cultures from blood, or pleural fluid culture unrelated to another space and obtained within 48 hours before and after respiratory sampling. Episodes of pneumonia obtained within the first 24 hours of admission were considered present on admission

Note: The mean number of days before the first episode of VAP was 9.2 in the antacid group and 9.3 in the sucralfate group, respectively.

Bonten 1995 (Continued)

- Duration of ICU stay
- All-cause mortality in ICU
- All-cause mortality in hospital

Outcomes sought but not reported in trial

- Duration of intubation
- Number of participants requiring blood transfusion
- Number of units of blood transfused
- Adverse events of interventions

Outcomes reported in report but not used in review

- Gastric pH monitoring
- Colonisation
- Post hoc analysis of the role of enteral feeding

Notes

Setting: University Hospital Maastricht, Maastricht, The Netherlands

Source of funding: Quote: "Supported by grant 28-2125 from the Praevention Foundation"

Conflicts of interest: -

Ethics approval: Quote: "The protocol was approved by the institutional review board of the hospital"

Informed consent: Quote: "... informed consent was obtained from all participants or if this was not possible because of the clinical condition, from a representative of the family"

Clinical trials registration: -

Sample size calculation: Quote: "The sample size of both groups of patients was calculated to detect a reduction in the incidence of VAP from an assumed 30% in the antacid group to an expected incidence of 10% in the sucralfate group ($\alpha = 0.05$ and $\beta = 0.2$)"

Additional notes: VAP was mainly polymicrobial in nature. *Pseudomonas aeruginosa* and *Staphylococcus aureus* were the 2 predominant pathogens cultured from participants with a diagnosis of VAP. The oropharynx was the initial site for colonisation of *Enterobacteriaceae*, whereas *Pseudomonas aeruginosa* and *Staphylococcus aureus* colonised in the upper respiratory tract first

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were stratified into two groups according to, the gastric pH values measured on the first day of admission which were < 3 ($n = 69$) or ≥ 3 ($n = 72$). These patients were later randomised to two treatment arms" Comment: not enough information on method of sequence generation reported
Allocation concealment (selection bias)	Unclear risk	Quote: "Sucralfate and antacids were compared in a double blind fashion and analysed according to a prospectively developed plan that used definition adopted before the treatment allocation code was broken" Comment: Allocation concealment might have been in place but not enough information was provided on method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study had a "double dummy model" design wherein participants receiving sucralfate received an antacid placebo at the same time when antacid was administered to the other group and vice versa"

Bonten 1995 (Continued)

		<p>Quote: "Sucralfate and antacids were compared in a double blind fashion and analysed according to a prospectively developed plan that used definition adopted before the treatment allocation code was broken. The attending physician was unaware of the cultural results of the oropharyngeal and gastric samples, or results of pH monitoring"</p> <p>Comment: Personnel (and participants) were unaware of therapy and results</p>
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	<p>Quote: "The study had a "double dummy model" design wherein participants receiving sucralfate received an antacid placebo at the same time when antacid was administered to the other group and vice versa"</p> <p>Comment: The trial by design inherently blinded trial personnel who were assigned to endoscopically detect upper GI bleeding; however, criteria for diagnosis of upper GI bleeding were not clearly reported</p>
Blinding (detection bias) Nosocomial pneumonia	Low risk	<p>Quote: "The study had a "double dummy model" design wherein participants receiving sucralfate received an antacid placebo at the same time when antacid was administered to the other group and vice versa"</p> <p>Comment: The trial by design inherently blinded trial personnel who were assigned to diagnose VAP. Criteria for diagnosis of VAP were clearly reported</p>
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	<p>Quote: "The study had a "double dummy model" design wherein participants receiving sucralfate received an antacid placebo at the same time when antacid was administered to the other group and vice versa"</p> <p>Comment: The trial by design inherently blinded outcome assessors. Therefore, the likelihood of detection bias is low</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Comment: No dropouts were reported, and all randomised participants were part of the final analysis. Therefore, there might not be an attrition bias</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: All intended outcomes were reported and were part of the analysis.. A subgroup analysis for participants who received enteral feeds was desirable</p>
Other bias	Low risk	<p>Comment: Trial was supported by grant 28-2125 from the Praevention Foundation. The role of the sponsor in the conduct and reporting of the trial is unclear</p>

Borrero 1984

Methods	Quasi-randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 100 participants</p> <p>Number analysed: 100 participants</p> <p>Antacids</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 57 (-) • Number of participants (n): 52 • Gender (male/female; n): 31/21 <p>Sucralfate</p>

Borrero 1984 (Continued)

- Age (years; mean (SD)): 62.2 (-)
- Number of participants (n): 49
- Gender (male/female; n): 27/21

Inclusion criteria

- Patient admitted to medical or surgical ICU

Exclusion criteria

- Receiving fluids or food by mouth
- Having undergone cardiac, gastric, or oesophageal surgery
- Evidence of gross upper GI bleeding upon entry into the trial

Baseline imbalances: Quote: "There was no statistically significant difference between the sucralfate treated and the antacid treated groups in number of patients, sex"

Comment: Average numbers of risk factors per group were also similar; 92.5 and 83 participants had undergone an operation just before trial entry

Interventions

Antacids (Mylanta II)

- Dose (total/d): varied
- Duration of treatment (days): Until oral feedings began, NG tube was removed and patient was discharged from the ICU
- Route: NG tube
- Intervention: initial dose of 30 mL via NG tube. With pH < 3.5, dosage was progressively doubled until subsequent pH was > 3.5. Amphojel was substituted for Mylanta II in participants with severe diarrhoea and renal failure. In case of GI bleed, the last dose was doubled and the participant continued to receive that dose every hour
- Concomitant medications: NG tube was clamped in all participants for 1 hour after administration. If regurgitation occurred around the tube, or if the volume exceeded 150 mL at the end of 1 hour, the tube was clamped for 30 minutes and suction applied for the next 30 minutes, until aspirate was < 150 mL

Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days): Until oral feedings began, NG tube was removed and participant was discharged from ICU
- Route: NG tube
- Intervention: 1 g of sucralfate was administered in 30 mL of normal saline solution through NG tube followed by an additional gram every 6 hours (no dose changes were performed based on pH determinations)
- Concomitant medications: In case of GI bleed, sucralfate was discontinued and antacids started. The NG tube was clamped in all participants for 1 hour after administration. If regurgitation occurred around the tube or if volume exceeded 150 mL at the end of 1 hour, the tube was clamped for 30 minutes and suction applied for the next 30 minutes, until aspirate was less than 150 mL

Adherence to regimen: Quote: "Of the 52 patients treated with antacids, failure to achieve a pH of 3.5 or greater occurred in 8 patients initially given 30 mL of antacid. Five subsequently required 60 mL/hour and three required 120 mL/hour. All patients receiving antacids maintained a gastric pH of mote than 5"

Comment: Iced saline solution lavage was given to all participants with diagnosis of upper GI bleed (by Gastrocult test)

Duration of trial: August 1983 to December 1983

Duration of follow up: probably until discharge or death

Borrero 1984 (Continued)

Outcomes

Outcomes sought in review and reported in trial

- Clinically important GI bleeding defined as occurrence of any one of the following 3 findings
 - Frank or occult bleeding every hour or 3 consecutive dark-blue reactions (Gastrocult paper test)
- Number of participants requiring blood transfusions (nil)
- All-cause mortality in ICU
- Adverse events of interventions

Note: antacids 9 and 10 hours after start of the drug and sucralfate; 8, 41, and 45 hours after initiation of prophylaxis

Outcomes sought but not reported in trial

- VAP
- Duration of ICU stay
- Duration of intubation
- All-cause mortality in hospital
- Number of units of blood transfused

Outcomes reported in trial but not used in review

- Cost-effectiveness
- Nursing time required

Notes

Setting: Queens Hospital Centre, New York, USA

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Additional notes: No deaths were due to GI bleeding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "100 patients admitted to medical and surgical intensive care units were randomised to receive either antacids and sucralfate depending on the year of birth (odd year, sucralfate; even year, antacid)" Comment: This was a quasi-randomised trial
Allocation concealment (selection bias)	High risk	Comment: This was a quasi-randomised trial, and no information on allocation concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no information on blinding reported
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: Blinding was not done. However, the outcome was measured as per the definition used in the trial protocol. Moreover, owing to the objective na-

Borrero 1984 (Continued)

		ture of the outcome of interest, the likelihood of detection and performance bias is low
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: The trial did not address this outcome
Blinding of outcome as- sessment (detection bias) Adverse reactions of inter- ventions	Unclear risk	Comment: no information on blinding or criteria to diagnose other outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were included in the final analysis
Selective reporting (re- porting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Source of funding is unclear. No other source of bias detected

Borrero 1985

Methods	Quasi-randomised trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 155 participants</p> <p>Number analysed: 155 participants</p> <p>Antacids</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 57 (-) • Number of participants (n): 75 • Gender (male/female; n): 43/32 <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 61 (-) • Number of participants (n): 80 • Gender (male/female; n): 45/35 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Participants with 1 or more of the following risk factors for GI bleeding <ul style="list-style-type: none"> ◦ Hypotension ◦ Major surgical procedure ◦ Multiple trauma ◦ Renal failure ◦ Jaundice ◦ Respiratory failure ◦ Sepsis • Participants from whom informed consent was obtained <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Patient not satisfying inclusion criteria

Borrero 1985 (Continued)

Baseline imbalances: no statistically significant difference between sucralfate-treated and antacid-treated groups in numbers, age, and gender of participants. 130 participants (61 and 69 in each group) had undergone a major operation just before trial entry

Interventions

Antacids (Mylanta or Maalox)

- Dose (total/d): varied
- Duration of treatment (days): 2.54
- Route: NG tube
- Intervention: hourly according to the following schedule: 30 mL if pH of the gastric aspirate was ≥ 3.5 and 60 mL if pH was < 3.5
- Concomitant medications: NG tube was clamped for 55 minutes after drug administration. There was constant monitoring of cardiac, pulmonary, renal, hepatic, haematological, metabolic, and neurological parameters. Special attention was paid to the frequency of bowel movements, serum magnesium levels, and the appearance of a skin rash

Sucralfate

- Dose (total/d): 5 g
- Duration of treatment (days): 2.9
- Route: NG tube
- Intervention: 1 g of sucralfate was administered in 10 mL of water every 6 hours
- Concomitant medications: NG tube was clamped for 55 minutes after drug administration. There was constant monitoring of cardiac, pulmonary, renal, hepatic, haematological, metabolic, and neurological parameters. Special attention was paid to the frequency of bowel movements, serum magnesium levels, and the appearance of a skin rash

Adherence to regimen: not clearly mentioned in the trial report

Duration of follow-up: Quote: "Patients were continued in the trial until the onset of gastrointestinal bleeding, until they were discharged from the critical care unit, or until nasogastric suction was discontinued. The patients' clinical course was followed until they were discharged from the hospital"

Outcomes

Outcomes sought in review and reported in trial

- Clinically important GI bleeding defined as the occurrence of any 1 of the following 3 findings
 - Frank blood or 'coffee ground' aspirate from the nasogastric tube
 - Melena and a decline in haematocrit
 - Three consecutive dark-blue reactions on Gastrocult slides
- All-cause mortality in ICU
- Participants requiring blood transfusion (nil)
- Adverse events of interventions

Note: GI bleeding was tested for antacids 9 and 10 hours after initiating prophylaxis, and for sucralfate 8, 41, and 43 hours after initiating prophylaxis

Outcomes sought but not reported in trial

- VAP
- Duration of ICU stay
- Duration of intubation
- All-cause mortality in hospital
- Number of units of blood transfused

Outcomes reported in trial but not used in review

- Cost-effectiveness
- Nursing time required
- Ease of administration

Borrero 1985 (Continued)

Notes

Setting: Long Island Jewish Medical Centre and Queens Hospital Centre

Source of funding: -

Conflicts of interest: -

Ethics approval: Quote: "The study protocol was approved by the institutional review boards at Long island Jewish Medical Centre and Queens Hospital Centre"

Informed consent: Quote: "Informed consent was obtained from the patient or immediate relative"

Clinical trials registration: -

Sample size calculation: -

Additional notes: None of the deaths were due to GI bleeding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Patients were randomly assigned to one of the two treatment regimens according to their date of birth"; "participants born on even days were given antacids and those born on odd days were administered sucralfate" Comment: This was a quasi-randomised trial
Allocation concealment (selection bias)	High risk	Comment: This was a quasi-randomised trial; no information on method of allocation concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial; the different interventions and their mode of administration might not have ensured blinding of personnel
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear on blinding of outcome assessors. However, the outcome was measured as per the definition used in the trial protocol. Moreover, owing to the objective nature of the outcome of interest, the likelihood of detection and performance bias was judged as low
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: The trial did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear on blinding of outcome assessors. However, outcomes of interest were objective in nature, so the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Source of funding is unclear. No other source of bias is suspected

Borrero 1986

Methods	Quasi-randomised trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 50 participants</p> <p>Number analysed: 50 participants</p> <p>Antacids</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 67.1 (-) • Number of participants (n): 25 • Gender (male/female; n): 19/6 <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 67.9 (-) • Number of participants (n): 25 • Gender (male/female; n): 19/6 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Underwent abdominal aortic surgery • Admitted to surgical ICU <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Simultaneously underwent gastric or duodenal surgery • History of peptic ulcer disease <p>Baseline imbalances: Quote: "There was no statistically significant difference between the sucralfate treated and the antacid treated groups in number of patients, sex, mean age [...] or number of risk factors per patient"</p> <p>Comment: All participants had undergone aortobifemoral artery Dacron graft placement</p>
Interventions	<p>Antacids (Mylanta II)</p> <ul style="list-style-type: none"> • Dose (total/d): 30 mL • Duration of treatment (days): until oral feedings began, NG tube was removed, and participant was discharged from ICU • Route: NG tube • Intervention: Participants received 30 mL of a commercial antacid through NG tube. Each hour, the tube was clamped and participant was placed on suction for 5 minutes • Concomitant medications: NG tube was clamped in all participants for 1 hour after administration. If regurgitation occurred around the tube, or if the volume exceeded 150 mL at the end of 1 hour, the tube was clamped for 30 minutes and suction applied for the next 30 minutes, until aspirate was less than 150 mL <p>Sucralfate</p> <ul style="list-style-type: none"> • Dose (total/d): 4 grams • Duration of treatment (days): until oral feedings began, NG tube was removed, and participant was discharged from ICU • Route: NG tube • Intervention: 1 gram suspended in 30 mL of normal saline solution through NG tube followed by 10 mL of normal saline solution every 6 hours to clear the NG tube of any adherent sucralfate • Concomitant medications: NG tube was clamped in all participants for 1 hour after administration. If regurgitation occurred around the tube, or if the volume exceeded 150 mL at the end of 1 hour, the

Borrero 1986 (Continued)

tube was clamped for 30 minutes and suction applied for the next 30 minutes, until aspirate was less than 150 mL

Adherence to regimen: Comment: Iced saline solution lavage was given to all participants with diagnosed upper GI bleeding

Duration of trial: August 1983 to December 1984

Duration of follow-up: not clearly mentioned in the trial report; probably until discharge or death

Outcomes	Outcomes sought in review and reported in trial Primary outcomes <ul style="list-style-type: none">• Clinically important GI bleeding defined as the occurrence of<ul style="list-style-type: none">◦ Frank blood in the aspirate◦ Uniformly dark blue reaction on 3 consecutive readings• All-cause mortality in ICU• Participants requiring blood transfusion• Adverse events of interventions Outcomes sought but not reported in trial report <ul style="list-style-type: none">• VAP• Duration of ICU stay• Duration of intubation• All-cause mortality in hospital• Number of units of blood transfused Outcomes reported in trial but not used in review <ul style="list-style-type: none">• Cost-effectiveness	
Notes	Settings: Long island Jewish Medical Centre, New Hyde Park, NY 11042 Source of funding: - Conflicts of interest: - Ethics approval: - Informed consent: - Clinical trials registration: - Sample size calculation: - Additional notes: None of the deaths were due to GI bleeding	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "...were randomised to receive either antacid or sucralfate, depending on their year of birth (odd year sucralfate, even year antacid)" Comment: quasi-randomised trial
Allocation concealment (selection bias)	High risk	Comment: This was a quasi-randomised trial; no information on method of allocation concealment was reported

Borrero 1986 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial; the different interventions and their mode of administration might not have ensured blinding of personnel
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear on blinding of outcome assessors. However, GI bleeding was an objective outcome that was detected as per the definition used in the trial report
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: The trial did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: unclear on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were included in the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Source of funding is unclear. No other source of bias is suspected

Bresalier 1987

Methods	Open-label parallel-group trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 83 participants</p> <p>Number analysed: 74 participants</p> <p>Antacids</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 50 (18) Number of participants (n): 36 Gender (male/female; n): 25/11 <p>Sucralfate</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 54 (19) Number of participants (n): 38 Gender (male/female; n): 29/9 <p>Inclusion criteria</p> <ul style="list-style-type: none"> Admitted to surgical, medical, or burn ICU Having major trauma, burns injury, postoperative complications, or major medical illness Entering the study within 48 hours of admission to ICU Remaining in the study for at least 12 hours Having a minimum of 2 risk factors necessary to predispose patient to stress-related mucosal injury at the time of injury, such as respiratory failure, documented respiratory insufficiency, or pneumonia requiring mechanical ventilator assistance for longer than 24 hours; hypotension/shock requiring the

Bresalier 1987 (Continued)

use of pressor agents; sepsis; burns; renal failure; hepatic failure; central nervous system injury or coma; or severe cardiac decompensation

Exclusion criteria

- Having oesophageal, gastric, or duodenal mucosal disease; oesophageal variceal bleeding; or oesophageal or gastric surgery within past 6 months
- Receiving salicylates or NSAIDs, anti-coagulants, or H2 receptor blocking agents
- Having GI bleeding (as demonstrated through nasogastric aspirates)
- Receiving oral feedings or tube feedings greater than 50 mL/h
- Age < 18 years
- Pregnancy

Baseline imbalances: The 2 groups were almost similar with respect to age, gender, and time from entry into ICU to random selection. However, the sucralfate group had more risk factors for bleeding on admission to the study when compared with the antacid group (respiratory failure was the most common - 34 and 37 participants, respectively). Three participants in the antacid group had coagulopathy vs 1 participant in the antacid group. Two participants in the antacid group were given a diagnosis of pneumonia on admission

Interventions

Antacids (Maalox Therapeutic Concentration)

- Dose (total/d): varied
- Duration of treatment (hours; mean (range)): 57 (14-297)
- Duration of follow-up (days; mean (SD)): 21 (20)
- Route: -
- Intervention: 30 mL every 2 hours for maintaining gastric pH ≥ 4 . If gastric pH was < 4, dosage was increased to 30 mL every hour, 60 mL every 2 hours, or 60 mL/h as needed to maintain pH ≥ 4
- Concomitant medications: -

Sucralfate

- Dose (total/d): 6 g
- Duration of treatment (hours; mean (range)): 60 (12-360)
- Duration of follow-up (days; mean (SD)): 20 (13)
- Route: NG tube
- Intervention: 1 g (10 mL) every 4 hours per nasogastric tube
- Concomitant medications: -

Adherence to regimen: Six participants from the antacid group (n = 42) and 3 from the sucralfate group (n = 41) were excluded from analysis for the following reasons: < 12 hours in the study (3 died, 2 enteral feeds, 1 severe diarrhoea, with treatment discontinued), received both interventions, had evidence of GI bleed before intervention, refused participation

Duration of trial: January 1984 to September 1985

Outcomes

Outcomes sought in review and reported in trial

- Incidence of clinically relevant upper GI bleeding defined as
 - Bright red blood in the nasogastric tube that was not cleared by a 2-liter saline lavage
 - Decrease in haematocrit by more than 3 percentage points in 24 hours, accompanied by
 - Stool that yielded positive results when tested for occult blood with Haemoccult and no evidence of lower gastrointestinal bleed, or a decrease in haematocrit level of more than 6 percentage points in 48 hours with no evidence of extra gastrointestinal source or no evidence of lower gastrointestinal bleeding
- All-cause mortality in ICU
- Number of participants requiring blood transfusion
- Adverse events of interventions

Bresalier 1987 (Continued)

Outcomes sought but not reported in trial

- VAP
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation

Outcomes reported in trial but not used in review

- Relationship between underlying risk factors and development of upper GI bleeding
- Gastric pH values
- Medicine doses missed

Notes

Setting: surgical, medical, or burn intensive care units at San Francisco General Hospital, USA

Source of funding: -

Conflicts of interest: -

Ethics approval: Quote: "The protocol was approved by the University of California, San Francisco, Hum and Environmental protection committees (approval number 251701-02)"

Informed consent: "obtained from all participants. If the participant was unable to provide informed consent, then the participant's next of kin or legally authorized representative provided consent. If they could not be contacted, then the participant's attending physician was asked to provide permission"

Clinical trials registration: -

Sample size calculation: -

Additional notes: One participant in each group had significant upper GI bleeding after the trial was completed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information on sequence generation reported
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: Participants and personnel involved in the trial were not blinded
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: GI bleeding was an objective outcome that was diagnosed as per the definition used in the trial protocol
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Trial did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: unclear whether outcome assessors were blinded. Moreover, criteria for diagnosis of other outcomes of interest not clearly reported

Bresalier 1987 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Not all randomised participants were included in the final analysis (83 were randomised, 74 were included in the analysis). A per-protocol analysis was done, as 9 participants were involved in the trial for less than 12 hours. There was no imbalance between groups. Therefore, low risk of bias is due to attrition
Selective reporting (reporting bias)	Unclear risk	Comment: not enough information reported on outcomes of relevance in the trial
Other bias	High risk	Comment: Source of funding is not clearly mentioned in the trial report. No other sources of bias are suspected, but insufficient information is reported in the trial abstract

Brophy 2010

Methods	Quasi-randomised trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 51 participants</p> <p>Number analysed: 51 participants</p> <p>Famotidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 37 (17) • Number of participants (n): 23 • Gender (male/female; n): 20/3 <p>Lansoprazole</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 43 (22) • Number of participants (n): 28 • Gender (male/female; n): 17/11 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admitted to neurosurgery ICU • Prescribed stress ulcer prophylactic therapy during the study period • Gastric pH < 4.0 before first dose of lansoprazole or famotidine • One of the following risk factors for stress-related mucosal disease (SRMD); head injury with altered mental status, acid-base disorder, multiple trauma, coagulopathy, multiple surgical procedures, hypotension > 1 hour, sepsis <p>Exclusion criteria</p> <ul style="list-style-type: none"> • GI bleeding • Prior use of an anti-secretory agent during admission • History of gastric or duodenal ulcer • Age < 18 years • Allergies to famotidine or lansoprazole; pregnancy • Anticipated need for stress ulcer prophylaxis (SUP) for < 3 days (OR) • Renal compromise (creatinine clearance < 50 mL/min) <p>Baseline imbalances: "There were significantly more males than females in the study. Over 75% of the patients had a Glasgow Coma Scale (GCS) < 9, and median GCS scores were similar between the two groups. All of the patients had at least two risk factors for SRMD, and each treatment group had a sim-</p>

Brophy 2010 (Continued)

ilar number of patients with traumatic brain injuries. The median baseline gastric pH was 3.0 for both famotidine and lansoprazole groups"

Comment: There were more women in the lansoprazole group than in the famotidine group

Interventions

Famotidine

- Dose (total/d): 60 mg
- Duration of treatment (days; mean (SD)): > 3 (-)
- Route: IV or PO
- Intervention: 20 mg IV every 12 hours, or orally 20 mg every 12 hours after 72 hours
- Concomitant medications: Most patients in this study received enteral nutrition by day 2

Lansoprazole

- Dose (total/d):
- Duration of treatment (days, mean (SD)): > 3 (-)
- Route: nasogastric tube
- Intervention: 30 mg suspended in 10 mL of an 8.4% sodium bicarbonate solution or apple juice, and administered via NG tube daily
- Concomitant medications: Most patients in this study received enteral nutrition by day 2

Adherence to regimen: -

Duration of trial: August 1999 to April 2005

Duration of follow-up: "Patients were followed until 24 hours after the discontinuation of SUP, the patient was discharged from the ICU, or if the patient expired, whichever came first"

Outcomes

Outcomes sought in review and reported in trial

- Incidence of clinically significant bleeding related to SRMD defined as the presence of at least 1 of the following
 - Endoscopic evidence of stress-related mucosal bleeding
 - Bright red blood per NG tube that did not clear after lavage
 - Overt bleeding (haematemesis, bloody gastric aspirate, melena, or haematochezia) plus either a decrease in blood pressure of 20 mmHg or a decrease of 2 g/dL in haemoglobin and 2 units of blood transfused within 24 hours
- Adverse events of interventions

Outcomes sought but not reported in trial

- VAP
- All-cause mortality in ICU
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Number of participants requiring blood transfusion
- Number of units of blood transfused

Outcomes reported in trial but not used in review

- Duration of pH $\geq$ 4.0
- Percentage of time gastric residual was < 28 mL

Notes

Setting: The Virginia Commonwealth University (VCU), 1000-bed, academic, level 1 trauma centre

Source of funding: Quote: "This study was funded by TAP Pharmaceuticals"

Brophy 2010 (Continued)

Conflicts of interest: -

Ethics approval: Quote: "The Virginia Commonwealth University (VCU) Institutional Review Board approved this study prior to subject enrolment, and this study was conducted in compliance with the Declaration of Helsinki"

Informed consent: Quote: "All subjects provided written informed consent prior to study commencement"

Clinical trials registration: -

Sample size calculation: Quote: "...we assumed that on day 3 of therapy, 85% of the patients receiving lansoprazole would have pH values ≥ 4.0 for 80% of the time compared to only 40% of the patients receiving famotidine. Using these proportions, $\alpha = 0.05$, $\beta = 0.20$, and a two-way statistical test, approximately 22 patients were needed in each group to show statistical significance"

Comment: This was after 30 people admitted to the neurosurgical unit were followed; it was assumed that approximately 40% of them receiving famotidine and 80% receiving lansoprazole maintained gastric pH ≥ 4 80% of the time

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Patients admitted into the unit during odd-numbered months received famotidine 20 mg IV every 12 hours; patients admitted during even numbered months received lansoprazole" Comment: This was a quasi-randomised trial in which sequence generation was not done
Allocation concealment (selection bias)	High risk	Quote: "Patients admitted into the unit during odd-numbered months received famotidine 20 mg IV every 12 hours; patients admitted during even numbered months received lansoprazole" Comment: This was a quasi-randomised trial in which allocation was not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial; the different interventions and their mode of administration could not have made it possible to blind trial personnel
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: This was an unblinded trial in which GI bleeding was detected as per the definition used in the trial protocol
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Trial did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: This was an unblinded trial; outcomes of interest were diagnosed as described in the trial protocol
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis. Therefore, no attrition bias is suspected

Brophy 2010 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: TAP Pharmaceuticals funded the trial. The role of the sponsor in the conduct and reporting of the trial is unclear. No other sources of bias are suspected

Burgess 1995

Methods	Double-blind parallel-group randomised placebo-controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 34 participants</p> <p>Number analysed: 34 participants</p> <p>Ranitidine</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 38.4 (4.5) Number of participants (n): 16 Gender (male/female; n): 11/5 <p>Placebo</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 34.5 (3.7) Number of participants (n): 8 Gender (male/female; n): 4/4 <p>Inclusion criteria</p> <ul style="list-style-type: none"> Severe head injury and Glasgow Coma Scale score < 10 Admitted to the University of Louisville surgical intensive care unit <p>Exclusion criteria</p> <ul style="list-style-type: none"> Concomitant peptic ulcer disease Other gastrointestinal injury Receiving anti-ulcer therapy Having any oral intake <p>Baseline imbalances: Quote: "All 34 patients were comatose on admission and required ventilatory support"; "No significant differences in demographic characteristics were present between the two treatment groups"</p> <p>Comment: The 2 groups were comparable with respect to mean Glasgow Coma Scale score (mean 8, range 4 to 10; and mean 6.7 range 3 to 10), mean Injury Severity Score (mean 32, range 25 to 41; and mean 30, range 25 to 57), and time from injury to study drug administration</p>
Interventions	<p>Ranitidine</p> <ul style="list-style-type: none"> Dose (total/d): 150 mg Duration of treatment (days; mean (SD)): Treatment period was complete when participant was withdrawn from the trial or had received study drug for 72 hours Route: IV Intervention: 6.25 mg/h continuous IV ranitidine infusion, prepared by diluting 11 mg parenteral ranitidine to a volume of 240 mL with 0.9% sodium chloride and delivered at a rate of 10 mL/h Concomitant medications: Antacid therapy, steroids and tube feedings were not allowed

Burgess 1995 (Continued)

Placebo

- Dose (total/day): -
- Duration of treatment (days; mean (SD)): The treatment period was complete when the patient was withdrawn from the trial or had received 72 hours of study drug
- Route: IV
- Intervention: 1.9% sodium chloride administered at 10 mL/h
- Concomitant medications: Antacid therapy, steroids and tube feedings were not allowed

Adherence to regimen: Quote: "All 34 patients were comatose on admission and required ventilatory support. Ten patients were withdrawn before completing 72-hour study period. Five of these patients were in the placebo treatment group and were withdrawn from the trial because of protocol-defined upper gastrointestinal tract bleeding. Of the remaining four patients, who were from the ranitidine group; one was withdrawn due to death secondary to severe head injury, two were withdrawn because they became combative and removed their NG tubes and pH probes, and the final patient was withdrawn from the trial when steroids were prescribed for an optic nerve injury by the attending physicians. One patient from the placebo group was removed due to withdrawal of NG tube"

Comment: 24 participants completed the prescribed 72 hours of the trial, and reasons for the remaining 10 not completing the 72-hour period are well documented

Duration of trial: February 1988 to November 1988

Duration of follow-up: 48 hours after study withdrawal

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Clinically important upper GI bleeding defined by haematemesis, haematochezia, bright red blood per NG tube, or 'coffee ground' NG tube aspirates. Participants with any of these signs plus a 5% decrease from baseline in haematocrit occurring at least 8 hours after study drug initiation were given diagnosis of upper gastrointestinal tract bleeding <p>Note: The 5 participants who bled belonged to the placebo group; bleeding occurred before 72 hours into the trial</p> <ul style="list-style-type: none"> • All-cause mortality in ICU • Participants requiring blood transfusion • Adverse events of interventions (no adverse reactions reported) <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • VAP • Duration of ICU stay • Duration of intubation • Number of units of blood transfused (mean and SD not provided) <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none"> • Intragastric pH values
Notes	<p>Setting: Department of Surgery, University of Louisville, School of Medicine, Louisville, Kentucky, USA</p> <p>Source of funding: Quote: "The study was supported by a grant from Glaxo Inc. Research Institute"</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The study was approved by the Human Studies Committee"</p> <p>Informed consent: Quote: "...informed consent was obtained from each patient's legal representative"</p> <p>Clinical trials registration: -</p>

Burgess 1995 (Continued)

Sample size calculation: -

Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Within 24 hr of injury, each patient was randomly assigned to receive either 6.25 mg/hr continuous intravenous ranitidine infusion or a saline placebo infusion in accordance with a computer-generated randomisation scheme" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the trial report
Allocation concealment (selection bias)	Unclear risk	Comment: No information on allocation concealment reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "To maintain the integrity of the study blinding and to avoid potential bias, the principal investigator did not have access to the pH data" Comment: This is a double-blind, placebo-controlled, parallel-group study design in which study personnel were blinded
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "To maintain the integrity of the study blinding and to avoid potential bias, the principal investigator did not have access to the pH data" Comment: The trial did investigate the relationship between intragastric pH values and the incidence of bleeding. Moreover, we are unclear whether it was the principal investigator who was also involved in outcome assessment. However, GI bleed was detected as per the study definition, and owing to the objective nature of the outcome, the likelihood of performance and detection bias is low
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Trial did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: Blinding for other outcome assessments is unclear. Criteria for diagnosis of other outcomes are not fully described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients completed at least 8 hours of investigational therapy and were included in the analysis" Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and included in the report
Other bias	Low risk	Comment: Trial was supported by a grant from Glaxo Inc. Research Institute; trial authors (number not sure) had affiliation with this company. No other sources of bias are suspected

Cannon 1987

Methods	Open-label randomised controlled trial
Participants	Baseline characteristics

Cannon 1987 (Continued)

Number randomised: 62 participants

Number analysed: 59 participants

Cimetidine

- Age (years; mean (SD)): 63.57 (2.86)
- Number of participants (n): 21
- Gender (male/female; n): -

Antacids

- Age (years; mean (SD)): 58.56 (13.80)
- Number of participants (n): 19
- Gender (male/female; n): -

Sucralfate

- Age (years; mean (SD)): 61.41 (5.94)
- Number of participants (n): 19
- Gender (male/female; n): -

Inclusion criteria

- Critically ill with acute (< 48 hours) respiratory failure defined by
 - Alveolar-to-arterial oxygen tension difference $\geq$ 350 mmHg
 - Vital capacity < 10 cc/kg of body weight
 - Alveolar hypoventilation with arterial pH < 7.25 or a ratio of dead space to tidal volume > 60%

Exclusion criteria

- Allergy to cimetidine antacids, sucralfate
- Active gastrointestinal tract bleeding or guaiac-positive stool
- Pregnancy or lactation
- Age < 18 or > 80 years
- Requiring dialysis
- Known bleeding diathesis
- Ventilator dependence for longer than 48 hours before the protocol was initiated
- GI tract surgery in the previous 48 hours

Baseline imbalances: The 3 groups were almost similar with respect to age, gender, number of participants, and risk factors thought to precipitate GI bleed. Most participants were medical participants with respiratory failure secondary to an intrathoracic process. There was no significant difference between groups with respect to major risk factors for GI bleeding (sepsis, peritonitis, jaundice, hypotension, and trauma). Only acute renal failure was more common with the antacid regimen than with cimetidine and sucralfate (however, the incidence of renal failure did not correlate with upper GI bleed)

Interventions
Cimetidine

- Dose (total/d): 1200 mg
- Duration of treatment (days; mean (SE)): 123.69 (24.24)
- Route: IV
- Intervention: cimetidine initial dose of 300 mg given intravenously every 6 hours; if serum creatinine level was > 2.0 mg/dL, the dosing interval was changed to every 12 hours
- Concomitant medications: enteral nutrition in 22 participants from the overall study population; intervention group unclear; intravenous aminophylline was administered to 5 patients in the cimetidine group

Antacids

Cannon 1987 (Continued)

- Dose (total/d): min 30 mL, max 120 mL
- Duration of treatment (days; mean (SD)): 115.25 (45.41)
- Route: NG tube
- Intervention: 30 mL of a commercial antacid, per nasogastric tube; if pH was > 4, the same dose was continued, or the dose given previously was doubled to reach a maximum of 120 mL
- Concomitant medications: enteral nutrition in 22 participants from the overall study population; intervention group unclear; intravenous aminophylline was administered to 4 patients in the cimetidine group

Sucralfate

- Dose (total/d): 120 mL
- Duration of treatment (days; mean (SD)): 91.22 (24.01)
- Route: NG tube
- Intervention: 30 mL dissolved in warm tap water via nasogastric tube every 6 hours
- Concomitant medications: enteral nutrition in 22 participants from the overall study population; intervention group unclear; intravenous aminophylline was administered to 6 participants in the cimetidine group

Adherence to regimen: sucralfate, H2 receptor antagonists, or antacids were used inadvertently in 3 patients who were excluded from the trial

Duration of trial: October 1985 to January 1986

Duration of follow-up: 24 hours after extubation

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Clinically important upper GI bleeding defined as having frank blood or 'coffee ground' aspirate with a uniformly blue reaction by pH-corrected indicator paper for occult blood • All-cause mortality in ICU • Duration of intubation • Adverse events of interventions <p>Outcomes sought but not reported in trial report</p> <ul style="list-style-type: none"> • VAP • All-cause mortality in hospital • Duration of intubation • Duration of ICU stay • Number of participants requiring blood transfusion <p>Outcomes reported in report but not sought in review</p> <ul style="list-style-type: none"> • Gastric pH values • Cost effectiveness
Notes	<p>Setting: Medical-Surgical Intensive Care Unit at Akron General Medical Centre, Ohio, USA</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The study was approved by the institutional review board at the Akron General Medical Centre"</p> <p>Informed consent: Quote: "A signed consent was obtained from patients or the next of kin after the potential complications and nature of the procedure were explained"</p> <p>Clinical trials registration: -</p>

Cannon 1987 (Continued)

Sample size calculation: -

Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Sixty-two patients were accepted for computerised randomised study between October 1985 and January 1986" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the trial report
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and mode of administration of drugs could not have allowed blinding of participants and personnel involved in the trial
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear if outcome assessors were blinded. However, GI bleeding was an objective outcome, which was detected as per the definition in the trial protocol
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: The trial did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: not enough information on criteria for diagnosis of other outcomes described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 62 patients originally entered into the study three were excluded because of the inadvertent concomitant use of sucralfate, H2 receptor antagonists or antacids in the study group" Comment: Groups to which these 3 participants belonged are unclear (ITT cannot be performed). These participants were excluded from the final analysis. Because loss to follow-up was < 10% and appeared to be balanced across groups, this would not have introduced any attrition bias into the trial
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Source of funding is not clearly mentioned in the trial report. No other form of bias is detected

Chan 1995

Methods	Parallel-group randomised controlled trial
Participants	Baseline characteristics Number randomised: - Number analysed: 101 participants Ranitidine

Chan 1995 (Continued)

- Age (years; mean (range)): 61 (17-84)
- Number of participants (n): 49
- Gender (male/female; n): 26/23

Placebo

- Age (years; mean (range)): 61 (32-89)
- Number of participants (n): 52
- Gender (male/female; n): 28/24

Inclusion criteria

- Suffering from nontraumatic neurological lesions with ≥ 2 of the following risk factors
 - Preoperative coma
 - Inappropriate secretion of ADH
 - Major PO complications requiring reoperation
 - Age ≥ 60 years
 - Pyogenic CNS infection

Exclusion criteria

- Failure to obtain consent (4 patients)
- Presence of GD bleeding before neurosurgery (10 patients)
- Past history of chronic GD disease or chronic ulcer, identified at endoscopy (9 patients)
- Concomitant major medical illnesses such as heart, lung, kidney, haematological, and liver problems (7 patients)

Baseline imbalances: The nature and location of diseases, types of operations, number of preoperative risk factors, and demographic data were comparable in the 2 groups

Interventions
Ranitidine

- Dose (total/d): 200 or 300 mg
- Duration of treatment (days): -
- Route: IV or PO
- Intervention: 200 mg IV, or 300 mg PO when enteric feeding started
- Concomitant medications: artificial ventilation with muscle paralysis using pancuronium and sedation with midazolam. Additional bolus doses of sedative and analgesic medications were given during endoscopy. Concomitant medications included dexamethasone, 4 mg every 6 hours, and a single dose of ceftriaxone (1 g), which was given intravenously as prophylaxis with the first dose of ranitidine or placebo. Subsequent antibiotic medications were administered only for treatment of culture proven infections. Those patients who required anticonvulsant therapy or prophylaxis received phenytoin (00 mg every 8 hours)

Placebo

- Dose (total/d): -
- Duration of treatment (days): -
- Route: IV, PO
- Intervention: normal saline
- Concomitant medications: artificial ventilation with muscle paralysis using pancuronium and sedation with midazolam, additional bolus doses of sedative and analgesic medications were given during endoscopy. Concomitant medications included dexamethasone, 4 mg every 6 hours, and a single dose of ceftriaxone (1 g), which was given intravenously as prophylaxis with the first dose of ranitidine or placebo. Subsequent antibiotic medications were administered only for treatment of culture proven infections. Participants who required anticonvulsant therapy or prophylaxis received phenytoin (00 mg every 8 hours)

Adherence to regimen: -

Chan 1995 (Continued)

Duration of trial: July 1988 to December 1989

Duration of follow-up: -

Outcomes	<p>Outcomes reported in trial and used in review</p> <ul style="list-style-type: none">• Gastroduodenal bleeding defined as<ul style="list-style-type: none">◦ Normal (without GD lesions),◦ Asymptomatic (presence of endoscopically documented acute GD lesions but no evidence of bleeding), and◦ Symptomatic from GD lesions (presence of endoscopic stigmata of recent haemorrhage, requiring blood transfusion and/or surgery to stop bleeding, or treatment of peritonitis as a result of perforation of acute GD tract ulcers)• All-cause mortality• Adverse events of interventions <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none">• VAP• Duration of ICU stay• Duration of intubation• Number of blood transfusions <p>Outcomes reported, but not used in review</p> <ul style="list-style-type: none">• Chest infection• Risk factors for development of symptomatic GD lesions• Neurological recovery	
Notes	<p>Setting: Neurological Intensive Care Unit, Department of Surgery, Queen Mary Hospital, University of Hong Kong</p> <p>Source of funding: University of Hong Kong Research Grant and Lee Wing Tat Research Grant</p> <p>Conflicts of interest: -</p> <p>Ethics approval: The protocol used in our trial was approved by the Ethics Committee of the Faculty of Medicine, at the University of Hong Kong</p> <p>Informed consent: Written consent was obtained from patients or their next of kin</p> <p>Clinical trials registration: -</p> <p>Sample calculation: 49 patients would be required in each arm of the trial with a power of 0.8 and a 0.95 significance level by 2-tailed test</p> <p>Comments: The endpoint of the trial was the development of symptomatic GD lesions defined as GD bleeding requiring blood transfusions and/or surgery for acute perforated ulcers</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised in a standard double blind manner" Comment: not enough information on sequence generation reported
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment reported

Chan 1995 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All patients were randomised in a standard double-blind manner to receive either ranitidine (50 mg) or placebo medication (normal saline) identical in appearance and volume"
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "Final outcomes were also assessed by an independent observer to ascertain whether they were a direct result of the GD lesions" "Endoscopic examination of the GD tract up to the second part of the duodenum was performed in all patients within 12 hours of surgery. Additional bolus doses of sedative and analgesic medications were given during endoscopy. A nasogastric tube was passed into the stomach after endoscopy; its position was confirmed by radiological means, and it was connected to a bag for free drainage. Aspiration from the tube was performed at 6-hour intervals and a pH paper was used to measure the pH of the gastric content. The total volume of daily gastric output was recorded"
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Trial did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: no details on criteria for diagnosis of other outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing outcome data. All participants randomised at baseline are also included in analyses of outcomes
Selective reporting (reporting bias)	High risk	Comment: Outcome data for blood transfusions were not reported by treatment group, but as totals. Other outcomes were reported completely. More outcomes were reported in the Results section than in the Methods section
Other bias	Low risk	Comment: no other sources of bias suspected

Cioffi 1994

Methods	Single-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 100 participants</p> <p>Number analysed: 100 participants</p> <p>Antacids + cimetidine</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 37.6 (2.5) Number of participants (n): 150 Gender (male/female; n): - <p>Sucralfate</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 36.7 (1.99) Number of participants (n): 50 Gender (male/female; n): - <p>Inclusion criteria</p>

Cioffi 1994 (Continued)

- Adult burn patients (> 18 years) admitted to the US Army Institute of Surgical Research within 48 hours of injury
- Greater than 20% body surface area burn

Exclusion criteria

- Prior history of peptic ulcer disease
- Preinjury H₂ receptor antagonist therapy
- Pneumonia diagnosed at the time of admission

Baseline imbalance: Quote: "There were no significant differences in age, burn size, the presence of inhalation injury and requirements for intubation. The groups were compared using severity index based upon age, burn size and the presence of inhalation injury. The severity findings were not different between the groups, indicating the similarity of the participant cohorts"

Comment: The 2 groups were comparable at baseline. Participants were admitted for thermal injury (burns). Inhalation injury was found in 22 and 27 participants from the cimetidine + antacid and sucralfate groups. Intubation was required in 29 and 28 participants, respectively

Interventions

Antacids + cimetidine

- Dose (total/d): 1200 mg cimetidine + 360 mL antacids
- Duration of treatment (days; mean (SE)): -
- Route: PO or NG tube
- Intervention: cimetidine (300 mg/6 h), dose subsequently adjusted based on participant's gastric pH (4.5) values (to continuous infusion) and renal function. Antacids (30 mL bolus orally or via NG tube every 2 hours); if gastric pH was < 4.5, dose was doubled or administered on an hourly basis
- Concomitant medications: Continuous enteral feeding began from postburn day 3 onwards for participants who were not able to meet the requirements orally

Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days; mean (SE)): -
- Route:
- Intervention: 1 g suspended in 20 mL of water, administered orally or via NG tube every 6 hours
- Concomitant medications: Continuous enteral feeding began from postburn day 3 onwards for participants who were not able to meet the requirements orally

Adherence to regimen: 100 participants were randomised to both groups - 50 each. There were 4 protocol violations (2 in each group), leaving 96 participants for evaluation. Continuous enteral feeding began from postburn day 3 onwards for participants who were not able to meet the requirements orally. The duration of intubation was longer in the sucralfate group owing to higher incidence of pneumonia. There were 9 deaths before postburn day 5 - 5 in the acid neutralising group and 4 in the sucralfate group. None of these participants had pneumonia. There were 5 deaths among participants who developed pneumonia after postburn day 5

Duration of trial: March 1990 to December 1992

Duration of follow-up: probably until death or discharge

Outcomes

Outcomes sought in review and reported in trial

- Clinically important upper GI bleeding diagnosed clinically or endoscopically
- VAP based on roentgenographic findings consistent with pneumonia, sputum leucocytosis > 25 white cells per high-power microscopic field, and growth of a predominant organism on sputum culture
- All-cause mortality in ICU
- Duration of intubation

Outcomes sought but not reported in trial

Cioffi 1994 (Continued)

- All-cause mortality in hospital
- Duration of ICU stay
- Blood transfusion
- Adverse events of interventions

Outcomes reported in trial but not used in review

- Gastric pH monitoring
- Colonisation

Notes

Setting: US Army Institute of Surgical Research, Fort Sam Huston, Texas

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Informed consent: Quote: "Consenting participants were randomised in a pair wise fashion"

Clinical trials registration: -

Sample size calculation: -

Additional notes: There was a higher incidence of pneumonia among participants who were intubated or had inhalation injury and were administered sucralfate. Mixed pneumonia (gram-positive and gram-negative pathogens) was most frequent in both groups. The percentage of participants in each group who developed positive sputum cultures was 100 and 98, and for gastric cultures 96 and 83, respectively (for any bacteria)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information on sequence generation reported
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the mode of administration of interventions could not have permitted blinding of participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: Outcome assessors were not blinded. Only the presence of gross bleeding was considered in the results
Blinding (detection bias) Nosocomial pneumonia	Low risk	Quote: "Chest roentgenograms were reviewed by staff surgeon and radiologist who were unaware of the participants' treatment group" Comment: Outcome assessors for this particular outcome were blinded
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: Outcome assessors were not blinded. Criteria for diagnosis of other outcomes were not clearly reported
Incomplete outcome data (attrition bias)	Low risk	Comment: Not all participants who were randomised were part of the final analysis. Two were excluded from each arm owing to protocol violations.

Cioffi 1994 (Continued)

All outcomes		Because the loss to follow-up of less than 10% is balanced between groups, this would not have introduced any attrition bias into the trial. Results were analysed in the review on the basis of ITT
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed
Other bias	Low risk	Comment: Source of funding is unclear. No other source of bias is suspected

Conrad 2005

Methods	Double-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 359 participants</p> <p>Number analysed: 359 participants</p> <p>Omeprazole</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 54.9 (18.3) • Number of participants (n): 178 • Gender (male/female; n): 105/73 <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 56.5 (18.5) • Number of participants (n): 181 • Gender (male/female; n): 105/76 <p>Note: 64 participants in both groups were over 65 years of age</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age ≥ 16 years • Hospitalised in an intensive care unit with anticipated stay > 72 hours • Requiring mechanical ventilation for ≥ 48 hours • Acute Physiology and Chronic Health Evaluation (APACHE II) score ≥ 11 at baseline • Having an intact stomach with a nasogastric or orogastric tube in place • Having ≥ 1 additional risk factor for upper GI bleeding <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Status of "no cardiopulmonary resuscitation", delay of > 48 hours from time of initial eligibility • History of gastric surgery, allergy to cimetidine or omeprazole • Active GI bleeding, significant risk of swallowing blood (e.g. severe facial trauma, oral lacerations, haemoptysis) • Enteral feeding required for first 2 days of the trial • Admission for upper GI surgery • Known upper GI lesions that might bleed (e.g. varices, polyps) • Unable to take a suspension by nasogastric tube • End-stage liver disease <p>Baseline imbalances: Quote: "The two groups were generally well matched, although the mean APACHE II score (indicating severity of critical illness) was higher in the omeprazole-suspension group"</p>

Conrad 2005 (Continued)

Comment: Coagulopathy was present in 37 and 26 participants, respectively, and acute renal failure was more common in the omeprazole group (47 and 33). The 2 groups were similar to each other with respect to age, gender, baseline gastric pH, and other risk factors known to precipitate GI bleeding in the ICU

Interventions
Omeprazole

- Dose (total/d): 40 mg
- Duration of treatment (days; mean (SE)): max 14, or until death, discharge, or extubation
- Route: PO
- Intervention: oral suspension (Zegerid, Santarus, San Diego, CA) and continuous intravenous infusion of placebo: Omeprazole suspension (40 mg omeprazole and 20 mEq sodium bicarbonate) was given initially, 6 to 8 hours later (loading-dose regimen), and once daily thereafter. The suspension was delivered via nasogastric or orogastric tube. If a patient's gastric pH was ≤ 4 on 2 consecutive determinations ≥ 1 hour apart on any day of treatment (defined as inadequate pH control), an additional single dose of the suspension (40 mg of omeprazole or placebo) was given only for that day
- Concomitant medications: Enteral feeding was allowed from day 3 but was held for 3 hours before and 1 hour after the suspension was administered

Cimetidine

- Dose (total/d): 1500 mg
- Duration of treatment (days; mean (SE)): max 14, or until death, discharge, or extubation
- Route: IV
- Intervention: continuous intravenous cimetidine and placebo oral suspension for up to 14 days: A 300-mg loading dose of intravenous cimetidine was given initially, followed by a continuous infusion at 50 mg/h (25 mg/h in patients with creatinine clearance of 30 mL/min). If a patient's gastric pH was ≤ 4 on 2 consecutive determinations ≥ 1 hour apart on any day of treatment (defined as inadequate pH control), doses of the intravenous study drug (cimetidine or placebo) were doubled for the remainder of the trial
- Concomitant medications: Enteral feeding was allowed from day 3 but was held for 3 hours before and 1 hour after the suspension was administered

Duration of trial: June 2002 to May 2003

Duration of follow-up: probably until death or discharge

Adherence to regimen: Quote: "A total of 56 patients in the intention-to-treat population were excluded from the per-protocol population (omeprazole, $n = 21$; cimetidine, $n = 35$) primarily due to failure to receive dose increases within 12 hours of observing the first of two pH values of 4 (omeprazole, $n = 4$; cimetidine, $n = 25$)"

"Participation in the trial was discontinued before 14 days in the event of death, discharge from the unit, or extubation (endotracheal or gastric tube)"

"...four patients who were discontinued from the trial while actively bleeding (omeprazole, $n = 1$; cimetidine, $n = 3$)"

Outcomes
Outcomes sought in review and reported in trial

- Clinically important upper GI bleeding defined as bright red blood not clearing after tube adjustment and 5 to 10 minutes of lavage with saline, 2.8 hours of persistent Gastrocult-positive 'coffee ground' material with aspirates (performed every 2 hours) not clearing with ≥ 100 mL of saline lavage on days 1 to 2, or 3. persistent Gastrocult-positive 'coffee ground' material over 2 to 4 hours on days 3 to 14 in 3 consecutive aspirates not clearing with ≥ 100 mL of saline lavage

Note: Five participants bled during the first 2 days of acid suppression therapy (omeprazole; $n = 1$; cimetidine; $n = 4$)

Conrad 2005 (Continued)

- VAP defined as diagnosis of nosocomial pneumonia (US Food and Drug Administration guidance document included the following):
 - Onset of symptoms ≥ 72 hours after admission and ≤ 7 days after discharge from a previous hospitalisation
 - New or evolving infiltrate on chest radiograph, not related to another condition
 - New onset of production of purulent sputum or increase in volume of purulent sputum and ≥ 1 of the following: fever (e.g. oral temperature $\geq 38^{\circ}\text{C}$) or hypothermia (e.g. oral temperature $\leq 35.5^{\circ}\text{C}$), total white blood cell count = $10,000/\text{mm}^3$ or $< 4500/\text{mm}^3$, or $> 15\%$ bands on white blood cell count differential. Diagnosis required confirmation by culture or gram-negative stain of a lower respiratory tract specimen
- All-cause mortality in ICU
- Participants requiring blood transfusions (red blood cells)

Outcomes sought but not reported in trial

- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Adverse events of interventions

Outcomes reported in trial but not used in review

- Median gastric pH on each trial day

Notes

Setting: 47 ICUs in the United States

Source of funding: supported, in part, by Santarus, San Diego, CA

Conflicts of interest: -

Ethics approval: Quote: "This trial was approved by the institutional review board at each site"

Informed consent: Quote: "Before any trial procedures were performed, each patient or his or her authorized legal representative gave written informed consent for trial participation"

Clinical trials registration: -

Sample size calculation: Quote: "Sample size calculations were based on an assumption of a 12% rate of upper GI bleeding in cimetidine-treated patients and a 6% rate in omeprazole suspension-treated patients. To establish the non-inferiority of omeprazole suspension with 90% power at the one-sided $\alpha = 0.25$ level, 142 patients were required in each treatment group. Assuming that 20% of randomised patients would not satisfy per-protocol requirements, enrolment of 178 patients per group was planned"

Additional notes: An additional 75 participants had overt upper GI bleeding but did not meet the primary endpoint of clinically significant upper GI bleeding as defined by the trial protocol. Moreover all participants who met the endpoint criteria of clinically significant upper GI bleeding were in the per-protocol population. Four of the 17 participants who had clinically significant bleeding died (omeprazole: $n = 2$; cimetidine: $n = 2$), but bleeding was not the cause of death for any of these participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the trial report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the trial report

Conrad 2005 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "Patients, trial site personnel, and the sponsor were blinded to patient treatment assignment"</p> <p>"Within each site, patients were randomly assigned to receive immediate-release omeprazole oral suspension (Zegerid, Santarus, San Diego, CA) and continuous intravenous infusion of placebo or continuous intravenous cimetidine and placebo oral suspension for up to 14 days"</p> <p>Comment: The presence of placebo in both arms might have ensured that participants and personnel were blinded</p>
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	<p>Quote: "Patients, trial site personnel, and the sponsor were blinded to patient treatment assignment"</p> <p>Comment: The presence of placebo in both arms ensured that participants and personnel and outcome assessors were blinded. Moreover, GI bleeding was an objective outcome that was detected as per the trial protocol, so the likelihood of performance and detection bias is low</p>
Blinding (detection bias) Nosocomial pneumonia	Low risk	<p>Quote: "Patients, trial site personnel, and the sponsor were blinded to patient treatment assignment"</p> <p>Comment: The presence of placebo in both arms ensured that participants and personnel and outcome assessors were blinded. Moreover, nosocomial pneumonia was an objective outcome that was detected as per the trial protocol, so the likelihood of performance and detection bias is low</p>
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	<p>Quote: "Patients, trial site personnel, and the sponsor were blinded to patient treatment assignment"</p> <p>Comment: The presence of placebo in both arms ensured that participants and personnel were blinded. Moreover, other outcomes of interest were objective in nature and were diagnosed according to the trial protocol, so the likelihood of performance and detection bias was low</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: "The intent-to-treat population included all randomised patients. The per-protocol population was used for the analysis of the primary efficacy end point; the intent-to-treat population was also used for the primary end point and for all other analyses"</p> <p>Comment: ITT analysis was performed for all outcomes of interest, so the likelihood of attrition bias was low</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: All outcomes intended in the trial were analysed and reported. However, there is no mention of the presence or absence of any adverse events</p>
Other bias	Unclear risk	<p>Comment: One of the trial interventions, omeprazole oral suspension, was sponsored by Zegerid, Santarus, San Diego, CA, which is also the sponsor of the trial. Analysis of data was performed by Santarus, the sponsor of the trial. Also the analysis used was a non-inferiority analysis, to compare rates of upper GI bleeding in the 2 treatment groups</p>

Cook 1998

Methods	Multi-centre blinded randomised placebo-controlled trial
Participants	Baseline characteristics

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

Cook 1998 (Continued)

Number randomised: 1200 participants

Number analysed: 1200 participants

Ranitidine

- Age (years; mean (SD)): 58.8 (18.1)
- Number of participants (n): 596
- Gender (male/female; n): 369/227

Sucralfate

- Age (years; mean (SD)): 58.7 (18.7)
- Number of participants (n): 604
- Gender (male/female; n): 354/250

Inclusion criteria

- Consecutive participants who were screened and admitted to 16 participating intensive care units (ICUs)
- Projected to require mechanical ventilation for ≥ 48 hours

Exclusion criteria

- Diagnosis of gastrointestinal bleeding or pneumonia on admission
- Gastrectomy
- Prognosis considered to be hopeless
- Previous randomisation in this or another trial
- Receipt of ≥ 2 previous doses of open-label prophylactic therapy

Baseline imbalance: Quote: "Demographic and baseline physiologic characteristics were similar in the two groups"

Comment: Mean and SD for APACHE II scores were 24.7 $\pm$ 7.1 and 24.6 $\pm$ 7.3 in the ranitidine and sucralfate groups. The main reasons for admission were medical: elective surgery or emergency surgery

Interventions
Ranitidine

- Dose (total/d): 150 mg
- Duration of treatment (days; mean (SE)): -
- Route: IV
- Intervention: administered in intravenous bolus form, with the dose adjusted for renal failure as follows: standard dose, 50 mg every 8 hours; dose for patients with an estimated creatinine clearance rate of 25 to 50 mL per minute, 50 mg every 12 hours; dose for patients with an estimated creatinine clearance rate below 25 mL per minute, 50 mg every 24 hours; and dose for patients dependent on dialysis, 50 mg every 12 hours. 70.3% received enteral feeding + sucralfate placebo
- Concomitant medications: "Fourteen patients in the ranitidine group (2.3%) and 16 in the sucralfate group (2.6%) received an additional drug as prophylaxis against stress ulcers outside of the study protocol"
- "Most patients received enteral nutrition (70.3% and 71.8%, respectively; $P = 0.55$). Enteral feeding was started a median of 3 days (interquartile range, 2 to 4) after admission to the ICU"

Sucralfate

- Dose (total/d): 2400 mg
- Duration of treatment (days; mean (SE)): -
- Route: NG tube
- Intervention: Sucralfate suspension was given through a nasogastric tube or orally. 71.8% received Enteral feeding + Ranitidine placebo

Cook 1998 (Continued)

- Concomitant medications: "Fourteen patients in the ranitidine group (2.3%) and 16 in the sucralfate group (2.6%) received an additional drug as prophylaxis against stress ulcers outside of the study protocol"
- "Most patients received enteral nutrition (70.3% and 71.8%, respectively; $P = 0.55$). Enteral feeding was started a median of 3 days (interquartile range, 2 to 4) after admission to the ICU"

Adherence to regimen: Quote: "No patient received active drug instead of the assigned placebo, or vice versa. Of the scheduled doses of ranitidine and sucralfate, 94.2% and 91.7%, respectively, were administered. Among patients who missed doses, the mean number of doses missed was 2.3 (median, 3; interquartile range, 2 to 3) for ranitidine and 2.9 (median, 4; interquartile range, 1 to 4) for sucralfate"

Duration of trial: October 1992 to May 1996

Duration of follow-up: probably until death or discharge

Outcomes
Outcomes sought in review and reported in trial:

- Clinically important GI bleeding defined as overt bleeding plus 1 of the following 4 features, in the absence of other causes:
 - Spontaneous drop of ≥ 20 mmHg in systolic or diastolic blood pressure within 24 hours after upper gastrointestinal bleeding
 - Increase in pulse rate of 20 beats per minute and decrease in systolic blood pressure of 10 mmHg on the patient's assuming an upright position
 - Decrease in haemoglobin concentration ≥ 2 g/dL in 24 hours and transfusion of 2 units of packed red cells within 24 hours after bleeding
 - Failure of haemoglobin concentration (in g/dL) to increase after transfusion by at least the number of units transfused minus 2 (i.e. if 4 units of packed cells were transfused, bleeding would be considered clinically important if the haemoglobin concentration did not rise by ≥ 2 g/dL)
- VAP defined according to the modified version of the criteria of the Centers for Disease Control and Prevention
 - New radiographic infiltrate that had persisted for ≥ 48 hours (as interpreted by designated study radiologists blinded to participants' treatment assignments) plus ≥ 2 of the following: temperature $> 38.5^{\circ}\text{C}$ or $< 35.0^{\circ}\text{C}$, a leucocyte count $> 10,000/\text{mm}^3$ or $< 3000/\text{mm}^3$, purulent sputum, or isolation of pathogenic bacteria from an endotracheal aspirate
 - Clinical Pulmonary Infection Score revised by Pugin et al (range, 0 to 12, with pneumonia defined by a score ≥ 7)
 - Criteria of the Memphis Ventilator-Associated Pneumonia Consensus Conference for Definite Ventilator-Associated Pneumonia (if there was radiographic evidence of abscess and a positive needle aspirate, or if there was histologic proof of pneumonia at biopsy or autopsy) and probable ventilator-associated pneumonia (if bronchoalveolar lavage or protected brush-catheter sampling yielded positive quantitative or semi-quantitative cultures, if there was a positive blood culture of an organism found within 48 hours of isolation in the sputum, if there was a positive pleural-fluid culture of an organism found within 48 hours of isolation in the sputum, or if histologic examination showed formation of an abscess or consolidation with polymorphonuclear cell infiltration)
 - Summary judgement based on all available information; disagreement was resolved through discussion
- All-cause mortality in ICU
- Duration of ICU stay (median and interquartile ranges)
- Duration of intubation (median and interquartile ranges)

Outcomes sought but not reported in trial

- All-cause mortality in hospital
- Number of participants requiring blood transfusion
- Number of units of blood transfused
- Adverse events of interventions

Outcomes reported in trial but not used in review

- Intragastric pH status (with and without enteral nutrition)

Cook 1998 (Continued)

- Gastric colonisation

Notes

Setting: 16 ICUs: McMaster University, Hamilton, The University of Toronto, Toronto, The University of Western Ontario, London, Dalhousie University, Halifax, Memorial University, St. John's, Newf, Queen's University, Kingston. University of British Columbia, University of Ottawa, Ottawa, University of Alberta, Edmonton Vancouver General Hospital, Vancouver, Royal Alexandra Hospital, Edmonton, Grey Nun's Hospital, Edmonton, Winnipeg Health Sciences Center, Winnipeg, Man., Toronto Hospital, General Division, Toronto; Wellesley Hospital, Toronto London Health Sciences Center (Victoria Campus), London, Ont., London Health Sciences Center (University Campus), London, Ont., St. Joseph's Health Center, London, Ont., St. Joseph's Hospital, Hamilton, Ont., Henderson Hospital, Hamilton, Ont., Kingston General Hospital, Kingston, Ont., Ottawa Civic Hospital, Ottawa, Ont., Health Sciences Center, St. John's, Newf, Victoria General Hospital, Halifax, N.S.

Source of funding: Quote: "Supported by the Medical Research Council of Canada and Hoechst Marion Roussel. Drugs were supplied by Glaxo Wellcome, Baxter, and Hoechst Marion Roussel. Dr. Cook is a Career Scientist of the Ontario Ministry of Health"

Conflicts of interest: -

Ethics approval: Quote: "The protocol was approved by the institutional review board of all participating centers ..."

Informed consent: Quote: "...and the patients or their proxies gave informed consent"

Clinical trials registration: -

Sample size calculation: Quote: "On the basis of data published through 1991, when our study was designed, we anticipated a 25 percent incidence of pneumonia and identified a 25 percent reduction in the risk of pneumonia associated with sucralfate as being plausible and clinically important. This led to the calculation of a sample size of 1200 patients as necessary to give the study 75 percent power to detect such a difference, assuming a two-sided significance test at the 0.05 level. We analysed all patients in the groups to which they were randomly assigned, according to the intention-to-treat principle"

Additional notes: Gram-negative bacilli and gram-positive cocci were the main isolates from endotracheal aspirates from patients with ventilator-associated pneumonia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to study groups in blocks of six, with stratification according to centre, by means of a computer generated random-number table prepared at the McMaster University Methods Center and managed by the ICU study pharmacist at each site" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the trial report
Allocation concealment (selection bias)	Low risk	Quote: "...managed by the ICU study pharmacist at each site who administered the coded drugs" Comment: Method to obtain allocation concealment is clearly mentioned in the trial report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients, research nurses, and all ICU care givers were unaware of the treatment assignments for the duration of the study. Therefore, clinicians did not monitor gastric pH" "The radiologists, outcome adjudicators, all investigators, and the study statistician were also blinded until all events had been adjudicated and the analyses completed"

Cook 1998 (Continued)

		Comment: Blinding was done, so the likelihood of performance bias and detection bias is low
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	<p>Quote: "The patients, research nurses, and all ICU care givers were unaware of the treatment assignments for the duration of the study. Therefore, clinicians did not monitor gastric pH"</p> <p>"The radiologists, outcome adjudicators, all investigators, and the study statistician were also blinded until all events had been adjudicated and the analyses completed"</p> <p>Comment: Blinding was done. Moreover the outcome of interest was objective in nature, so the likelihood of performance bias and detection bias is low</p>
Blinding (detection bias) Nosocomial pneumonia	Low risk	<p>Quote: "The patients, research nurses, and all ICU care givers were unaware of the treatment assignments for the duration of the study. Therefore, clinicians did not monitor gastric pH"</p> <p>"The radiologists, outcome adjudicators, all investigators, and the study statistician were also blinded until all events had been adjudicated and the analyses completed"</p> <p>Comment: Blinding was done. Moreover the outcome of interest was objective in nature, so the likelihood of performance bias and detection bias is low</p>
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	<p>Quote: "The patients, research nurses, and all ICU care givers were unaware of the treatment assignments for the duration of the study..."</p> <p>Comment: Blinding was done. Moreover all other outcomes of interest were objective in nature</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All participants who were randomised to the 2 groups were analysed
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were reported
Other bias	Low risk	Comment: Hoechst Marion Roussel supported the trial and also sponsored sucalfate needed for administering to study participants. The role of the sponsor in the conduct and reporting of the trial is unclear. No other sources of bias are suspected

Darlong 2003

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 52 participants</p> <p>Number analysed: 52 participants</p> <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 43.95 (18.46) • Number of participants (n): 24 • Gender (male/female; n): 11/13

Darlong 2003 (Continued)

Sucralfate

- Age (years; mean (SD)): 39.6 (15.24)
- Number of participants (n): 21
- Gender (male/female; n): 14/7

No prophylaxis

- Age (years; mean (SD)): 39.16 (19.52)
- Number of participants (n): 7
- Gender (male/female; n): 3/4

Inclusion criteria

- Intubated for mechanical ventilation likely to last > 24 hours
- Nasogastric tube in place was included in the study

Exclusion criteria

- Active upper gastrointestinal haemorrhage receiving antacids, H2 receptor antagonist, or sucralfate in the previous 24 hours
- Receiving anticoagulants
- Coagulopathy

Baseline imbalances: There were no major differences in demographic profiles between study groups

Comment: Participants were from medical and surgical units, in equal proportions across the 3 groups. However, the underlying reason for admission is not mentioned in the trial report

Interventions

Ranitidine

- Dose (total/d): 150 mg
- Duration of treatment (days; mean (SE)): -
- Route: IV
- Intervention: intravenous ranitidine at a standard dose of 50 mg every 8 hours
- Concomitant medications: Nutrition was provided through the parenteral route until completion of the trial

Sucralfate

- Dose (total/d): 3 g
- Duration of treatment (days; mean (SE)): -
- Route:
- Intervention: sucralfate tablet, 1 g 8-hourly crushed to powder
- Concomitant medications: Nutrition was provided through the parenteral route until completion of the trial

No prophylaxis

- Dose (total/d): -
- Duration of treatment (days; mean (SE)): -
- Route: -
- Intervention: -
- Concomitant medications: Nutrition was provided through the parenteral route until completion of the trial

Adherence to regimen: -

Duration of trial: -

Darlong 2003 (Continued)

Duration of follow-up: probably until death or discharge

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> Clinically Important GI bleeding defined as observation of fresh blood or blood of 'coffee ground' colour in the gastric aspirate <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> VAP All-cause mortality in ICU All-cause mortality in hospital Duration of ICU stay Duration of intubation Number of participants requiring blood transfusion Number of units of blood transfused Adverse events of interventions <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none"> Intragastric pH status Gastric colonisation Gastric ulcerations BAL cultures
Notes	<p>Setting: All India Institute of Medical Sciences (AIIMS), New Delhi, India</p> <p>Source of funding: Quote: "Supported by the Medical Research Council of Canada and Hoechst Marion Roussel. Drugs were supplied by Glaxo Wellcome, Baxter, and Hoechst Marion Roussel. Dr. Cook is a Career Scientist of the Ontario Ministry of Health"</p> <p>Conflicts of interest: -</p> <p>Ethics approval: -</p> <p>Informed consent: -</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional Notes: Gram-negative organisms were found in the gastric culture of 18 ranitidine participants and 6 sucralfate participants, and the control group had no pathogenic organisms. <i>Pseudomonas</i> was the most common organism in the gastric and BAL cultures of the ranitidine and sucralfate groups</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the trial report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the trial report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the mode of administration of interventions could not have permitted blinding of participants. Therefore, high risk of performance bias

Darlong 2003 (Continued)

Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: not clearly mentioned in the trial report. However owing to the objective nature of the outcome, which was detected as per the trial protocol, the likelihood of performance and detection bias is low
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Trial did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: No other outcomes of interest were assessed in this trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	High risk	Comment: unclear on source of funding. Baseline imbalance on the numbers randomised to the 3 groups as the no prophylaxis arm had only 7 participants compared with 21 in the sucralfate arm and 24 in the ranitidine arm

Davies 2012

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 182 participants</p> <p>Number analysed: 181 participants</p> <p>Nasojejunal nutrition</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 51 (19) • Number of participants (n): 91 • Gender (male/female; n): 62/29 <p>Nasogastric nutrition</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 54 (18) • Number of participants (n): 89 • Gender (male/female; n): 71/18 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age ≥ 16 years • ICU stay < 72 hours • Receiving narcotic infusion at any dose <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Previous anatomy altering upper gastrointestinal surgery • Gastric malignancy • Oesophageal varices • Current peptic ulceration

Davies 2012 (Continued)

- Mechanical bowel obstruction
- Presence of gastrostomy or jejunostomy
- Nutrition therapy before ICU admission
- Severe coagulopathy
- Pregnancy
- Suspected brain death
- Death expected within 24 hours
- Suspected hypoxic-ischaemic encephalopathy

Baseline imbalances: Baseline characteristics of the groups were similar

Interventions	<p>Nasojejunal nutrition</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days (range)): 8 (6–12) • Route: nasojejunal • Intervention: enteral nutrition. Spontaneously migrating frictional nasojejunal tube inserted using a standardised method • Concomitant medications: intravenous administration of 250 mg erythromycin, and hourly 10-cm tube advancement to a maximum of 100 cm from the nostril. Patients with clinical manifestations of EN intolerance received metoclopramide (10 mg intravenously every 6 hours), followed by erythromycin (250 mg intravenously every 2 hours) if required. Other recommended treatments for all patients were head of bed elevation to 45 degrees and ranitidine for stress ulcer prophylaxis (except for patients receiving a proton pump inhibitor before ICU admission). Metoclopramide was administered to 82 (90%) patients in the early nasojejunal and 81 (91%) in the nasogastric groups, respectively ($P = .84$). Erythromycin was more commonly used in the early nasojejunal group than in the nasogastric group (79 [87%] vs 55 [62%] patients; $P = .001$) <p>Nasogastric nutrition</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days (range)): 8 (5–14) • Route: NG tube • Intervention: enteral nutrition through a nasogastric tube already in situ • Concomitant medications: intravenous administration of 250 mg erythromycin and hourly 10-cm tube advancement to a maximum of 100 cm from the nostril. Patients with clinical manifestations of EN intolerance received metoclopramide (10 mg intravenously every 6 hours), followed by erythromycin (250 mg intravenously every 2 hours) if required. Other recommended treatments for all patients were head of bed elevation to 45 degrees and ranitidine for stress ulcer prophylaxis (except for patients receiving a proton pump inhibitor before ICU admission). Metoclopramide was administered to 82 (90%) patients in the early nasojejunal and 81 (91%) in the nasogastric groups, respectively ($P = .84$). Erythromycin was more commonly used in the early nasojejunal group than in the nasogastric group (79 [87%] vs 55 [62%] patients; $P = .001$) <p>Adherence to treatment: -</p> <p>Duration of trial: -</p> <p>Duration of follow-up: 28 days</p>
Outcomes	Outcomes sought in review and reported in trial

Davies 2012 (Continued)

- Clinically important upper GI bleeding defined as major or minor using the following criteria
 - Major haemorrhage was epistaxis or overt GI haemorrhage, plus ≥ 1 of the following in the absence of other causes:
 - Spontaneous drop ≥ 20 mmHg in the systolic, diastolic, or mean blood pressure within 24 hours after upper GI bleeding
 - An increase in the pulse rate of 20 bpm and a decrease in the systolic blood pressure of 10 mmHg upon the patient assuming an upright position
 - A decrease in the haemoglobin concentration of ≥ 2 g/dL in 24 hours and transfusion of 2 units of packed red cells within 24 hours after bleeding
 - Spontaneous drop ≥ 20 mmHg in systolic, diastolic, or mean blood pressure within 24 hours after upper GI bleeding
 - Failure of haemoglobin concentration (ing/dL) to increase after transfusion by $\geq$ number of units transfused minus 2
 - Minor haemorrhage was defined as epistaxis or overt GI haemorrhage in the absence of other causes that was not defined as major
- VAP defined as receiving mechanical ventilation for > 72 hours AND either new or worsening radiographic infiltrate and any use of new antibiotics or persistent radiographic infiltrate and any use of new antibiotics in the absence of a clear non-pulmonary source of sepsis, and ≥ 1 of the following:
 - Temperature $> 38.5^{\circ}\text{C}$ or $< 35.0^{\circ}\text{C}$
 - Leucocyte count $> 10 \times 10^9/\text{L}$ or $< 3 \times 10^9/\text{L}$
 - Purulent sputum
 - Isolation of bacteria from an endotracheal aspirate or bronchoalveolar lavage (defined as "growth on culture of a named organism on the report, not including a light growth of oral, mixed respiratory or skin flora")
- All-cause mortality in hospital
- Duration of ICU stay (only mean and IQR reported, could not be formally analysed)
- Duration of mechanical ventilation (no standard deviation or standard error reported, could not be formally analysed)
- Adverse events of interventions

Outcomes sought but not reported in trial

- Number of units blood transfusion
- Number of patients requiring blood transfusion

Outcomes reported in trial but not used in review

1. Mean energy delivery

Notes

Setting: Medical-Surgical ICUs, Alfred Hospital, Melbourne, Australia

Sponsorship source: Cook Critical Care provided the frictional nasojunal tubes

Conflicts of interest: no conflicts of interest disclosed

Comments: Other recommended treatment includes ranitidine

Ethics approval: All sites received institutional human research ethics committee approval

Informed consent: Prior written informed consent was obtained from the patient's surrogate decision-maker

Clinical trials registration: -

Sample size calculation: 180-patient sample size provided 80% power with 2-sided significance of 0.05 to detect a 12% difference in mean energy delivery

Risk of bias

Davies 2012 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "They were randomly assigned to early nasojejunal nutrition or naso-gastric nutrition using a computer-generated randomisation schedule with variable block size"
Allocation concealment (selection bias)	Low risk	Quote: "Treatment assignments were concealed before randomisation using a centralized voice-recognition phone system"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "There was no blinding after randomisation" Comment: high for personnel; indifferent for patients
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "gastrointestinal haemorrhage ([was measured as] defined as major or minor based on definitions from a previous trial)" Comment: detailed description provided in supplementary material to the trial. Outcome measurement unlikely to introduce bias to the trial
Blinding (detection bias) Nosocomial pneumonia	Low risk	Quote: "chest radiograph images" Comment: Outcome measurement was objective and therefore was unlikely to introduce bias
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Quote: "The collected information was provided to a blinded adjudication panel of two intensivists and one respiratory physician for each patient. To maintain blinding, the radiograph images had the enteral tube shadows in the mediastinum and upper abdomen obscured. Panel members individually adjudicated the diagnosis of VAP using objective criteria (Supplemental Digital Appendix A, Supplemental Digital Content 1, http://links.lww.com/CCM/A454). Patients were formally categorized as meeting the VAP outcome if at least two of the three adjudicators determined the presence of VAP and this occurred after the patient had been mechanically ventilated for >72 hrs. A Data Monitoring Committee regularly viewed data on safety aspects with blinding maintained and did not recommend study cessation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Data were analyzed according to the intention-to-treat principle with no imputation of missing values" Comment: No incomplete outcome data were suspected. All participants enrolled at baseline were treated and analysed
Selective reporting (reporting bias)	Low risk	Comment: All prespecified outcomes listed in the Methods section were reported in the Results section. No selective outcome reporting was suspected
Other bias	Low risk	Comment: No other sources of bias were suspected

De Azevedo 2000

Methods	Randomised controlled trial
Participants	Baseline characteristics Number randomised: - Number analysed: -

De Azevedo 2000 (Continued)

Ranitidine

- Age (years; mean (SD)): 57.3 (19.3)
- Number of participants (n): 38
- Gender (male/female; n): 19/19

Sucralfate

- Age (years; mean (SD)): 56.9 (20.5)
- Number of participants (n): 32
- Gender (male/female; n): 18/14

Omeprazole

- Age (years; mean (SD)): 56.0 (18.9)
- Number of participants (n): 38
- Gender (male/female; n): 19/19

Inclusion criteria

- Age > 14 years
- Admitted to São Domingos Hospital during the period 28 Feb. 1997 to 06 Apr 1998
- Having ≥ 1 risk factor for stress ulcer bleeding (stroke with Glasgow score < 10, coagulopathy, steroid therapy, anticoagulant therapy, liver failure, acute renal failure, respiratory failure, severe acute pancreatitis, burns > 30% of body surface, sepsis and septic shock, head injury with Glasgow score < 10)

Exclusion criteria

- Pregnancy
- Stress ulcer bleeding at admission

Baseline imbalances: Groups were similar to each other with respect to demographic characteristics. APACHE II scores were 55.7 ± 23.2 , 54.1 ± 21.7 , and 56.1 ± 23.7 in the ranitidine, sucralfate, and omeprazole groups, respectively. Pneumonia was present in 2, 3, and 3 participants in the 3 groups

Interventions
Ranitidine

- Dose (total/d): 150 mg
- Duration of treatment (days): -
- Route: IV
- Intervention: 150 mg of continuous intravenous infusion per day, diluted in 100 mL saline, administered with the aid infusion pump
- Concomitant medications: corticosteroids

Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days): -
- Route: intragastric tube
- Intervention: tablet of 1 g of sucralfate, homogenised and diluted in 20 mL of water every 6 hours by tube feeding; In patients who showed siphoning probe, the tube was held closed for 1 hour after drug administration
- Concomitant medications: corticosteroids

Omeprazole

- Dose (total/d): 80 mg
- Duration of treatment (days): -
- Route: IV
- Intervention: intravenous, 40 mg every 12 hours

De Azevedo 2000 (Continued)

- Concomitant medications: corticosteroids

Adherence to regimen: -

Duration of trial: February 1997 to April 1998

Duration of treatment: Duration of treatment that was established was based on clinical evaluation, control of risk factors, clinical improvement, and full nutritional support, oral or enteral

Duration of follow-up: during the period that participants were in the ICU. Probably until death or discharge

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> Clinically important upper GI bleeding VAP All-cause mortality in ICU Number of participants requiring blood transfusion <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> Number of units of blood transfused All-cause mortality in hospital Duration of ICU stay Duration of intubation Adverse events of interventions <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none"> Intragastric pH status Gastric colonisation
Notes	<p>Setting: Intensive Care Unit, Hospital São Domingos, Sao Luis do Maranhão, Brasil</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: -</p> <p>Informed consent: -</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned for one of the three groups when they were admitted for the intensive unit care, they used a simple technique of randomisation, and sealed envelopes" Comment: not enough information on sequence generation reported
Allocation concealment (selection bias)	Unclear risk	Comment: Trial authors described that they used sealed envelopes. It was not stated whether they were numbered and opaque
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: not enough information reported

De Azevedo 2000 (Continued)

All outcomes

Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: not enough information reported on criteria for assessment of upper GI bleeding
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: not enough information reported on criteria for assessment of pneumonia
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear; however all other outcomes of interest were objective outcomes. Therefore the likelihood of performance and detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were analysed
Selective reporting (reporting bias)	Low risk	Comment: All outcomes described in the Methods section were analysed in the Results section
Other bias	Low risk	Comment: no other source of bias detected

Driks 1987

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 130 participants</p> <p>Number analysed: 130 participants</p> <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 53.9 (18.9) • Number of participants (n): 61 • Gender (male/female; n): 47/14 <p>Antacid and/or H2 receptor antagonists</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 55.2 (20.1) • Number of participants (n): 69 • Gender (male/female; n): 42/27 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Patients admitted to the surgical medical or coronary intensive care units • Intubated with in the previous 24 hours receiving mechanical ventilation • Nasogastric tube in place <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Active upper gastrointestinal tract haemorrhage • Receiving antacids, H2 blocker, or sucralfate within the previous 48 hours • Duration of mechanical ventilation < 24 hours

Driks 1987 (Continued)

Baseline imbalances: Quote: "The two treatment groups were similar in terms of demographic characteristics and severity of illness on admission to the study"

"The distribution of underlying diseases, indications for intubation and surgical procedures according to the site were similar in both the groups"

"Thirty two of the 61 patients in the sucralfate group and twenty nine of the 69 participants in the antacid H2 group had infiltrates at baseline evaluation (n = 38), adult respiratory distress syndrome (n = 8), or congestive heart failure (n = 15), making it difficult to diagnose new infiltrates on a chest film"

Comment: similar distribution with respect to demographic and baseline risk factors. However, a total of 35 participants (sucralfate: n = 16; antacid and/or H2: 19) had pneumonia on admission and/or had infiltrates (as mentioned above)

Interventions
Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days; mean (SE)): -
- Route: NG tube
- Intervention: 1 g every 6 hours sucralfate was suspended in 20 mL of sterile water and administered by nasogastric tube, which was then flushed with 10 mL of sterile water to prevent clogging
- Concomitant medications: 21 participants in the sucralfate group received tube feeds; treating physician sometimes added antacids if gastric pH could not be maintained at a level ≥ 4

Antacid and/or H2 receptor antagonists

- Dose (total/d): 5 g
- Duration of treatment (days; mean (SE)): -
- Route: NG tube
- Intervention: conventional therapy with antacids, H2 blockers (cimetidine or ranitidine), or both antacids and H2 blockers. Standard regimens of various antacid preparations were administered by nasogastric tube. In some patients, the dosage was titrated to maintain gastric pH ≥ 4 . Similarly standard doses of intravenous cimetidine or ranitidine were prescribed. The treating physician sometimes added antacids if gastric pH could not be maintained at a level ≥ 4 . In all, 39 participants received antacids alone, 17 received H2 blockers (cimetidine or ranitidine), and 13 received both H2 blockers and antacids
- Concomitant medications: 34 participants in the antacid-H2 group received tube feeds; the treating physician sometimes added antacids if gastric pH could not be maintained at a level ≥ 4

Adherence to regimen: Quote: "Six patients who were initially assigned to sucralfate but subsequently assigned to antacids or H2 blockers by the treating physician were included in the sucralfate group (for analysis), no patients were switched from antacids or H2 blockers to sucralfate. Four of the six patients who were crossed over had evidence of upper GI tract bleeding, the other two who were switched to antacids 5 and 11 days after randomisation had no evidence of such bleeding. Two of the six patients had pneumonia after the crossover occurred but were included in the sucralfate group"

"Four patients in the sucralfate group and 17 in the antacid-H₂ group underwent tracheostomy"

Comment: ITT was performed for the review and not per-protocol analysis

Duration of trial: April 1986 to February 1987

Duration of follow-up: until 48 hours after extubation

Outcomes
Outcomes sought in review and reported in trial

- Clinically important upper GI bleeding: nasogastric aspirates examined for bright red blood, 'coffee ground' material, occult blood as detected by guaiac test

Driks 1987 (Continued)

- VAP diagnosed if chest film showed a new and persistent infiltrate that was consistent with pneumonia and ≥ 3 of the following findings:
 - Purulent sputum that showed > 25 leucocytes on gram staining, < 10 squamous epithelial cells per low-powered field, and numerous bacteria per oil immersion field
 - An important respiratory or nosocomial pathogen isolated from culture of a tracheal aspirate. Peripheral leucocytosis $> 10,000$ cells/mm³ and fever (temperature $> 38^{\circ}\text{C}$). Episodes of pneumonia that occurred within the first 24 hours of intubation were included; only the first episode was included for each patient

Note: Pneumonia developed after 9.6 (4.6) days in sucralfate group and after 9.6 (6.3) days in antacid H2 group

- All-cause mortality in ICU
- Duration of ICU stay
- Duration on ventilation
- Participants requiring blood transfusion

Outcomes sought but not reported in trial

- All-cause mortality in hospital
- Number of units of blood transfused
- Adverse events of interventions

Outcomes reported in trial but not used in review

- Intragastric pH status
- Bacteriological examination

Notes

Setting: surgical, medical, or coronary intensive care units, Boston City Hospital

Source of funding: -

Conflicts of interest: -

Ethics approval: Quote: "The study protocol was reviewed and approved by the hospital institutional review board for human studies"

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Additional notes: Quantitative data were extracted for the 2 randomised groups alone (sucralfate and antacid - H2 receptor groups). Data were not extracted separately for participants treated with antacid or H2 receptor alone, as this would break the randomisation. Of bacteria isolated from the tracheal aspirates of participants treated with pneumonia, gram-negative bacilli were predominant; *Pseudomonas aeruginosa* in the sucralfate group; Enterobacteriaceae in antacid-H2 group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the trial report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the trial report

Driks 1987 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the mode of administration of the interventions would not have permitted blinding of participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear whether outcome assessors were blinded, but GI bleeding was an objective outcome that was detected as per the definition in the trial protocol
Blinding (detection bias) Nosocomial pneumonia	Low risk	Quote: "Chest roentgenograms were interpreted by at least one of us, who had no knowledge on the patient's treatment group after randomisation" Comment: Blinding was done. Moreover, pneumonia was an objective outcome that was detected as per the definition in the trial protocol
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear whether outcome assessors were blinded. Moreover the outcomes of interest were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Intention-to-treat analysis was performed wherein all participants who were initially randomised to each of the 2 study groups were part of the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes have been reported
Other bias	Low risk	Comment: Source of funding is not clearly mentioned in the trial report. No other form of bias was detected

Eddleston 1991

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 60 participants</p> <p>Number analysed: 60 participants</p> <p>Sucralfate</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 44.3 (3.5) Number of participants (n): 30 Gender (male/female; n): 21/9 <p>Ranitidine</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 54.1 (3.1) Number of participants (n): 30 Gender (male/female; n): 17/13 <p>Inclusion criteria</p> <ul style="list-style-type: none"> Expected to require mechanical ventilation support for at least 4 days Admitted with the following risk factors: hypotension (mean arterial blood pressure < 65 mmHg), sepsis, renal dysfunction, hepatic dysfunction, CNS injury, coma Age 15 to 78 years

Eddleston 1991 (Continued)

Exclusion criteria

- History of peptic ulcer disease, gastric surgery, fresh blood on nasogastric aspirate, and clinical evidence of pulmonary aspiration
- Participants with pneumonia
- Pregnancy
- Treatment within previous 4 weeks with H2 receptor antagonists, antacids, omeprazole, or NSAIDs

Baseline imbalances: Participants in the ranitidine group were relatively older. The acute physiology and chronic health evaluation (APACHE II) score was 11.6 (1.3) for sucralfate and 12.4 (1.5) for ranitidine

Admission diagnosis: More participants in the sucralfate group had both CNS injury (11/30) and trauma (8/30), and CNS injury and respiratory failure were the most common diagnoses on admission among participants in the ranitidine group (8/30) and (7/30)

Interventions
Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days; mean (SE)): 105 (-)
- Route: NG tube
- Intervention: (1 g/5 mL) every 6 hours via NG tube, flushed with 10 mL of sterile water
- Concomitant medications: Prophylactic antibiotics were given to 21 participants in the sucralfate group

Ranitidine

- Dose (total/d):
- Duration of treatment (days; mean (SE)): 98 (-)
- Route: IV
- Intervention: ranitidine (50 mg) IV every 6 hours + 15 mL sterile water, via NG tube; sodium citrate (30 mL of 0.3 M), NG tube (gastric pH < 3.5), via NG tube if pH level < 3.5
- Concomitant medications: Prophylactic antibiotics were given to 17 participants in the ranitidine group; 11 participants in the ranitidine group who had a gastric pH value < 3.5 were given between 1 and 10 doses of 0.3 M sodium citrate

Adherence to regimen: All participants were subjected to treatment within 6 hours after ICU admission. Enteral nutrition was given (exact numbers and interventional groups not specified)

Duration of trial: -

Duration of follow-up: probably until death or discharge

Outcomes
Outcomes sought in review and reported in trial

- Diagnosis of secondary pneumonia: defined as per the criteria of a new and progressive infiltrate on chest radiograph, an unexplained reduction in PaO₂; positive culture with a tracheal aspirate with pyrexia (>38°C) or an increase in blood leucocyte count (> 3 × 10⁹ WBCs/L). Furthermore the same organism had to be colonised in ascending order: stomach, oropharynx, and trachea
- Clinically important upper GI bleeding reported as fresh blood (< 50 mL) in the nasogastric aspirate
- Duration of endotracheal Intubation
- Duration of ICU stay
- All-cause mortality in ICU
- Duration of endotracheal Intubation
- Duration of ICU stay
- All-cause mortality in ICU

Note: GI bleeding in 2 participants (day 3 in the participant from the sucralfate group and day 5 in the participant from the ranitidine group)

Outcomes sought but not reported in trial

Eddleston 1991 (Continued)

- Participants requiring blood transfusions
- Adverse events of interventions

Outcomes reported in trial but not sought in review

- Gastric pH noted through aspiration using NG tube (every 6 hours)
- Inflammation, erosion, and ulceration of the gastric and duodenal mucosa through endoscopy within 24 hours and on fourth day (if patient still receiving mechanical ventilation)
- Gastric colonisation; from nasogastric aspirate taken at admission daily for 4 days and repeated on seventh and tenth days, thereafter twice weekly until death or discharge
- Duration of mechanical ventilation

Notes

Setting: ICU, Manchester Royal Infirmary, Manchester, UK

Source of funding: -

Ethics approval: Quote: "The protocol for the study was approved by the hospital ethics committee"

Informed consent: Quote: "Informed consent was obtained from the patient's next of kin"

Clinical trials registration: -

Sample size calculation: -

Additional notes: Retrograde colonisation from stomach to oropharynx was found in 6 participants in the sucralfate group and 14 participants in group B. From the oropharynx to the trachea, colonisation occurred in 5 of the 6 participants in group A and in 12 of the 14 participants in group B. Colonisation occurred relatively later in sucralfate-treated participants. More pneumonia cases were reported in group B, and the pathogens were mainly similar in both groups (mainly gram-negative bacilli)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were allocated by the use of a random sampling table into two groups" Comments: Method adopted to obtain random sequence generation is clearly mentioned in the trial report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the trial report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering the study interventions would not have made it possible to blind the study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "Endoscopic evolution of the gastric and the duodenal mucosa was performed within 24 hours of admission by an operator who was blinded to the randomisation and was repeated on day 4 if the participant was still receiving mechanical ventilation" Comment: Endoscopy was performed if there was fresh blood (< 50 mL) in the nasogastric aspirate, but the endoscopist was blinded. Moreover, the outcome of interest was objective in nature
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: no mention of blinding of radiologists, lab technicians, or physicians. However, pneumonia was diagnosed as per the study definition and due to the objective nature of the outcome

Eddleston 1991 (Continued)

Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: not clear on blinding assessors for other outcomes of interest. However given the objective nature of the outcomes, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All 60 randomised participants were included in the final analysis. Therefore there is low risk of attrition bias
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were reported. No mention of any adverse events
Other bias	Low risk	Comment: Source of funding is not clearly mentioned in the trial report. No other sources of bias are suspected

Eddleston 1994

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 26 participants</p> <p>Number analysed: 26 participants</p> <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 47.6 (5.4) • Number of participants (n): 14 • Gender (male/female; n): 9/5 <p>Placebo</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 54.9 (5.7) • Number of participants (n): 12 • Gender (male/female; n): 8/4 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Expected to require mechanical ventilator support for ≥ 4 days • Participants diagnosed with risk factors to develop stress ulceration <ul style="list-style-type: none"> ◦ Sepsis ◦ Hypotension (mean arterial pressure < 65 mm) ◦ Respiratory failure ◦ Renal dysfunction ◦ Hepatic dysfunction <p>Exclusion criteria</p>

Eddleston 1994 (Continued)

- Participants who had the following conditions:
 - Previous history of peptic ulcer disease
 - Gastric surgery
 - Fresh blood in nasogastric aspirate
 - Clinical evidence of pulmonary aspiration
 - Pneumonia
 - CNS injury or coma
 - Pregnancy
- Treatment within previous 4 weeks with histamine receptor antagonists, antacid, omeprazole, or NSAIDs

Baseline imbalances: Participants in the placebo group were relatively older. Acute Physiology and Chronic Health Evaluation II (APACHEII) scores were 12.5 (1.7) and 14.7 (2.2), respectively. Trauma was the most common cause for admission (6 in sucralfate group and 4 in the placebo group)

Interventions
Sucralfate

- Dose (total/d): 6 g
- Duration of treatment (days; mean (SD)): -
- Route: NG tube
- Intervention: 2 g/10 mL every 8 hours via NG tube flushed with 10 mL of sterile water
- Concomitant medications: Prophylactic antibiotics were administered to 11 participants from both groups

Placebo

- Dose (total/d): -
- Duration of treatment (days; mean (SD)): -
- Route: NG tube
- Intervention: 20 mL of sterile water every 8 hours via NG tube
- Concomitant medications: Prophylactic antibiotics were administered to 11 participants from both groups

Adherence to regimen: Treatment began within 8 hours of ICU admission. Endoscopy performed on day 3 in the placebo group revealed acute ulcerations in 5 participants, as a result of which they were withdrawn and put on sucralfate 2 g every 8 hours. On day 6, 2 more patients from placebo group were switched over to sucralfate owing to acute gastric ulceration. Mucosal deterioration and acute ulceration were significant in the placebo group. The study was halted after recruitment of 26 participants for ethical reasons

Duration of trial: -

Duration of follow-up: -

Outcomes
Outcomes sought in review and reported in trial

- Incidence of pneumonia, defined as per the criteria of a new and progressive infiltrate on chest radiograph, an unexplained reduction in PaP₂; positive culture with a tracheal aspirate with pyrexia (> 38°C) or an increase in blood leucocyte count (> 3 × 10⁹ WBCs/L). Furthermore the same organism had to be colonised in ascending order: stomach, oropharynx, and trachea
- Clinically important GI bleeding reported as fresh blood in the nasogastric tube
- All-cause mortality in ICU

Note: GI bleeding occurred in 1 participant from placebo group on 20th day of the trial

Outcomes sought but not reported in trial

- All-cause mortality in hospital
- Participants requiring blood transfusions

Eddleston 1994 (Continued)

- Adverse events of interventions

Outcomes reported in trial but not used in review

- Intragastric pH status (with and without enteral nutrition)
- Inflammation, erosion, and ulceration of gastric and duodenal mucosa through endoscopy within 24 hours; third, sixth, and tenth days if patient still on mechanical ventilator and cardiovascularly stable
- Gastric colonisation
- Duration of endotracheal intubation (subgrouped for participants with and without erosions and ulcerations)
- Length of stay in ICU (subgrouped for participants with and without erosions and ulcerations)

Notes	<p>Setting: Department of Surgery, Critical Care Unit, Department of Microbiology, Manchester Royal Infirmary, Manchester, UK</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The protocol for the study was approved by the hospital ethics committee"</p> <p>Informed consent: Quote: "...informed consent was obtained from the patient's next of kin"</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: Oropharyngeal retrograde colonisation occurred in 1 participant in the sucralfate group and in 2 participants in the placebo group. Tracheal colonisation occurred in 2 participants from the sucralfate group and in 1 participant from the placebo group. However only the latter developed pneumonia. Mortality in ICU was attributed to multiple organ failure</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were allocated by the use of a random sampling table into two groups..." Comment: Method adopted to obtain random sequence generation is clearly mentioned in the trial report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the trial report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This was a placebo-controlled trial, and the mode of administering the interventions was similar. However, unclear whether personnel and participants were blinded
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "Endoscopic evaluation of the gastric and the duodenal mucosa was performed within 24 hours of admission by an operator who was blinded to the randomisation code and was repeated on day 3, 6 and 10 if the participant was still receiving mechanical ventilation" Comment: Interim gastroscopy was performed if there was fresh blood in the nasogastric aspirate, but the endoscopist was blinded. However, the outcome of interest was objective in nature

Eddleston 1994 (Continued)

Blinking (detection bias) Nosocomial pneumonia	Low risk	Comment: no mention of blinding of radiologists, lab technicians, or physicians. However, pneumonia was diagnosed as per the study definition and due to the objective nature of the outcome
Blinking of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: no clear mention of blinding of outcome assessors. However owing to the objective nature of the outcomes, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All participants randomised were included in the analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes are reported, although unclear on adverse events
Other bias	Low risk	Comment: Source of funding is not clearly mentioned in the trial report. No other sources of bias are suspected

Ephgrave 1998

Methods	Double-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 140 participants</p> <p>Number analysed: 140 participants</p> <p>Antacids</p> <ul style="list-style-type: none"> • Age (years; mean (range)): - • Number of participants (n): 70 • Gender (male/female; n): - <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (range)): - • Number of participants (n): 70 • Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Participants at the Veterans Affairs Medical Center, Iowa City, Iowa, scheduled for major elective surgical procedures requiring postoperative nasogastric intubation <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Participants who did not give informed consent <p>Baseline imbalances: Quote: "The patients who were randomly assigned to receive antacid or sucralfate stress ulcer prophylaxis were similar in most risk factors for postoperative complications but they differed in the percentage of patients with a history of treatment for chronic obstructive pulmonary disease (COPD). Significantly more patients with a clinical diagnosis of COPD preoperatively were randomly assigned to receive sucralfate (COPD was found to be an independent risk factor for development of pneumonia)"</p>

Ephgrave 1998 (Continued)

Comment: Baseline age and gender distributions are not mentioned; however the distribution of all risk factors except COPD is normal across the 2 groups. Most participants from both groups were admitted for general surgery of the abdomen (23 in antacid group and 27 in sucralfate group, respectively)

Interventions	<p>Antacid</p> <ul style="list-style-type: none"> • Dose (total/d): max 180 mL • Duration of treatment (days): "One hundred twenty-two participants received 3 or more days of stress ulcer prophylaxis with the study drugs, while only 25 received 7 or more days" • Route: PO or NG tube (unclear) • Intervention: double-strength antacids (15 mL every 2 hours while in the intensive care unit, every 4 hours after transfer to the surgical ward) + sham sucralfate preparation • Concomitant medications: enteral nutrition in 21%; gastric pH was monitored hourly while patient was in the intensive care unit, and administration of the antacid (or sham antacid) was repeated after 1 hour if pH persisted at < 4.0. Antibiotics (IV; all patients for wound infections). Antibiotic orally + bowel preparation was given to 35% of participants overall <p>Sucralfate</p> <ul style="list-style-type: none"> • Dose (total/d): 4 g • Duration of treatment (days): "One hundred twenty-two participants received 3 or more days of stress ulcer prophylaxis with the study drugs, while only 25 received 7 or more days" • Route: PO or NG tube (unclear) • Intervention: sucralfate suspension (1 g in 10 mL every 6 hours) + sham antacid preparation • Concomitant medications: enteral nutrition in 20%; gastric pH was monitored hourly while patient was in the intensive care unit, and administration of antacid (or sham antacid) was repeated after 1 hour if pH persisted at < 4.0. Antibiotics (IV; all patients for wound infections). Antibiotic orally + bowel preparation was given to 35% of participants overall <p>Adherence to regimen: Quote: "One hundred twenty-two participants received 3 or more days of stress ulcer prophylaxis with the study drugs, while only 25 received 7 or more days. Many patients were treated with intravenous H2-receptor blockers after 3 days postoperatively, which was when the study drugs were generally discontinued"</p> <p>Duration of trial: June 1990 to April 1992</p> <p>Duration of follow-up: Quote: "Daily assessment for gastrointestinal tract bleeding, infections, and other postoperative complications was continued until discharge from the hospital or death for all 140 patients"</p>
Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Incidence of GI bleeding defined as appearance of grossly bloody fluid in the nasogastric aspirate that failed to clear with 100-mL saline lavage • Incidence of pneumonia diagnosed by consensus of 2 investigators not involved with clinical care by means of the following criteria: a new or progressive infiltrate on chest roentgenogram, plus 3 of the following: <ul style="list-style-type: none"> ◦ Purulent sputum with more than 25 white blood cells per high-power field ◦ Isolation of respiratory pathogens from an adequate sputum sample ◦ Peripheral leucocytosis ◦ Temperature > 38.3°C • All-cause mortality in ICU <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • All-cause mortality in hospital • Duration of ICU stay • Duration of intubation • Number of participants requiring blood transfusion

Ephgrave 1998 (Continued)

- Number of units of blood transfused
- Adverse events to interventions

Outcomes reported in trial but not used in review

- Intragastric pH values
- Infections; wound/urinary tract
- Drug effects on microbial appearance and transmission
- Intubation time (only mean number of days, SD not provided)

Notes

Setting: The Surgical Service, Veterans Affairs Medical Center, Iowa City, Iowa

Source of funding: Quote: "This study was funded through a Veterans Affairs Merit Review grant."

Conflicts of interest: -

Ethics approval: Quote: "...approved for human subjects by the appropriate committees of the University of Iowa College of Medicine and the Iowa City Veterans Affairs Medical Center"

Informed consent: Quote: "Patients were contacted before their elective surgical procedures, and less than 10% of the patients asked to participate refused to do so. Patients who declined entry into the study were not monitored further"

Clinical trials registration: -

Sample size calculation: Quote: "A biostatistician calculated that an 80% likelihood of detection of a 50% improvement in the expected postoperative pneumonia rate of 15% to 20% would require entry of more than 300 patients into each arm of the study. With pilot work showing that more than 50% of patients in the surgical intensive care unit harboured pathogens in their gastric contents, we determined that approximately 70 patients in each arm would give an 80% likelihood of detecting an effect by the stress ulcer prophylactic agent on the gastric microbial flora"

Comment: Sample size was calculated for the primary endpoint of pneumonia

Additional notes: Study endpoints of pneumonia and GI bleeding were diagnosed postoperatively. Many participants received H2 antagonists 3 days postoperatively; study drugs were discontinued by then. Pulmonary colonisation with gastric micro-organism occurred in 16% of antacid-treated and 15% of sucralfate-treated participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed in blocks of 20 patients before the study began, to ensure that both treatment groups would be evenly represented throughout the 2 years of patient accrual" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Low risk	Quote: "In keeping with the double-blind design, the treatment group assignment of each patient was known only to the pharmacy service until all the clinical and microbial data collection was complete" Comment: Allocation concealment was done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The sham agents were designed to be similar in colour and viscosity to the active agents, and free of acid-neutralizing properties" Comment: This was a double-blind study in which participants and trial personnel appear to be blinded. Therefore the likelihood of performance bias is low

Ephgrave 1998 (Continued)

Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "The sham agents were designed to be similar in colour and viscosity to the active agents, and free of acid-neutralizing properties" Comment: This was a double-blind study in which participants and trial personnel appear to be blinded. Moreover the outcome of GI bleed was detected as per the definition in the study protocol owing to the objective nature of the outcome
Blinding (detection bias) Nosocomial pneumonia	Low risk	Quote: "Pneumonia was diagnosed by consensus of 2 investigators not involved with the clinical Care"; "The sham agents were designed to be similar in colour and viscosity to the active agents, and free of acid-neutralizing properties" Comment: Blinding of outcome assessors was done. Moreover the outcome of pneumonia was detected as per the definition in the study protocol owing to the objective nature of the outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Quote: "The sham agents were designed to be similar in colour and viscosity to the active agents, and free of acid-neutralizing properties" Comment: Blinding of outcome assessors was done. Moreover because of the objective nature of the outcomes, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were analysed for the outcomes of interest
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes have been reported
Other bias	Low risk	Comment: Funding was through a Veterans Affairs Merit Review grant. The role of the sponsor in the conduct and reporting of the trial is unclear. No other bias was detected

Fabian 1993

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 616 participants</p> <p>Number analysed: 278 participants</p> <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (range)): overall 35 (18 - 78) • Number of participants (n): 206 • Gender (male/female; n): overall 221/66 <p>Cimetidine bolus</p> <ul style="list-style-type: none"> • Age (years; mean (range)): overall 35 (18 - 78) • Number of participants (n): 204 • Gender (male/female; n): overall 221/66 <p>Cimetidine continuous</p>

Fabian 1993 (Continued)

- Age (years; mean (range)): overall 35 (18 - 78)
- Number of participants (n): 206
- Gender (male/female; n): overall 221/66

Inclusion criteria

- Admission to trauma ICU
- Endotracheal intubation at the time of enrolment
- Nasogastric intubation at enrolment
- Age > 18 years

Exclusion criteria

- History of peptic ulcer disease
- Receiving anti-ulcer medications
- Pregnancy

Baseline imbalances: After exclusion, 99 participants received sucralfate, 114 received cimetidine (bolus), and 65 received cimetidine as continuous infusion. Blunt trauma was the most common cause for admission in 72% and penetrating trauma in 28% (86% of these were gunshot wounds; 14% were stab wounds). The APACHE II scores were 14 (5) (mean, SD) for the sucralfate group, 14 (8) (mean, SD) for the cimetidine bolus group, and 13 (6) (mean, SD) for the cimetidine infusion group

Interventions

Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days): ≥ 3 days
- Route: NG tube
- Intervention: 1 g of sucralfate suspended in 20 mL of water given via nasogastric tube or orally every 6 hours (NG tube was clamped for 30 minutes after instillation)
- Concomitant medications: corticosteroids, vasopressors, and antibiotics

Cimetidine bolus

- Dose (total/d): 900 mg
- Duration of treatment (days): ≥ 3 days
- Route: IV
- Intervention: 300 mg of cimetidine every 8 hours via 15-minute IV infusions
- Concomitant medications: corticosteroids, vasopressors, and antibiotics

Cimetidine continuous

- Dose (total/d): 300 mg + 960 mg
- Duration of treatment (days): ≥ 3 days
- Route: IV
- Intervention: 300 mg cimetidine IV as loading dose, followed by continuous infusion at an initial dose of 40 mg/h; if gastric pH < 4, it was increased by 20 mg/h to a maximum of 100 mg/h. If pH was ≥ 7 , the dose was decreased by 20 mg/h to a minimum of 20 mg/h
- Concomitant medications: corticosteroids, vasopressors, and antibiotics

Adherence to regimen: 616 participants were initially randomised to 3 treatment groups. Data on 338 participants were excluded from analysis for the following reasons:

- 177 participants spent less than 48 hours in the ICU (sucralfate: 52, cimetidine bolus: 52, and cimetidine continuous: 73)
- 28 participants were younger than 18 years of age (sucralfate: 9, cimetidine bolus: 7, and cimetidine continuous: 12)
- 8 participants had adverse reactions (cimetidine bolus: 6 and cimetidine continuous: 2)

Fabian 1993 (Continued)

- 125 participants for protocol violations (sucralfate: 46, cimetidine bolus: 25, and cimetidine continuous: 54)

The remaining 278 participants were part of the study until discharge or death

Duration of trial: January 1990 to April 1991

Duration of follow-up: Quote: "Evaluable patients were studied until discharge or death"

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Incidence of stress ulcer bleeding defined as clinically important or overt bleeding. Clinically important GI bleeding was considered present only when blood transfusion was required because of endoscopically diagnosed stress ulcers. Overt bleeding was classified as frank blood or 'coffee ground' material in nasogastric aspirate that cleared with irrigation. The presence of guaiac-positive material was not considered indicative of overt bleeding • Incidence of pneumonia defined as presence of persistent infiltrate on chest roentgenography, presence of purulent tracheal aspirate, isolation of respiratory pathogen on culture, temperature > 38°C, and white blood cell count > 15 × 10³/L <p>Note: Pneumonia developed 5.6 (1.6) (mean, SD) days after injury</p> <ul style="list-style-type: none"> • All-cause mortality in ICU • Duration of ICU stay • Participants requiring blood transfusion • Adverse reactions to Interventions <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • All-cause mortality in hospital • Duration of intubation <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none"> • Bacterial isolates from participants who developed pneumonia
Notes	<p>Setting: Department of Surgery and Clinical Pharmacy, Presley Regional Trauma Centre, University of Tennessee, Memphis</p> <p>Source of funding: Quote: "Supported in part by educational grant from Smith Kline Beecham Inc"</p> <p>Conflicts of interest:</p> <p>Ethics approval: Quote: "The protocol was approved by the Institutional Review Board of The University of Tennessee, Memphis"</p> <p>Informed consent: -</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: Quote: "Power analysis was made using a significance level of 0.5 a power of 0.8 and a two sided alternative hypothesis"</p> <p>Additional notes: In the bacterial isolates of 81 participants, <i>Staphylococcus aureus</i> was the most predominant followed by <i>Haemophilus influenzae</i>. H2 receptor antagonists were combined to form a common interventional arm vs sucralfate, as the review does not aim to investigate</p>
Risk of bias	
Bias	<p>Authors' judgement</p> <p>Support for judgement</p>
Random sequence generation (selection bias)	<p>Low risk</p> <p>Quote: "Patients were randomly assigned to one of the three prophylaxis groups by random number table"</p>

Fabian 1993 (Continued)

		Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial. Moreover, the mode of administration of study drugs would not have permitted blinding
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: GI bleeding was an objective outcome that was diagnosed as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: Pneumonia was an objective outcome that was diagnosed as per the definition in the study protocol
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Yes, around 55% of all participants who were randomised were excluded from the final analysis because of less time spent in the ICU (< 48 hours), adverse reactions, younger than 18 years of age (which was clearly an exclusion criterion), and other protocol violations. Although a per-protocol analysis was done, there appears to be an imbalance between groups with respect to the number of participants available for analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes are clearly mentioned in the study report
Other bias	Low risk	Comment: The study was supported in part by an educational grant from Smith Kline Beecham Inc. The role of the sponsor in the conduct and reporting of the trial is unclear. No other sources of bias are suspected

Fan 2016

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: participants</p> <p>Number analysed: participants</p> <p>Enteral plus parenteral nutrition</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 42.31 (14.18) • Number of participants (n): 40 • Gender (male/female; n): 23/17 <p>Enteral nutrition</p> <ul style="list-style-type: none"> • Age (years, mean (SD)): 40.12 (11.25) • Number of participants (n): 40 • Gender (male/female; n): 18/22

Fan 2016 (Continued)

Parenteral nutrition

- Age (years, mean (SD)): 41.56 (15.10)
- Number of participants (n): 40
- Gender (male/female; n): 21/19

Inclusion criteria

- Glasgow Coma Scale score: 6-8
- Nutritional Risk Screening: ≥ 3

Exclusion criteria

- Use of glucocorticoid and blood products during study
- Haemodynamic instability
- Use of immunosuppressive drug in the past 6 months
- Radiotherapy or chemotherapy in the past 1 year
- Injured more than 12 hours early before admission
- Died within 3 weeks
- Had previous history of metabolic disease such as diabetes mellitus (irritable hyperglycaemia due to injury was exceptional)

Baseline imbalances: There was no significant difference among the 3 groups in terms of age, sex, weight, and serum-albumin at baseline ($P > 0.05$)

Interventions

Enteral plus parenteral nutrition

- Dose (total/day): varies
- Duration of treatment (days): -
- Route: enteral/IV
- Intervention: Increase in dosage to maximum of 1000 mL/d was made gradually over 7 days, with pumping speed not exceeding 50 mL/h. Insufficient energy was supplied by PN. All patients were given energy as 105-126 kJ/kg·d
- Concomitant medications

Enteral nutrition

- Dose (total/d): varies
- Duration of treatment (days): -
- Route: enteral
- Intervention: nasogastric tube accompanied by subsequent suctioning gastric juice and pumping EN (energy density 6.28 kJ/mL, Nutrison Fibre, NUTRICIA, Holland) within 48 hours after admission. An increase in dosage to the maximum (1500 mL/d) was made gradually over 7 days with pumping speed < 75 mL/h. Only normal sodium, glucose, and saline were given as medicamentous dissolvent in the vein. All patients were given energy as 105 to 126 kJ/kg·d
- Concomitant medications: nasogastric tube intubation and central venous catheterisation; supplements such as vitamins, microelement, natrium, and kalium were given according to patients' status; and the headstock was raised to 30 degrees to avoid the counterflow conventionally if necessary

Parenteral nutrition

- Dose (total/d): varies
- Duration of treatment (days): -
- Route: IV
- Intervention: fully parenteral alimentation through central venous catheter within 48 hours after admission. PN was prepared by Intravenous drug dispensing centre with ratio of 2:1 for carbohydrates to lipids, and ratio of 100:1 for calorie nitrogen ratio. All patients were given energy as 105 to 126 kJ/kg·d

Fan 2016 (Continued)

- Concomitant medications: nasogastric tube intubation and central venous catheterisation; supplements such as vitamins, microelement, natrium, and kalium were given according to patients' status; and the headstock was raised to 30 degrees to avoid the counterflow conventionally if necessary

Adherence to regimen: -

Duration of trial: January 2009 to May 2012

Duration of follow-up: -

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none">• Incidence of clinically important GI bleeding• Incidence of VAP• Duration of ICU stay• Duration of intubation• All-cause mortality in hospital• Adverse events of interventions <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none">• All-cause mortality in ICU• Blood transfusions <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none">• T lymphocyte subsets• Plasma levels of IgA, IgM• Serum total protein• Albumin• Prealbumin and haemoglobin• Intracranial infection• Pyaemia	
Notes	<p>Setting: Neurological Intensive Care Unit</p> <p>Source of funding: Natural Science Foundation of Shandong Province (Y2008C35) and Technology Supporting Program of Qingdao (12-1-3-5-(1)-nsh)</p> <p>Conflicts of interest: -</p> <p>Ethics approval: This study had been approved by the local institutional review board and the Human Ethics Committee of the Affiliated Hospital of Qingdao University</p> <p>Informed consent: Informed consent had been provided by patients’ guardians</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: -</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	<p>Quote: "patients were assigned to EN group, PN group and EN+PN groups randomly according to the sequence of their assigned hospital record number"</p> <p>Comment: method of randomisation not adequate</p>

Fan 2016 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: no information reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information about blinding reported
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: No definition of criteria was used to diagnose upper GI bleeding as reported
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: No definition of criteria was used to diagnose nosocomial pneumonia was reported
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: no information reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to allow judgement; once 120 patients were enrolled, but no information on how many patients fitted eligibility criteria
Selective reporting (reporting bias)	Low risk	Comment: All outcomes listed in the Methods section are also reported in the Results section
Other bias	Low risk	Comment: no other sources of bias suspected

Fang 2014

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 120</p> <p>Number analysed: 120</p> <p>Early onset drug treatment</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 47.62 (5.33) • Number of participants (n): 40 • Gender (male/female; n): 27/13 <p>Late onset drug treatment</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 46.57 (5.71) • Number of participants (n): 40 • Gender (male/female; n): 26/14 <p>Enteral nutrition</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 47.08 (5.26) • Number of participants (n): 40 • Gender (male/female; n): 28/12

Fang 2014 (Continued)

Inclusion criteria:

- Open craniocerebral injury
- Brain contusion
- Skull fracture
- Subarachnoid haemorrhage
- Diffuse axonal injury
- Glasgow Coma Scale score 3 to 8

Exclusion criteria

- Peptic ulcer disease before admission
- Gastrointestinal ulcer before admission
- Coagulopathy or other severe comorbidity

Baseline imbalances: no baseline difference in sex, age, BMI, and causes of brain injury

Interventions

Early-onset drug treatment

- Dose (total/d):
- Duration of treatment (days):
- Route: IV or PO
- Intervention: omeprazole (80 mg/d) or lansoprazole (60 mg/d), plus sucralfate (4 g/d), starting 12 to 24 hours after admission
- Concomitant medications

Late-onset drug treatment

- Dose (total/d):
- Duration of treatment (days):
- Route: IV or PO
- Intervention: omeprazole (80 mg/d) or lansoprazole (60 mg/d), plus sucralfate (4 g/d), starting 48 to 72 hours after admission
- Concomitant medications

Enteral nutrition

- Dose (total/d):
- Duration of treatment (days):
- Route: IV or NG tube
- Intervention: IV nutrition (within 24 hours of admission) and early enteral nutrition (12 to 24 hours after admission), no drug treatment
- Concomitant medications: -

Adherence to regimen: -

Duration of follow-up: -

Duration of trial: May 2011 to May 2013

Outcomes

Outcomes sought in review and reported in trial

- Clinically important GI bleeding

Outcomes sought in review and not reported in trial

- Ventilator-associated pneumonia
- Duration of ICU stay
- All-cause mortality
- Duration of intubation

Fang 2014 (Continued)

- Participants requiring blood transfusion
- Units blood transfused
- Adverse events of interventions

Outcomes reported in trial, but not used in review

- Gastric pH after treatment
- Peptic ulcer healing time

Notes	<p>Setting: Department of Nursing, First People's Hospital of Yunnan Province, Kunming, Yunnan Province, China</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: -</p> <p>Informed consent: -</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: randomisation by random number tables
Allocation concealment (selection bias)	Unclear risk	Comment: no information reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information reported
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: no definition of criteria used to diagnose upper GI bleeding as reported
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: no information reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All participants were observed and analysed after intervention
Selective reporting (reporting bias)	Low risk	Comment: All observed results were reported, including stress ulcer bleeding rate in group A; the correlation between gastric pH and ulcer healing time in group A; incidence of stress ulcer bleeding rate by different gastric pH and different blood sugar level in group C; clinical therapeutic effects

Fang 2014 (Continued)

Other bias	Low risk	Comment: no other sources of bias suspected
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Fink 2003

Methods	Open-label randomised controlled trial
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Participants
Baseline characteristics

Number randomised: not clearly mentioned in study abstract

Number analysed: 189 participants

Overall

- Age (years; mean (range)): -
- Number of participants (n): 152
- Gender (male/female; n): -

Inclusion criteria

Study design, inclusion and exclusion criteria similar to [Martin 1993](#)

- Signed consent from patient or legal guardian before randomisation
- Male
- Not lactating, not pregnant women
- Age ≥ 16 years
- Nasogastric tube in place
- Admitted to ICU for minimum anticipated period of 36 hours
- At least 1 of the following risk factors for upper GI haemorrhage
 - Major surgery
 - Multiple trauma to head, neck, abdomen, solid organs, or limbs
 - Hypotension
 - Hypovolumic shock
 - Sepsis (including peritonitis)
 - Confirmed bacteraemia
 - Complex fever
 - Increased WBC count
 - Bacteriologically determined source of infection
 - Acute respiratory failure
- Need for assisted mechanical ventilation
- Severe hypoxia (oxygen deficit (FiO₂ OF 0.31 by mask or ≥ 2 L/min by nasal prongs)
- Acute hypoventilation
- Burns involving $\geq 30\%$ of body surface area
- Jaundice (plasma bilirubin (> 30 mg/dL)

Exclusion criteria

- > 24 hours has elapsed since they have become eligible for enrolment into the study
- Patients intubated for longer than 24 hours
- ICU admission following gastric, oesophageal, or duodenal surgery
- Patients with a history of gastrectomy or upper GI lesions that are likely to bleed
- Patients on H₂ receptor antagonists within 12 hours of admission into the study, or patients receiving omeprazole, anticoagulants (except low-dose heparin), aspirin, or NSAIDs within 24 hours before admission

Fink 2003 (Continued)

- Treatment with investigational drug within last 30 days
- Presence of blood in either of the 2 gastric aspirates that were taken 30 minutes apart during screening of potential participants

Baseline imbalances: not clearly mentioned in study abstract

Interventions

Pantoprazole

- Dose (total/d): 40 mg
- Duration of treatment (days): -
- Route: -
- Intervention: pantoprazole IV 40 m QD
- Concomitant medications: -

Pantoprazole

- Dose (total/d): 80 mg
- Duration of treatment (days): -
- Route: -
- Intervention: pantoprazole IV 40 mg bid
- Concomitant medications: -

Pantoprazole

- Dose (total/d): 80 mg
- Duration of treatment (days): -
- Route: -
- Intervention: pantoprazole IV 80 mg QD
- Concomitant medications: -

Pantoprazole

- Dose (total/day): 160 mg
- Duration of treatment (days): -
- Route: -
- Intervention: Pantaprazole IV 80mg bid
- Concomitant medications: -

Cimetidine

- Dose (total/d): 15,000 mg
- Duration of treatment (days): -
- Route: -
- Intervention: cimetidine; 300 mg + 50 mg per hour
- Concomitant medications: -

Adherence to regimen: -

Duration of trial: -

Duration of follow-up: -

Outcomes

Outcomes sought in review and reported in trial

- Incidence of upper GI haemorrhage
- All-cause mortality in ICU

Outcomes sought but not reported in trial report

- Incidence of ventilator-associated pneumonia

Fink 2003 (Continued)

- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Participants requiring blood transfusion
- Units of blood transfused
- Adverse events of interventions

Outcomes reported in report but not used in review

- Mean APS II scores in participants who died and in those who survived

Notes

Setting: -

Adherence to regimen: -

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Additional notes: Quote: "Overall patients with a mean APSII score of 16.8 or greater tended to die while those with 15.33 or less, tended to survive"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in study abstract
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in study abstract
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: unblinded, open trial
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unblinded, open trial. The definition for detecting GI bleeding is not clearly mentioned in the study abstract. However, GI bleeding was an objective outcome
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unblinded, open trial. However owing to the objective nature of the outcomes of interest, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "189 patients received at least 1 dose of medication and had sufficient data points to be included in the analysis"

Fink 2003 (Continued)

		Comment: unclear on how many were randomised initially to the different arms. Therefore, unclear on attrition bias
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes appear to be reported
Other bias	Low risk	Comment: Source of funding remains unclear. No other sources of bias are suspected

Fogas 2013

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 94 participants</p> <p>Number analysed: 79 participants</p> <p>Proton pump inhibitors</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 67 (56-77) • Number of participants at baseline (n): 38 • Gender (male/female; n): 23/15 <p>H2 receptor antagonists</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 72 (58-79) • Number of participants at baseline (n): 41 • Gender (male/female; n): 25/16 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Mechanically ventilated for longer than 48 hours <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Admission diagnosis of pneumonia or other acute inflammatory pulmonary disease • Severe sepsis/septic shock • Regular use of proton pump inhibitors or H2 receptor antagonists <p>Baseline imbalances: no significant difference ($P > 0.05$) between groups regarding demographics</p>
Interventions	<p>Proton pump inhibitors</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days): - • Route: - • Concomitant medications: - • Intervention: - <p>H2 receptor antagonists</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days): - • Route: - • Concomitant medications: - • Intervention: -

Fogas 2013 (Continued)

Adherence to treatment: -

Duration of follow-up: -

Duration of trial: -

Outcomes	<p>Outcomes reported in trial and used in review</p> <ul style="list-style-type: none">• Clinically important upper GI bleeding• VAP diagnosed by leucocytosis, increased PCT level, fever, purulent tracheal secretion, positive microbiological result of tracheal sample, and new/increased infiltrate on chest X-ray <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none">• Mortality• Duration of ICU stay• Duration of intubation• Blood transfusion• Adverse events of interventions <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none">• Nil
Notes	<p>Setting: General ICU, University of Szeged, Hungary</p> <p>Sponsorship source: -</p> <p>Conflicts of interest: -</p> <p>Comments: conference abstract</p> <p>Ethics approval: Quote: "After ethics committee approval ..."</p> <p>Informed consent: -</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: Quote: "However, the completion of the study on the planned 198 patients is required to come to the final conclusions"</p>
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Unclear risk Comment: no details reported
Allocation concealment (selection bias)	Unclear risk Comment: no details reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk Comment: no details reported, but lack of blinding unlikely to introduce bias to the outcome and outcome measures
Blinding (detection bias) Clinically important upper GI bleeding	High risk Comment: no details reported, and no diagnostic criteria described

Fogas 2013 (Continued)

Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: Pneumonia was an objective outcome that was diagnosed as per the definition in the study protocol
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: no details reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no incomplete reporting of outcome data. Patient flow was reported transparently; attrition was unlikely to have introduced bias to the results
Selective reporting (reporting bias)	Low risk	Comment: All outcomes listed are reported in the Results section. Conference abstract
Other bias	Unclear risk	Comment: no other sources of bias suspected, but not enough details reported in conference abstract

Friedman 1982

Methods	Double-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 36 participants</p> <p>Number analysed: 36 participants</p> <p>Placebo</p> <ul style="list-style-type: none"> • Age (years; mean (range)): - • Number of participants (n): 14 • Gender (male/female; n): - <p>Antacids (Mylanta)</p> <ul style="list-style-type: none"> • Age (years; mean (range)): - • Number of participants (n): 11 • Gender (male/female; n): - <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (range)): - • Number of participants (n): 11 • Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admitted on the medical services of the University of West Virginia Hospital • Receiving mechanical ventilation for less than 12 hours <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Participants with renal insufficiency (creatinine > 3 mg/dL) • Active GI bleeding at the time of initiation of ventilatory support • Receiving antacids and or cimetidine immediately before ventilation • Pregnancy • Participants or their immediate family members from whom informed consent was not obtained

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

Friedman 1982 (Continued)

Baseline imbalances: The 3 groups were comparable except for a significantly higher number of participants with chronic obstructive pulmonary disease in the antacid group as compared with the control group. They were also similar with respect to the mean number of risk factors per individual in any of the groups

Interventions	<p>Placebo</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days): until a patient developed GI bleeding, was weaned from ventilator, or died • Route: IV • Intervention: placebo cimetidine IV every 6 hours and placebo antacids, 30 mL per nasogastric tube every 1 hour • Concomitant medications <p>Antacid</p> <ul style="list-style-type: none"> • Dose (total/d): 120 mL • Duration of treatment (days): until a patient developed GI bleeding, was weaned from ventilator, or died • Route: IV • Intervention: received antacids (Mylanta II), 30 mL per nasogastric tube, and placebo cimetidine IV every 6 hours. Alternagel was administered instead of Mylanta II to participants who developed severe diarrhoea • Concomitant medications <p>Cimetidine</p> <ul style="list-style-type: none"> • Dose (total/d): 1200 mg • Duration of treatment (days): until a patient developed GI bleeding, was weaned from ventilator, or died • Route: IV • Intervention: 300 mg cimetidine IV q 6 hours and placebo antacids, 30 mL per nasogastric tube q 1 hour • Concomitant medications <p>Adherence to regimen: 6 participants were unable to complete the protocol: 5 from the antacid group (4 had severe diarrhoea, and 1 had severe hypophosphataemia and hypomagnesaemia) and 1 from the control group (severe diarrhoea). However, intention to treat was performed by study authors</p> <p>Duration of trial: December 1978 to May 1980</p> <p>Duration of follow-up: not clearly mentioned in the study report. Probably until death or discharge</p>
Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Clinically important upper GI bleeding <ul style="list-style-type: none"> ◦ Overt bleeding: fresh or old blood in the nasogastric aspirate that failed to clear with lavage in 15 minutes or melena ◦ Occult bleeding: a drop in haematocrit ≥ 5 points, associated with positive tests for stool occult blood for 3 consecutive days without obvious non-upper GI bleeding <p>Note: Only data on overt bleeding were extracted, as they were considered to be clinically significant</p> <ul style="list-style-type: none"> • Adverse events of interventions <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • VAP • All-cause mortality in ICU • All-cause mortality in hospital

Friedman 1982 (Continued)

- Duration of ICU stay
- Number of participants requiring blood transfusion

Outcomes reported in trial but not used in review

- Duration of ventilation among different treatment groups (SD not provided)
- Number of units of blood transfused (SD not provided)

Notes	<p>Setting: Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA 22908</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The protocol was approved by the Human Investigation Committee of the University of Virginia in February 1978"</p> <p>Informed consent: Quote: "Informed consent was obtained from the patients or from a member of their immediate family"</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: According to the study report, no participant died of haemorrhage and overt bleeding ceased when participants were administered cimetidine and antacids</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	<p>Quote: "If a participant developed severe diarrhoea, an independent referee broke the treatment code and substituted alternagel in those participants receiving Mylanta II"</p> <p>Comment: Study must have had some sort of allocation concealment to make the above statement materialise. However, method used for allocation concealment is not clear</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "If a participant developed severe diarrhoea, an independent referee broke the treatment code and substituted Alternagel in those participants receiving Mylanta II and the investigators were not informed of the outcomes of the referees intervention"</p> <p>Comment: Investigators might have been blinded in the rest of the study too because this was a placebo-controlled trial; each treatment arm (with the actual intervention) received a placebo form of the other drug (with which it was being compared) and vice versa</p>
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: This was a placebo-controlled trial; each treatment arm (with the actual intervention) received a placebo form of the other drug (with which it was being compared) and vice versa. Moreover, this was an objective outcome detected as per the definition provided in the study
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias)	Low risk	Comment: This was a placebo-controlled trial; each treatment arm (with the actual intervention) received a placebo form of the other drug (with which it

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

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Friedman 1982 (Continued)

Adverse reactions of interventions		was being compared) and vice versa. Moreover, owing to the objective nature of the outcome of interest, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were accounted for in the analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: unclear on source of funding. No other form of bias detected

Groll 1986

Methods	Double-blind randomised placebo-controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: unclear on how many were initially randomised. Study report mentions that 531 participants were eligible for the trial, of whom 221 participants completed the trial with reasons for excluding of the remaining participants</p> <p>Number analysed: 221 participants</p> <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 58(16-90) • Number of participants (n): 114 • Gender (male/female; n): 75/39 <p>Placebo</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 57 (15-88) • Number of participants (n): 107 • Gender (male/female; n): 68/39 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admitted to Kingston General Hospital medical-surgical ICU <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Participants who had bleeding on admission to the ICU • Pregnancy • Renal failure requiring haemodialysis or peritoneal dialysis • Drug overdosage • Acute myocardial infarction • Use of antacids • Stay in the unit was less than 24hours • Inability to obtain early consent • Refusal to enter the study • Death within the first 24 hours • Accidental omission by house staff • Miscellaneous reasons <p>Baseline imbalances: Quote: "The drug and placebo groups were similar for demographic features and risk factors. The number of patients with each risk factor known to predispose to stress ulceration</p>

Groll 1986 (Continued)

and the mean number of risk factors per patient were similar in both groups such as minor operative procedure, respiratory failure, renal failure, sepsis, shock, trauma, coma and liver failure"

Interventions
Cimetidine

- Dose (total/d): 1200 mg
- Duration of treatment (days, mean (range)): 3.8 (1-23 days)
- Route: IV
- Intervention: 300 mg in 20 mL normal saline given intravenously every 6 hours
- Concomitant medications: -

Placebo

- Dose (total/d): -
- Duration of treatment (days, mean (range)): 3.6 (1-20 days)
- Route: IV
- Intervention: prepared in an identical manner to cimetidine, given intravenously every 6 hours
- Concomitant medications

Adherence to regimen: Quote: "Of the remaining 531 eligible patients 221 completed the trial (41%). The remainder were excluded because of inability to obtain early consent (n = 69), refusal to enter the study (n = 83), death within the first 24 hours (n = 48), accidental omission by house staff (n = 86), and miscellaneous reasons (n = 24)"

Comment: not sure when randomisation took place and exact numbers of participants who were initially randomised

Duration of trial: 21 months

Duration of follow-up: not clearly mentioned in the study report. Probably until death or discharge

Outcomes
Outcomes sought in review and reported in trial

- Clinically important upper GI bleeding diagnosed as
 - Frank haematemesis or gastric aspirate of > 50 mL fresh blood
 - Malaena or fresh blood per rectum with an upper source of haemorrhage verified by endoscopy if the gastric aspirate was clear
 - A fall in haemoglobin level > 2 g/dL in a 24-hour period associated with either 4+ occult blood in the stools or 'coffee ground' gastric drainage of at least 100 mL. Upper gastrointestinal endoscopy was not a prerequisite for entry into the study, as its routine use was considered unwarranted in critically ill patients

Note: Data were not provided separately for overt and occult bleeds. Of the 70% of participants who were in the study for 1 to 3 days, 9 of the 11 placebo and 5 of the 6 cimetidine participants bled

- All-cause mortality in ICU

Outcomes sought but not reported in trial

- VAP
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of Intubation
- Participants requiring blood transfusion
- Adverse events of interventions

Outcomes reported in report but not used in review

- Volumes of packed cells administered (mean and ranges provided)
- Intragastric pH status

Groll 1986 (Continued)

- Gastric colonisation

Notes	Setting: Kingston General Hospital, Ontario, Canada	
	Source of funding: Quote: "This project was supported by Smith Kline and French Canada Ltd"	
	Conflicts of interest: -	
	Ethics approval: Quote: "The study was approved by the Institutional Review Board and Grant agency at the Misnistry of Healthof Chez Republic"	
	Informed consent: Quote: "The study was approved by the committee on human research, Depart-ment of Medicine, Queen's University"	
	Clinical trials registration: -	
	Sample size calculation: -	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Quote: "Patients were randomised in a double blind method to receive injec- tions of either cimetidine 300 mg in 20 mL normal saline or placebo prepared in an identical manner, given intravenously every 6 hours" Comment: This was a placebo-controlled trial, and participants and personnel were blinded
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "Patients were randomised in a double blind method to receive injec- tions of either cimetidine 300 mg in 20 mL normal saline or placebo prepared in an identical manner, given intravenously every 6 hours" Comment: This was a placebo-controlled trial, and GI bleeding was detected as per the definition in the study owing to the objective nature of the outcome of interest
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome as- sessment (detection bias) Adverse reactions of inter- ventions	Low risk	Comment: This was a placebo-controlled trial, and participants and personnel were blinded. Moreover owing to the objective nature of the outcomes of in- terest, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of the remaining 531 eligible patients 221 completed the trial (41%). The remainder were excluded because of inability to obtain early consent (n = 69), refusal to enter the study (n = 83), death within the first 24 hours (n = 48), accidental omission by house staff (n = 86), and miscellaneous reasons (n = 24)" Comment: not sure when randomisation took place and exact numbers of par- ticipants who were initially randomised. Therefore unclear on attrition bias

Groll 1986 (Continued)

Selective reporting (re-reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: This project was supported by Smith Kline and French Canada Ltd. The role of the sponsor in the conduct and reporting of the trial is unclear. No other sources of bias suspected

Halloran 1980

Methods	Double-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 50 participants</p> <p>Number analysed: 50 participants</p> <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 29.6 (15 - 54) • Number of participants (n): 26 • Gender (male/female; n): 23/3 <p>Placebo</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 30.6 (8-62) • Number of participants (n): 24 • Gender (male/female; n): 18/6 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Severe head injury • Hospitalised within 12 hours of injury • Managed in an ICU according to a uniform diagnostic and therapeutic protocol. • Minimal neurologic criterion for entry into this study: inability of the patient to obey simple commands after closed head injury <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Apnoeic patients with fixed dilated pupils and no motor response to painful stimuli on arrival • Peptic ulcer disease • Pregnancy • Concomitant injury of the upper gastrointestinal tract • Severe hepatic or renal disease <p>Baseline imbalances: Both groups were comparable with respect to age, gender, and underlying disorders</p>
Interventions	<p>Cimetidine</p> <ul style="list-style-type: none"> • Dose (total/d): 1800 mg • Duration of treatment (days): 3 weeks • Route: IV • Intervention: 300 mg of cimetidine, given as an intravenous bolus dose every 4 hours • Concomitant medications: oral preparation administered when tube feeding or a diet was started; gastric secretions were drained by nasogastric intubation. Steroids were administered to each partic-

Halloran 1980 (Continued)

ipant (dexamethazone or methylprednisolone) along with prophylactic anticonvulsant therapy and muscle relaxants

Placebo

- Dose (total/d): -
- Duration of treatment (days): 3 weeks
- Route: IV
- Intervention: intravenous bolus dose every 4 hours after patient was resuscitated and baseline studies were completed
- Concomitant medications: oral preparation administered when tube feeding or a diet was started, and gastric secretions were drained by nasogastric intubation. Steroids were administered to each participant (dexamethazone or methylprednisolone) along with prophylactic anticonvulsant therapy and muscle relaxants

Adherence to regimen: no dropouts mentioned

Duration of trial: July 1977 to March 1979

Duration of follow-up: -

Outcomes	<p>Outcomes sought in review and reported in trial</p> <p>Primary outcomes</p> <ul style="list-style-type: none"> • Incidence of GI bleeding defined by bright red blood or a 4+ positive guaiac in the gastric aspirate for 3 consecutive 8-hour periods if no oropharyngeal source of bleeding was present <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Number of participants requiring blood transfusion • Number of units of blood transfused • Adverse reactions of interventions (no adverse events reported) <p>Outcomes sought but not reported in trial report</p> <ul style="list-style-type: none"> • Incidence of ventilator-associated pneumonia • All-cause mortality in hospital • Duration of ICU stay • All-cause mortality in ICU • Duration of intubation <p>Outcomes reported in report but not used in review</p> <ul style="list-style-type: none"> • None
Notes	<p>Setting: Departments of Medicine and Surgery, Medical College, Virginia, USA</p> <p>Source of funding: Quote: "The work was supported by Smith Kline and French Laboratories. clearly mentioned in the study report"</p> <p>Ethics approval: Quote: "The study was approved by the committee on the conduct of clinical research. Medical College of Virginia, Virginia commonwealth university"</p> <p>Informed consent: Quote: "Informed consent was obtained from the patients closest relative or legal agent and later from the patient if sufficient neurologic recovery ensued"</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p>

Risk of bias

Halloran 1980 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly given coded medication in a standard double blind fashion" Comment: Allocation concealment might have been done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients were randomly given coded medication in a standard double blind fashion" Comment: This was a placebo-controlled double-blind trial, so study personnel would have been blinded
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: not clearly mentioned, but this was a placebo-controlled double-blind trial, and GI bleeding was an objective outcome that was detected as per the study definition
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: not clearly mentioned, but this was a placebo-controlled double-blind trial, and outcomes of interest were objective in nature and were detected as per the study definition
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All outcomes stated were reported in the Results
Other bias	Low risk	Quote: "The work was supported by Smith Kline and French Laboratories" Comment: The role of the sponsor in the conduct and reporting of the trial is unclear. No other source of bias is suspected

Hanisch 1998

Methods	Double-blind randomised controlled trial
Participants	Baseline characteristics Number randomised: 827 participants Number analysed: 158 participants Ranitidine <ul style="list-style-type: none"> Age (years; mean (range)): 55 (22 - 88) Number of participants (n): 57 Gender (male/female; n): - Pirenzepine

Hanisch 1998 (Continued)

- Age (years; mean (range)): 53 (18 - 86)
- Number of participants (n): 44
- Gender (male/female; n): -

Placebo

- Age (years; mean (range)): 58 (22 - 88)
- Number of participants (n): 57
- Gender (male/female; n): -

Notes: Age not given for all randomised participants, but only for those who were in mechanical ventilation for longer than 48 hours

Inclusion criteria

- All adult patients referred to ICU of the surgical department of John Wolfgang Goethe University, Frankfurt

Exclusion criteria

- Patients with active peptic ulcer disease and concomitant ulcer medications
- Existing upper GI bleeding
- Age < 18 years
- 4.transplanted patients (kidney, liver, heart)
- Pre-existing pneumonia and gastric resection

Baseline imbalances: Groups were similar with respect to age and APACHE II score

Interventions

Ranitidine

- Dose (total/d): 150 mg
- Duration of treatment (days): -
- Route: IV
- Intervention: sostril: 3 × 50 mg IV
- Concomitant medications

Pirenzepine

- Dose (total/d): 30 mg
- Duration of treatment (days): -
- Route: IV
- Intervention: gastrozepin: 3 × 10 mg IV
- Concomitant medications

Placebo

- Dose (total/d): -
- Duration of treatment (days): -
- Route: IV
- Intervention: placebo
- Concomitant medications: -

Adherence to regimen: All 827 randomised patients completed the trial. However, only 158 participants who were on mechanical ventilation for ≥ 48 hours were part of the analysis, as the primary outcome was pneumonia rate

Duration of trial: December 1991 to December 1992

Duration of follow-up: not clearly mentioned in the study report. Probably until death or discharge

Hanisch 1998 (Continued)

Outcomes

Outcomes sought in review and reported in trial

Primary outcome

- Incidence of pneumonia in patients under mechanical ventilation ≥ 48 hours (defined according to Daschner as "radiological signs of pneumonia and purulent tracheal secretion or positive microbiological findings in tracheal aspiration and temperature $> 38^{\circ}\text{C}$ and leucocytosis $> 10,000 \text{ mm}^3$ ")

Secondary outcomes

- Incidence of clinically relevant stress bleeding: defined as bright red blood via gastric tube or melena combined with haemodynamic changes (systolic blood pressure $< 100 \text{ mmHg}$, tachycardia > 100 beats per minute) and requirement of blood transfusion (fall in haemoglobin $> 2 \text{ g/dL}$ within 24 hours) and endoscopic identification of bleeding site and activity
- All-cause mortality in ICU
- Duration of ICU stay (standard deviation not reported)
- Duration of mechanical ventilation (standard deviation not reported)
- Participants requiring blood transfusion
- Units of blood transfused (mean and SD not reported)

Outcomes sought but not reported in trial report

- All-cause mortality in hospital
- Adverse events of interventions

Outcomes reported in report but not used in review

- Duration of Intubation (standard deviation not reported)
- Duration of ICU stay (standard deviation not reported)

Notes

Setting: Department of Surgery, Division of General and Trauma Surgery, Johann Wolfgang Goethe University, Frankfurt am Main, Germany

Source of funding: -

Conflicts of interest: -

Ethics approval: approved by the Ethics Committee of Johann Wolfgang Goethe University, Frankfurt/Main

Informed consent: -

Clinical trials registration: -

Sample size calculation: Quote: "Assuming a pneumonia rate of 25% in ranitidine treated patients and a pneumonia rate of 15% in placebo treated patients, the complete sample size was calculated to be at least 100 patients ($\alpha = 0.05$ and $\beta = 0.20$)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A complete and balanced randomisation schedule was generated by the institute of biomathematics of the university of Frankfurt" Comment: method adopted to obtain random sequence generation clearly mentioned in the study report
Allocation concealment (selection bias)	Low risk	Quote: "At the time of entering the ICU patients were assigned to a consecutive study number, the application of a blinded drug regimen was started"

Hanisch 1998 (Continued)

		<p>"...the drugs were prepared in advance by a staff who were not involved in the treatment of patients and identified by the above mentioned consecutive study number i.e. the code was located exclusively with this group during the trial"</p> <p>Comment: Randomisation code was used exclusively with staff who were not involved in the treatment of patients, and these staff were responsible for preparing the 3 interventions through a similar mechanism (dissolving each in 100 mL of 5% glucose) to avoid detection during treatment</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "Blinding of drugs (placebo, ranitidine, pirenzepine) was achieved by dissolving them in glucose (100 mL; 5% Braun, Melsungen, Germany) resulting in an equal infusion volume for each patient. Drugs were prepared by staff who were not involved in the treatment of patients and identified by the above mentioned consecutive study number"; "All blinded drugs (only identifiable by their consecutive study number) were given to the patients by a staff nurse in the ICU"</p> <p>Comment: This was a placebo-controlled nature of the study design in which the 3 interventions were prepared in a similar manner (dissolving each in 100 mL of 5% glucose) to ensure adequate blinding because of which the details of interventions received were not known. Participants and personnel were blinded, ensuring no performance bias</p>
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	<p>Quote: "Data documentation for each patient was performed prospectively and daily by a different staff not involved in the treatment of patients in the randomised assignment of the drugs"</p> <p>Comment: not clear whether they were involved in outcome assessment. Moreover, GI bleeding was detected as per the definition in the study protocol and was an objective outcome</p>
Blinding (detection bias) Nosocomial pneumonia	Low risk	<p>Quote: "Data documentation for each patient was performed prospectively and daily by a different staff not involved in the treatment of patients in the randomised assignment of the drugs"</p> <p>Comment: not clear whether they were involved in outcome assessment. Moreover, pneumonia was detected as per the definition in the study protocol and was an objective outcome</p>
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	<p>Quote: "Data documentation for each patient was performed prospectively and daily by a different staff not involved in the treatment of patients in the randomised assignment of the drugs"</p> <p>Comment: not clear whether they were involved in outcome assessment. However, outcomes of interest were objective in nature</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Comment: 741 patients randomised, but only 158 completed 48 hours of mechanical ventilation and were reported in the trial</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: Data on all randomised participants were not included in the results. Only outcomes for participants who were on mechanical ventilation for longer than 48 hours are reported. Of 827 randomised patients, a total of 158 were mechanically ventilated for ≥ 48 hours. Data on the remaining 669 patients were not available. However, this does not account for reporting bias, as the study intended to report its primary outcome of pneumonia only for participants who completed ≥ 48 hours on mechanical ventilation. All intended outcomes were reported only for participants who spent ≥ 48 hours in the ICU</p>

Hanisch 1998 (Continued)

Other bias	Low risk	Comment: unclear on the source of funding. No other sources of bias suspected
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Hastings 1978

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 100 participants</p> <p>Number analysed: 100 participants</p> <p>Antacids</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 60.7 • Number of participants (n): 51 • Gender (male/female; n): 31/20 <p>No prophylaxis</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 62.3 • Number of participants (n): 49 • Gender (male/female; n): 20/29 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Informed consent given by the physician and a relative or themselves • Hospitalised in the Respiratory-Surgical Intensive Care Unit of the Beth Israel Hospital during the study period • Diagnosed with multiple trauma, major operative procedures, respiratory failure, vital capacity < 10 mL/kg, ratio of dead space to tidal volume > 0.6 or alveolar hypoventilation with arterial pH < 7.25, hypotension (defined as systolic pressure < 100 mmHg for longer than 2 hours before and after randomisation), sepsis (including participants with peritonitis, proved bacteraemia or the complex of fever, elevated white cell count, and hypotension with proved bacteriologic source), jaundice, and renal failure <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Receiving fluids or food by mouth • Having undergone gastric, cardiac, or oesophageal operations • Primary disease was burn trauma or neurological disease • Evidence of gross upper GI bleeding <p>Baseline imbalances: Quote: "Fifty one of the 100 participants entered into the study were randomised to receive antacid prophylaxis. Six major risk factors were analysed for each participant in each group. These risk factors were respiratory failure, extra abdominal sepsis, peritonitis, jaundice, renal failure and hypotension. There were 110 risk factors in 51 participants in the antacid group, a mean of 2.2 risk factors per participant. There were 115 risk factors in 49 participants in the group not receiving antacid prophylaxis, a mean of 2.4 risk factors per participant. All participants in respiratory failure were treated with constant-volume ventilators. The severity of respiratory failure was judged by the alveolar-atrial oxygen. The mean highest value was 363+/- 25 mm Hg (SEM) in the participants receiving antacid and 324+/- 29 mm Hg in those not receiving Antacid prophylaxis ($p > 0.05$). The difference in mean blood urea nitrogen values (96+/- 10 mm/dl in the Antacid group vs. 90+/- 10 mm Hg in those not receiving antacid prophylaxis) was not statistically significant between the two groups. The extent of jaundice was also similar in the two groups"</p>

Hastings 1978 (Continued)

Comment: Both groups were similar with respect to their baseline characteristics. The major risk factor was respiratory failure

Interventions
Antacids

- Dose (total/d): 720 mL
- Duration of treatment (days): 2.6
- Route: IV
- Intervention: Mylanta II in 46 participants and aluminium hydroxide in 5 participants: 30 mL at the beginning, at the end of each hour. 30 mL of antacids was instilled at the beginning of each subsequent hour, provided gastric pH was ≥ 3.5 . If pH < 3.5 , 60 mL of antacid was instilled. The nasogastric tube was flushed with 10 mL of tap water after each instillation, to ensure complete delivery. Then the tube was clamped for 60 minutes
- Concomitant medications

No prophylaxis

- Dose (total/d): -
- Duration of treatment (days): 3.1
- Route: IV
- Intervention: -
- Concomitant medications: -

Adherence to regimen: Quote: "The study was ended when oral feedings were begun and the nasogastric tube was removed, or the participant was discharged from the intensive care unit"

Comment: In 2 participant who had diarrhoea, antacid was stopped, and in 2 other participants, a different antacid was administered. In 1 participant from antacid group with elevated magnesium levels, antacid was changed to a preparation that did not contain magnesium

Duration of trial: March 1972 to March 1977

Notes duration of treatment: Mean duration for the entire study of 100 participants was 2.9 ± 0.29 days (SEM). Study was terminated when oral feedings were begun and the nasogastric tube was removed, or when the participant was discharged from the ICU

Duration of follow-up: -

Outcomes
Outcomes sought in review and reported in trial

Primary outcome

(outcomes are not categorised as primary and secondary, but from the study report we feel GI Bleeding was the primary outcome)

- Incidence of acute GI bleeding. Gastric aspirate was checked for frank or occult blood every 4 hours with the bench guaiac test or the haemoccult paper test. Any participant who had frank blood in his aspirate or had a 4+ positive guaiac test or a uniformly dark blue reaction with the haemoccult paper test on 3 consecutive readings was considered to have GI bleed, and prophylaxis was considered a failure
- Number of participants requiring blood transfusion
- Adverse reactions of interventions
- All-cause mortality in ICU

Outcomes sought but not reported in trial report

- Incidence of ventilator-associated pneumonia
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation

Hastings 1978 (Continued)

Outcomes reported in report but not used in review

- Intragastric pH status
- Number of units of blood transfused (number provided, not mean or SD)

Notes

Setting: Respiratory-Surgical Intensive Care Unit of the Beth Israel Hospital, 300 Brookline Avenue, Boston, MA, 02215

Source of funding: Quote: "we are indebted to Stuart Pharmaceuticals, Division of I.C.I United States, Inc., Wilmington, DE (manufacturers of Mylanta II), whose generous contribution in part made this study possible..."

Conflicts of interest: -

Ethics approval: Quote: "The study was approved by the Committee on Cliniccal Investigations, New procedures and new forums of therapy of the Beth Israel Hospital"

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...the patients were randomised by a table of random numbers" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not enough information on allocation concealment reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering the study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	High risk	Comment: no clear definition for the diagnosis of upper GI bleeding or blinding of outcome assessors reported
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the analysis. Therefore there is no attrition bias
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported in the study

Hastings 1978 (Continued)

Other bias	Low risk	<p>Quote: "we are indebted to Stuart Pharmaceuticals, Division of I.C.I United States ,Inc., Wilmington, DE (manufacturers of Mylanta II), whose generous contribution in part made this study possible..."</p> <p>Comment: The above mentioned organisation also manufactured the antacid used as intervention in this study, which is suggestive of potential conflict of interest. The role of the sponsor in the conduct and reporting of the trial is unclear. No other sources of bias are suspected</p>
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Hata 2005

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 210 participants</p> <p>Number analysed: 210 participants</p> <p>Tepterone</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 65.0 (7.0) • Number of participants (n): 70 • Gender (male/female; n): - <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 62.6 (10.0) • Number of participants (n): 70 • Gender (male/female; n): - <p>Rabeprazole</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 66.1 (9.0) • Number of participants (n): 70 • Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Participants admitted to Nihon University Hospital of Medicine • Having undergone open heart surgery • No history of upper GI diseases • Informed consent <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Participants not satisfying the inclusion criteria <p>Baseline imbalances: Quote: "Prevalence of hypertension, diabetes, renal insufficiency (serum creatinine level of more than 2.0 mg/dl), and smoking history were similar. The rates of operative characteristics such as CABG, valve replacement, and aortic surgery were also similar. There were also no differences regarding CPB duration, postoperative maximum creatine kinase (CK)-MB levels"</p> <p>Comment: Participants had undergone an open heart surgery</p>
Interventions	<p>Tepterone</p> <ul style="list-style-type: none"> • Dose (total/d): 150 mg • Duration of treatment (days): starting after first day after operation

Hata 2005 (Continued)

- Route: PO
- Intervention: tablet form
- Concomitant medications: see notes

Ranitidine

- Dose (total/day): 300 mg
- Duration of treatment (days): starting after first day after operation
- Route: PO
- Intervention: tablet form
- Concomitant medications: see notes

Rabenzaprazole

- Dose (total/d): 10 mg
- Duration of treatment (days): starting after first day after operation
- Intervention: Tablet form
- Concomitant medications: see notes

Adherence to regimen: Quote: "There was hematemesis complications in 4 patients during postoperative days 4 and 6 in each of groups I and II. Otherwise, those with active ulcers were completely healed by PPI administered for 2 weeks, and confirmed by GFS. These patients required a blood transfusion and all had emergency GFS. In contrast, in group III, no patients developed upper GI bleeding"

Notes concomitant medication: Quote: "Systemic heparinization (10,000 U/day) was delayed until the second postoperative day. Patients undergoing CABG or aortic surgery had aspirin (81 mg/day) and those with valve replacement were administered Warfarin (2–3 mg/day) from the first postoperative day. Even though there was no complaints in relation to the upper GI system, gastric fibroscopy was used in all patients postoperatively during days 5 to 7"

Concomitant medications: as mentioned in concurrent medication

Duration of trial: January 2001 to December 2003

Duration of treatment: -

Duration of follow-up: not clearly mentioned in the study report. Most probably until discharge or death (although mortality is not reported)

Outcomes
Outcomes sought in review and reported in trial
Primary outcomes

- Incidence of GI bleeding

Secondary outcomes

- Participants requiring blood transfusion

Outcomes sought but not reported in trial report

- Incidence of ventilator-associated pneumonia
- All-cause mortality in the ICU
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Number of units of blood transfused
- Adverse events of interventions

Outcomes reported in report but not used in review

- Incidence of oesophagitis, superficial gastritis, erosive gastritis and haemorrhagic gastritis

Hata 2005 (Continued)

- Gastric pain
- Duration of hospital stay

Notes	<p>Setting: Department of Cardiovascular Surgery, Nihon University School of Medicine, Tokyo, Japan</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The Ethics committee of Nihon University School of Medicine approved the current trial"</p> <p>Informed Consent: Quote: "All patients gave written informed consent"</p> <p>Clinical trials registration: -</p> <p>Sample Size calculation: -</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This was not a placebo-controlled trial, and the study is unclear on blinding of study personnel and participants. Therefore, it is unclear on performance bias
Blinding (detection bias) Clinically important upper GI bleeding	High risk	Comment: unclear on blinding of outcome assessors, and there was no clear definition for detecting clinically significant upper GI bleeding. Therefore high risk of performance and detection bias
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear on blinding of outcome assessors. However owing to the objective nature of the outcome of interest, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis. Therefore there is no attrition bias
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported in the study
Other bias	Low risk	Comment: unclear on the source of funding. No other bias detected

He 2017

Methods	Parallel-group randomised controlled trial
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He 2017 (Continued)

Participants

Baseline characteristics

Number randomised: 120 participants

Number analysed: 120 participants

Naloxone

- Age (years; mean (SD)): 63.1 (6.2)
- Number of participants (n): 60
- Gender (male/female; n): 35/25

Naloxone + pantoprazole

- Age (years, mean (SD)): 65.1 (6.7)
- Number of participants (n): 60
- Gender (male/female; n): 37/23

Inclusion criteria

- Age of about 50 years
- No clinical manifestations of respiratory failure before admission
- No naloxone allergy history
- No liver, kidney dysfunction and other diseases
- Signed informed consent
- Voluntarily joined the clinical study

Exclusion criteria: -

Baseline imbalances: no significant difference in primary disease, sex, age, and course of disease between study group and control group

Interventions

Naloxene

- Dose (total/d): -
- Duration of treatment (days): -
- Route: PO
- Intervention: 0.8 mg of naloxone hydrochloride 2 mL : 2 mg (Shandong Xinhua Pharmaceutical Co., Ltd. production) added to 100 mL of 10% glucose water 6 times/d. When the blood gas situation improved, treatment dose was reduced by 50%
- Concomitant medications: In addition to comparative treatment, 2 groups of patients were given the same regular treatment, including anti-infective treatment, low-flow oxygen therapy, phlegm treatment, correct electrolyte imbalance and maintain acid-base balance, given the treatment of milk and timely nutrition

Naloxene + pantoprazole

- Dose (total/d): -
- Duration of treatment (days): -
- Route: PO
- Intervention: -
- Concomitant medications: In addition to comparative treatment, 2 groups of patients were given the same regular treatment, including anti-infective treatment, low-flow oxygen therapy, phlegm treatment, correct electrolyte imbalance and maintain acid-base balance, given the treatment of milk and timely nutrition

Adherence to regimen: -

Duration of trial: May 2009 to May 2014

He 2017 (Continued)

Duration of follow-up: -

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Incidence of clinically important GI bleeding • All-cause mortality in hospital • Adverse events of interventions <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • Incidence of VAP • Duration of ICU stay • Duration of intubation <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none"> • Duration of hospital stay • Blood gas values
Notes	<p>Setting: ICU</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: -</p> <p>Informed consent: Signed informed consent was required by all participants</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: -</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient information to allow judgment
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to allow judgment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: insufficient information to allow judgment
Blinding (detection bias) Clinically important upper GI bleeding	High risk	Comment: no details about criteria for diagnosis of upper GI bleeding or blinding of outcome assessors reported
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: insufficient information to allow judgement

He 2017 (Continued)

Adverse reactions of interventions

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to allow judgement
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in Methods section also reported in Results
Other bias	Unclear risk	Comment: insufficient information to allow judgement

Israsena 1987

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 86 participants</p> <p>Number analysed: 64 participants</p> <p>Sucralfate</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 55.05 (21.86) Number of participants at baseline (n): 40 Gender (male/female; n): 25/15 <p>Antacid</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 51.07 (18.22) Number of participants at baseline (n): 46 Gender (male/female; n): 31/15 <p>Inclusion criteria</p> <ul style="list-style-type: none"> Requiring mechanical ventilation for longer than 24 hours <p>Exclusion criteria</p> <ul style="list-style-type: none"> Failure to obtain consent from the patients, the relatives, or the attending physicians Evidence of GI bleeding before commencing the study History of upper GI disease <p>Baseline imbalances: None of the differences was statistically significant</p>
Interventions	<p>Sucralfate</p> <ul style="list-style-type: none"> Dose (total/d): 4 g Duration of treatment (days): until the patient developed gastrointestinal bleeding or was discharged from the unit Route: PO or nasogastric tube Intervention: 1 g of sucralfate every 6 hours, orally or via the NG tube (suspended in 10 mL of water) Concomitant medications: Patients who bled were treated with conventional antacids or H1-receptor antagonists. Gastroscopy was performed only in physically suitable patients with evidence of continued bleeding <p>Antacid</p>

Israsena 1987 (Continued)

- Dose (total/d): 720 mEq
- Duration of treatment (days): until the patient either developed gastrointestinal bleeding or was discharged from the unit
- Route: PO or nasogastric tube
- Intervention: hospital-made antacid containing aluminium/magnesium hydroxide gel, with acid neutralising activity of 2 mEq/mL every 2 hours orally or via the NG tube
- Concomitant medications: Patients who bled were treated with conventional antacids or H1 receptor antagonists. Gastroscopy was performed only in physically suitable patients with evidence of continued bleeding

Adherence to regimen: -

Duration of trial: April 1985 to March 1986

Duration of follow-up: -

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Gastrointestinal bleeding defined as the occurrence of any 1 of the following findings: (a) haematemesis, (b) melena and a drop in haematocrit (> 5% in 24 hours), or (c) frankly bloody or 'coffee ground' aspirate from the nasogastric tube • All-cause mortality in the hospital • Duration of ICU stay • Duration of ventilation • Serious adverse events leading to discontinuation of treatment, prolongation of ICU stay, or disability <p>Outcome sought in review but not reported in trial</p> <ul style="list-style-type: none"> • VAP • Blood transfusions <p>Outcomes reported in trial, but not used in review</p> <ul style="list-style-type: none"> • Nil
Notes	<p>Setting: Medical Intensive Care Unit, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand</p> <p>Sponsorship source: Siam Pharmaceutical Company, Bangkok</p> <p>Ethics approval: -</p> <p>Informed consent: Failure to receive informed consent is mentioned under exclusion criteria</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Comments: -</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "108 subjects were divided into acute and chronic cases of respiratory failure and were allocated by means of a table of random numbers to receive either sucralfate or antacid"
Allocation concealment (selection bias)	Unclear risk	Comment: no details reported

Israsena 1987 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no details about blinding reported, but lack of blinding unlikely to introduce bias to findings
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: Study did not address this outcome
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: GI bleeding was an objective outcome that was diagnosed as per the definition in the study protocol. Therefore the likelihood of performance or detection bias is low
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: no details reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 16 patients were excluded from analysis in the sucralfate group and 6 from the antacid group, without a described reason
Selective reporting (reporting bias)	Low risk	Comment: no selective reporting of outcomes suspected; all outcomes listed in the Methods section and objectives are also reported in the Results section
Other bias	Low risk	Comment: funded by pharmaceutical industry. No other sources of bias suspected

Kantorova 2004

Methods	Single-center randomised placebo-controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 323 participants</p> <p>Number analysed: 287 participants</p> <p>Omeprazole</p> <ul style="list-style-type: none"> Age (years; mean (range)): 44 +/-15 Number of participants (n): 72 Gender (male/female; n): 48/24 <p>Famotidine</p> <ul style="list-style-type: none"> Age (years; mean (range)): 47+/-17 Number of participants (n): 71 Gender (male/female; n): 44/27 <p>Sucralfate</p> <ul style="list-style-type: none"> Age (years; mean (range)): 51 +/- 18 Number of participants (n): 69 Gender (male/female; n): 50/19 <p>Placebo</p>

Kantorova 2004 (Continued)

- Age (years; mean (range)): 18,46 +/-19.
- Number of participants (n): 75
- Gender (male/female; n): 50/25

Inclusion criteria

- Age ≥ 18 years
- Projected to require mechanical ventilation for at least 48 hours
- Having coagulopathy
- Having a nasogastric tube in place

Exclusion criteria

- Expected stay in ICU ≤ 48 hours
- History of oesophagogastric surgery including vagotomy
- Evidence of GI bleeding at the time of admission to the ICU and during the previous year
- Pneumonia
- Treatment with PPIs, H2 blockers, antacids, or sucralfate during previous 72 hours
- Documented peptic ulcer disease during the year
- Use of systemic anticoagulants, high-dose oral corticosteroids, or thrombolytic agents during previous week
- Renal insufficiency requiring haemodialysis
- Thrombocytopaenia $< 30,000/\text{mL}$
- Participants with life expectancy < 3 months
- Participants not able or willing to give informed consent

Baseline imbalances: Quote: "At randomisation no statistically significant difference was found among the four groups in demographic and baseline physiological characters. The distribution of risk factors such as participants who had trauma, surgery or coagulopathy at ICU admission were also similar in all groups"

Comment: no significant difference between the 2 groups with respect to demographic and baseline risk factors. Trauma was the main reason for admission. Coagulopathy was diagnosed in 31 participants at baseline (7, 10, 6, and 8 in each of the 4 groups, respectively)

Interventions

Omeprazole

- Dose (total/d): 40 mg
- Duration of treatment (days): -
- Route: IV
- Intervention: 40 mg of omeprazole intravenously once daily
- Concomitant medications: Enteral feeding was administered to 30 participants, antibiotic therapy to 65 participants

Famotidine

- Dose (total/d): 80 mg
- Duration of treatment (days): -
- Route: IV
- Intervention: 40 mg twice a day at 12-hour intervals by slow intravenous injection
- Concomitant medications: Enteral feeding was administered to 25 participants, antibiotic therapy to 62 participants

Sucralfate

- Dose (total/d): -
- Duration of treatment (days): -
- Route: -

Kantorova 2004 (Continued)

- Intervention: administered every 6 hours as 1 g of suspension
- Concomitant medications: Enteral feeding was administered to 29 participants, antibiotic therapy to 66 participants

Placebo

- Dose (total/d): -
- Duration of treatment (days): 3.1
- Route: IV
- Intervention: not clearly reported. Probably 100 mL in saline solution IV (like group 1 and group 2 interventions)
- Concomitant medications: Enteral feeding was administered to 26 participants, antibiotic therapy to 71 participants

Notes for placebo intervention: A placebo group was included in the protocol design because at study initiation and during the study period, no drug was approved for prophylaxis of stress-related upper gastrointestinal bleeding by the FDA. The European Medicines Evaluation Agency required a placebo comparison group for registration of studies in this indication

Adherence to regimen: Quote: "Of the 323 randomised patients 36 were subsequently excluded from analysis (1 patient died suddenly within 2 hours after randomisation, 18 underwent mechanical ventilation < 48 hours and 16 were not assessable because of missing important data"

Thus only 287 patients could be analysed. No drug-related adverse events were seen during the whole study, possibly related adverse events were rare, and in no patient was discontinuation of therapy necessary.

Duration of trial: February 2000 to June 2002

Duration of follow-up: -

Outcomes

Outcomes sought in review and reported in trial

- Clinically important upper GI bleeding (haematemesis, melena, positive nasogastric aspirate, or haematochezia) defined as overt bleeding plus at least 1 of the following:
 - Drop in systolic blood pressure within 24 hours after upper GI bleeding of 20 mmHg or increase in pulse rate ≥ 20 beats per minute with more than 24 hours of upper GI bleeding
 - Drop in haemoglobin concentration ≥ 2 g/dL in the absence of a clear explained reason
- VAP
 - Purulent tracheal aspirate with more than 25 leucocytes per low-power field
 - Episodes of pneumonia diagnosed within first 24 hours of admission were considered to be present on admission
 - Peripheral leucocytes $> 11 \times 10^9/L$ or $> 10\%$ bands
 - Central body temperature $> 38.4^\circ C$
 - Isolation of pathogens from tracheal aspirate, bronchoalveolar lavage
 - Positive haemo culture or pleural fluid culture unrelated to another source

Secondary outcomes

- All-cause mortality in ICU
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Participants requiring blood transfusion (could not be analysed owing to low incidence of bleeding)
- Units of blood transfused (could not be due to low incidence of bleeding)
- Adverse events of interventions (no adverse events reported)

Outcomes sought but not reported in trial report

- Nil

Kantorova 2004 (Continued)

Outcomes reported in trial but not used in review

- Intragastric pH status
- Gastric colonisation

Notes

Setting: Traumatological Hospital Brno, a Czech republic ministry of health teaching and research facility

Source of funding: Quote: "The study was supported by a grant of IGA MZ CB ND 5932-3/2000"

Conflicts of interest:

Ethics approval: Quote: "The study was approved by the Institutional Review Board and Grant agency at the Ministry of Health of the Czech Republic"

Informed consent: Quote: "participants not able or willing to give informed consent were excluded from the study"

Clinical trials registration: not provided in the study report

Sample size calculation: not mentioned in the study report

Additional notes: GI bleeding occurred more commonly in participants with coagulopathies (3/31, 10% vs 4/245, 2%, $P = 0.006$). The most common pathogens in participants with pneumonia were *Staphylococcus* and *Streptococcus*. ICU stay and mortality were greater in participants with investigated complications of GI bleed and pneumonia but were not influenced by prophylaxis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to study group by means of computer generated random number table to generate a random treatment list" Comment: method adopted to obtain random sequence generation clearly mentioned in the study report
Allocation concealment (selection bias)	Low risk	Quote: "Treatment regimens were included in opaque sealed numbered envelopes and the envelope with the lowest number was always used for the consecutive patient" Comment: method adopted to allocation concealment clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Blinding of the drug administered intravenously was achieved by dissolving them in 100 mL of saline solution drug were prepared by staff not involved in the study according to the randomisation. All blinded drugs were identifiable by their study number and were given to the patients by the study nurse" Comment: Blinding is mentioned only for groups that received intravenous medications (omeprazole, famotidine, and placebo), not sucralfate. Unclear whether this would have led to performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: mentioned that outcome assessment was done blinded to intervention. The presence of 1 or more macroscopic abnormalities (erythema or oedema, erosions, ulcerations, and naso-gastric tube lesions) and GI bleeding was assessed, blinded to intervention, at endoscopy by a single experienced gastroenterologist Quote: "assessed, blinded to intervention, at endoscopy by a single experienced gastroenterologist"

Kantorova 2004 (Continued)

Blinding (detection bias) Nosocomial pneumonia	Low risk	Quote: "Chest radiographs were interpreted by two independent radiologists" Comment: Blinding of outcome assessors was done. Pneumonia was an objective outcome detected as per the study protocol
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature, so the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Of the 323 randomised patients, 36 were subsequently excluded from analysis. Groups to which they were initially randomised remain unclear though. Thus only 287 participants were available for analysis. However, the number of dropouts and their characteristics were comparable in all 4 arms. Therefore there is no likelihood of risk of attrition bias
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported in the study
Other bias	Low risk	Comment: Study was funded by a grant of IGA MZ CB ND 5932-3/2000. The role of the sponsor in the conduct and reporting of the trial is unclear. No other sources of bias were detected

Kappstein 1991

Methods	Parallel-group quasi-randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 104 participants</p> <p>Number analysed: 104 participants</p> <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 40.6 (21.1) • Number of participants at baseline (n): 49 • Gender (male/female; n): 38/11 <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 46.2 (21.0) • Number of participants at baseline (n): 55 • Gender (male/female; n): 46/9 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admitted to the anesthesiology intensive care unit • Requiring mechanical ventilation for at least 24 hours • Having a nasogastric tube in place <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Upper abdominal or thoracic surgical interventions • Being tube-fed

Kappstein 1991 (Continued)

Baseline imbalances: The 2 groups were largely similar according to demographic characteristics, underlying diseases, and diagnoses at admission. However, there were slight imbalances with regard to age, gender, polytrauma, and acute respiratory failure

Interventions	<p>Sucralfate</p> <ul style="list-style-type: none"> Dose (total/d): 4 g Duration of treatment (days): - Route: nasogastric tube Intervention: 1 g sucralfate every 6 hours through the nasogastric tube, which was subsequently rinsed with 10 mL of sterile water to avoid residues of the suspension in the tube lumen. Tubes were then clamped for about 1 hour to prevent reflux Concomitant medications: - <p>Cimetidine</p> <ul style="list-style-type: none"> Dose (total/d): 2000 mg or 1200 mg Duration of treatment (days): - Route: IV Intervention: not pH adjusted. There was no difference in mean gastric pH levels of patients receiving cimetidine continuously (2000 mg/d) or intermittently (3 × 400 mg/d) Concomitant medications: - <p>Adherence to treatment: -</p> <p>Duration of trial: May 1986 to January 1989</p> <p>Duration of follow-up (days): -</p>
Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> GI bleeding: Macroscopically visible blood in gastric aspirates was taken for evidence of stress bleeding Ventilator-associated pneumonia: Diagnosis of pneumonia was established if there was a new and persistent infiltrate on chest X-ray and at least 3 of the following signs consistent with infection: (a) purulent tracheal secretions (> 25 polymorphonuclear leucocytes and < 10 squamous epithelial cells per low- power field); (b) a pathogen known to cause lung infection isolated from tracheal secretions; and (c) blood leucocytosis > 10,000 cells/mm³ and fever with body temperature > 38°C. Shock was defined by systolic blood pressure < 90 mmHg. Sepsis was diagnosed if there was bacteriologically confirmed or clinical sepsis Mortality Duration of ventilation <p>Outcomes sought in review, but not reported in trial</p> <ul style="list-style-type: none"> Duration of ICU stay Blood transfusion Adverse events of interventions <p>Outcomes reported in trial but not sought in review</p> <ul style="list-style-type: none"> Gastric colonisation Gastric pH levels
Notes	<p>Setting: ICU, Department of Hospital Epidemiology, Medical Biometry and Anaesthesiology, University Hospital Freiburg, Germany</p> <p>Sponsorship source: -</p> <p>Conflicts of interest: -</p>

Kappstein 1991 (Continued)

Ethics approval: -

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Comment: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "and tube-fed patients were excluded. Patients were assigned to stress ulcer prophylaxis with either sucralfate or cimetidine by setting up groups of 10 patients who received one prophylactic regimen followed by the next 10 patients receiving the other regimen. Patients received either intravenous" Judgement comment: quasi-randomisation. Patients were assigned to stress ulcer prophylaxis with either sucralfate or cimetidine by setting up groups of 10 patients who received 1 prophylactic regimen followed by the next 10 patients receiving the other regimen
Allocation concealment (selection bias)	Unclear risk	Judgement comment: Provided the sequence was consecutive, patients were known in each group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement comment: no blinding reported, but lack of blinding is unlikely to introduce bias. Outcome measures and outcomes are objectively measured
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "Macroscopically visible blood in gastric aspirates was taken for evidence of stress bleeding" Comment: outcome measured objectively
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: criteria for the diagnosis of pneumonia clearly reported in the trial
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	High risk	Quote: "The chest x-ray was interpreted by a radiologist who was not aware of the particular prophylactic regimen" Judgement comment: but investigators and personnel were unblinded for other criteria for pneumonia and for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: All outcomes have included all patients. No incomplete reporting of data suspected. Attrition was low and was reported transparently
Selective reporting (reporting bias)	Low risk	Judgement comment: no incomplete reporting of outcomes suspected. All outcomes listed in the Methods section are also reported in the Results section
Other bias	Low risk	Comment: no other sources of bias suspected

Karlstadt 1990

Methods

Multi-centre double-blind randomised placebo-controlled trial

Karlstadt 1990 (Continued)

Participants

Baseline characteristics

Number randomised: 87 participants

Number analysed: 87 participants

Cimetidine

- Age (years; mean (SD)): 56.5 (22.8)
- Number of participants (n): 54
- Gender (male/female; n): 31/23

Placebo

- Age (years; mean (SD)): 61.9 (18.8)
- Number of participants (n): 33
- Gender (male/female; n): 16/17

Inclusion criteria

Participants admitted to ICUs were eligible for entry into the trial if they had at least 1 of the following conditions generally regarded as risk factors for bleeding:

- Major thoracic or abdominal surgery
- Major multiple trauma
- Hypotension, defined as a decrease in blood pressure greater than 30/20 mmHg (systolic/diastolic)
- Hypovolemic shock, defined as a syndrome of inadequate tissue perfusion characterised by systolic blood pressure < 90 mmHg (or a decrease of 30 mmHg in previously hypertensive patients)
- Sepsis, defined by the presence of peritonitis, confirmed bacteraemia, or the complex of fever, elevated white blood cell count, and hypotension with a bacteriologically determined source of infection
- Acute respiratory failure, defined as the need for assisted ventilation for longer than 24 hours

Exclusion criteria

- Active upper GI bleeding, history of peptic ulcer or upper gastrointestinal surgery
- Severe chronic hepatic failure, defined by the presence of portal systemic encephalopathy or ascites secondary to chronic liver disease
- Renal failure, defined by elevated serum creatinine, indicating creatinine clearance < 30 mg/min
- Treatment with other drugs such as antacids, other H2-receptor antagonists, and sucralfate that would interfere with evaluation of investigative treatment effects
- Pregnancy or lactation
- Age < 16 years
- Known hypersecretory disorders (e.g. peptic ulcer, burns) or patients considered likely to bleed from non-stress-related conditions (e.g. varices, uraemic gastritis)

Baseline imbalances: Quote: "Patient demographics and risk factors for bleeding on entry into the study show that the treatment groups were comparable"

Comment: Participants from 14 centres were comparable with respect to demographic characteristics and baseline risk factors. Almost 40% of study participants had acute respiratory failure at baseline, of whom 14% had pneumonia

Interventions

Cimetidine

- Dose (total/d): 1500 mg
- Duration of treatment (days): probably 7 days
- Route: IV
- Intervention: continuous intravenous 50 mg/h infusion. Patients received an initial 300 mg dose of cimetidine

Karlstadt 1990 (Continued)

- Concomitant medications: Average number of medications administered concomitantly during the trial was 8 (range, 1 to 20) in the cimetidine group and 7 (range, 2 to 23) in the placebo group. All participants had a nasogastric tube in place

Placebo

- Dose (total/d): -
- Duration of treatment (days): probably 7 days
- Route: IV
- Intervention: placebo; 0.9% saline infused over 15 to 20 minutes, followed by continuous infusion by IVAC or IMED
- Concomitant medications: Average number of medications administered concomitantly during the trial was 8 (range, 1 to 20) in the cimetidine group and 7 (range, 2 to 23) in the placebo group. All participants had a nasogastric tube in place

Adherence to regimen: Quote: "The average time in the study was longer for patients treated with cimetidine (mean, 83 hours $\pm$ 53) than for patients treated with placebo (mean, 53 hours $\pm$ 41). This difference was because more patients treated with placebo bled and left the study early"

"Two patients being treated with cimetidine experienced adverse events for which they were withdrawn from the study: one developed moderate nausea and vomiting and one developed a change in mental status. In both cases, the adverse experiences were reversible. No patients treated with placebo were withdrawn from treatment, but adverse experiences attributed to placebo treatment included one case of mental confusion"

Duration of trial: -

Duration of follow-up: not clearly mentioned in the study report. Probably until death or discharge

Outcomes

Outcomes sought in review and reported in trial

Primary outcomes

- Upper GI haemorrhage in critically ill patients defined by 1 of the following:
 - Haematemesis or the presence of more than 10 mL of bright red blood in a single aspirate
 - Melena or haematochezia (unless upper GI endoscopy clearly indicated that the melena did not arise from an upper GI site)
 - Presence of 'coffee grounds' positive for haemoglobin by Gastrocult (Smith Kline Diagnostics, Sunnyvale, CA) in the nasogastric aspirate on each of 3 consecutive 6-hourly observations (over 12 hours) and a 1-gram decrease in haemoglobin over 24 hours
 - Gastrocult-positive 'coffee grounds' aspirate that did not clear with lavage

Secondary outcomes

- Incidence of pneumonia
- All-cause mortality in ICU
- Adverse reactions of interventions

Outcomes sought but not reported in trial

- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Number of participants requiring transfusion of more than 2 units of blood
- Number of units of blood transfused

Outcomes reported in trial but not used in review

- Time until occurrence of bleeding
- Stress-related upper gastrointestinal mucosal damage

Karlstadt 1990 (Continued)

Notes

Setting: The study was a multi-centric study involving 14 centres; University of Kentucky, Lexington, KY; Boston City Hospital, Boston, King Drew Medical Center, Los Angeles, CA; Winthrop University Hospital, Mineola, NY; Ellis Hospital, Schenectady, NY; Detroit Rec. Hospital, Detroit, MI; Mt. Sinai Medical Center, New York, Hartford Hospital, Hartford, CT; St. Thomas Hospital, Akron, OH; Cleveland Metro General Hospital, Cleveland, OH; University of Oklahoma Health Science Center, Oklahoma City, OK; Ravenswood Hospital, Chicago, IL; Brookdale Hospital, Brooklyn, NY; University of Texas Health Science Center, San Antonio, TX

Source of funding: Study appears to have been funded by Smith Kline & French Laboratories, Philadelphia, PA, although this is not clearly mentioned in the study report

Conflicts of interest:

Ethics approval: Quote: "The study was approved by all institutional review boards"

Comment: This study was approved by the ethics committees at all 14 centres

Informed consent: Quote: "...and all patients (or their legal guardians) provided written, informed consent"

Comment: For participating in the trial, informed consent was obtained from participants or their legal guardians

Clinical trials registration: not provided in the study report

Sample size calculation: not clearly mentioned in the study report

Additional Notes: *Staphylococcus aureus* was the organism found to have caused pneumonia. One participant treated with cimetidine had melena, but the upper GI source could not be detected, so this participant was not categorised as having an upper GI bleed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not enough information about sequence generation reported
Allocation concealment (selection bias)	Unclear risk	Comment: not enough information about allocation concealment reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This was a placebo-controlled trial; unclear about whether participants and study personnel were blinded
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear whether outcome assessors were blinded. GI bleeding was an objective outcome detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	High risk	Comment: Outcome assessors were not blinded. Study had no clear mention of the definition to detect pneumonia. Moreover 14% of participants had pneumonia on entry into the study. Lack of blinding could have influenced detection of this condition, as it is mentioned that the physician did not attribute pneumonia to the study medication
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: Outcomes of interest were in part objective in nature; for other outcomes, the definition is not described and no blinding is in place

Karlstadt 1990 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients who received study drugs were included in the denominator for analysis" Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Lead author is affiliated with Smith Kline & French Laboratories, Philadelphia, PA. Clear conflict of interest. No other sources of bias suspected

Kaushal 2000

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 75 participants</p> <p>Number analysed: 75 participants</p> <p>Famotidine</p> <ul style="list-style-type: none"> Age (years; mean (range)): 32.92 +/- 10.93 Number of participants (n): 25 Gender (male/female; n): 24/1 <p>Sucralfate</p> <ul style="list-style-type: none"> Age (years; mean (range)): 32.7 +/- 12.79 Number of participants (n): 25 Gender (male/female; n): 24/1 <p>No prophylaxis</p> <ul style="list-style-type: none"> Age (years; mean (range)): 36.34 +/- 15.58 Number of participants (n): 25 Gender (male/female; n): 24/1 <p>Inclusion criteria</p> <ul style="list-style-type: none"> Head injury of < 24 hours' duration Glasgow Coma Scale (GCS) score < 10 Need for nasogastric intubation Admitted to Neurosurgery Unit Informed consent (could not be taken directly from patients); it was taken from the next of kin <p>Exclusion criteria</p> <ul style="list-style-type: none"> History of acid peptic disease Upper GI bleed Use of ulcer-modifying drugs over preceding 4 weeks Presence of significant hepatic/renal disease Bleeding diathesis or significant injury requiring anaesthesia Ventilation or surgery, except tracheostomy or minor wound suturing

Kaushal 2000 (Continued)

Baseline imbalances: Age, gender, and clinical features of participants in the 3 groups were comparable. Participants were people who required ICU care after head injury (mainly because of road side accident)

Interventions

Famotidine

- Dose (total/d): 40 mg
- Duration of treatment (days): -
- Route:
- Intervention: prophylactic famotidine (20 mg) twice daily
- Concomitant medications: In case of 3 consecutive positive tests for occult blood in any group, the protocol allowed use of antacids in addition to drugs patients were already receiving

Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days): -
- Route:
- Intervention: prophylactic sucralfate 2g twice daily
- Concomitant medications: In case of 3 consecutive positive tests for occult blood in any group, the protocol allowed use of antacids in addition to drugs patients were already receiving

No prophylaxis

- Dose (total/d): -
- Duration of treatment (days): -
- Route:
- Intervention: no regular prophylactic antiulcer treatment
- Concomitant medications: In case of 3 consecutive positive tests for occult blood in any group, the protocol allowed use of antacids plus famotidine (20 mg twice daily) or sucralfate (2 g twice daily)

Adherence to regimen: Quote: "Out of 56 patients who had upper GI bleeding, 39 started bleeding within 3 days of head injury"

Comment: Only 1 patient in the famotidine group required escape treatment as compared with 3 in the sucralfate group and 8 in the no prophylaxis group. The exact reason for escape of treatment is not mentioned but could be attributed to untimely death or upper GI bleed that was clinically significant as per the study protocol. The 56 participants with upper GI bleed are inclusive of all grades of bleeding according to the study protocol. Interventions were discontinued if at least 3 consecutive positive occult blood readings were detected

Duration of trial: -

Duration of follow-up: 15 days

Outcomes

Outcomes sought in review and reported in trial
Primary outcomes

- Incidence of upper GI bleeding; haemorrhage was graded as grade 0 if test for occult blood was negative; grade 1 if test for occult blood was positive; grade 2 if there was also red or brown discolouration of the aspirate; and grade 3 if severity of haemorrhage necessitated blood transfusion

Note: Among the 56 participants who bled, 39 of them started to bleed within 3 days of head injury. Data on occult bleeding were not used in the review

Secondary outcomes

- All-cause mortality in ICU
- Participants requiring blood transfusion (none)
- Units of blood transfused (no participant required this)

Kaushal 2000 (Continued)

Outcomes sought but not reported in trial

- Incidence of VAP
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Adverse events of interventions

Outcomes reported in trial but not used in review

- Incidence of upper GI bleeding with respect to Glasgow Coma Scale (GCS)

Notes

Setting: Neurosurgery Unit of Medical College and Hospital, Ludhiana, India

Source of funding: -

Ethics approval: Quote: "After approval from Hospital Ethics Committee, the study was conducted in 75 consecutive patients"

Comment: The ethics committee of the concerned institution had approved the study

Informed consent: Quote: "Since informed consent could not be taken directly from patients, it was taken from the next of kin"

Comment: Informed consent was obtained

Clinical trials registration: -

Sample size calculation: -

Additional notes: According to the study report, data on endoscopy could not be analysed because of small numbers of participants who underwent the procedure. Occult bleeding occurred in 38 participants (no prophylaxis: 11, famotidine: 12, and sucralfate: 15)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and 1 arm received no prophylaxis; this would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear whether outcome assessors were blinded. However GI bleeding was an objective outcome that was detected as per the definition in the study
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear whether outcome assessors were blinded. All other outcomes of interest were objective in nature

Kaushal 2000 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis in the study report
Selective reporting (reporting bias)	Low risk	Comment: The intended outcome of GI bleeding was reported in the study report
Other bias	Low risk	Comment: unclear on the source of funding. No other form of bias detected

Khorvash 2014

Methods	Parallel-group quasi-randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 148 participants</p> <p>Number analysed: 137 participants</p> <p>Pantoprazole</p> <ul style="list-style-type: none"> Age (years; mean (range)): 51.5 (21.4) Number of participants (n): 74 Gender (male/female; n): 55/16 <p>Sucralfate</p> <ul style="list-style-type: none"> Age (years; mean (range)): 49.8 (19.5) Number of participants (n): 74 Gender (male/female; n): 50/16 <p>Inclusion criteria</p> <ul style="list-style-type: none"> Admitted to ICU Accepting to cooperate <p>Exclusion criteria</p> <ul style="list-style-type: none"> Early discharge from ICU Death before 10 days Inception of antibiotic before incidence of pneumonia or Sensitivity to the drug <p>Baseline imbalance: -</p>
Interventions	<p>Pantoprazole</p> <ul style="list-style-type: none"> Dose (total/d): - Duration of treatment (days): - Route: - Intervention: - Concomitant medications: <p>Sucralfate</p> <ul style="list-style-type: none"> Dose (total/d): - Duration of treatment (days): - Route: -

Khurvash 2014 (Continued)

- Intervention: -
- Concomitant medications: -

Adherence to regimen: -

Duration of trial: early 2010 to mid-2011

Duration of follow-up: -

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Ventilator-associated pneumonia • Duration of ventilation • Duration of hospital stay • All-cause mortality • Adverse events <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • Clinically important GI bleeding <p>Outcomes reported but not used in review</p> <ul style="list-style-type: none"> • Consolidation in X-ray • Cavitation • Chronic infiltration • Purulent sputum • Risk factors for ventilator-associated pneumonia
Notes	<p>Setting: ICU, Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Study was approved by the medical universities ethics committee at Isfahan University of Medical Sciences</p> <p>Informed consent: Quote: "after they agreed to cooperate"</p> <p>Comment: included in the trial report</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Patients were consecutively assigned to each group. The first patient was selected randomly" Comment: no randomisation, quasi-randomised study
Allocation concealment (selection bias)	High risk	Comment: consecutive pattern of allocation
Blinding of participants and personnel (performance bias)	Low risk	Comment: no blinding reported, but lack of blinding is unlikely to introduce bias to outcome measures or outcomes

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

Khorvash 2014 (Continued)

All outcomes

Blinking (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: Study did not address this outcome
Blinking (detection bias) Nosocomial pneumonia	Low risk	Quote: "Ventilator-associated pneumonia is defined as a group of pneumonias that occur 48 hours after the patient is ventilated if the patient did not have primary signs of the infection at the time of arriving ICU. VAP is one of the most prevalent nosocomial infections and pneumonia is causes 27% of infections in ICU" Comment: Criteria for diagnosis of the outcome were reported objectively
Blinking of outcome as- essment (detection bias) Adverse reactions of inter- ventions	Unclear risk	Comment: no blinding of outcome assessors described
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: "11 patients were excluded for different reasons like not using the drug, changing the drug by the physician, and so on. Three of them were from the pantoprazole and 8 of them were from sucralfate group"
Selective reporting (re- porting bias)	Unclear risk	Comment: no outcomes of interest described in the Methods section; assess- ment of selective outcome reporting difficult
Other bias	Low risk	Comment: no other sources of bias suspected

Kingsley 1985

Methods	Randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 263 participants</p> <p>Number analysed: 249 participants</p> <p>Antacids</p> <ul style="list-style-type: none"> • Age (years; mean (range)): - • Number of participants (n): 61+64 • Gender (male/female; n): - <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (range)): - • Number of participants (n): 64+59 • Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Suffering from a variety of illnesses classified II or greater by therapeutic intervention scoring system (TISS) <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Patients receiving oral intake • History of peptic ulcer or coagulopathy or gastrointestinal bleeding

Kingsley 1985 (Continued)

- Having undergone oesophageal or gastric operation before admission to the study

Baseline imbalances: Quote: "The patients were randomised to the four different groups were fairly homogenous and were exposed to essentially the same risk factors"

Comment: no clear mention of gender, age, and type of risk factor distribution in the study report. In all participants, a variety of illness classified II or greater by therapeutic intervention scoring system (TISS) were diagnosed

Interventions

Antacids bolus

- Dose (total/d): 7200 mL
- Duration of treatment (days): until enteric feeding was begun, or patient was discharged from the critical care unit or died
- Route: NG tube
- Intervention: antacid bolus at a rate of 90 mL every 3 hours. Nasogastric tube was clamped until the subsequent instillation; if regurgitation occurred around the nasogastric tube, it was unclamped and connected to low suction
- Concomitant medications: Gastric pH was measured and recorded hourly. Gastric contents were tested for frank or occult bleeding every 3 hours by guaiac tests

Antacids continuous

- Dose (total/d): 1440 mL
- Duration of treatment (days): until enteric feeding was begun, or until patient was discharged from the critical care unit or died
- Route: IV
- Intervention: continuous antacid drip (AA-D) at the rate of 60 mL per hour
- Concomitant medications: Gastric pH was measured and recorded hourly. Gastric contents were tested for frank or occult bleeding every 3 hours by guaiac tests

Cimetidine bolus

- Dose (total/d): 1200 mg
- Duration of treatment (days): until enteric feeding was begun, or patient was discharged from the critical care unit or died
- Route: IV
- Intervention: IV cimetidine bolus 300 mg every 6 hours
- Concomitant medications: Gastric pH was measured and recorded hourly. Gastric contents were tested for frank or occult bleeding every 3 hours by guaiac tests

Cimetidine continuous

- Dose (total/d): 1200 mg
- Duration of treatment (days): until enteric feeding was begun, or patient was discharged from the critical care unit or died
- Route: IV
- Intervention: continuous cimetidine drip at a dose of 50 mg per hour
- Concomitant medications: Gastric pH was measured and recorded hourly. Gastric contents were tested for frank or occult bleeding every 3 hours by guaiac tests

Adherence to regimen: Quote: "...14 patients initially admitted to the study were excluded for failure to follow protocol", "Any patient who developed severe diarrhoea was given alternagel instead of Mylanta"

Comments: not sure which groups the 14 participants belonged to. Nine participants needed to be switched to alternagel

Duration of trial: -

Kingsley 1985 (Continued)

Duration of follow-up: not clearly mentioned in the study report. Probably until death or discharge

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> Incidence of clinically important upper GI bleeding defined as presence of bright blood in the naso-gastric tube, which would not clear with iced saline lavage or if melena occurred. Guaiac-positive aspirate, not accompanied by a fall in haematocrit or obvious bleeding; was not considered significant All-cause mortality in ICU Number of participants requiring blood transfusion (does not appear entirely due to GI bleeding) Units of blood transfused (total units of blood transfused provided; no mean and SD) Adverse events of interventions <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> VAP All-cause mortality in the hospital Duration of intubation <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none"> Gastric pH values Superior mode of delivery for both the interventions Endoscopic evaluation of gastric mucosa
Notes	<p>Setting: Hurley Medical Centre, Michigan, USA</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: -</p> <p>Informed consent: -</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: Mean blood transfusion due to gastrointestinal haemorrhage was 1335 mL (range: 0 to 4500 mL). This is not mentioned separately for both groups. Irreversible haemorrhagic shock was the cause of death in 2 cimetidine participants</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Given the mode of administration and dosing regimens, it would not have been possible to blind study personnel. Therefore unclear whether this would have caused any performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear whether the outcome assessor was blinded. GI bleeding was an objective outcome that was detected as per the definition in the study protocol

Kingsley 1985 (Continued)

Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "...14 patients initially admitted to the study were excluded for failure to follow protocol" Comment: unclear on which groups the 14 participants were initially randomised to. But this accounts to be around 5% of total participants and is uniformly distributed across groups
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: unclear on the source of funding. No additional biases suspected

Kitler 1990

Methods	Randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 401 participants</p> <p>Number analysed: 298 participants</p> <p>Overall</p> <ul style="list-style-type: none"> Age (years; mean (range)): - (19 to 65) Number of participants (n): 298, n = 85 bioflavonoid (Maciadanol), n = 100 sucralfate, n = 113 antacids Gender (male/female; n): 197/101 <p>Inclusion criteria</p> <ul style="list-style-type: none"> Patients admitted to surgical ICU of Johns Hopkins and Francis Scott Key Medical Centres in Baltimore Patients who consented to enter the study <p>Exclusion criteria</p> <ul style="list-style-type: none"> Patient refusal to enter the study or surgeon refusal to allow the patient entry Patients with active bleeding of the GI tract Recent acute symptoms of peptic ulcers Recent operations of the stomach or oesophagus Known renal failure <p>Baseline imbalances: Most participants were referred for cardiac surgical treatment. Groups were similar in demographic characteristics such as age and race. The sucralfate group had the fewest women. Ten participants assigned to receive meciadanol had a history of peptic ulcer disease (3 with a history of bleeding); 14 with sucralfate had a history of peptic ulcer disease (5 with a history of bleeding), and 13 assigned to receive antacid had a history of peptic ulcer disease (4 with bleeding)</p>
Interventions	<p>Bioflavonoid (Maciadanol)</p> <ul style="list-style-type: none"> Dose (total/d): 3000 mg

Kitler 1990 (Continued)

- Duration of treatment (days): -
- Route: NG tube
- Intervention: 500 mg ever 6 hours through NG tube. Maciadanol was dissolved in sterile normal saline (10 mL) immediately before administration
- Concomitant medications: aspirin, steroids, indomethacin, sodium warfarin, and heparin

Sucralfate

- Dose (total/d): 5000 mg
- Duration of treatment (days): -
- Route: NG tube
- Intervention: 1000 mg (1g) in sterile normal saline solution through NG tube every 6 hours. Tablets were crushed immediately before administration and the resulting powder was suspended in sterile normal solution
- Concomitant medications: aspirin, steroids, indomethacin, sodium warfarin and heparin

Antacids (Maalox, magnesium aluminium hydroxide gel)

- Dose (total/d): 360 mL
- Duration of treatment (days): -
- Route: -
- Intervention: dosage mentioned as an initial dose of 15 mL every hour (in abstract) "in a manner similar to the protocol reported by others"
- Concomitant medications: aspirin, steroids, indomethacin, sodium warfarin, and heparin

Adherence to regimen: Overall 401 patients had entered the study and 298 had completed the study. Those who did not complete the study could not be evaluated or were excluded because of protocol error (receiving other antacids or antiulcer drugs), by physician request, or by their own request. Participants who remained in SICU for less than 24 hours were also excluded from the study. 85 participants completed the maciadanol arm, 100 the sucralfate arm, and 113 the antacid arm

Duration of trial: 16 months

Duration of follow-up: -

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Clinically important upper GI bleeding (frank bleed) determined visually (frank blood in gastric contents) or by guaiac testing • All-cause mortality in ICU (not reported for each arm) • Duration of ICU stay (mean and SD not reported) • Participants requiring blood transfusions <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • VAP • All-cause mortality in hospital • Units of blood transfused • Duration of intubation • Adverse events of interventions <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none"> • Intragastric pH
Notes	<p>Setting: Surgical Intensive Care Unit of Johns Hopkins Medical Institutions, Baltimore, and Francis Scott Key Medical Centre, Baltimore</p> <p>Source of funding: Zyma, S. A., Nyon, Switzerland</p>

Kitler 1990 (Continued)

Conflicts of interest:

Ethics approval: Quote: "The study was approved by the institutional review board of Johns Hopkins Medical Center and the Francis Scott Key Medical Center"

Informed consent: mentioned in the study report

Clinical trials registration: -

Sample size calculation: Quote: "The power calculations resulting from study sample size were one tailed with an alpha of 0.05 and a power of 80.0 per cent..."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised by a table of random numbers..." Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering the study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "All data were collected by an observer unaware of the results" Comment: not clear how this would have contributed to blinding. GI bleeding was detected as per the definition in the study. However, owing to the objective nature of the outcome of interest, the likelihood of performance and detection bias is low
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Quote: "All data were collected by an observer unaware of the results" Comment: unclear on blinding of outcome assessors. However, all other outcome data were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Overall 401 patients had entered the study and 298 had completed the study. Study did a per-protocol analysis for outcomes. Participants in the Maciadanol arm were 24% less than in the antacid arm. Unclear whether this could have influenced outcomes
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported in the study report
Other bias	Low risk	Comment: Source of funding is mentioned. The role of the sponsor in the conduct and reporting of the trial is unclear. No other sources of bias are suspected

Krakamp 1989

Methods	Double-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 30 participants</p> <p>Number analysed: 30 participants</p> <p>Overall</p> <ul style="list-style-type: none"> • Age (years; mean (range)): - • Number of participants (n): 15 in each group • Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Participants in neurosurgical ICU • Age > 20 years • Participants selected based on expected survival owing to underlying disease after 2 days at ICU <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Diagnosis of upper GI bleeding • Diagnosis of septicaemia • Diagnosis of pneumonia <p>Baseline imbalances: Quote: "... groups were comparable in terms of age, gender and degree of consciousness"</p> <p>Comment: Participants were people who were admitted to the neurosurgical ICU</p>
Interventions	<p>Ranitidine + placebo</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days): 7 • Route: - • Intervention: - • Concomitant medications: - <p>Ranitidine + pirenzepine</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days): 7 • Route: - • Intervention: - • Concomitant medications: - <p>Adherence to regimen: no dropouts. There does not seem to be any change in dosage, nor were any adverse events mentioned</p> <p>Duration of trial: -</p> <p>Duration of follow-up: no information given. It seems that there was no further follow-up after the end of the study</p>
Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Clinically important upper GI bleeding and related complications (haematemesis, melena, haematin in the gastric tube, haemoglobin fall > 2 g% in 48 hours) were considered as indication for endoscopy • VAP (nil)

Krakamp 1989 (Continued)

- All-cause mortality in ICU
- Adverse events of interventions (nil)

Outcomes sought but not reported in trial

- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Number of participants requiring blood transfusion
- Units of blood transfused

Outcomes reported but not used in review

- Intragastric pH

Notes

Setting: Neurosurgical ICU, Cologne, Germany

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Informed consent : -

Clinical trials registration: -

Sample size calculation: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Study mentions that it is double-blinded, but it does not describe clearly who was blinded or how this was done. However, because this is a placebo-controlled trial, we assume that participants and study personnel were the ones blinded
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: Study mentions that it is double-blinded, but it does not describe clearly who was blinded or how this was done. Moreover GI bleeding was an objective outcome that was detected as per the study definition
Blinding (detection bias) Nosocomial pneumonia	High risk	Comment: Study mentions that it is double-blinded, but it does not describe clearly who was blinded or how this was done. The definition for VAP was not clearly mentioned in the study report
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: Study mentions that it is double-blinded, but it does not describe clearly who was blinded or how this was done. Moreover outcomes were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis

Krakamp 1989 (Continued)

Selective reporting (re-reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: unclear on the source of funding. No additional biases were suspected

Kuusela 1997

Methods	Single-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 53 participants</p> <p>Number analysed: 53 participants</p> <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (months; mean (range)): 31 (29 - 33) • Number of participants (n): 26 • Gender (male/female; n): <p>No prophylaxis</p> <ul style="list-style-type: none"> • Age (months; mean (range)): 32 (29 - 32) • Number of participants (n): 27 • Gender (male/female; n): <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Start of mechanical ventilation during first 2 hours of life <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Other infants treated in the neonatal ICU • No informed consent given by parents <p>Baseline imbalances: The 2 groups were comparable with respect to gestational age, birth weight, Apgar score, cord blood pH, and gender. Participants were preterm and full-term infants</p>
Interventions	<p>Ranitidine</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days): 4 • Route: - • Intervention: 5 mg/kg body weight/d divided into 3 doses • Concomitant medications: Enteral feeding was administered to 17 infants. Morphine only to 4 patients who received gastroscopy. 40 participants received either morphine or phenobarbital for reasons not related to endoscopy <p>No prophylaxis</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days): - • Route: • Intervention: no prophylaxis

Kuusela 1997 (Continued)

- Concomitant medications: Enteral feeding was administered to 17 infants. Morphine only to 4 patients who received gastroscopy. 40 participants received either morphine or phenobarbital for reasons not related to endoscopy

Adherence to regimen: Of 53 participants who were randomised, only 48 were analysed as there were 5 dropouts due to early death (2 participants at gestational age < 33 weeks and 1 participant at gestational age ≥ 33 weeks) and oesophageal atresia (n = 2). 3 infants belonged to the ranitidine group and 2 belonged to the control group

Duration of trial: 10-Month period

Duration of treatment : 4 days; study was discontinued when significant results of the first block of 20 preterm infants randomised were available for interpretation

Duration of follow-up: Routine follow-ups were made at 7 days, then afterwards weekly up to 4 weeks

Outcomes
Outcomes sought in review and reported in trial

- Clinically important upper GI bleeding, detected through endoscopic findings (not extractable)

Note: The intervention was given for 4 days only, whereas endoscopic findings were done at 3 and 6 days (even after treatment), the results of which could not be extracted separately

- All-cause mortality in ICU
- Duration of intubation (mean and range provided, but the range exceeds the study period of 4 days)

Outcomes sought but not reported in trial

- VAP
- All-cause mortality in ICU
- All-cause mortality in hospital
- Duration of ICU stay
- Participants requiring blood transfusions
- Number of units of blood transfused
- Adverse events of interventions

Outcomes reported but not used in review

- Gastric colonisation
- Intragastric pH

Notes

Setting: Department of Neonatal Intensive Care, University Hospital, Tampere, Finland

Source of funding: Quote: "Supported in part by the Finnish Foundation of Pediatric Research"

Conflicts of interest: -

Ethics approval: Quote: "The study protocol was approved by the Ethics Committee of the Tampere University Hospital"

Informed consent: Quote: "The parents received both oral and written information on the study; their informed consent was obtained"

Clinical trials registration: -

Sample size calculation: -

Additional notes: Randomisation of participants was performed after infants were stratified into 2 groups (infants at less than and more than 33 weeks' gestational age) because infants usually less than 33 weeks are ventilated more often. Thus balance was achieved with respect to gestational age for both groups. Study was discontinued after significant results for the first 20 preterm infants (the first block)

Kuusela 1997 (Continued)

were available. When the study was stopped, results for a second block of 10 preterm infants and a third block of 7 preterm infants were available, along with results for a block of 16 and 20 mature infants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The first randomisation block included 20 envelopes in random order for both groups (gestational age < 33 weeks and gestational age ≥ 33 weeks). Followed by two randomisation blocks of 10 envelopes for more preterm infants. Babies closer to term were randomised in one block with 20 envelopes" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Low risk	Quote: "The first randomisation block included 20 envelopes in random order for both groups (gestational age < 33 weeks and gestational age ≥ 33 weeks). Followed by two randomisation blocks of 10 envelopes for more preterm infants. Babies closer to term were randomised in one block with 20 envelopes" Comment: Method adopted to conceal allocation is clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Only the sequence number of the patient were written in the patients records by the nurse responsible for medication; thus the attending physicians the endoscopist and the pathologist remained blinded as to the treatment group" Comment: Study personnel were blinded to treatments. Moreover outcomes of interest were objective in nature
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "Only the sequence number of the patient [was] written in the patient records by the nurse responsible for medication; thus the attending physicians, the endoscopist, and the pathologist remained blinded as to the treatment group" Comment: The endoscopist was blinded to whether or not the participant received prophylaxis. Moreover the outcome measured was objective in nature
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Quote: "Only the sequence number of the patient [was] written in the patient records by the nurse responsible for medication; thus the attending physicians, the endoscopist, and the pathologist remained blinded as to the treatment group" Comment: Outcome assessors were blinded. Moreover owing to the objective nature of the outcomes of interest, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 5 babies were not part of the analysis (3 in treatment and 2 in control groups). A sensitivity analysis was done in which it was assumed that the 3 dropout neonates randomised to the treatment group had mucosal abnormalities, and the 2 dropout neonates randomised to the control group had no mucosal abnormalities. Results of this assumption still indicate that ranitidine was effective in preventing gastric mucosal lesions in infants under stress
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were reported and analysed

Kuusela 1997 (Continued)

Other bias	Low risk	Comment: The Finnish Foundation of Pediatric Research funded the study. The role of the sponsor in the conduct and reporting of the trial is unclear. No other sources of bias are suspected
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Lacroix 1986

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 40 participants</p> <p>Number analysed: 38 participants</p> <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (SE)): 1.59 (3.0) • Number of participants (n): 19 • Gender (male/female; n): 7/12 <p>Placebo</p> <ul style="list-style-type: none"> • Age (years; mean (SE)): 2.13 (3.4) • Number of participants (n): 21 • Gender (male/female; n): 8/13 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • All children from birth to 18 years of age • Admitted to the PICU with illness that precludes any oral or enteral nutrition for at least 2 days <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Admission to the PICU more than 24 hours previously • Burns or surgical problems • Weight < 2.5 kg • Admission because of GI tract bleeding • Need for oral or enteral feeding • Congenital cardiac disease • Creatinine > 3 mg/dL • Renal failure or cerebral death • Intoxication in which the toxic substances ingested could interact with cimetidine • Treatment requiring administration of cimetidine, antacids, anticoagulants, or theophylline, or dialysis <p>Baseline imbalances: Mechanical ventilation was used in 2 times more patients in the placebo group</p>
Interventions	<p>Cimetidine</p> <ul style="list-style-type: none"> • Dose (total/d): 0.13 mL/kg (20 mg/kg), up to a maximum of 6.66 mL/d (1000 mg/d) • Duration of treatment (days): 10 • Route: IV • Intervention: Ampules for intravenous injection of drug contained 2 mL solution of cimetidine at 150 mg/mL (300 mg per ampoule). Ampules were prepared and grouped so that all those used for 1 patient contained or did not contain cimetidine • Concomitant medications: steroids, mechanical ventilation, blood transfusion in some

Lacroix 1986 (Continued)

Placebo

- Dose (total/d): same amount of placebo solution
- Duration of treatment (days): 10
- Route: IV
- Intervention: Ampules for intravenous injection of drug contained 2 mL placebo solution. Ampules were prepared and grouped so that all those used for 1 patient contained or did not contain cimetidine
- Concomitant medications: steroids, mechanical ventilation, blood transfusion in some

Adherence to treatment: -

Duration of trial: -

Duration of follow-up (days): -

Outcomes	Outcomes sought in review and reported in trial <ul style="list-style-type: none">• Clinically important upper GI bleeding• Number of participants requiring blood transfusions Outcome sought in review and not reported in trial <ul style="list-style-type: none">• VAP• All-cause mortality• Duration of ICU stay• Duration of intubation• Adverse events of interventions Outcomes reported in trial and not sought in review <ul style="list-style-type: none">• Gastric pH• Bleeding-free survival	
Notes	Setting: PICU, Department of Pediatrics, Pediatric intensive Care Unit, Hopital Sainte-Justine, University of Montreal, Canada Sponsorship source: Smith Kline & French Laboratories Conflicts of interest: - Ethics approval: Study was approved by the Ethics Committee of Hopital Sainte-Justine Informed consent: Written informed consent was obtained from a parent or guardian of each patient Clinical trials registration: - Sample size calculation: We calculated a necessary sample size of 37 participants	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Allocation of treatment followed a double-blind pattern, according to a list set up by the Smith Kline & French Laboratories from a table of random numbers" Judgement comment: list of random number set up by study sponsor. Some risk of bias suspected

Lacroix 1986 (Continued)

Allocation concealment (selection bias)	Unclear risk	Quote: "Allocation of treatment followed a double-blind pattern, according to a list set up by the Smith Kline & French Laboratories from a table of random numbers" Judgement comment: no details about allocation concealment reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: "double-blind pattern". Procedures for blinding not explicitly reported, but lack of blinding is unlikely to introduce bias to the outcomes or outcome measures
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "UGIB noted from the nasogastric tube, which had been inserted in each patient. Outcome was assessed by the appearance of UGIB and by gastric fluid pH. Massive UGIB was defined as red or brown haemorrhage from the nasogastric tube associated with a decrease in arterial blood pressure of >20 mm Hg or with an acute decrease in haemoglobin level of >2 gm/dl; obvious UGIB was defined as red or brown haemorrhage from the nasogastric tube without a decrease in arterial blood pressure or in haemoglobin level of >2 gm/dl; slight UGIB was defined as minimal bleeding appearing only at the aspiration of gastric fluid" Comment: criteria for diagnosis of this outcome reported objectively
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: no details about blinding of outcome assessors reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no incomplete outcome data suspected. All participants randomised at baseline were included in analyses
Selective reporting (reporting bias)	Low risk	Comment: All outcomes listed in the Methods section (GI bleeding) were also reported in the Results section
Other bias	High risk	Comment: Industry participates in providing drugs and conducting the trial. Mechanical ventilation (risk factor for GI bleeding) was used more often in placebo group

Laggner 1988

Methods	Open-label randomised controlled trial
Participants	Baseline characteristics Number randomised: 84 participants Number analysed: 84 participants Ranitidine <ul style="list-style-type: none"> • Age (years; mean (SD)): 57.3 (18.8) • Number of participants (n): 43 • Gender (male/female; n): 25/18

Laggner 1988 (Continued)

Sucralfate

- Age (years; mean (SD)): 51.1 (17.7)
- Number of participants (n): 41
- Gender (male/female; n): 23/18

Inclusion criteria

- Admitted to the ICU unit with expected duration > 3 days' stay
- High risk for upper GI bleeding
 - History of ulcer
 - Creatinine clearance < 10 mL/min/1.73 m²
 - Respiratory support
 - Thrombocytes < 50,000/mm³
 - Heparin therapy
 - Extracorporeal therapy, e.g. haemodialysis, haemofiltration

Notes: not clear whether any at all, 1, or more of these risk factors is required to be classified as high risk

Exclusion criteria

- Acute upper GI bleeding

Baseline imbalance: Both groups were comparable with respect to age, underlying disorders, and factors predisposing to development of stress ulcers

Interventions
Ranitidine

- Dose (total/d): 300 mg
- Duration of treatment (days, mean (SD)): 8.6 (4.6)
- Route: IV
- Intervention: 6 × 50 mg/d IV as bolus injection; doubling of dose if stomach pH < 3.5
- Concomitant medications: had a Nasogastric tube in place. Anticoagulants were administered to 15 participants

Sucralfate

- Dose (total/d): 6 g
- Duration of treatment (days, mean (SD)): 8.9 (6.1)
- Route: NG tube
- Intervention: 6 × 1 g/d via gastric tube
- Concomitant medications: had a Nasogastric tube in place. Anticoagulants were administered to 15 participants

Adherence to regimen: no dropouts mentioned; however, after bleeding was detected, 1 participant in the sucralfate group was switched over to ranitidine. 2 individuals in the ranitidine group who had bleeding were switched to the sucralfate group, 1 to pirenzepine; in 3, enteral feeding was started

Duration of trial: 18 months

Duration of treatment: until participant was discharged from ICU or when acute problem improved, so that bleeding prophylaxis was no longer deemed necessary

Duration of follow-up: until patient was discharged from ICU or prophylaxis was no longer required (unclear how this was determined)

Outcomes
Outcomes sought in review and reported in trial

- Incidence of stress ulcer bleeding defined as presence of macroscopically visible blood in gastric aspirates and/or haematemesis.

Laggner 1988 (Continued)

- All-cause mortality in ICU
- Duration of intubation (all participants were not intubated)

Outcomes sought but not reported in trial

- VAP
- All-cause mortality in hospital
- Duration of ICU stay
- Number of participants requiring blood transfusion
- Units of blood transfused
- Adverse events

Outcomes reported but not used in review

- Adverse reactions of interventions (no clear numbers provided)
- Gastric pH values
- Bacteriological test (blood culture, bronchial aspirate in ventilated patients)
- Thrombocyte counts
- Liver function tests
- Body temperature

Notes

Setting: ICU Medical University Hospital, Wien, Austria

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Additional notes: Positive bacterial cultures were obtained from bronchial secretions of (43.3% of 74 bronchial secretions in participants receiving ranitidine and 18.6% of 59 bronchial secretions in those receiving sucralfate). Only 30 participants in the ranitidine group and 25 participants in the sucralfate group needed mechanical ventilation. The duration of this was 8.6 ± 4.6 in the ranitidine group and 8.9 ± 6.1 in the sucralfate group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: GI bleeding was detected as per the definition in the study protocol, and the the nature of the outcome of interest is objective

Laggner 1988 (Continued)

Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature, so the likelihood of performance bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants completed the trial and were included in the final analysis. No treatment withdrawals and no trial group changes
Selective reporting (reporting bias)	High risk	Quote: "There was no difference in side effects between the two medication groups" Comment: Adverse reactions due to the interventions are not clearly mentioned in the study report. This would have caused reporting bias in the study report. All other intended outcomes are reported
Other bias	Low risk	Comment: no mention of the source of funding. No additional biases were detected

Laggner 1989

Methods	Single-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 32 participants</p> <p>Number analysed: 32 participants</p> <p>Sucralfate</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 47 (19) Number of participants (n): 16 Gender (male/female; n): 11/5 <p>Ranitidine</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 60 (15) Number of participants (n): 16 Gender (male/female; n): 7/9 <p>Inclusion criteria</p> <ul style="list-style-type: none"> Participants with acute onset of respiratory illness that required mechanical ventilation of more than 48 hours. <p>Exclusion criteria</p> <ul style="list-style-type: none"> Age < 18 and > 80 years Bleeding from nasopharynx, upper gastrointestinal tract Requiring mechanical ventilation of < 49 hours, or > 12 hours before the study commenced Known allergy to sucralfate and ranitidine <p>Baseline imbalances: Quote: "Male: female ratios and mean age of the two treatment groups appear not quite similar, but we could not detect any significant difference"</p>

Laggner 1989 (Continued)

Comment: All participants were long-term ventilated persons

Interventions	<p>Sucralfate</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days, mean (SD)): 11.8 (7.9) • Route: NG tube • Intervention: sucralfate gastric tube every 4 hours. After administration of sucralfate, tubes were clamped for 60 minutes • Concomitant medications: All participants were receiving total parenteral nutrition. All participants received mechanical ventilation with volume-cycled ventilators and had soft nasogastric tubes. Antibiotics <p>Ranitidine</p> <ul style="list-style-type: none"> • Dose (total/d): 300 mg • Duration of treatment (days, mean (SD)): 10.1 (3.6) • Route: IV • Intervention: intravenously as bolus injections of 50 mg every 4 hours. If gastric pH was < 3.5, ranitidine dosage was increased to 100 mg • Concomitant medications: All participants were receiving total parenteral nutrition. All participants received mechanical ventilation with volume-cycled ventilators and had soft nasogastric tubes. Antibiotics <p>Adherence to regimen: -</p> <p>Duration of trial: -</p> <p>Note duration of treatment: Quote: "The study was terminated when the patient was dismissed from the intensive care unit or died"</p> <p>Duration of follow-up: not clearly mentioned in the study report</p>
Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Clinically important upper GI bleeding diagnosed in participants with gastric aspirates and/or haematemesis • VAP diagnosed by appearance of an infiltrate on the chest radiograph with concomitant bronchial colonization, leucocytosis > 15,000/mm³, and fever higher than 38.5°C • All-cause mortality in ICU • Participants requiring blood transfusion • Duration of ICU stay <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • All-cause mortality in hospital • Duration of intubation • Units of blood transfused • Adverse events of interventions <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none"> • Gastric pH • Bacterial colonisation of bronchial secretions
Notes	<p>Setting: Department of Medicine, University of Vienna, Austria</p> <p>Source of funding: -</p> <p>Conflicts of interest:</p>

Laggner 1989 (Continued)

Ethics approval: Quote: "The study was approved by the local ethical committee"

Informed consent: Quote: "...and informed consent was obtained from the next of kin after the potential complications of the procedures were explained"

Comment: Consent was obtained

Clinical trials registration: -

Sample size calculation: -

Additional notes: Quote: "During mechanical ventilation, upper gastrointestinal bleeding developed in three sucralfate- and seven ranitidine-treated patients (18.7 versus 43.7 percent, $p < 0.05$). Until the end of the study, bleeding developed in only three sucralfate- but nine ranitidine treated patients (18.7 versus 56.2 percent, $p \sim 0.05$)"

Comment: Data for 9 participants (in ranitidine) were taken for analysis because it was felt that this occurred when participants were still in the ICU. One death in each group was attributed to GI bleed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... 32 mechanically ventilated patients were randomly assigned, according to a preset table, to receive either ranitidine or sucralfate" Comment: not clear on how the sequence was generated in the "preset table"
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial. Moreover the different modes of administering study drug would not have made it possible to blind participants. Therefore the likelihood of performance bias is high
Blinding (detection bias) Clinically important upper GI bleeding	High risk	Comment: unclear whether outcome assessors were blinded to this outcome. The definition of this outcome was not clearly described in the study report
Blinding (detection bias) Nosocomial pneumonia	Low risk	Quote: "Analysis of chest radiographs was performed by a radiologist, who was not aware of the radiologist, who was not aware of the clinical status or the therapy of the patients" Comment: Outcome assessors for nosocomial pneumonia were blinded
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear whether outcome assessors were blinded to other outcomes of interest. However, outcomes were objective in nature. Therefore the likelihood of performance and detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were reported in the study
Other bias	Low risk	Comment: unclear on the source of funding. No other sources of bias suspected

Lamothe 1991

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 57 participants</p> <p>Number analysed: 57 participants</p> <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 58 (-) • Number of participants (n): 15 • Gender (male/female; n): 11/4 <p>Famotidine</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 61 (-) • Number of participants (n): 18 • Gender (male/female; n): 15/3 <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 65 (-) • Number of participants (n): 19 • Gender (male/female; n): 13/6 <p>Antacids</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 68 (-) • Number of participants (n): 5 • Gender (male/female; n): 2/3 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • About to undergo elective coronary artery bypass graft surgery <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of ulcer disease <p>Baseline imbalances: Quote: "There were no statistically significant difference in age distribution or sex distribution among the four treatment groups"</p> <p>Comment: all participants about to undergo elective coronary artery bypass graft surgery</p>
Interventions	<p>Cimetidine</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days): - • Route: - • Intervention: cimetidine 300 mg IV every 6 hours • Concomitant medications: all participants NG tube postoperatively. Participants with gastroscopic evidence of gastric erosions requiring blood transfusion would be considered treatment failures and would be placed on a combination of another H2 receptor antagonist and sucralfate with or without an antacids with meals <p>Famotidine</p> <ul style="list-style-type: none"> • Dose (total/d): -

Lamothe 1991 (Continued)

- Duration of treatment (days): -
- Route: -
- Intervention: famotidine 20 mg IV every 12 hours
- Concomitant medications: All participants had an NG tube postoperatively. Patients with gastroscopic evidence of gastric erosions requiring blood transfusion would be considered treatment failures and would be placed on a combination of another H2 receptor antagonist and sucralfate with or without an antacids with meals

Ranitidine

- Dose (total/d): -
- Duration of treatment (days): -
- Route: -
- Intervention: ranitidine 50 mg IV every 8 hours
- Concomitant medications: All participants had an NG tube postoperatively. Patients with gastroscopic evidence of gastric erosions requiring blood transfusion would be considered treatment failures and would be placed on a combination of another H2 receptor antagonist and sucralfate with or without an antacids with meals

Antacids (Mylanta II)

- Dose (total/d): -
- Duration of treatment (days): -
- Route: -
- Intervention: antacid 30 mL by nasogastric tube every 4 hours
- Concomitant medications: All participants had an NG tube postoperatively. Patients with gastroscopic evidence of gastric erosions requiring blood transfusion would be considered treatment failures and would be placed on a combination of another H2 receptor antagonist and sucralfate with or without an antacids with meals

Adherence to regimen: All participants received the drugs at least 12 hours before surgery and continued to receive them postoperatively. All participants used NG tube postoperatively

Duration of trial: -

Duration of follow-up: until discharge from hospital

Outcomes

Outcomes sought in review and reported in trial

- Clinically important upper GI bleeding (no participant had this outcome); determined by the need to transfuse blood in a haemodynamically unstable participant because of documented acute gastric erosions. Other clinical signs and symptoms of hypotension and nausea with hematemesis, changes in haematocrit and haemoglobin values as recorded on first and seventh days of treatment, as endoscopy was not used in the study
- Participants requiring blood transfusion (none because of GI bleeding, as there were no reports of the latter)
- Adverse events of interventions

Outcomes sought but not reported in trial report

- VAP
- All-cause mortality in ICU
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Units of blood transfused

Outcomes reported in report but not used in review

Lamothe 1991 (Continued)

- Intragastric pH

Notes	<p>Setting: cardiac surgery at the Medical Centre of Delaware</p> <p>Adherence to regimen: -</p> <p>Source of funding: -</p> <p>Ethics approval: -</p> <p>Informed consent: Quote: "A consent form was signed by all patient before surgery"</p> <p>Comment: Consent was obtained</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: H2 receptor antagonists were combined to form a common interventional arm vs antacids, as the review did not aim to investigate intraclass effects among included interventions. Blood transfusions were done but were not attributed to GI bleeding</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear on blinding of outcome assessors. GI bleeding was an objective outcome that was detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: All other outcomes were objective in nature, which was detected as per the definition in the study protocol. Therefore the likelihood of performance and detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: All randomised participants were accounted in the final analysis
Selective reporting (reporting bias)	Unclear risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: unclear on source of funding. No other known form of bias detected

Larson 1989

Methods	Double-blind placebo-controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 31 participants</p> <p>Number analysed: 31 participants</p> <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (range)): - • Number of participants (n): 13 • Gender (male/female; n): - <p>Placebo</p> <ul style="list-style-type: none"> • Age (years; mean (range)): - • Number of participants (n): 18 • Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Severe head injury admitted to ICU (Glasgow Coma Scale ≥ 10) • Expected ICU stay > 3 days • Participants with no history of upper GI bleeding <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Participants who did not satisfy the inclusion criteria <p>Baseline imbalances: Comment: All participants are admitted with severe head injury</p>
Interventions	<p>Ranitidine</p> <ul style="list-style-type: none"> • Dose (total/d): 150 mg • Duration of treatment (days): - • Route: IV • Intervention: continuous infusion of IV ranitidine (6.25 mg/h) • Concomitant medications: - <p>Placebo</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days): - • Route: - • Intervention: 0.9% NaCl • Concomitant medications: - <p>Adherence to regimen: Comment: 1 participant died owing to the underlying cause of severe head injury on day 2, 1 participant removed pH electrode on day 3, and 5 participants in the placebo group had upper GI bleeding</p> <p>Duration of trial: -</p> <p>Duration of follow-up: -</p>
Outcomes	<p>Outcomes sought in review and reported in trial</p> <p>Primary outcomes</p>

Larson 1989 (Continued)

- Upper GI bleeding diagnosed when blood or 'coffee ground' drainage was seen in NG tube accompanied by $\geq 5\%$ decrease in haematocrit

Secondary outcomes

- All-cause mortality in ICU (not clearly mentioned in which arm)

Outcomes sought but not reported in trial report

- Incidence of ventilator-associated pneumonia
- All-cause mortality in ICU
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Number of participants requiring blood transfusion
- Units of blood transfused
- Adverse reactions of interventions

Outcomes reported in report but not used in review

- Gastric pH

Notes

Setting: University of Louisville, Louisville, KY

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: This was a double-blind placebo-controlled trial. Therefore the likelihood of performance bias is low
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: not clearly mentioned in the study report. GI bleeding was an objective outcome that was detected as per the definition in the study
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias)	Low risk	Comment: not clearly mentioned in the study report. However, the outcome was an objective outcome. Therefore, the likelihood of detection bias is low

Larson 1989 (Continued)

Adverse reactions of interventions

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	High risk	Comment: unclear on source of funding and baseline characteristics of participants

Lee 2014

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 60 participants</p> <p>Number analysed: 60 participants</p> <p>Esomeprazole</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 56.2 (18.4) • Number of participants at baseline (n): 30 • Gender (male/female; n): 20/10 <p>Famotidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 59.2 (15.0) • Number of participants at baseline (n): 30 • Gender (male/female; n): 16/14 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age $\geq$ 18 years • Admitted to ICU or management of severe cerebrovascular accident <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Age < 18 years • History of allergy to either famotidine or esomeprazole • Feeding through a nasogastric tube not possible • Having gastrointestinal bleeding on admission <p>Baseline imbalances: no significant difference for sex, age, GCS, AP-II, intracranial pressure, and operation time between these 2 groups</p>
Interventions	<p>Esomeprazole</p> <ul style="list-style-type: none"> • Dose (total/d): 40 mg • Duration of treatment (days): 7 • Route: nasogastric tube • Intervention: 40 mg (Nexium, AstraZeneca, Sodertaije, Sweden) dissolved in water through a nasogastric tube once per day for 7 days

Lee 2014 (Continued)

- Concomitant medications: Every patient received ventilator support and nasogastric feeding when admitted to the ICU

Famotidine

- Dose (total/d): 40 mg
- Duration of treatment (days): 7
- Route: IV
- Intervention: intravenous famotidine (20 mg, Gaster, Astellas, Shizuoka, Japan) infusion every 12 hours for 7 days
- Concomitant medications: Every patient received ventilator support and nasogastric feeding when admitted to the ICU

Adherence to regimen: -

Duration of trial: March 2007 to March 2010

Duration of follow-up: 30 days

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • GI bleeding (overt or occult) defined as tarry stool, haematemesis, drainage of more than 60 mL 'coffee ground' substance from nasogastric tube, or decreased haemoglobin level > 2 g/dL with proven lesions by endoscopic examination. We also defined positive stool occult blood test as occult bleeding • Ventilator-associated pneumonia defined as pneumonia occurring after 48 hours of ventilator use that fulfils ≥ 3 of the following 4 criteria: (1) presence of persistent (> 48 hours) or new-onset infiltration in CXR; (2) positive sputum smear (with < 10 epithelial cells per low-power field, 100×, and > 25 white blood cells per low-power field or presence of polymorphonuclear cells with phagocytosis); (3) fever with body temperature > 38.3°C; and (4) leucocytosis > 12 × 10⁹/L • Mortality (30 days) • Duration of ICU stay <p>Outcomes sought in review but not reported in trial</p> <ul style="list-style-type: none"> • Blood transfusion • Adverse events of interventions • Duration of intubation <p>Outcome reported in trial but not used in review</p> <ul style="list-style-type: none"> • 30-Day survival
Notes	<p>Setting: Neurosurgical ICU, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei, Taiwan</p> <p>Source of funding: Quote: "This study was performed in the Far Eastern Memorial Hospital and was supported by the research grant FEMH-94-C-016 from the Far Eastern Memorial Hospital"</p> <p>Conflicts of interest: Quote: "All contributing authors declare no conflicts of interest"</p> <p>Ethics approval: Quote: "This study was approved by the Research Ethics Review Committee of the Far Eastern Memorial Hospital"</p> <p>Informed consent: Quote: "After explaining the study purpose and obtaining written consent from their family members"</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Sponsorship source: supported by the research grant FEMH-94- C-016 from the Far Eastern Memorial Hospital</p>

Lee 2014 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly allocated to two groups" Comment: not enough details reported
Allocation concealment (selection bias)	Unclear risk	Comment: no details reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: no details on blinding reported, but lack of blinding is unlikely to introduce bias to the outcomes or outcome measures
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "[We] defined upper gastrointestinal bleeding as tarry stool, haematemesis, drainage of more than 60 mL coffee ground substance from nasogastric tube, or decreased haemoglobin level more than 2 g/dL with proved lesions by endoscopic examination. We also defined positive stool occult blood test as occult bleeding" Comment: Outcome was measured objectively
Blinding (detection bias) Nosocomial pneumonia	Low risk	Quote: "We defined ventilator-associated pneumonia as pneumonia occurring after 48 hours of ventilator use that fulfils three or more of the following four criteria: (1) presence of persistent (> 48 hours) or new onset infiltration in CXR; (2) positive sputum smear (with < 10 epithelial cells per low-power field, 100×, and > 25 white blood cells per low-power field or presence of polymorphonuclear cells with phagocytosis); (3) fever with body temperature > 38.3°C; and (4) leukocytosis > 12 × 10 ⁹ /L" Comment: Outcome was measured objectively
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: no details reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no incomplete outcome data; all participants randomised at baseline were included in analyses
Selective reporting (reporting bias)	Low risk	Comment: no incomplete reporting of outcomes suspected. All outcomes listed in the Methods section were also reported in the Results section
Other bias	Low risk	Comment: no other sources of bias suspected

Levy 1997

Methods	Open-label randomised controlled trial
Participants	Baseline characteristics Number randomised: 70 participants

Levy 1997 (Continued)

Number analysed: 67 participants

Ranitidine

- Age (years; mean (SD)): 56.9 (17.5)
- Number of participants (n): 35
- Gender (male/female; n): 20/15

Omeprazole

- Age (years; mean (SD)): 57.3 (23.5)
- Number of participants (n): 35
- Gender (male/female; n): 17/18

Inclusion criteria

- Affected by at least 1 of 9 risk factors regarded as strong indications for stress ulcer prophylaxis: burns, coagulopathy, acute hepatic failure, major neurologic insult, acute renal failure, respiratory failure, sepsis, shock, and trauma

Acute Physiologic and Chronic Health Evaluation (APACHE II) scores were calculated at baseline

Exclusion criteria

- Age < 18 years
- Pregnancy
- Admitted for a gastrointestinal haemorrhage
- Contraindication to the use of 5-enteral medications
- Admitted to the ICU more than 24 hours before identification for enrolment

Baseline imbalances: Quote: "There were no statistically significant differences between the ranitidine-treated and the omeprazole-treated groups for age, gender, race, or APACHE II scores. Ranitidine subjects had significantly more risk factors at baseline. There were no significant differences in the number of patients who required mechanical ventilation: ranitidine, 26/35 (72%) and omeprazole 16/32 (50%)"

Comment: More participants in the ranitidine group had major neurological insults or trauma. 7 and 5 participants in both groups had coagulopathy at baseline

Interventions
Ranitidine

- Dose (total/d): 150 mg
- Duration of treatment (days): -
- Route: IV
- Intervention: ranitidine-primed infusion 50-mg bolus followed by 150 mg daily by continuous intravenous infusion or bolus administration 50 mg intravenously every 8 hours. In patients with renal insufficiency, the ranitidine dose was adjusted on the basis of the manufacturer's recommendation
- Concomitant medications: -

Omeprazole

- Dose (total/d): 40 mg
- Duration of treatment (days): -
- Route: PO or NG tube
- Intervention: 40 mg once daily orally or by nasogastric tube, if clinically necessary. If given by nasogastric tube, the omeprazole capsule was opened but the enteric-coated granules were not crushed, so as to preserve delayed-release activity. The 40-mg dose of omeprazole was selected on the basis of its pharmacokinetics, and because it is a dose comparable with that used in related disorders
- Concomitant medications: -

Levy 1997 (Continued)

Adherence to regimen: "Seventy patients formed the study group. Thirty five were randomised to the ranitidine treatment group, 35 received omeprazole. Three omeprazole subjects were excluded from data analysis because of errors in randomisation or enrolment criteria protocol violations, resulting in 32 omeprazole-treated patients included in the final analysis"

Duration of trial: over a 10-month period

Duration of follow up: -

Outcomes	<p>Outcomes sought in review and reported in trial</p> <p>Primary outcomes</p> <ul style="list-style-type: none"> Clinically important bleeding, haemodynamic instability resulting from gross bleeding as manifest by haematemesis, aspiration of 'coffee ground' material from the nasogastric tube, or melena. Clinically important bleeding was also defined by a decrease in haemoglobin > 2 g/dL complicated by the need for transfusion or haemodynamic instability. The haemoglobin value obtained 24 hours after admission was used as the baseline to allow for initial fluid equilibration. Oesophagogastroduodenoscopy was done only if deemed clinically indicated by the attending physician <p>Secondary outcomes</p> <ul style="list-style-type: none"> Nosocomial pneumonia as clinically diagnosed Duration of ventilation Duration of ICU stay All-cause mortality in ICU <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> All-cause mortality in hospital Adverse events Participants requiring blood transfusion Units of blood transfused <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none"> Nil
Notes	<p>Setting: New Hanover Regional Medical Center and the Coastal AHEC, Wilmington, North Carolina, and Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "This study was approved by the Institutional Review Board"</p> <p>Informed consent: Quote: "...informed consent was obtained from each patient or their legally authorized representative"</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: Mortality was related to increased APACHE II scores. Endoscopy was performed on 27 participants (ranitidine 15 and omeprazole 15) and stress ulcers were detected in all but 2 participants (from each group). The source of bleeding in these participants could not be determined, but it was presumed to be due to stress ulcerations</p>
Risk of bias	
Bias	<p>Authors' judgement Support for judgement</p>

Levy 1997 (Continued)

Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear on blinding of outcome assessors. GI bleeding was detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	High risk	Comment: unclear on blinding of outcome assessors. The definition of nosocomial pneumonia is not clearly mentioned in the study report
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear on blinding of outcome assessors. However, owing to the objective nature of the outcomes of interest, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comments: Three participants (from the omeprazole group) were not part of the final analysis for legitimate reasons such as errors in randomisation or enrolment criteria protocol violations. However, we did an intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	High risk	Comment: Source of funding was not clearly mentioned in the study report. Baseline differences between groups were detected

Lin 2016

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 120 participants</p> <p>Number analysed: 120 participants</p> <p>Lansoprazole</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 66.7 (16.8) Number of participants at baseline (n): 60 Gender (male/female; n): 38/22 <p>Other medications</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 64.8 (18.6) Number of participants at baseline (n): 60 Gender (male/female; n): 37/23 <p>Inclusion criteria</p>

Lin 2016 (Continued)

- Receiving mechanical ventilation for > 48 hours
- Underwent nasogastric tube intubation
- Prepared to be weaned from the ventilator
- Difficult to wean patients (not weaned off the mechanical ventilator 48 to 72 hours after resolution of their underlying disease process)

Exclusion criteria

- Pregnancy
- Age < 18 years
- Allergic to lansoprazole
- Having active UGI bleeding
- Receiving PPIs or H2RAs within 1 week

Baseline imbalances: no difference in gender, age, and mean number of comorbidities between the 2 groups. Use of ulcerogenic medications was similar between the 2 groups. There was no significant difference between the 2 groups in GCS scores, initial APACHE II score in the medical or surgical ICUs, ventilator-dependent days before starting to be weaned, rapid shallow index (a weaning parameter), and baseline albumin and haemoglobin levels before weaning

Interventions

Lansoprazole

- Dose (total/d): 30 mg
- Duration of treatment (days): 14
- Route: NG tube
- Intervention: lansoprazole OD 30 mg once daily (takepron OD 30 mg/tab, TAKEDA Pharmaceutical Company, Ltd., Osaka, Japan) via NG tube
- Concomitant medications: bolus feeding from the NG tube, NSAID, aspirin, steroids, anticoagulant in some patients

Other medications

- Dose (total/d): -
- Duration of treatment (days): 14
- Route: NG tube
- Intervention: no PPIs or other medications for treating peptic ulcers
- Concomitant medications: bolus feeding from the NG tube, NSAID, aspirin, steroids, anticoagulant in some patients

Adherence to treatment: -

Duration of trial: June 2009 - February 2012

Duration of follow-up: 30 days

Outcomes

Outcomes sought in review and reported in trial

- Gastrointestinal bleeding defined as follows: (1) a 'coffee ground' substance from the NG aspirate $\geq$ 60 mL; (2) fresh blood from the NG tube; or (3) passage of tarry stool. UGI bleeding definition: UGI bleeding with haemoglobin level decrease $\geq$ 2 g/dL or in need of a blood transfusion of > 2 units
- Ventilator-associated pneumonia defined as clinical pulmonary infection score > 6, with scoring system composed of body temperature, white blood cell count, purulent secretions, diffuse or localised pulmonary infiltrate in XR, progression of infiltrate, and culture of secretions
- Mortality

Outcomes sought in review but not reported in trial

- Duration of ICU stay
- Duration of intubation

Lin 2016 (Continued)

- Blood transfusion
- Adverse events of interventions

Outcomes reported in trial but not used in review

- Successful weaning rate

Notes	<p>Setting: Respiratory Care Center, Division of Gastroenterology and Hepatology, Far Eastern Memorial Hospital, New Taipei City, Taiwan</p> <p>Sponsorship source: Quote: "This study was supported by a grant from Far Eastern Memorial Hospital (FEMH) (FEMH-2008-C-043)"</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The protocol was approved by the Research Ethics Review Committee of the Far Eastern Memorial Hospital"</p> <p>Informed consent: Quote: "After obtaining written consent from their families..."</p> <p>Clinical trials registration: ClinicalTrials.gov ID: NCT00708149,</p> <p>Sample size calculation: -</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "They were randomly allocated into two groups using blocked randomisation"
Allocation concealment (selection bias)	Unclear risk	Comment: no details reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "non-double-blind" Comment: Performance bias is a possibility, even if outcomes are objective
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: outcome measured objectively as defined in the trial report
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: outcome measured objectively as defined in the trial report
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Quote: "randomised, non-double-blind" Comment: no blinding in place, lack of blinding unlikely to influence outcome measures and outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no incomplete reporting suspected; all participants randomised at baseline are also included in analyses
Selective reporting (reporting bias)	Low risk	Quote: "(ClinicalTrials.gov ID: NCT00708149). Outcome measures. The primary end point of our study was apparent UGI bleeding 2,20 within 2 weeks of enrolment, which was defined as follows: (1) a 'coffee ground' substance from the NG aspirate 60 mL; (2) fresh blood from the NG tube; or (3) passage of tarry stool. Secondary end points included clinically significant UGI bleeding 2,20 (definition: UGI bleeding with haemoglobin level decrease !2 gm/dL or in need

Lin 2016 (Continued)

of a blood transfusion of > 2 units), successful weaning rate, ventilator-associated pneumonia (definition: clinical pulmonary infection score 21 > 6, a scoring system composed of body temperature, white blood cell count, purulent secretions, diffuse or localized pulmonary infiltrate in CXR, progression of infiltrate, and culture of secretions), and a 30-day survival rate"

Comment: All outcomes reported in the Methods section are also reported in the Results

Other bias	Low risk	Comment: no other sources of bias suspected
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Lopez-Herce 1992

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 165 participants</p> <p>Number analysed: 140 participants</p> <p>Overall</p> <ul style="list-style-type: none"> Age (years; mean (range)): 4.6 years (0 days - 20 years) Number of participants (n): 140 (no prophylaxis n = 35, Almagate n = 35, Ranitidine n = 35, Sucralfate n = 35) Gender (male/female; n): 85/55 <p>Inclusion criteria</p> <ul style="list-style-type: none"> Admitted in the paediatric ICU One of the following criteria: shock, acute cardiac failure, acute respiratory failure, acute liver failure, acute renal failure, sepsis or serious focal infection, coagulopathy, acute nephrologic dysfunction, multiple trauma, severe metabolic acidosis following major surgery <p>Exclusion criteria</p> <ul style="list-style-type: none"> Nasal or pharyngeal bleeding (difficulty in distinguishing from upper GI bleed) <p>Baseline imbalances: Groups were similar when compared using indexes (Therapeutic Intervention Scoring System, Physiological Stability Index, Multi Organ System Failure Scoring System, Zinner and Tryba). Detailed baseline characteristics for each group are not provided in the study report</p>
Interventions	<p>No prophylaxis</p> <ul style="list-style-type: none"> Dose (total/d): - Duration of treatment (days): - Route: - Intervention: no prophylaxis Concomitant medications: All patients had a nasogastric tube in place and gastric fluid drained by gravity. The position of the stomach was confirmed by radiograph. Patients were not fed during the study. Pressor drugs, dopamine, dobutamine, isoproterenol and epinephrine sedatives, barbiturates, diazepam, opiates, and muscle relaxants <p>Almagate</p> <ul style="list-style-type: none"> Dose (total/d): varies Duration of treatment (days): - Route: NG tube

Lopez-Herce 1992 (Continued)

- Intervention: 0.25 mL/kg every 2 hours via NG tube. If this dose did not increase the gastric pH to ≥ 4 , then dosage was increased by 0.25 mL/kg up to a maximum dose of 1 mL/kg
- Concomitant medications: All patients had a nasogastric tube in place and gastric fluid drained by gravity. The position of the stomach was confirmed by radiograph. Patients were not fed during the study. Pressor drugs, dopamine, dobutamine, isoproterenol and epinephrine sedatives, barbiturates, diazepam, opiates, and muscle relaxants

Ranitidine

- Dose (total/d): varies
- Duration of treatment (days): -
- Route: IV
- Intervention: 1.5 mg/kg of ranitidine every 6 hours via IV
- Concomitant medications: All patients had a nasogastric tube in place and gastric fluid drained by gravity. The position of the stomach was confirmed by radiograph. Patients were not fed during the study. Pressor drugs, dopamine, dobutamine, isoproterenol and epinephrine sedatives, barbiturates, diazepam, opiates, and muscle relaxants

Sucralfate

- Dose (total/d): varies
- Duration of treatment (days): -
- Route: NG tube
- Intervention: Children < 10 kg received 0.5 g sucralfate via nasogastric tube. Children > 10 kg received 1 g every 6 hours via nasogastric tube (tablets were dissolved in 5 to 10 mL of water, and drug was administered by nasogastric tube; the tube was subsequently flushed with 2 to 3 mL of water to prevent tube obstruction)
- Concomitant medications: All patients had a nasogastric tube in place and gastric fluid drained by gravity. The position of the stomach was confirmed by radiograph. Patients were not fed during the study. Pressor drugs, dopamine, dobutamine, isoproterenol and epinephrine sedatives, barbiturates, diazepam, opiates, and muscle relaxants.

Adherence to regimen: 165 randomised, 25 "excluded because of protocol reasons"; 1 patient in the Amalgamate group had watery diarrhoea and treatment was switched to ranitidine. In 6 patients from the control group (no prophylaxis) who developed GI bleed, 2 were given Amalgamate, 2 were given sucralfate, and 2 were given amalgamate

Duration of trial: June 1986 to June 1988

Duration of follow-up: -

Outcomes	Outcomes sought in review and reported in trial
	Primary outcome <ul style="list-style-type: none"> • GI haemorrhage microscopic or macroscopic: non-haemorrhagic, slight ('coffee grounds' or small amounts of red blood) and important (with haematological and/or haemodynamic repercussion (e.g. a decrease in haematocrit $> 15\%$ or need for transfusion, hypotension, or need for volume and/or pressors))
	Secondary outcomes <ul style="list-style-type: none"> • Adverse events of interventions
	Outcomes sought in review but not reported in trial <ul style="list-style-type: none"> • All-cause mortality in the hospital • Duration of ICU stay • Duration of intubation • Number of participants requiring blood transfusions • Units of blood transfused

Lopez-Herce 1992 (Continued)

Outcomes reported in trial but not used in review

- Incidence of nosocomial pneumonia (data unclear)
- Intragastric pH
- All-cause mortality in ICU (data unclear for each interventional arm)

Notes

Setting: Pediatric ICU, LaPaz Children's Hospital, Madrid, Spain

Source of funding: -

Conflicts of interest: -

Ethics approval: Quote: "The study was approved by the institutional review board"

Clinical trials registration: -

Sample size calculation: -

Additional notes: One of the 7 participants in the control group with GI bleeding did not receive any treatment; the others were given the following: amalgamate to 2 participants, ranitidine to 2 participants, and sucralfate to 2 participants. The last participant needed ranitidine too to decrease the intensity of bleeding. In the antacid group, 1 child died of haemorrhage, and the other was given ranitidine and sucralfate to contain the bleeding. In the ranitidine group, 1 participant improved within the first 24 hours, without receiving any other drug. In the second participant, the intensity of bleeding decreased when amalgamate was added, and the third participant died. In the sucralfate group, the status of the lone participant with haemorrhage improved without any addition of another drug

It is mentioned that there was no incidence of nosocomial pneumonia, but under "side effects", the study reports 5 incidences of the same and goes on to say that there was a difference between groups with respect to this outcome. The incidence in each group remains unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: no blinding of outcome assessors reported, but GI bleeding was detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	High risk	Comment: no blinding of outcome assessors reported, and definition for detecting pneumonia was not clearly mentioned in the study protocol. Moreover the outcome was not clearly reported in the study
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: The outcome of interest was objective in nature, so the likelihood of performance and detection bias is low
Incomplete outcome data (attrition bias)	Low risk	Comment: Although it mentions that 165 children were randomised and 25 were excluded because of various protocol violations, it is not clear to which

Lopez-Herce 1992 (Continued)

All outcomes		of the 4 study groups these 25 children belonged. A per-protocol analysis was done, and there appears to be no imbalance between groups with respect to the number of participants available for analysis. Therefore, the likelihood of bias due to attrition is low
Selective reporting (reporting bias)	High risk	<p>Comment: A high mortality rate of 38.4% is found in patients with important (major) upper GI bleeding, but counts for each intervention are not given separately.</p> <p>Data on macroscopic upper GI bleeding, slight (microscopic) upper GI bleeding, and mortality are not reported for each intervention separately but are reported for the entire study. Data for pneumonia are not clear</p>
Other bias	Low risk	Comment: Study is unclear on source of funding. No other known source of bias

Luk 1982

Methods	Double-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 182 participants</p> <p>Number analysed: 182 participants</p> <p>Cimetidine</p> <ul style="list-style-type: none"> Age (years; mean (SD)): - Number of participants (n): 62 Gender (male/female; n): - <p>Antacids</p> <ul style="list-style-type: none"> Age (years; mean (SD)): - Number of participants (n): 59 Gender (male/female; n): - <p>Placebo</p> <ul style="list-style-type: none"> Age (years; mean (SD)): - Number of participants (n): 61 Gender (male/female; n): - <p>No prophylaxis</p> <ul style="list-style-type: none"> Age (years; mean (SD)): - Number of participants (n): 128 (not included in randomisation) Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> Not admitted for GI bleeding <p>Exclusion criteria: -</p> <p>Baseline imbalance: "All 4 groups were similar in age, sex, clinical severity of illness and mortality (25%)"</p>

Luk 1982 (Continued)

Interventions

Cimetidine

- Dose (total/d): 1200 mg
- Duration of treatment (days): -
- Route: IV
- Intervention: cimetidine (300 mg IV q 6 hours and placebo antacid 30 mL PO q 3 hours)
- Concomitant medications:

Antacids

- Dose (total/d): 240 mL
- Duration of treatment (days): -
- Route: PO
- Intervention: antacids (similar in potency to Mylanta II) 30 mL PO q 3 hours + placebo IV drug q 6 hours
- Concomitant medications:

Placebo

- Dose (total/d): -
- Duration of treatment (days): -
- Route: IV and PO
- Intervention: placebo IV drug and placebo antacid
- Concomitant medications: -

No prophylaxis

- Dose (total/d): -
- Duration of treatment (days): -
- Route: -
- Intervention: -
- Concomitant medications: -

Adherence to regimen: -
Duration of trial: -
Duration of follow-up: -

Outcomes

Outcomes sought in review and reported in trial

- Gastrointestinal bleeding defined as a decrease in haematocrit of 5% or requirement for transfusion and haemoccult-positive stool or gastric aspirate; endoscopy was performed when clinically feasible

Outcomes sought in review but not reported in trial report

- Incidence of ventilator-associated pneumonia
- All-cause mortality in ICU
- All-cause mortality in the hospital
- Duration of ICU stay
- Duration of intubation
- Number of participants requiring blood transfusion
- Units of blood transfused

Outcomes reported in report but not used in review

- Relationship between GI bleeding and respiratory illness

Notes

Setting: Johns Hopkins University, Baltimore, Maryland, USA

Luk 1982 (Continued)

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Clinical trials registration: -

Sample size calculation: -

Additional notes: Cimetidine and placebo helped reduce the incidence of GI bleeding in participants with respiratory illness

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: This was a double-blind placebo-controlled trial. Study personnel were blinded. Therefore the likelihood of performance bias is low
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: This was a double-blind placebo-controlled trial, and GI bleed was an objective outcome that was diagnosed as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: No other outcome of interest was mentioned in this study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: unclear on source of funding. No other sources of bias suspected

Maasoumi 2016

Methods	Parallel-group randomised controlled trial
Participants	Baseline characteristics
	Number randomised: 90 participants
	Number analysed: 90 participants

Maasoumi 2016 (Continued)

Ranitidine

- Age (years, mean (SD)): - (-)
- Number of participants (n): 45
- Gender (male/female; n): -

Pantoprazole

- Age (years; mean (SD)): - (-)
- Number of participants (n): 45
- Gender (male/female; n): -

Inclusion criteria

- Candidates for coronary artery bypass graft surgery

Exclusion criteria: -

Baseline imbalances: -

Interventions

Ranitidine

- Dose (total/d): -
- Duration of treatment (days): until ICU discharge
- Route: -
- Intervention: ranitidine before and after surgery
- Concomitant medications: -

Pantoprazole

- Dose (total/d): -
- Duration of treatment (days): until ICU discharge
- Route: -
- Intervention: pantoprazole before and after surgery
- Concomitant medications: -

Adherence to regimen: -

Duration of trial: -

Duration of follow-up: -

Outcomes

Outcomes sought in review and reported in trial

- Adverse events of interventions

Outcomes sought but not reported in trial

- Clinically important GI bleeding
- VAP
- Duration of ICU stay
- All-cause mortality in ICU
- All-cause mortality in hospital
- Duration of intubation
- Blood transfusions

Outcomes reported in trial but not used in review

- Duration of hospital stay
- Gastrological symptoms (such as abdominal distension and vomiting)

Maasoumi 2016 (Continued)

Notes

Setting: ICU

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Additional notes: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not enough detail reported. Quote: "randomly divided"
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to allow judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no information about blinding reported; no definitions for diagnosis of outcomes reported
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: Study did not address this outcome
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: no incomplete reporting of data suspected
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no incomplete reporting of data suspected
Selective reporting (reporting bias)	Unclear risk	Comment: no selective reporting of outcomes suspected. Outcome reported in the Methods section is also reported in the Results section
Other bias	Unclear risk	Comment: not enough detail reported in conference abstract to assess risk of other biases

Macdougall 1977

Methods Open-label randomised controlled trial

Participants **Baseline characteristics**
Interventions for preventing upper gastrointestinal bleeding in people admitted to intensive care units (Review)

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Macdougall 1977 (Continued)

Number randomised: 75 participants

Number analysed: 75 participants

Antacids

- Age (years; mean (SD)):-
- Number of participants (n): 13
- Gender (male/female; n):-

No prophylaxis

- Age (years; mean (SD)):-
- Number of participants (n): 12
- Gender (male/female; n): -

Inclusion criteria

- Admitted in the paediatric ICU
- At least 1 of the following criteria: shock, acute cardiac failure, acute respiratory failure, acute liver failure, acute renal failure, sepsis or serious focal infection, coagulopathy, acute nephrologic dysfunction, multiple trauma, severe metabolic acidosis following major surgery

Exclusion criteria: -

Baseline imbalances: -

Interventions

Antacids

- Dose (total/d): 120 mL
- Duration of treatment (days): -
- Route: NG tube
- Intervention: 20 mL magnesium hydroxide 4-hourly via nasogastric tube, which was then clamped for 1 hour
- Concomitant medications: No corticosteroids were administered

No prophylaxis

- Dose (total/d): -
- Duration of treatment (days): -
- Route: -
- Intervention: -
- Concomitant medications: No corticosteroids were administered

Adherence to regimen: The first 25 participants received either antacids or no prophylaxis. The trial was discontinued when H2 receptor antagonists became available. Of the 50 remaining participants, 10 received metiamide and 16 received cimetidine (after case reports of agranulocytosis by metiamide). The remaining 24 got no prophylaxis

Duration of trial: January 1975 to July 1976

Duration of follow-up: -

Outcomes

Outcomes sought in review and reported in trial

- Clinically important upper GI bleeding defined as aspiration of fresh blood via nasogastric tube
- All-cause mortality in ICU (data unclear for each interventional arm)
- Units of blood transfused (only mean provided)
- Adverse events of interventions (no event recorded)

Outcomes sought in review but not reported in trial

Macdougall 1977 (Continued)

- VAP (data unclear)
- All-cause mortality in the hospital
- Duration of ICU stay
- Duration of intubation
- Number of participants requiring blood transfusion

Outcomes reported in trial but not used in review

- Nil

Notes

Setting: Liver Unit, King's College Hospital and Medical School, Denmark Hill, London SES

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Clinical trials registration: -

Sample size calculation: -

Additional notes: Only data for the comparison of antacid with no prophylaxis were extracted for the review, as it was felt that the second part of the trial, which compared H2 receptor antagonist vs no prophylaxis, was not a properly randomised trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the trial was stopped and H2 receptors administered instead of antacids
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear on blinding of outcome assessors, but the definition for diagnosis of GI bleeding is mentioned in the study report
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear on blinding of outcome assessors, but outcomes of interest were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	High risk	Comment: Data are not reported separately for participants who received cimetidine and metiamide. Mortality data are clubbed for both groups of controls (those compared with antacids and H2 receptor antagonists)

Macdougall 1977 (Continued)

Other bias	High risk	Comment: unclear on source of funding and baseline characteristics of participants
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Mahul 1992

Methods	Single-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 158 participants</p> <p>Number analysed: 145 participants</p> <p>Overall</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 57.9 (18.5) • Number of participants (n): 145 (antacids n = 72, sucralfate n = 73) • Gender (male/female; n): 105/40 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admitted to ICU • Intubation for more than 3 days (probably) <p>Exclusion criteria</p> <ul style="list-style-type: none"> • No intubation (n = 79) • Tracheostomy (n = 9) • Intubated < 3 days (n = 163) • Intubated > 3 days (n = 19) • Vital risk for new intubation (n = 15) • Intubated before ICU (n = 1) • Gastric bleeding (n = 1) • Oesogastrectomy (n = 2) <p>Baseline imbalances: 48 participants had 'primitive pneumonia' on admission, 14 had tracheobronchitis, and bacterial colonisation was noted in 36 participants, respectively (not clear to which intervention these participants belonged)</p>
Interventions	<p>Antacids</p> <ul style="list-style-type: none"> • Dose (total/d): 80 mL • Duration of treatment (days): - • Route: NG tube • Intervention: aluminium hydroxide prescribed in 20 mL/6 h via NG tube • Concomitant medications: enteral feeding in 13 participants. Gastric pH was assessed every 6 hours directly before administration of the assigned drug. When continuous enteral nutrition was performed, stress ulcer prophylaxis was maintained but gastric pH measures were discontinued. No selective decontamination of the digestive tract was performed <p>Sucralfate</p> <ul style="list-style-type: none"> • Dose (total/d): 6 g • Duration of treatment (days): - • Route: NG tube • Intervention: sucralfate:1 g/6 h via NG tube

Mahul 1992 (Continued)

- Concomitant medications: enteral feeding in 14 participants. Gastric pH was assessed every 6 hours directly before administration of the assigned drug. When continuous enteral nutrition was performed, stress ulcer prophylaxis was maintained but gastric pH measures were discontinued. No selective decontamination of the digestive tract was performed

Adherence to regimen: Quote: "A single blind randomisation was performed within 12 hours of admission according to a simultaneous and independent dual randomisation. The first randomisation involved mechanical SSD versus no-SSD. The second randomisation involved ulcer prophylaxis with aluminium hydroxide versus sucralfate. At the end, 4 random classes were defined"

"158 of them were randomly selected on the probability of intubation for more than 3 days, 13 were then excluded because of death (n = 5) or extubation (n = 8) before day 3"

Duration of trial: 14 months

Duration of follow-up: not clearly mentioned in the study report

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> Incidence of nosocomial pneumonia: A new and persistent infiltrate on the chest X-ray occurring after 2 days of intubation was considered as nosocomial pneumonia, with an aerobic micro-organism on BAL ≥ 10.5 cfu/mL. In the first 2 days, it was considered to be an early pneumonitis and was included with primary pneumonia Incidence of GI bleeding All-cause mortality in ICU <p>Outcomes sought but not reported in trial report</p> <ul style="list-style-type: none"> All-cause mortality in hospital Duration of ICU stay Duration of intubation Number of participants requiring blood transfusions Number of units of blood transfused Adverse events of interventions <p>Outcomes reported in report but not used in review</p> <ul style="list-style-type: none"> Prevention of aspiration by mechanical drainage of subglottic secretions (SSD) above the tracheal cuff Prevention of gastric colonization by prophylaxis of ulcer bleeding Association between SSD and gastric colonization rates and gastric pH values Association between stress ulcer prophylaxis and gastric colonization rates and gastric pH values
Notes	<p>Setting: Hospital Nord, CHRU St. Etienne, France</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: -</p> <p>Informed consent: -</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p>
Risk of bias	
Bias	Authors' judgement Support for judgement

Mahul 1992 (Continued)

Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "A single blind randomisation was performed within 12 hours of admission according to a simultaneous and independent dual randomisation" Comment: not clear who were blinded. Therefore, unclear on the likelihood of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Quote: "A single blind randomisation was performed within 12 hours of admission according to a simultaneous and independent dual randomisation" Comment: unclear on blinding of outcome assessors. The definition for detecting GI bleeding is not clearly mentioned in the study report
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: unclear on blinding of outcome assessors. Nosocomial pneumonia was detected as per the definition in the study protocol
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear on blinding of outcome assessors. However outcomes of interest were objective in nature, so the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Of the 158 randomised participants, only 145 were part of the final analysis. There were 13 dropouts for the reasons mentioned above. The group to which they were randomised is not clearly mentioned in the study report, and an intention-to-treat analysis was not done. However, the dropouts accounted for less than 10% of randomised participants and appear to be equally distributed (given the double randomisation design of the study). Therefore, the likelihood of attrition bias is low
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	High risk	Comment: source of funding and baseline imbalances of antacid and sucralfate groups unclear

Maier 1994

Methods	Open-label randomised controlled trial
Participants	Baseline characteristics Number randomised: 98 participants Number analysed: 98 participants Ranitidine <ul style="list-style-type: none"> Age (years; mean (SD)): 34.2 (13.3) Number of participants (n): 51 Gender (male/female; n): 37/14 Sucralfate

Maier 1994 (Continued)

- Age (years; mean (SD)): 34.2 (16.4)
- Number of participants (n): 47
- Gender (male/female; n): 39/8

Inclusion criteria

- Endotracheal intubation on admission with anticipation of at least 72 hours of ICU care before extubation
- Presence of NG tube at the time of admission
- Age > 18 years

Exclusion criteria

- Early extubation
- Protocol violation
- Initiation of gastric feeding,
- Thrombocytopaenia
- Death
- Inability to obtain consent

Baseline imbalances: The 2 groups were similar with respect to gender distribution, age, admission APACHE II scores, Injury Severity Score, Revised Trauma Score, and history of smoking. Overall, patterns of injury were also similar in both groups

Interventions

Ranitidine

- Dose (total/d): unclear
- Duration of treatment (days): 72 hours to until the participant was extubated or was fed via the stomach. Study patients were enrolled an average of 4.3 days
- Route: IV
- Intervention: hydrochloride continuous infusion at 0.25 mg/kg bw/h, after a loading dose of 0.5 mg/kg bw
- Concomitant medications: antacids 30 to 60 mL PRN via NG tube for persistent pH < 4, antibiotics in n = 38

Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days): 72 hours to when participant was extubated or was fed via the stomach. Study patients were enrolled an average of 4.3 days
- Route: NG tube
- Intervention: 1 g as a slurry every 6 hours via NG tube
- Concomitant medications: antibiotics in n = 32

Adherence to regimen: All 98 participants were admitted for a minimum of 72 hours in ICU

Duration of trial: April 1991 to October 1993

Duration of follow-up: up to 2 weeks

Outcomes

Outcomes sought in review and reported in trial

- Incidence of pneumonia diagnosed by criteria previously established by the Centres for Disease Control and included the following:
 - Positive sputum gram stain and culture for specific pathogen(s)
 - Chest radiograph demonstrating a new focal infiltrate
 - Temperature > 38.5°C or < 36.5°C
 - White blood cell count > 15,000

Maier 1994 (Continued)

- Incidence of gastric bleeding was determined on NG aspirates and classified as
 - Occult detected by guaiac only
 - Overt for gross blood described as 'coffee grounds', red/brown fluid, or red blood (BRB)
 - Clinically significant - requiring transfusion of blood or operative intervention
- Duration of intubation
- Duration of ICU stay
- All-cause mortality in ICU
- Number of participants requiring blood transfusion

Outcomes sought but not reported in trial report

- All-cause mortality in hospital
- Adverse events of interventions

Outcomes reported in report but not used in review

- Duration of hospital stay
- Units of blood transfused (9 for the participant from ranitidine group; the study reports only "massive transfusions" for the participant from sucralfate group)

Notes	<p>Setting: Harborview Medical Center, 325 Ninth Avenue ZA - 16, Seattle, WA 98104</p> <p>Source of funding: Quote: "Supported in part by grant C#R49/CCR002570"</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The study was approved by the University of Washington Human Subjects Review Board"</p> <p>Informed consent: Quote: "Informed consent was obtained from each patient or patient representative within 24 hours of study enrolment"</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: Of the 12 participants who were classified as having gross bleeding, 7 in ranitidine and 5 in sucralfate groups had 'coffee-ground' aspirates</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear on blinding of outcome assessors. However, GI bleeding was an objective outcome that was detected as per the definition in study protocol

Maier 1994 (Continued)

Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: unclear on blinding of outcome assessors. However, nosocomial pneumonia was an objective outcome that was detected as per the definition in the study protocol
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear on blinding of outcome assessors. However, all other outcomes of interest were objective in nature. Therefore, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants completed the trial and were included in the final analysis. There are no treatment withdrawals and no trial group changes. Therefore, there is no attrition bias
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Trial is supported by a grant from the Centers for Disease and Control and Prevention CDC#R49/CCR002570. The role of the sponsor in the conduct and reporting of the trial is unclear. No other source of bias detected

Martin 1980

Methods	Quasi-randomised trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 77 participants</p> <p>Number analysed: 77 participants</p> <p>Antacids</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 30.5 (15.3) Number of participants (n): 37 Gender (male/female; n): 32/5 <p>Cimetidine</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 29.9 (14) Number of participants (n): 40 Gender (male/female; n): 30/10 <p>Inclusion criteria</p> <ul style="list-style-type: none"> Admitted to Louisville General Hospital surgical intensive care unit Admitted for at least 3 days in ICU Requiring gastric drainage by nasogastric or gastrostomy tube <p>Exclusion criteria</p> <ul style="list-style-type: none"> GI haemorrhage at the time of admission <p>Baseline imbalances: no difference between antacid and cimetidine groups in age and gender. The main reasons for admission were head injury and orthopaedic injury</p>
Interventions	<p>Antacids</p> <ul style="list-style-type: none"> Dose (total/d): 1440 mL

Martin 1980 (Continued)

- Duration of treatment (days): until discharged from intensive care or after initiation of feedings
- Route: NG or gastrostomy tube
- Intervention: given as an hourly dose of 60 mL (Gelusil, Warner/Chilcott, Morris Plains, NJ with buffering capacity of 1.3 m Eq/mL) through the NG or gastrostomy tube followed by a 10-mL flush of tap water, then connected to low continuous suction for 30 minutes. The sequence was repeated every hour provided the gastric pH was 4 or greater. If gastric pH was less than 4 on any 3 of 6 consecutive hourly measurements, it was increased to 90 mL/h. If the pH was still less than 4, dose was increased to 120 mL/h and cimetidine was added at a dose of 300 mg IV every 4 hours. It was increased to 300 mg every 3 hours if pH of less than 4 persisted
- Concomitant medications: hydrochloride (ranitidine), continuous infusion at 0.25 mg/kg/h, after a loading dose of 0.5 mg/kg combined with antacids (30 to 60 mL PRN via NG tube for persistent pH < 4)

Cimetidine

- Dose (total/d): 1800 mg
- Duration of treatment (days): until discharged from intensive care or after initiation of feedings
- Route: IV
- Intervention: 300 mg IV every 4 hours (if gastric pH was less than 4 on any 3 of 6 consecutive hourly aspirations, the rate of administration of the drug was increased to every 3 hours. If the pH was still not maintained, then Gelusil was added at 60 mL/h through NG or gastrostomy tube followed by a 10-mL flush of tap water, and the tube was clamped 30 of every 60 minutes. The dose of antacids was progressively raised according to protocol while the dose of cimetidine was maintained at 300 mg IV every 3 hours (if renal failure was diagnosed, cimetidine was administered at 300 mg every 12 hours)
- Concomitant medications: -

Adherence to regimen: 49 participants in both groups maintained a gastric pH ≥ 4 (29 in antacid and 20 in cimetidine). Fifteen participants required increase in dosage, as they were not able to maintain a gastric pH ≥ 4 at the initial dose (6 in antacid and 7 in cimetidine). For 4 participants who were on cimetidine, an additional antacid administration was required. Nine participants failed to maintain a pH ≥ 4 despite maximum dose as per the study protocol (2 in antacid and 7 in cimetidine)

Duration of trial: January 1979 to August 1979

Duration of follow-up: Quote: "Patients were observed throughout their hospitalisation for GI bleeding and if it developed they were readmitted to the study and to intensive care unit"

Outcomes	Outcomes sought in review and reported in trial
	<ul style="list-style-type: none"> • Incidence of GI bleeding defined as <ul style="list-style-type: none"> ◦ Gastric aspirate that was 3+/4 positive (or grossly bloody) on 3 of 4 consecutive hourly examinations ◦ Red blood that was returned through the nasogastric or gastrostomy tube that did not immediately clear with 500 mL lavage of normal saline solution ◦ Melena that developed after initiation of therapy • All-cause mortality in ICU • Participants requiring blood transfusion • Adverse events of interventions (nil) • Incidence of pneumonia (unintended reporting)
	Outcomes sought but not reported in trial
	<ul style="list-style-type: none"> • Duration of intubation • Duration of ICU stay • All-cause mortality in hospital • Units of blood transfused
	Outcomes reported in trial but not used in review
	<ul style="list-style-type: none"> • Gastric pH values

Martin 1980 (Continued)

Notes

Setting: Louisville General Hospital surgical intensive care unit

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Additional notes: It is mentioned that 19 participants had pneumonia (7 in antacid and 12 in cimetidine), but it was not an outcome intended to be reported in the study. Not sure if this was present on admission

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "patients were assigned to either antacid or cimetidine treatment group according to odd or even date of admission" Comment: This was a quasi-randomised trial, so sequence generation was not done
Allocation concealment (selection bias)	High risk	Quote: "patients were assigned to either antacid or cimetidine treatment group according to odd or even date of admission" Comment: This was a quasi-randomised trial in which allocation was not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: Blinding was not done, and GI bleeding was an objective outcome that was detected as per the definition in the study objectives
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Blinding was not done, and there was no intention to report pneumonia in the study objectives. It was reported when it was diagnosed in participants and was the main cause of sepsis in participants. Unclear whether pneumonia was present on admission
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature; because of this, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All participants were included in the final analysis. There was no attrition bias
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported. Pneumonia was reported although it was not intended. However this was an outcome of interest for the review. Therefore it could have caused reporting bias

Martin 1980 (Continued)

Other bias	Low risk	Comment: Source of funding is unclear from the study report. No other sources of bias are suspected
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Martin 1992

Methods	Double-blind randomised, double-dummy trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 127 participants</p> <p>Number analysed: 127 participants</p> <p>Misoprostol</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 60.2 (15.2) • Number of participants (n): 63 • Gender (male/female; n): 39/24 <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 59.9 (17.5) • Number of participants (n): 64 • Gender (male/female; n): 40/24 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Adults • Undergone a surgical procedure requiring general anaesthesia within 14 days before meeting the other entry criteria • Intubated requiring mechanical ventilation support • Experience an episode of either hypotension or sepsis <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Pregnancy • Psychiatric disorder requiring medication • Upper GI malignancies • Inflammatory bowel disease • Active peptic ulcer disease and burns • Recent central nervous system damage head injury requiring neurosurgical intervention or unstable spinal fractures • Having had UCI surgery proximal to the ampoules of water within 30 days • Receiving non-steroidal anti-inflammatory agents, antiulcer agents or antineoplastic agents • Known allergies to either study medication <p>Baseline imbalances: Quote: "The groups were clinically equivalent at entry with respect to age, gender race, risk factors such as hypotension, sepsis, coagulopathy, renal failure, hepatic failure, cardiac failure, adult respiratory distress syndrome (ARDS), gastric and duodenal lesions"</p> <p>Comment: no significant difference between the 2 groups with respect to demographic and baseline risk factors. Most participants were given a diagnosis of hypotension at baseline. Coagulopathy was present in 15 and 14 participants in both groups. Only 15 and 19 participants in both groups were free of any haemorrhagic gastric lesions at baseline</p>
Interventions	Misoprostol

Martin 1992 (Continued)

- Dose (total/d): 1200 mg
- Duration of treatment (days): see below
- Route: NG tube
- Intervention: 200 g mixed in 20 mL of water every 4 hours through their NG tube and IV placebo every 6 hours, or placebo tablet mixed in water through the NG tube
- Concomitant medications:

Cimetidine

- Dose (total/d): 1200 mg
- Duration of treatment (days): see below
- Route: IV
- Intervention: cimetidine (IV) 300 mg every 6 hours and a placebo tablet mixed in water through the NG tube
- Concomitant medications: -

Adherence to regimen: Quote: "Patients meeting the above criteria for bleeding underwent an endoscopic evaluation within 12 hours and were removed from the study if a upper GI bleeding source was confirmed. All patients still in the study at 72 hours underwent a follow-up endoscopy to determine whether the condition of the gastric or duodenal mucosa had changed. When possible, patients also underwent an endoscopy on exit from the study. If a patient underwent more than one follow-up endoscopy, the score that represented the most severe damage was used"

Duration of trial: July 1986 to January 1988.

Duration of follow up: Quote: "All patients still in the study at 72 hours underwent a follow-up endoscopy to determine whether the condition of the gastric or duodenal mucosa had changed"

Notes duration of treatment: Patients were studied until 1 of 3 events occurred:

- 2 weeks of ICU management was completed
- Improvement allowed discharge from the ICU
- Significant upper gastrointestinal haemorrhage developed

Outcomes
Outcomes sought in review and reported in trial

- Incidence of upper GI bleeding considered a sign of organ failure and defined by any one of the following:
 - Occurrence of haematemesis, melena, or haematochezia.
 - Presence of bright red blood in the NG aspirate that did not immediately clear after lavage with 250 mL normal saline
 - Drop in haemoglobin concentration over 2 consecutive measurements of at least 2 mg/dL with stools that had positive Hematest (Smith Kline Beckman, Sunnyvale, CA) results that were not attributable to other causes

Note: GI bleeding developed 3 to 14 days after the first dose of study medication

- All-cause mortality in ICU

Outcomes sought but not reported in trial

- VAP
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Number of participants requiring blood transfusion
- Units of blood transfused
- Adverse events of interventions

Outcomes reported in the trial but not used in review

Martin 1992 (Continued)

- Participants with organ failure
- Gastric lesion scores

Notes

Setting: 25 medical centres in United States: Medical University of South Carolina, Charleston, South Carolina; Our Lady of Mercy Center, Bronx, New York; Cook County Hospital, Chicago, Illinois; Medical Center of Central George, Macon, Georgia; VA Medical Center, Dayton, Ohio, St. Francis Medical Center, Trenton, New Jersey; Maine Medical Center, Portland, Maine; VA Medical Center, Detroit, Michigan; Buffalo General Hospital, Buffalo, New York; University of South Alabama, Mobile, Alabama; Butterworth Hospital, Grand Rapids, Michigan; Indiana University Medical Center, Indianapolis, Indiana; Brackenridge Hospital, Austin, Texas; Meharry Medical Center, Nashville Tennessee; 6196 Eagle Crest Drive, Huntington Beach, California; Humana Hospital-University, Louisville, Kentucky; Hershey Medical Center, Hershey, Pennsylvania; University Hospital, Columbia, Missouri; Denver General Hospital, Denver, Colorado; Truman Medical Center, Kansas City, Missouri; VA Medical Center, Long Beach, California; Chicago Medical School, North Chicago, Illinois; St. Louis University Medical Center, St. Louis, Missouri; Buffalo VA Medical Center, Buffalo, New York; University of Chicago, Chicago, Illinois

Source of funding: -

Conflicts of interest: -

Ethics approval: Quote: "At each of the 25 institutions, the protocol was approved by the institutional review board"

Informed consent: Quote: "Written informed consent was obtained from the patient or surrogate before study entry"

Clinical trials registration: -

Sample size calculation: -

Additional notes: Mortality was significantly associated with adult respiratory distress syndrome (ARDS), at baseline or at subsequent development, upper GI haemorrhage and additional organ system failure. 87 participants were given diagnosis of haemorrhagic lesions, and 10 participants met the criteria of upper GI haemorrhage as per the study definition

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: This was a double-blind 'double-dummy study' in which placebo was administered to both groups. There personnel involved were blinded, and so the likelihood of performance bias is low
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: This was a double-blind 'double-dummy study' in which placebo was administered to both groups. GI bleeding was an objective outcome that was detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias)	Low risk	Comment: unclear whether outcome assessors were blinded. However, owing to the objective nature of the outcome of interest, the likelihood of detection bias is low

Martin 1992 (Continued)

Adverse reactions of interventions

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants completed the trial and were included in the final analysis. There are no treatment withdrawals and no trial group changes. Therefore there is no attrition bias
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Source of funding is unclear. No other sources of bias are suspected

Martin 1993

Methods	Multi-centre double-blind randomised placebo-controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 131 participants</p> <p>Number analysed: 131 participants</p> <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 59 (19) • Number of participants (n): 65 • Gender (male/female; n): 41/24 <p>Placebo</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 60 (17) • Number of participants (n): 48/18 • Gender (male/female; n): 66 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Signed consent from patient or legal guardian before randomisation • Males or non-lactating, non-pregnant women ≥ 16 years of age • Nasogastric tube in place and admitted to ICU for a minimum anticipated period of 36 hours • At least 1 of the following risk factors for upper GI haemorrhage <ul style="list-style-type: none"> ◦ Major surgery ◦ Multiple trauma to head, neck, abdomen, solid organs, or limbs ◦ Hypotension ◦ Hypovolumic shock ◦ Sepsis (including peritonitis) ◦ Confirmed bacteraemia ◦ Complex fever ◦ Increased WBC count ◦ Bacteriologically determined source of infection ◦ Acute respiratory failure ◦ Need for assisted mechanical ventilation ◦ Severe hypoxia (oxygen deficit (FiO₂ OF 0.31 by mask or at least 2 L/min by nasal prongs) ◦ Acute hypoventilation ◦ Burns involving $\geq 30\%$ of body surface area ◦ Jaundice (plasma bilirubin > 30 mg/dL)

Martin 1993 (Continued)

Exclusion criteria

- > 24 hours since becoming eligible for enrolment into the study
- Intubated for longer than 24 hours
- ICU admission following gastric, oesophageal, or duodenal surgery
- History of gastrectomy or upper GI lesions that are likely to bleed
- Patients on H2 receptor antagonists within 12 hours of admission into the study, or patients receiving omeprazole, anticoagulants (except low-dose heparin), aspirin, NSAIDs within 24 hours before admission
- Treatment with investigational drug within the last 30 days
- Presence of blood in either of the 2 gastric aspirates that were taken 30 minutes apart during screening of potential participants

Baseline imbalances: The 2 treatment groups were similar in terms of demographic and clinical characteristics at baseline, including age, sex, race, type and number of risk factors for bleeding, and nasogastric pH. Most participants had major surgery (40 in cimetidine and 49 in placebo groups). Pneumonia was diagnosed at baseline in 9 and 5 participants, respectively

Interventions
Cimetidine

- Dose (total/d): 1200 mg
- Duration of treatment (days): minimum of 36 hours and maximum of 7 days
- Route: IV
- Intervention: 50-mL loading dose of coded medication (300 mg) in 5% dextrose in water was infused over a 20-minute period. This loading dose was followed immediately by a continuous infusion of coded medication at 50 mg per hour (in 5% dextrose in water at a rate of approximately 10.4 mL/h, using an infusion pump)
- Concomitant medications: Enteral feeding was administered through a Dobhoff tube or through a jejunostomy tube. Phenytoin, diazepam or chlordiazepine, xanthines or lidocaine and propranolol

Placebo

- Dose (total/d): -
- Duration of treatment (days): minimum of 36 hours and maximum of 7 days
- Route: IV
- Intervention: 50-mL loading dose of coded medication (8 mL) in 5% dextrose in water was infused over a 20-minute period. This loading dose was followed immediately by a continuous infusion of coded medication (placebo) in 5% dextrose in water at a rate of approximately 10.4 mL/h, using an infusion pump
- Concomitant medications: Enteral feeding was administered through a Dobhoff tube or through a jejunostomy tube. Phenytoin, diazepam, or chlordiazepine, xanthines or lidocaine and propranolol

Adherence to regimen: Patients with renal failure were given 25 mg/h. Patients with pH below 4 on two different occasions (1 hour apart) 100 mg/h (if renally impaired 50 mg/h)

Duration of trial: September 1988 to March 1989

Duration of follow up: In participants who developed GI bleeding, transfusion monitoring was continued for an additional 24-hour period and a chest radiograph was taken, 48 hours after the medications were discontinued

Outcomes
Outcomes sought in review and reported in trial

- Incidence of upper GI bleeding defined as
 - Haematemesis or bright red blood that did not clear after nasogastric tube adjustment and a 5 to 10 minute lavage or
 - Persistent 'coffee ground' material (8 consecutive hours) that was Gastroocult positive, not clearing with 100 mL lavage, and/or
 - Accompanied by a 5% decrease in haematocrit

Martin 1993 (Continued)

- Incidence of nosocomial pneumonia requiring a new and persistent (at least 24 hours) infiltrate on the chest radiograph that is consistent with pneumonia, and sputum that shows on gram stain, > 25 leucocytes and < 10 squamous cells per low-power field, numerous bacteria per oil immersion field, and a positive sputum culture
- All-cause mortality in ICU

Outcomes sought but not reported in trial report

- All-cause mortality in the hospital
- Duration of ICU stay
- Duration of intubation
- Number of units of blood transfused

Outcomes reported in report but not used in review

- Gastric pH values
- Number of participants requiring blood transfusions (not given separately for each group)

Notes	<p>Setting: multi-centre study (20 institutions)</p> <p>Source of funding: Smith Kline Beecham Pharmaceuticals</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The study was approved by the institutional review board"</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: Quote: "The study was designed as a multi centred trial with 200 randomised participants. The sample size was derived from the assumption that the population failure rate for placebo infused patients would be 20% vs. 5% for cimetidine infused patients. Thus, 100 patients per group (200 patients total) would be required to provide a power of 90%, with a two sided type 1 error of 0.05"</p> <p>Comment: Study was designed to include 200 participants but was terminated after enrolment of 131 participants because of the statically significant reduction in bleeding among participants treated with cimetidine</p> <p>Additional notes: Enteral feeding was given to 5 participants (4 in cimetidine and 1 in placebo groups, and among these a participant from the cimetidine group had protocol defined GI bleeding). An intention to treat was done for the incidence of nosocomial pneumonia (although it was present at baseline in 9 and 5 participants, respectively) as the study definition required new and persistent infiltrates on the chest radiograph. Mortality was not attributed to upper GI haemorrhage</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Low risk	<p>Quote: "All the patients received a one time, 50 mL loading dose of coded medication (cimetidine or placebo) in 5% dextrose in water that was infused over a 20 minute period. This loading dose was followed immediately by a continuous infusion of coded medication (cimetidine or placebo) in 5% dextrose in water at a rate of approximately 10.4 mL/hour, using an infusion pump"</p> <p>Comment: Allocation concealment might have been done since the medication is coded</p>

Martin 1993 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All the patients received a one time, 50 mL loading dose of coded medication (cimetidine or placebo) in 5% dextrose in water that was infused over a 20 minute period" Comments: This was a placebo-controlled study in which medications administered were coded and participants and personnel involved in the trial were blinded
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "To prevent bias in the interpretation of endpoints and safety data each institution designated one investigator to monitor pH and a second investigator, blinded to the pH determinations, to monitor signs and symptoms of upper GI haemorrhage, pneumonia and other safety parameters" Comment: This was a placebo-controlled study in which medications administered were coded and the outcome assessor who monitored signs and symptoms of GI bleeding was unaware of the gastric pH value of respective participants. Moreover GI bleeding was an objective outcome detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Low risk	Quote: "To prevent bias in the interpretation of endpoints and safety data each institution designated one investigator to monitor pH and a second investigator, blinded to the pH determinations, to monitor signs and symptoms of upper GI haemorrhage, pneumonia and other safety parameters" Comment: This was a placebo-controlled study in which medications administered were coded and the outcome assessor who monitored signs and symptoms for pneumonia was unaware of the gastric pH value of respective participants. Moreover, nosocomial pneumonia was an objective outcome detected as per the definition in the study protocol
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: This was a placebo-controlled trial in which medications administered were coded. This would have ensured blinding for other outcome assessments. Moreover, outcomes of interest were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were included in the final analysis. There are no treatment withdrawals and no trial group changes
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Smith Kline Beecham Pharmaceuticals funded part of the study. The role of the sponsor in the conduct and reporting of the trial is unclear. No other sources of bias are suspected

Metz 1993

Methods	Multi-centre double-blind randomised controlled trial
Participants	Baseline characteristics Number randomised: 167 participants Number analysed: 167 participants Ranitidine

Metz 1993 (Continued)

- Age (years; mean (SE)): 35.4 (1.91)
- Number of participants (n): 86
- Gender (male/female; n): 67/19

Placebo

- Age (years; mean (SE)): 32.5 (1.86)
- Number of participants (n): 81
- Gender (male/female; n): 56/25

Inclusion criteria

- Severe head injury, defined as Glasgow Coma Score (12) of ≥ 10
- Age ≥ 18 years
- Participants who had NG tube in place
- Expected ICU stay longer than 72 hours

Exclusion criteria

- Active GI bleeding at baseline
- Severe burns (more than 20% of body surface area)
- Renal insufficiency (serum creatinine concentration > 3 mg/dL [265.2 μ mol/L])
- Documented peptic ulcer diseases within last 6 months
- Baseline count of $< 50,000$ thrombocytes/ μ L
- History of usage of antacids within last 4 hours or histamine 2 receptor antagonist within last 24 hours of study entry

Baseline imbalances: Quote: "No statistically significant difference was present between treatment groups with regard to any demographic variables"

Comment: The imbalance between the 2 groups was only with respect to number of people on mechanical ventilation at study entry. 65 in placebo group and 80 in the ranitidine group. The other baseline characteristics were comparable. Nosocomial pneumonia was present on entry in 2 participants in both groups, respectively. Prothrombin time $>$ upper limit was present in 31/77 and 28/83 participants, respectively

Interventions
Ranitidine

- Dose (total/d): 150 mg
- Duration of treatment (days): Investigational therapy was administered for a maximum of 5 days
- Route: IV
- Intervention: 6.25 mg/h continuous ranitidine infusions
- Concomitant medications: Concurrent enteral nutrition and treatment with H2 receptor antagonists (other than the study drug), antacids, prostaglandins, somatostatin analogues, propranolol, digitalis, and salicylates were not allowed

Placebo

- Dose (total/d): 150 mg
- Duration of treatment (days): Investigational therapy was administered for a maximum of 5 days
- Route: IV
- Intervention: placebo 6.25 mg/h continuous infusion
- Concomitant medications: Concurrent enteral nutrition and treatment with H2 receptor antagonists (other than the study drug), antacids, prostaglandins, somatostatin analogues, propranolol, digitalis, and salicylates were not allowed

Adherence to regimen: If upper GI bleeding was detected according to the definition, then participant was withdrawn from the study. All participants adhered to the prescribed study regimen

Duration of trial: January 1990 to September 1991

Metz 1993 (Continued)

Duration of follow-up: probably until discharge or untimely death

Outcomes
Outcomes sought in review and reported in trial
Primary outcomes

- Incidence of upper GI bleed: Bleeding assessments were performed at 8-hour intervals and were recorded throughout the study monitoring period and consisted of evaluation of the following:
 - Presence of Gastrooccult
 - Positive nasogastric tube drainage
 - Presence of bright red blood per nasogastric tube
 - Haematemesis
 - Haemoccult positive stool
 - Melena and haematochezia

If any of the preceding variables were present, the following 4 questions were addressed to establish the diagnosis of stress ulcer GI bleeding:

- Was the gastric drainage occult blood positive and were 'coffee grounds' present for previous 8 hours?
- Was there minimum 50 mL bright red blood aspirated per NG tube?
- Did the patient experience haematemesis in the last 8 hours?
- Was there endoscopic or surgical confirmation of an upper GI source of bleeding?

If the answer to any of the preceding 4 questions was "yes", the participant was considered to have GI bleeding

Secondary outcomes

- Incidence of nosocomial pneumonia diagnosed on the basis of chest radiograph indicating pulmonary infiltrates and 1 of the following groupings of clinical findings established by Centers for Diseases Control and Prevention
 - Adequate sputum (< 10 epithelial cells per lower-power field) cultures revealing a respiratory pathogen consistent with the sputum gram stain
 - Positive culture from thoracentesis, transtracheal aspirate, or bronchoscopic brush consistent with sputum gram stain
 - Adequate sputum as discussed above
 - Positive blood culture
 - No other source of infection except pulmonary
 - Sputum positive by DNA probe for *Legionella*, e.g. diagnostic single antibody titre (immunoglobulin [IgG] IgM) or 4-fold increase in paired serum samples (IgG) for pathogen
 - Histopathologic evidence of pneumonia

Outcomes sought but not reported in trial

- All-cause mortality in ICU
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Participants requiring blood transfusions
- Units of blood transfused
- Adverse events of interventions

Outcomes reported in report but not used in review

- Incidence of upper GI bleeding with respect to risk factors

Notes

Setting: 10 ICUs from across the United States of America

Metz 1993 (Continued)

Source of funding: Quote: "This study was supported in part by a research grant from Glaxo Pharmaceuticals"

Ethics approval: Quote: "The study was approved by the institutional review boards of all participating sites."

Comment: ethics approval obtained from all 10 participating sites

Informed consent: Quote: "Informed consent was obtained from patient or a legally authorized representative"

Clinical trials registration: -

Sample size calculation: -

Additional notes: Two participants who were diagnosed with pneumonia at baseline were excluded from the denominator of participants who subsequently developed nosocomial pneumonia during the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were then randomised to treatment with 6.25 mg/hour continuous ranitidine or placebo infusion according to a computer generated randomisation scheme" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: This is a placebo-controlled trial in which both the intervention and the control were administered at the same rate as per a computer-generated randomisation scheme, which suggests that participants and study personnel were blinded. Therefore the likelihood of performance bias is low
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: This was a placebo-controlled trial, and GI bleeding was an objective outcome that was detected as per the definition in the study report
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: This is a placebo-controlled trial, and nosocomial pneumonia was an objective outcome detected as per the definition in the study report
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: This is a placebo-controlled trial, and all other outcomes of interest were objective in nature. Therefore the likelihood of performance or detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants completed the trial and were included in the final analysis. There are no treatment withdrawals and no trial group changes. Therefore the likelihood of attrition bias is low
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: This study was supported in part by a research grant from Glaxo Pharmaceuticals, and some of the equipment used was provided by this or-

Metz 1993 (Continued)

ganisation. The role of the sponsor in the conduct and reporting of the trial is unclear. No other form of bias was detected

Mustafa 1994

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 31 participants</p> <p>Number analysed: 31 participants</p> <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 42.43 (18.5) • Number of participants (n): 16 • Gender (male/female; n): - <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 40.12 (13.6) • Number of participants (n): 15 • Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> • People with risk factors for developing stress ulceration and bleeding: hypotension (mean arterial pressure < 65 mmHg), sepsis, renal dysfunction, central nervous system injury or pulmonary dysfunction <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Clinical evidence of pulmonary aspiration • Clinical evidence of pneumonia • Pregnancy • Clinical evidence of Intestinal tract infection precluding administration of sucralfate <p>Baseline imbalances: no significant difference between the 2 groups with respect to demographic and baseline risk factors. Most participants were admitted post surgery</p>
Interventions	<p>Ranitidine</p> <ul style="list-style-type: none"> • Dose (total/d): 300 g • Duration of treatment (days): Treatments began within 6 hours of admission and continued throughout the participant's stay in the ICU • Route: IV • Intervention: 100 g intravenously every 8 hours • Concomitant medications: nutritional support (enteral/parenteral), antibiotics <p>Sucralfate</p> <ul style="list-style-type: none"> • Dose (total/d): 8 g • Duration of treatment (days): Treatments began within 6 hours of admission and continued throughout the participant's stay in the ICU • Route: NG tube • Intervention: 2 g every 6 hours via NG tube, which was flushed with 10 mL of sterile water • Concomitant medications: nutritional support (enteral/parenteral), antibiotics

Mustafa 1994 (Continued)

Adherence to regimen: All participants appear to have adhered to the regimen to which they were randomised

Duration of trial: -

Duration of follow-up: probably until discharge or untimely death of the participant

Outcomes	<p>Outcomes sought in review and reported in trial</p> <p>Primary outcomes</p> <ul style="list-style-type: none"> • Incidence of GI bleeding • Incidence of secondary pneumonia diagnosed with following criteria <ul style="list-style-type: none"> ◦ Persistent new infiltrate on chest radiograph ◦ Fever ($>39^{\circ}\text{C}$) ◦ Leucocytosis (an increase of $> 3 \times 10^8$ WBC/L) ◦ Unexplained reduction in PaO_2 ◦ Positive culture from tracheal aspirates <p>Secondary outcomes</p> <ul style="list-style-type: none"> • All-cause mortality in ICU • Duration of intubation <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • Duration of ICU stay • All-cause mortality in the hospital • Number of participants requiring blood transfusion • Units of blood transfused • Adverse events of interventions <p>Outcomes sought but not used in review</p> <ul style="list-style-type: none"> • Intragastric pH status • Gastric colonisation
Notes	<p>Setting: Department of Intensive Care Unit, Karadeniz Teknik University, Trabzon, Turkey</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: -</p> <p>Informed consent: -</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: Only 3 participants treated with ranitidine and 1 with sucralfate had secondary pneumonia due to some bacterial agent isolated from the stomach. Colonisation of the oropharynx and tracheostomy were more common in participants treated with ranitidine</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report

Mustafa 1994 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and blinding of study personnel or participants was not possible owing to the different modes of administration of study drugs
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: The definition for detecting GI bleeding was not clearly mentioned in the study report, and the study is unclear on blinding of outcome assessors
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: The definition for detecting secondary pneumonia was clearly mentioned in the study report. Still, the study is unclear on blinding of outcome assessors
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes were objective in nature, so the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants completed the trial and were included in the final analysis. There are no treatment withdrawals and no trial group changes.
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were reported
Other bias	Low risk	Comment: No mention of the source of funding. No additional biases were detected

Ng 2012

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 313</p> <p>Number analysed: 311</p> <p>Esomeprazole</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 64.3 (13.8) • Number of participants at baseline (n): 164 • Gender (male/female; n): 126/37 <p>Famotidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 63.1 (13.2) • Number of participants at baseline (n): 149 • Gender (male/female; n): 107/41 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admitted for ACS or acute STEMI • Requiring active treatment with aspirin, clopidogrel, and one of enoxaparin or thrombolytics

Ng 2012 (Continued)

Exclusion criteria

- Known active peptic ulcer disease
- GI bleeding within 8 weeks
- Known iron deficiency anaemia
- Mechanical ventilation with endotracheal intubation
- Active cancer
- Liver cirrhosis
- End-stage renal failure
- Life expectancy < 1 year
- Known allergy to aspirin, clopidogrel, enoxaparin, famotidine, or esomeprazole
- Pregnancy
- Lactation
- Child-bearing potential in the absence of contraception
- Co-prescription of NSAIDs, corticosteroid, or warfarin
- Non-oral feeding
- Impaired gastrointestinal absorption, for example, vomiting, already treated with a PPI for > 1 day or another clinical trial drug for ulcer disease
- Vulnerable subjects
- Age < 18 years
- Persons related unequally to investigators (students and employees)
- Mentally or cognitively disabled people

Baseline imbalances: The 2 treatment groups were similar with respect to baseline demographic characteristics, history of ulcers, cardiac disease, percutaneous coronary stenting, baseline haemoglobin and serum creatinine levels, and use of enoxaparin or thrombolytics

Interventions

Esomeprazole

- Dose (total/d): 20 mg
- Duration of treatment (days): minimum of 4 weeks and maximum of 52 weeks
- Route: PO
- Intervention: oral esomeprazole 20 mg (Nexium, AstraZeneca, Södertälje, Sweden) before bedtime, at least 1 hour after dinner
- Concomitant medications: In patients without prior antiplatelet therapy, the loading dose of aspirin was 300 mg in chewable form, while the loading dose of clopidogrel was 300 mg. Patients were maintained with aspirin 80 to 160 mg daily and clopidogrel 75 mg daily. Patients with implantation of drug-eluting coronary stents were maintained with aspirin 160 mg daily for 3 months. Enoxaparin was given subcutaneously at a dose of 1 mg/kg twice daily in conjunction with oral aspirin and clopidogrel therapy until clinical stabilisation, for a minimum of at least 2 days. In patients with renal impairment, the frequency of enoxaparin was reduced to 1 mg/kg once daily if the estimated creatinine clearance was below 30 mL/min. Anti-Xa activity was not monitored. The protocol for administration of thrombolytics was that of the American Heart Association — Guidelines for the Management of Patients with STEMI 2004

Famotidine

- Dose (total/d): 40mg
- Duration of treatment (days): minimum of 4 weeks and maximum of 52 weeks
- Route: PO
- Intervention: oral famotidine 40 mg (2 tablets of FAMOLTA 20 mg; Jean-Marie Pharmacal, Hong Kong) before bedtime, at least 1 hour after dinner
- Concomitant medications: In patients without prior antiplatelet therapy, the loading dose of aspirin was 300 mg in chewable form, while the loading dose of clopidogrel was 300 mg. Patients were maintained with aspirin 80 to 160 mg daily and clopidogrel 75 mg daily. Patients with implantation of drug-eluting coronary stents were maintained with aspirin 160 mg daily for 3 months. Enoxaparin was given subcutaneously at a dose of 1 mg/kg twice daily in conjunction with oral aspirin and clopidogrel therapy until clinical stabilisation, for a minimum of at least 2 days. In patients with renal impairment,

Ng 2012 (Continued)

the frequency of enoxaparin was reduced to 1 mg/kg once daily if the estimated creatinine clearance was below 30 mL/min. Anti-Xa activity was not monitored. The protocol for administration of thrombolytics was that of the American Heart Association — Guidelines for the Management of Patients with STEMI 2004

Adherence to regimen: Compliance was assessed by pill count. Good compliance with study drugs ($\geq 90\%$): 100% in famotidine group and 98.8% in esomeprazole group

Duration of trial: July 2008 to September 2010

Duration of follow-up: minimum of 4 weeks and maximum of 52 weeks

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> Gastrointestinal bleeding classified as <ul style="list-style-type: none"> Overt bleeding of gastroduodenal origin (confirmed by means of upper gastrointestinal endoscopy) defined as haematemesis, melena, or both, with a non-malignant ulcer or bleeding erosions found on endoscopy or at surgery Overt upper gastrointestinal bleeding of unknown origin defined as haematemesis, melena, or both, without endoscopy performed or Occult gastrointestinal bleeding (confirmed by upper gastrointestinal endoscopy) defined as a decrease of ≥ 2 g/dL in the haemoglobin level, with a non-malignant ulcer or > 5 erosions found on endoscopy All-cause mortality in the hospital Adverse events <p>Outcomes sought in review but not reported in trial</p> <ul style="list-style-type: none"> VAP Duration of ICU stay Duration of intubation Blood transfusions <p>Outcomes reported in trial, but not used in review</p> <ul style="list-style-type: none"> Time to composite outcome
Notes	<p>Setting: acute medical wards, cardiac care unit, and intensive care unit, Department of Medicine and Geriatric, Ruttonjee Hospital, Hong Kong</p> <p>Sponsorship source: Cardiac Research Fund, Ruttonjee Hospital</p> <p>Conflict of interest: Quote: "Potential competing interests: None"</p> <p>Ethics approval: Quote: "The study protocol was approved by the Ethics Committee of the Hong Kong East Cluster"</p> <p>Informed consent: Quote: "All patients gave their written, informed consent"</p> <p>Clinical trials registration: This study was registered at http://www.clinicaltrials.gov (Identifier NCT00683111)</p> <p>Sample size calculation: Yes, described under statistical analysis</p>
Risk of bias	
Bias	<p>Authors' judgement</p> <p>Support for judgement</p>
Random sequence generation (selection bias)	<p>Low risk</p> <p>Quote: "Ward clerks at the four acute medical wards, the cardiac ward, and the intensive care ward generated 50 treatment codes labelled A and 50 codes la-</p>

Ng 2012 (Continued)

		belled B. These were sealed in identical, blinded envelopes that were shuffled randomly"
Allocation concealment (selection bias)	Low risk	Quote: "Ward clerks at the four acute medical wards, the cardiac ward, and the intensive care ward generated 50 treatment codes labelled A and 50 codes labelled B. These were sealed in identical, blinded envelopes that were shuffled randomly. The investigators drew a blinded envelope randomly, and the pharmacist dispensed the repackaged medication. The investigators and patients were blinded to the treatment-group assignments"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The investigators drew a blinded envelope randomly, and the pharmacist dispensed the repackaged medication. The investigators and patients were blinded to the treatment-group assignments. The treatment codes were released after approval of the completion of the study by the Ethics Committee"
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "overt bleeding of gastroduodenal origin (confirmed by means of upper endoscopy), overt upper GIB of unknown origin, bleeding of occult gastrointestinal origin (confirmed by means of upper gastrointestinal endoscopy), obstruction, or perforation" Comment: objective criteria for the measurement of GI bleeding reported
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Quote: "The investigators drew a blinded envelope randomly, and the pharmacist dispensed the repackaged medication. The investigators and patients were blinded to the treatment-group assignments. The treatment codes were released after approval of the completion of the study by the Ethics Committee"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patients were lost to follow-up. Premature termination occurred in 34 (20.9%) and 31 (20.9%) patients in the esomeprazole and famotidine groups, respectively. No patient in the esomeprazole group and three (2.1%) patients in the famotidine group refused to continue the study. In the famotidine group, one patient with significant dyspepsia withdrew consent, while the remaining two patients did not give specific reasons" Comment: Flow chart of participant flow is included, and no incomplete reporting of outcome data is suspected
Selective reporting (reporting bias)	Low risk	Comment: All outcomes that are listed in the Methods section are also reported in the Results section
Other bias	Low risk	Comment: no other sources of bias suspected

Noseworthy 1987

Methods	Open-label randomised controlled trial
Participants	Baseline characteristics Number randomised: 86 participants Number analysed: 86 participants Ranitidine

Noseworthy 1987 (Continued)

- Age (years; mean (SD)): 50 (20)
- Number of participants (n): 42
- Gender (male/female; n): 31/11

Antacids

- Age (years; mean (SD)): 57 (21)
- Number of participants (n): 44
- Gender (male/female; n): 32/12

Inclusion criteria

- Adult ICU patients

Exclusion criteria

- Patients with active duodenal or gastric ulcers
- Patients diagnosed with GI bleeding during admission
- Patients on antacids or H₂ receptor antagonists within the previous 12 hours

Baseline imbalances: Groups were similar with respect to age, gender, and admission diagnosis. Acute and chronic respiratory failure were the most common causes for admission

Interventions

Ranitidine

- Dose (total/d): 200 mg
- Duration of treatment (days): 23 of 42 participants continued up to 72 hours
- Route: IV
- Intervention: 50 mg IV every 6 hours or 75 mg IV every 6 hours if gastric pH not maintained at or above 4 for at least 50% of hourly observations during 6-hour interval between doses
- Concomitant medications: Corticosteroids and heparin were given to 1 participant

Antacids

- Dose (total/d): 720 mL
- Duration of treatment (days): 25 participants of the 44 continued up to 72 hours
- Route: NG tube
- Intervention: antacids (Maalox n = 42 and Amphogel n = 3) (TC magnesium hydroxide, aluminium hydroxide) 30 mL/hour via NG tube
- Concomitant medications: Corticosteroids and heparin were given to 1 participant

Adherence to regimen: Quote: "Eightysix patients were randomised, 42 received ranitidine, 44 received antacids (maalox: 42 and amphogel:3), 38 receiving ranitidine completed 48 hours of study while 23 continued up to 72 hours. Of the patients receiving antacids, 39 completed 48 hours of study, while 25 continued up to 76 hours"

Duration of trial: -

Duration of follow-up: -

Outcomes

Outcomes sought in review and reported in trial

- Incidence of upper GI bleeding
- All-cause mortality in ICU
- Adverse events of interventions

Outcomes sought but not reported in trial

- Incidence of ventilator associated pneumonia
- All-cause mortality in hospital

Noseworthy 1987 (Continued)

- Duration of ICU stay
- Duration of intubation
- Participants requiring blood transfusions
- Units of blood transfused

Outcomes reported in trial but not used in review

- Intragastric pH status (with and without enteral nutrition)
- Creatinine levels and its subsequent clearance

Notes

Setting: Department of Adult Intensive Care, Royal Alexandra Hospitals, Edmonton, and the Division of Critical Care Medicine, University of Alberta, Edmonton, Alberta, Canada

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Clinical trials registration: -

Sample size calculation: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a computer generated table of numbers, patients were assigned by restricted randomisation..." Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Low risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	High risk	Comment: There was no clear definition for detecting clinically significant upper GI bleeding, and it is unclear whether the unblinded nature of the study influenced this outcome, which was otherwise objective in nature
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature. Therefore the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Although 1 participant withdrew from each group during the course of the study, all randomised participants were part of the final analysis. Therefore there was no attrition bias
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes have been reported

Noseworthy 1987 (Continued)

Other bias	Low risk	Comment: no mention of the source of funding. No additional biases were detected
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Ortiz 1998

Methods	Open-label randomised controlled trial
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Participants

Baseline characteristics

Number randomised: 78 participants

Number analysed: 78 participants (for outcomes of interest to this review)

Cimetidine bolus

- Age (years; mean (SD)): 62.2 (14.2)
- Number of participants (n): 14
- Gender (male/female; n): 7/7

Cimetidine continuous

- Age (years; mean (SD)): 61.2 (18.8)
- Number of participants (n): 12
- Gender (male/female; n): 6/6

Sucralfate

- Age (years; mean (SD)): 64.1 (18.8)
- Number of participants (n): 12
- Gender (male/female; n): 5/7

No prophylaxis

- Age (years; mean (SD)): -
- Number of participants (n): 26
- Gender (male/female; n): -

Inclusion criteria

- Respiratory failure for which more than 72 hours of mechanical ventilation was expected

Exclusion criteria

- Age < 18 years
- No nasogastric tube in place
- Prior gastric ablation and contraindication to stress ulcer prophylaxis
- Pneumonia or GI haemorrhage

Baseline imbalances: Baseline characteristics for participants who met the criteria for early withdrawal from the study (for reasons mentioned below) are not mentioned. Nearly 40 participants were withdrawn from the study

Interventions

Cimetidine bolus

- Dose (total/d): 900 mg
- Duration of treatment (days): 7 days
- Route: IV
- Intervention: 300 mg by intravenous bolus every 8 hours

Ortiz 1998 (Continued)

- Concomitant medications: antibiotics

Cimetidine continuous

- Dose (total/d): 900 mg
- Duration of treatment (days): 7 days
- Route: IV
- Intervention: 900 mg by continuous intravenous infusion over 24 hours
- Concomitant medications: antibiotics

Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days): 7 days
- Route: NG tube
- Intervention: 1 gram by NG tube every 6 hours
- Concomitant medications: antibiotics

No prophylaxis

- Dose (total/d): -
- Duration of treatment (days): -
- Route: -
- Intervention: gastric feeding
- Concomitant medications: antibiotics

Adherence to regimen: Quote: "Patients who met criteria for early withdrawal (< 3 days) were not included in the final analysis"

Comment: Withdrawal was mainly due to GI bleeding, gastric colonisation on entry, extubation, mortality, and inability to aspirate GI secretions and change to tube feedings

Duration of trial: -

Duration of follow-up: not clearly mentioned in the study report. Probably until death or discharge

Outcomes

Outcomes sought in review and reported in trial (none of them were the primary outcomes in the study)

- Clinically significant upper GI bleeding defined as a continuous lavage of red blood from the nasogastric aspirate and the need for at least 1 unit of packed red blood cells. This was the definition followed for including/excluding participants. It can be assumed that this definition was followed later on as well during the course of the study and all participants detected with GI bleed required transfusion as well
- All-cause mortality in ICU (within the first 3 days and later on)
- Participant requiring blood transfusions; It can be assumed that this definition was followed later on as well during the course of the study and all participants detected with GI bleed required transfusion from the definition above.

Note to 1: Only those that occurred within the first 3 days and caused withdrawal were reported

Outcomes sought but not reported in trial report

- Incidence of VAP
- Duration of ICU stay
- Units of blood transfused
- Adverse events if interventions

Outcomes reported in report but not used in review

- Duration of intubation (mentioned for only participants who did not withdraw from the study)

Ortiz 1998 (Continued)

- Gastric colonisation
- All-cause mortality in hospital (overlap with ICU mortality suspected)

Notes

Setting: Department of Critical Care Medicine, Saint Vincent Hospital, Worcester, Massachusetts, and Department of Surgery, New England Medical Centre, Boston, Massachusetts

Source of funding: Smith Kline Beecham, Inc., Philadelphia, Pennsylvania

Informed consent: -

Ethics approval: Quote: "The study was approved by the institutional review board"

Clinical trials registration: -

Sample size calculation: -

Comment: Power analysis has been done at the end of the study to detect a correlation of less than 0.4

Additional notes: Cimetidine arms were combined to form a common interventional arm as the review did not aim to investigate efficacy on the basis of dose or mode of administration in the same drug

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "All other patients were randomised (table of random numbers) into one of the three groups" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: This is an unblinded trial, and GI bleeding was detected as per the definition in the trial protocol
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: This is an unblinded trial, and all other outcomes of interest were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 40 randomised participants were withdrawn from the study (more than 50%) for protocol violations and were excluded from the final analysis. However, relevant data (for GI bleed, ICU mortality) could be obtained from the study
Selective reporting (reporting bias)	High risk	Comment: The duration of intubation, hospital mortality and participants requiring antibiotics are mentioned only for participants who were part of the final analysis, and this excluded earlier withdrawals. This accounts for selective reporting

Ortiz 1998 (Continued)

Other bias	High risk	Comment: This study was supported by a grant from Smith Kline Beecham, and some of the equipment used was received from this organisation. However, the role of the sponsor in the conduct and reporting of the trial is unclear. Baseline characteristics for 40 participants (excluded owing to early withdrawal) are not mentioned in the study report
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Pan 2004

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 30 participants</p> <p>Number analysed: 30 participants</p> <p>Pantoprazole</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 46.4 (11.5) • Number of participants (n): 20 • Gender (male/female; n): - <p>Famotidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 49.7 (10.5) • Number of participants (n): 10 • Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Severe acute pancreatitis (SAP) • Admitted to ICU within the Department of Gastroenterology <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Not clearly stated in the study report. Probably participants who did not satisfy the inclusion criteria <p>Baseline imbalances: -</p>
Interventions	<p>Pantoprazole</p> <ul style="list-style-type: none"> • Dose (total/d): 20 mg • Duration of treatment (days): 7 • Route: PO • Intervention: 20 mg od (8 am every morning) for 1 week, oral • Concomitant medications: Somatostatin was used IV drip continuously in all patients; no other anti-acid drugs were used <p>Famotidine</p> <ul style="list-style-type: none"> • Dose (total/d): 80 mg • Duration of treatment (days): 7 • Route: IV • Intervention: 40 mg IV drip, twice daily for 1 week • Concomitant medications: Somatostatin was used IV drip continuously in all patients; no other anti-acid drugs were used <p>Adherence to regimen: no loss to follow-up; all finished treatment</p>

Pan 2004 (Continued)

Duration of trial: -

Duration of follow-up: not clearly mentioned in the study report. Probably until death or discharge from the hospital

Outcomes

Outcomes sought in review and reported in trial

Primary outcome

- Incidence of GI bleeding not defined in the Methods section; however, in the Results section defined on the basis of whether patients had haematemesis, melena, and positive nasogastric tube drainage occult blood test results

Outcomes sought but not reported in trial report

- Incidence of ventilator-associated pneumonia
- All-cause mortality in ICU
- All-cause mortality in hospital
- Duration of intubation
- Duration of ICU stay
- Number of participants requiring blood transfusions
- Units of blood transfused
- Adverse events of interventions

Outcomes reported in report but not used in review

- Intragastric pH

Notes

Setting: -

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: not clearly mentioned in the study report. However, this was not a placebo-controlled trial, and modes of interventions were different. Therefore it might not have been possible to blind personnel, so the likelihood of performance bias is low
Blinding (detection bias) Clinically important upper GI bleeding	High risk	Comment: not clearly mentioned in the study report. However, GI bleeding was an objective outcome, but the definition was not clearly mentioned in the study report

Pan 2004 (Continued)

Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: No other outcomes of interest were part of this study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All outcomes of interest were analysed and reported
Other bias	Low risk	Comment: unclear on the source of funding. No other source of bias detected

Peura 1985

Methods	Double-blind randomised placebo-controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 39 participants</p> <p>Number analysed: 39 participants</p> <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 61.2 (17.8) • Number of participants (n): 21 • Gender (male/female; n):15/6 <p>Placebo</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 51.1 (18.2) • Number of participants (n): 18 • Gender (male/female; n): 13/5 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • All patients admitted to medical ICU with an illness of sufficient severity to expect a minimum of 5 days care in the unit <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Age < 18 years • Presence of acute myocardial infraction • Pregnancy • Prior gastric surgery • Contraindications to upper gastrointestinal endoscopy • Clinical evidence of active or recent GI bleeding, such as hematemesis, melena, haemoccult positive stools, or nasogastric aspirate <p>Baseline imbalances: Quote: "The treatment groups were similar in the number of patients, sex and severity of illness as determined by the primary diagnosis. The cimetidine group tended to be older, but this difference was not statistically significant. Both treatment arms were also similar in the initial pretreatment endoscopic classification"</p>

Peura 1985 (Continued)

Comment: The 2 groups appear to be similar in their demographic and other characteristics, suggesting no imbalance between the 2 at baseline. Mosg in both groups were diagnosed with cardiopulmonary disease

Interventions
Cimetidine

- Dose (total/d): 1200 mg
- Duration of treatment (days): 3 to 14; treatment was stopped when the participant was transferred from the ICU
- Route: IV
- Intervention: 300 mg intravenously every 6 hours
- Concomitant medications: Quote : "Medical management of patients in the study was standard as their underlying conditions allowed"
- Comment: The specific names of medications administered were not mentioned. It seems that almost all participants were on oral feeding when their condition was stable. Participants with compromised renal function received cimetidine or placebo every 8 to 12 hours rather than every 6 hours. Use of ulcerogenic drugs (salicylates, NSAIDs) and antacids was not permitted according to the study protocol

Placebo

- Dose (total/d): -
- Duration of treatment (days): 3 to 14; treatment was stopped when the participant was transferred from the ICU
- Route: IV
- Intervention: IV injection of placebo every 6 hours
- Concomitant medications: Quote : "Primary treatment of the admitting diagnosis as was the medical management of patients in the study was standard as their underlying conditions allowed"
- Comment: The specific names of medications administered were not mentioned. It seems that almost all participants were on oral feeding when their condition was stable. Participants with compromised renal function received cimetidine or placebo every 8 to 12 hours rather than every 6 hours. Use of ulcerogenic drugs (salicylates, NSAIDs) and antacids was not permitted according to the study protocol

Adherence to regimen: -

Duration of trial: -

Duration of follow-up: not clearly mentioned in the study report. Probably until death or discharge from the hospital

Outcomes
Outcomes sought in review and reported in trial
Primary outcome

- Incidence of GI bleeding (mucosal anomalies were determined endoscopically and the incidence of bleeding, thus determined can be considered as primary outcome)

Secondary outcomes

- All-cause mortality in ICU
- Adverse events of interventions

Outcomes sought but not reported in trial report

- Incidence of ventilator-associated pneumonia
- All-cause mortality in hospital
- Duration of intubation
- Duration of ICU stay

Outcomes reported but not used in review

Peura 1985 (Continued)

- Number of participants requiring blood transfusions (not clear whether it is due to persisting bleeding or newly developed bleed)
- Units of blood transfused (not clear whether it was in participants with persisting bleeding or newly developed bleed)
- Gastro duodenal mucosal examination through endoscopy

Notes

Setting: Gastroenterology Service, Department of Medicine, Walter Reed Army Medical Center, Washington, DC

Source of funding: -

Conflicts of interest: -

Ethics approval: Quote: "This protocol was approved by the Clinical Investigation and Human Use Committees of the Walter Reed Army Medical Center"

Informed consent: Quote: "Each patient or guardian gave informed consent"

Clinical trials registration: not provided in the study report

Sample size calculation: -

Additional notes: On initial endoscopy, it was found that there were endoscopic signs of bleeding in 14 of 29 participants with mucosal abnormalities. 3 participants from the placebo arm developed new signs of bleeding during the study, when serial endoscopy was done. One death in the placebo group was attributed to upper GI bleed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The group not receiving cimetidine received an intravenous injection of placebo every 6 hours to ensure the double blind nature of the study" Comment: This suggests that participants and personnel were blinded to the interventions
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "All endoscopic examinations were done by a single investigator and witnessed by a second investigator who observed the procedure through a lectroscope. During the endoscopy, findings were discussed and agreed on by both investigators before an entry was made on the report form. Both investigators were uninformed as to the patient's treatment group" Comment: Outcome assessors were blinded. The definition for detecting GI bleed was not clearly mentioned. However, it was an objective outcome detected through endoscopy. Therefore the likelihood of performance or detection bias is low
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias)	Low risk	Comment: All other outcomes of interest were objective in nature

Peura 1985 (Continued)

Adverse reactions of interventions

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were reported and analysed in the study
Other bias	Low risk	Comment: unclear on the source of funding. No additional biases were detected

Phillips 1998

Methods	Multi-centre randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: not clear</p> <p>Number analysed: 58 participants</p> <p>Omeprazole</p> <ul style="list-style-type: none"> Age (years; mean (SD)): - Number of participants (n): 33 Gender (male/female; n): - <p>Ranitidine</p> <ul style="list-style-type: none"> Age (years; mean (SD)): - Number of participants (n): 25 Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> Critically ill with 2 or more risk factors for stress ulcer, one of which was respiratory failure/mechanical ventilation for longer than 48 hours Gastric pH measured at bedside <p>Exclusion criteria: not clearly mentioned in the study report, most probably participants who did not satisfy the inclusion criteria</p> <p>Baseline imbalances: Quote: "APACHE II, ISS scores and other variables were comparable in both the groups"</p> <p>Comment: The 3 groups appeared to be comparable at baseline</p>
Interventions	<p>Omeprazole</p> <ul style="list-style-type: none"> Dose (total/day): 20 mg Duration of treatment (days): - Route: - Intervention: omeprazole suspension (2 × 40 mg on day 1, then 20 mg/d) Concomitant medications: <p>Ranitidine</p>

Phillips 1998 (Continued)

- Dose (total/d): 150 to 200 mg
- Duration of treatment (days): -
- Route: IV
- Intervention: ranitidine; continuous infusion 150 to 200 mg/24 h, after a loading dose of 50 mg, 13 participants received 150 mg and 12 participants received 200 mg of ranitidine
- Concomitant medications: NG tube present in all participants

Adherence to regimen: -

Duration of trial: -

Duration of follow-up: -

Outcomes	Outcomes sought in review and reported in trial Primary outcomes <ul style="list-style-type: none">• Incidence of GI bleeding (not clearly defined) Secondary outcomes <ul style="list-style-type: none">• Incidence of pneumonia Outcomes sought but not reported in trial <ul style="list-style-type: none">• All-cause mortality in ICU• All-cause mortality in hospital• Duration of ICU stay• Duration of intubation• Number of participants requiring blood transfusions• Number of units of blood transfused Outcomes reported but not used in review <ul style="list-style-type: none">• Intragastric pH values• Costs of acquisition and administration• Adverse events of interventions (not specified what adverse events)	
Notes	Setting: University Hospitals and Clinics, Department of Surgery, 1 Hospital Drive, 65212, USA Source of funding: - Ethics approval: - Informed consent: - Clinical trials registration: - Sample size calculation: - Additional notes: This was a poster presented at Society of Critical Care Medicine; 27th Educational and Scientific Symposium; San Antonio, Texas, USA; February 4 to 8	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report

Phillips 1998 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	High risk	Comment: no clear mention of blinding of outcome assessors. Moreover, there is no clear definition to detect GI bleeding
Blinding (detection bias) Nosocomial pneumonia	High risk	Comment: no clear mention of blinding of outcome assessors. Moreover, there is no clear definition to detect pneumonia
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: No other outcomes of interest were reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Report says there were 58 evaluable participants; it does not specify the number randomised
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: unclear on source of funding. No other source of bias suspected

Pickworth 1993

Methods	Open-label quasi-randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 92 participants</p> <p>Number analysed: 83 participants</p> <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 26.8 (-) • Number of participants (n): 39 • Gender (male/female; n): - <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 27.3 (-) • Number of participants (n): 44 • Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Multiple injured persons • Age 15 to 42 years • Admitted to the 15-bed surgical intensive care unit • Participants who were endotracheally intubated within 24 hours of admission

Pickworth 1993 (Continued)

- NG tube was required for drug administration

Exclusion criteria

- Inclusion in another study
- Transferred from another hospital > 24 hours after injury
- Active GI bleeding
- Having taken antacid, histamine-2 blockers or sucralfate up to 48 hours before admission
- Spinal cord injury
- Treatment with high dose of methylprednisolone

Baseline imbalances: Quote: "There were no significant differences between the two groups in demographic data, trauma score, revised trauma score, Injury severity score and APACHE II score"

Interventions

Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days): until initiation of enteral feeding, extubation, placement of tracheotomy, transfer from ICU, or death
- Route: NG tube
- Intervention: sucralfate 1 g dissolved in 15 mL of sterile water, administered through NG tube every 6 hours
- Concomitant medications: Antibiotics were given, and most participants in both arms were given cefazoline (n = 22)

Ranitidine

- Dose (total/d): 200 mg
- Duration of treatment (days): until initiation of enteral feeding, extubation, placement of tracheotomy, transfer from ICU, or death
- Route: IV
- Intervention: ranitidine 50 mg intravenously every 6 hours
- Concomitant medications: Antibiotics were given, and most participants in both arms were given cefazoline (n = 24)

Adherence to regimen: Of the 92 participants, 9 were subsequently excluded for protocol breaks: 4 patients because they did not meet age criteria, 3 patients because admitting chest radiographic films were abnormal, and 2 patients because of inadvertent extubation

Duration of trial: January 1989 to August 1991

Duration of follow-up: All patients were followed until hospital discharge or death

Outcomes

Outcomes sought in review and reported in trial

Primary outcomes

- Incidence of nosocomial pneumonia based on new infiltrate in the chest roentgenogram and 3 of the following 4 criteria: rectal temperature > 38.5°C, white blood cell count > 10,000 cells/mm³, positive sputum culture obtained by leukins trap, or sputum sample obtained by leukins trap with gram stain containing many white blood cells (> 25 white blood cells, < 10 epithelial cells, and numerous bacteria per high-power field)

Secondary outcomes

- Significant GI bleeding (no episodes of significant upper GI bleeding)
- All-cause mortality in ICU
- Blood transfusions (no participants required transfusions)
- Duration of intubation (data for each intervention not provided separately, SD for each intervention not provided)

Pickworth 1993 (Continued)

- Duration of ICU stay (data for each intervention not provided separately, SD for each intervention not provided)

Outcomes sought but not reported in trial report

- Adverse drug reactions

Outcomes reported in report but not used in review

- Duration of hospital stay (SD not provided)

Notes	<p>Setting: SICU, Grant Medical Centre, Columbus, Ohio, USA</p> <p>Source of funding: Quote: "Supported in part by a Roche Hospital Pharmacy Research Grant"</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Study was approved and monitored by the Institutional Review Board</p> <p>Informed consent: Consent for therapy was considered consent for study inclusion, and specific informed consent was waived by the Institutional Review Board</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: Quote: "The present study was designed to produce a power of 90% with a 30% difference in pneumonia rates between the groups"</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Randomisation occurred by the use of computer generated random number table. Odd numbered patients received ranitidine 50 mg every 6 hours and even numbered patients received sucralfate 1 g dissolved in 15 mL of sterile water ..." Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report but is not adequate to generate a random sequence
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Different modes of administering study drugs and absence of placebo would not have made it possible to blind the study
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: Study report is unclear on blinding of outcome assessors. However GI bleeding was an objective outcome detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: Study report is unclear on blinding of outcome assessors. However, nosocomial pneumonia was detected as per the definition in the study protocol
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: Study report is unclear on blinding of outcome assessors. However, all other outcomes were objective in nature
Incomplete outcome data (attrition bias)	Low risk	Quote: "Nine patients were subsequently excluded for protocol breaks: four patients because they did not meet the age criteria, three patients because ad-

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

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Pickworth 1993 (Continued)

All outcomes

mitting chest radiographic films were abnormal and two patients had inadvertent extubation. These patients had been evenly distributed between study groups and none of the excluded patients developed pneumonia"

Comment: Although 92 participants were enrolled in the study, only 83 were analysed. The interventional arms to which these 9 participants were randomised are not clearly mentioned in the study report, but it does say that participants were evenly distributed between study groups, and none of them developed pneumonia. Therefore the likelihood of attrition bias is minimal

Selective reporting (reporting bias)

Low risk

Comment: All intended outcomes were part of the final analysis

Other bias

Low risk

Comment: Study was supported in part by a Roche Hospital Pharmacy Research Grant. However, the role of the sponsor in the conduct and reporting of the trial is unclear. No other sources of bias suspected

Pinilla 1985

Methods

Parallel-group randomised controlled trial

Participants

Baseline characteristics

Number randomised: 143

Number analysed: 126

Antacid

- Age (years; mean (range)): 43.0 (17 - 85)
- Number of participants at baseline (n): 65
- Gender (male/female; n): 47/18

No intervention

- Age (years; mean (range)): 42.4 (16 - 82)
- Number of participants at baseline (n): 61
- Gender (male/female; n): 46/15

Inclusion criteria

Critically ill with 1 or more of the following risk factors for acute erosive gastritis:

- Acute respiratory failure
- Adult respiratory distress syndrome
- Shock
- Acute renal failure
- Acute liver failure
- Burns > 40% of body surface area
- Sepsis
- Head injury
- Multiple trauma
- Major operative procedure
- Miscellaneous

Exclusion criteria

- Gastric surgery within 1 week of admission to the surgical ICU

Pinilla 1985 (Continued)

- History of potential or active bleeding lesions in the stomach or oesophagus
- Gross upper GI bleeding immediately before initiation of the study
- Coagulation defects
- Inability to introduce a nasogastric tube
- Failure to randomised within 24 hours of admission to the surgical ICU
- Facial fractures
- Antacids, cimetidine or salicylate administration within 48h before admission to the surgical ICU
- Age < 16 years
- Data collection errors

Baseline imbalances: -

Interventions

Antacid

- Dose (total/d): 720 mL
- Duration of treatment (days, mean (range)): 2.6 (1 - 14); when the patient's NG tube was removed, tube feedings were initiated, the oral diet was prescribed, or the patient was discharged from the ICU
- Route: NG tube
- Concomitant medications: Moderate or severe bleeding in either group was followed by gastroscopy and/or angiography to determine the source of bleeding, as well as treatment with antacid titration of gastric contents and 300 mg of iv cimetidine every 6 hours
- Intervention: 30 mL of an antacid solution containing 200 mg of magnesium hydroxide and 288 mg of aluminium hydroxide (Maalox), every hour as necessary to maintain a gastric pH of at least 5. The nasogastric tube was removed from suction and was clamped for 30 minutes after each administration of Maalox. The 30-mL aliquot of Maalox was increased as required to control gastric pH

No intervention

- Dose (total/d): -
- Duration of treatment (days, mean (range)): 3.0 (1 to 21); until patient's nasogastric tube was removed, tube feedings were initiated, the oral diet was prescribed, or the patient was discharged from the ICU
- Route: -
- Concomitant medications: -
- Intervention: no intervention

Adherence to regimen: -

Duration of follow-up: -

Duration of trial: January 1981 to June 1983

Outcomes

Outcomes sought in review and reported in trial

- GI bleeding quantitated in the following manner: microscopic, defined as a small, moderate, or large chemical reaction. Moderate, defined as less than 200 mL of blood visible at any time, or severe, defined as more than 200 mL of blood, or as moderate bleeding recurring at least three times in 6 hours, or as moderate bleeding with worsening vital signs during 6 hours of observation.
- Ventilator-associated pneumonia
- Mortality
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of ventilation (mean; range)
- Number of participants requiring transfusion
- Number of units of blood transfused
- Serious adverse events leading to discontinuation of treatment, prolongation of ICU stay or disability
- Any other adverse events

Outcomes sought in review and not reported in trial

Pinilla 1985 (Continued)

- All-cause mortality in ICU

Outcomes reported in trial but not used in review

- Risk factors for requiring mechanical ventilation
- pH of gastric aspirate

Notes	<p>Setting: ICU, Department of Surgery, University Hospital and the Department of Mathematics University of Saskatchewan</p> <p>Sponsorship source: none</p> <p>Conflicts of interest: -</p> <p>Comments: 28% of patients in the control group and 32% of patients in the treatment group were in the study for 1 day</p> <p>Ethics approval: -</p> <p>Informed consent: -</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were assigned randomly to control or treatment group using a table of random numbers, for groups of four"
Allocation concealment (selection bias)	Unclear risk	Comment: no information reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no details reported, but lack of blinding is unlikely to bias outcome measures and outcomes
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	<p>Quote: "The pH of the gastric aspirate was tested every 2 hours using phenolphthalein paper (Nitrazine, Squibb; or Colorphast. E. Merck), and observed and tested for blood every 4 hours using cumene hydroperoxide; 3,3',5,5'-tetramethylbenzidine (Ames Lab-stix). Upper GI bleeding was quantitated in the following manner: microscopic, defined as a small (+), moderate (++) or large (+++) chemical reaction; moderate, defined as less than 200 mL of blood visible at any time; or severe, defined as more than 200 mL of blood, or as moderate bleeding recurring at least three times in 6 hours, or as moderate bleeding with worsening vital signs during 6 hours of observation"</p> <p>Comment: objective criteria for the diagnosis of GI bleeding reported</p>
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: no details reported, but lack of blinding is unlikely to bias outcome measures and outcomes

Pinilla 1985 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of 143 eligible patients, nine control patients and eight treatment patients were excluded because of an insufficient number of gastric pH measurements (six patients), missing protocol sheets (five patients), randomisation error (four patients), or clotting abnormalities (two patients)" Comment: Of 143 eligible patients 17 were excluded for various reasons unrelated to treatment
Selective reporting (reporting bias)	Unclear risk	Comment: no selective outcome reporting suspected. All outcomes listed in the Methods section were reported in the Results section
Other bias	Low risk	Comment: no other sources of bias suspected

Poleski 1986

Methods	Single-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 44</p> <p>Number analysed: 38 (for the primary outcome of GI bleed), 44 (for all other outcomes of importance to the review)</p> <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 64 (16) • Number of participants (n): 23 • Gender (male/female; n): 11/10 <p>Antacid</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 58.3 (21.2) • Number of participants (n): 21 • Gender (male/female; n): 8/8 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Participates in ICU, at risk of developing gastric erosions due to the following reasons <ul style="list-style-type: none"> ◦ Respiratory Failure, defined as a need for assisted ventilation ◦ Shock (Systolic blood pressure at 90 or below for less than an hour) ◦ Sepsis (positive blood culture with other evidence of infection such as fever, leucocytosis etc) ◦ Renal Insufficiency defined as creatinine > 3 ◦ Liver Failure (cirrhosis or acute encephalopathy) • Signed informed consent (from patients or their immediate relatives) <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Recent head and neck surgery • Patients with prior GI bleeding on admission • Oesophageal gastric surgery • History of ASA ingestion within 72 hours • Recent myocardial infarction <p>Baseline imbalances: The 2 groups were almost similar with respect to age, gender, and number of participants. Most participants were diagnosed with respiratory failure or sepsis, and this was equally distributed in both groups</p>

Poleski 1986 (Continued)

Interventions

Cimetidine

- Dose (total/day): min 1200 mg
- Duration of treatment (days): 72 hours, after endoscopy was performed
- Route: IV
- Intervention: 300 mg IV every 6 hours (if gastric pH remained below 4 on 1 or more occasions in this 6-hour period, 300 mg IV every 4 hours, if the pH was still below 4, dosage increased to 400 mg every 4 hours)
- Concomitant medications: -

Antacids

- Dose (total/d): varies
- Duration of treatment (days): 72 hours, after endoscopy was performed
- Route: NG tube
- Intervention: Antacids (Mylanta II): initial dose of 30 mL of Mylanta II instilled in the stomach via a nasogastric tube. At the end of each hour, the contents of the stomach were aspirated and the pH recorded. If the pH was less than or equal to 3, 60 mL of antacids is instilled and no patient required more than 90 mL of Mylanta II per hours in this study to control pH
- Concomitant medications: -

Adherence to regimen: Two patients in the cimetidine group were removed from the protocol (n = 23) owing to refusal of endoscopy and protocol error, respectively. From the antacid group (n = 21), 5 patients were removed; 4 could not be endoscoped (2 refused endoscopy and 2 developed cardiac complications), and 1 patient with severe ileus (developed nausea and vomiting). Amphogel was substituted for Mylanta II in patients with severe diarrhoea and renal failure

Duration of trial: -

Duration of follow-up: not mentioned in the study report. Probably until death or discharge

Outcomes

Outcomes were not classified as primary or secondary in the study report; however outcomes reported were:

Outcomes sought in review and reported in trial

- Incidence of stress ulcer related GI bleeding determined through endoscopy at 72 hours after study entry (no participant had this outcome)
- All-cause mortality in ICU
- Adverse events of interventions

Outcomes sought but not reported in trial

- Incidence of ventilator-associated pneumonia
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Participants requiring blood transfusions
- Units of blood transfused

Outcomes reported but not used in review

- Gastric erosions (grades 1 to 4)
- Gastric pH values

Notes

Setting: McGill University, Sir Mortimer B. Davis-Jewish Hospital, Montreal, Quebec, Canada

Source of funding: Smith Kline and French Canada Ltd., and Park Davis Canada Ltd.

Conflicts of interest: -

Poleski 1986 (Continued)

Ethics approval: Quote: "The study was approved by the ethics committee on clinical investigations of the Sir Mortimer B.Davis-Jewish General Hospital"

Informed consent: Quote: "A signed consent was obtained from patients or their immediate relations"

Clinical trials registration: -

Sample size calculation: -

Additional notes: Trial reports that NG aspirates were frequently positive for occult bleeds and were not a useful tool for determining clinically significant upper GI bleeding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "After approximately 72 hours all patients were gastroscoped by a single endoscopist who had no knowledge about which therapy the patient was on..." Comment: GI bleeding was an objective outcome that was detected as per the definition in the study protocol; the outcome assessor was blinded
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: This was not an outcome of interest in this study
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear on blinding of outcome assessors. However, all other outcomes were objective in nature, so the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 6 participants were excluded from analysis of the primary outcome of diagnosing GI bleed endoscopically (as endoscopy could not be done on these participants) for reasons mentioned under "adherence to the regimen". An intention-to-treat analysis was done for other outcomes of interest
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were reported and analysed
Other bias	Low risk	Comment: Study was funded by Smith Kline and French Canada Ltd., and Park Davis Canada Ltd., and some of the equipment used was received from this organisation. The role of the sponsor in the conduct and reporting of the trial is unclear

Powell 1993

Methods	Single-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 41 participants</p> <p>Number analysed: 41 participants</p> <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 59.5 (10.1) • Number of participants (n): 11 • Gender (male/female; n): 8/3 <p>Omeprazole (bolus)</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 57.7 (6.9) • Number of participants (n): 10 • Gender (male/female; n): 7/3 <p>Omeprazole (infusion)</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 55.6 (9.6) • Number of participants (n): 10 • Gender (male/female; n): 7/3 <p>Placebo</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 53.3 (10.8) • Number of participants (n): 10 • Gender (male/female; n): 10/0 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Participants scheduled for coronary bypass graft surgery • Participants who gave their informed consent on the eve of the operation <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Active peptic ulcer diseases • Previous definitive acid lowering operation • Current treatment with an H₂ antagonists or other gastric antiseecretory agents • History of severe allergy • Concomitant renal or liver disease • Receiving treatments with warfarin or phenytoin • Having received any non licensed drug within the preceding 30 days <p>Baseline imbalances: Quote: "There was no difference between the groups with regard to sex, age, ethnic origin, the presence of droperidol in the premedication and the drugs used after the operation"</p> <p>Comments: The 4 groups of participants who were scheduled for CABG appear to be similar to each other with respect to demographic characteristics and medications given</p>
Interventions	<p>Ranitidine</p> <ul style="list-style-type: none"> • Dose (total/d): 150 mg • Duration of treatment (days): not clearly mentioned in the study record. Most probably until discharge • Route: IV • Intervention: 50 mg IV every 8 hours

Powell 1993 (Continued)

- Concomitant medications: Papaveretum, hyoscine and droperidol, thiopentone, fentanyl, pancuronium, nitrous oxide, droperidol and midazolam, glyceryl trinitrate (GTN), sodium nitroprusside (SNP), pentolinium, phentolamine, atropine (4 participants during surgery and 5 after surgery), heparin, gentamycin and flucloxacillin or cefuroxime, potassium chloride

Omeprazole (bolus)

- Dose (total/d): 120 mg
- Duration of treatment (days): not clearly mentioned in the study record. Most probably until discharge
- Route: IV bolus
- Intervention: 80-mg IV loading dose, then 40 mg every 8 hours by IV bolus
- Concomitant medications: Papaveretum, hyoscine and droperidol, thiopentone, fentanyl, pancuronium, nitrous oxide, droperidol and midazolam, glyceryl trinitrate (GTN), sodium nitroprusside (SNP), pentolinium, phentolamine, atropine (4 participants during surgery and 5 after surgery), heparin, gentamycin and flucloxacillin or cefuroxime, potassium chloride

Omeprazole (infusion)

- Dose (total/d): 120 mg
- Duration of treatment (days): not clearly mentioned in the study record. Most probably until discharge
- Route: IV infusion
- Intervention: 80 mg IV loading dose, then 40 mg every 8 hours by IV infusion
- Concomitant medications: Papaveretum, hyoscine and droperidol, thiopentone, fentanyl, pancuronium, nitrous oxide, droperidol and midazolam, glyceryl trinitrate (GTN), sodium nitroprusside (SNP), pentolinium, phentolamine, atropine (4 participants during surgery and 5 after surgery), heparin, gentamycin and flucloxacillin or cefuroxime, potassium chloride

Placebo

- Dose (total/d): -
- Duration of treatment (days): not clearly mentioned in the study record. Most probably until discharge
- Route: IV
- Intervention: 0.9% (150 mmol/L) saline 20 mL IV every 8 hours
- Concomitant medications: Papaveretum, hyoscine and droperidol, thiopentone, fentanyl, pancuronium, nitrous oxide, droperidol and midazolam, glyceryl trinitrate (GTN), sodium nitroprusside (SNP), pentolinium, phentolamine, atropine (4 participants during surgery and 5 after surgery), heparin, gentamycin and flucloxacillin or cefuroxime, potassium chloride

Adherence to regimen: -
Duration of trial: -

Duration of follow-up: not clearly mentioned in the study record. Most probably until discharge

Outcomes

Outcomes sought in review and reported in trial (none of these were primary outcomes for this study)

- Incidence of upper GI bleeding
- All-cause mortality in ICU

Outcomes sought but not reported in trial

- Incidence of ventilator-associated pneumonia
- All-cause mortality in the hospital
- Duration of ICU stay
- Duration of intubation
- Number of participants requiring blood transfusions
- Number of units of blood transfused
- Adverse events of interventions

Powell 1993 (Continued)

Outcomes reported but not used in review

- Gastric pH, 24 hour acid output, total pepsin activity
- Haematological, urea, creatinine, and electrolyte data

Notes

Setting: Department of Anaesthetics and Department of Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, London W120NN, UK

Source of funding: not clearly mentioned in the study report. However, it is mentioned that Astra Clinical Research Unit, Edinburgh, supplied the drugs and supported the trial

Conflicts of interest: -

Ethics approval: Quote: "41 patients who were scheduled for CABG were entered into the study, which was approved by the local ethics committee"

Informed consent: Quote: "Informed consent was obtained from each patient on the eve of the operation"

Clinical trials registration: -

Sample size calculation: -

Additional notes: The omeprazole arms were combined to form a common interventional arm as the review did not aim to investigate efficacy on the basis of dose or mode of administration of the same drug

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were assigned to one of the four treatment groups from a random list" Comment: Random sequence generation is not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were assigned to one of the four treatment groups from a random list" Comment: unclear on how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The personnel collecting the aspirates did not know which treatment the patient received" Comment: This was a placebo-controlled trial. Blinding of personnel was done for the primary outcomes of measuring gastric pH and volume of gastric secretion. The likelihood of performance bias is low
Blinding (detection bias) Clinically important upper GI bleeding	High risk	Comment: not clear whether outcome assessors were blinded. The definition for diagnosing GI bleed, which was an objective outcome, was not clearly mentioned in the study report
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: not clear whether outcome assessors were blinded. Moreover, the outcome of interest was objective in nature, so the likelihood of detection bias is low

Powell 1993 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: It is mentioned that Astra Clinical Research Unit, Edinburgh, supplied the drugs and supported the trial. But it is unclear whether they had any influence on the results of the trial. No other sources of bias detected

Prakash 2008

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: Unclear</p> <p>Number analysed: 50 participants</p> <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 35.12 (14.10) • Number of participants (n): 25 • Gender (male/female; n): 19/6 <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 27.48 (16.64) • Number of participants (n): 25 • Gender (male/female; n): 13/12 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admitted to the adult ICU • Receiving mechanical ventilation for at least 24 hours • Having a nasogastric tube in place • Having an expected ICU stay of at least 3 days <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Anticipated to require mechanical ventilation for less than 24 hours, • Receiving antacids, H2 blockers or sucralfate within the previous 48 hours • Active GI bleeding • Evidence of infiltrates on the chest radiograph at the time of admission • Taking steroids • Having undergone gastric or oesophageal surgery • Pregnancy <p>Baseline imbalances: Quote: "There were no significant differences between the groups with respect to age, sex, distribution of underlying diseases, the severity of illness, prophylactic antibiotic therapy, and gastric pH at admission"</p> <p>Comment: no significant difference between the 2 groups with respect to demographic and baseline risk factors. Laparotomy was the most common cause for admission in both groups. The APCHE II score was 14.21 ± 5.44 and 13.34 ± 6.03 in the ranitidine and sucralfate groups, respectively</p>

Prakash 2008 (Continued)

Interventions

Ranitidine

- Dose (total/d): 200 mg
- Duration of treatment (days): -
- Route: IV
- Intervention: 50 mg administered intravenously every 6 hours
- Concomitant medications: -

Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days): -
- Route: NG tube
- Intervention: sucralfate administered as 1 g of suspension diluted in 20 mL sterile water through a nasogastric tube every 6 hours. The nasogastric tube was flushed with 10 mL sterile water and clamped for 30 minutes after instillation
- Concomitant medications: -

Adherence to regimen: Quote: "Seven patients were extubated and one patient died before four days of observation and could not be analysed for the development of late onset pneumonia. 42 patients observed for more than four days"

Comment: Of the initial number of participants who were randomised, only those who were eventually intubated for longer than 24 hours were part of the study analysis

Duration of trial: -

Duration of follow-up: Patients were followed up for a period of 7 days with daily chest radiograph, complete blood count with differential, serum electrolytes, and gastric pH measurements

Outcomes

Outcomes sought in review and reported in trial
Primary outcomes

- Incidence of ventilator-associated pneumonia defined as an infiltrate on chest X-ray plus three of the following criteria
 - Leucocytosis > 10,000 cells/mm³
 - Pathogenic bacteria on a tracheal or blood culture
 - Gram stain of tracheal aspirate showing moderate to heavy bacteria or polymorphs-neutrophils > 25/HPF
 - Temperature > 38°C, using the criteria of Langer and colleagues

15 early-onset and late-onset cases of pneumonia were diagnosed if they occurred during the first 4 days of or 4 days after initiation of mechanical ventilation, respectively. Patients observed for longer than 4 days and were evaluated for the development of late-onset pneumonia

Secondary outcomes

- Significant upper GI bleeding defined as considered to be present in the event of haematemesis, melena, haematochezia, or fresh blood per nasogastric tube, which did not clear after lavage with 500 mL sterile saline
- Participants requiring blood transfusions (no participant required blood transfusions)
- All-cause mortality in ICU

Outcomes sought but not reported in trial

- Duration of ICU stay
- Duration of intubation
- Adverse events of interventions

Prakash 2008 (Continued)

Outcomes reported but not used in review

- Gastric colonisation
- Intragastric pH values

Notes	<p>Setting: Department of Anaesthesia and Intensive Care, Vardhman Mahavir Medical College and Safdarjang Hospital, New Delhi</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The study protocol was approved by the institutional ethics committee"</p> <p>Informed consent: Quote: "...informed consent was obtained from the patients or, if this was not possible because of the clinical condition, from a relative of the family"</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: Of the 25 participants who developed pneumonia, 11 (44%) had the source traced to gastric colonisation (10 in ranitidine and 1 in sucralfate group). <i>Klebsiella</i> species was the most commonly isolated (gastric and tracheal aspirates). Late-onset pneumonia was more common in the ranitidine group than in the sucralfate group (10 and 2; $P = 0.001$), and there was no significant difference in early-onset pneumonia between the 2 groups (5 and 8; $P = 0.098$)</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done using a computer generated random number table" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: no clear mention of blinding the outcome assessor to this outcome. But GI bleeding was an objective outcome detected as per the definition in the study report
Blinding (detection bias) Nosocomial pneumonia	Low risk	Quote: "Chest radiographs were interpreted by a radiologist who had no knowledge of the patients' treatment group after randomisation" Comment: VAP was detected as per the definition in the study report, and the radiologist was blinded to the interventions
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: no clear mention of blinding outcome assessors. However, outcomes were objective in nature, so the likelihood of detection bias is low

Prakash 2008 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Although 50 participants in each treatment arm were evaluated, we are not sure of the number of participants who were initially randomised to each of these arms
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: The source of funding is not mentioned. No additional biases were detected

Priebe 1980

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 75 participants</p> <p>Number analysed: 75 participants</p> <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 62 (-) • Number of participants (n): 38 • Gender (male/female; n): 19/19 <p>Antacids</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 63 (-) • Number of participants (n): 37 • Gender (male/female; n): 22/15 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Participants who were admitted to respiratory surgical intensive care unit of Beth Israel Hospital <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Receiving fluids or food by mouth if having undergone cardiac, gastric, or oesophageal operations • Any evidence of gross upper GI tract bleeding before the beginning of the study <p>Baseline imbalances: Quote: "Of the 38 participants in the cimetidine group, 19 were male and 19 were female, and the mean age was 62 years. Of the 37 participants in the antacid group 22 were male and 15 were female participants. and their mean age was 63 years. The principle diagnosis of both the groups were almost similar (most of them had intra abdominal diseases ; antacid group (7) and cimetidine group (10). There was no statistically significant difference between the two groups with respect to risk factors such as major operative procedures, respiratory failure, sepsis, peritonitis, multiple trauma, renal failure, hypotension and jaundice"</p> <p>"Before administration of any medication, the initial gastric pH values were below 3.5 in 16 of the cimetidine treated participants and 16 of the antacid treated participants. The guaiac test was initially positive in 11 participants in cimetidine group and 9 in antacid group. None of these 20 participants had gross evidence of GI bleeding and were included in the study"</p> <p>Comment: Both of these groups were similar with respect to their baseline characteristics</p>
Interventions	<p>Antacids</p> <ul style="list-style-type: none"> • Dose (total/d): unclear

Priebe 1980 (Continued)

- Duration of treatment (days): until oral feedings began or NG tube was removed, or until the participant was discharged from ICU
- Route: NG tube
- Intervention: initial dose of 30 mL of Mylanta II instilled into the stomach. At the end of each hour, the nasogastric tube was unclamped and the pH of the gastric aspirate was tested. If the pH was less than 3.5, the dosage of Mylanta II was doubled until the pH of the subsequent sample aspirated was greater than 3.5. No patient required more than 120 mL of Mylanta II
- Concomitant medications: The NG tube was clamped for 1 hour in both drugs after administration of the drug. If regurgitation occurred around the NG tube, or if the volume of aspirate exceeded 150 mL, at the end of a 1-hour period, the tube was clamped for 30 minutes after each administration of the drug, and intermittent suction was applied for 30 minutes of each hour until the aspirate was less than 150 mL

Cimetidine

- Dose (total/d): min 1200 mg
- Duration of treatment (days): until oral feedings began or NG tube was removed or until the participant was discharged from ICU
- Route: IV
- Intervention: cimetidine received as initial dose of 300 mg given intravenously and repeated every 6 hours. If the gastric pH remained below 3.5 on 1 or more occasions during the 6-hour period, the interval between subsequent administrations was decreased to 4 hours. If the gastric pH still remained below 3.5, the dosage was increased to 400 mg every 4 hours. No further dosage adjustments were made
- Concomitant medications: The NG tube was clamped for 1 hour in both groups after administration of the drug. If regurgitation occurred around the NG tube, or if the volume of aspirate exceeded 150 mL, at the end of a 1-hour period, the tube was clamped for 30 minutes after each administration of drug, and intermittent suction was applied for 30 minutes of each hour until the aspirate was less than 150 mL

Adherence to regimen: Quote: "In 38 participants treated with cimetidine, failure to achieve a pH of 3.5 or greater on one or more occasions occurred in 18 participants who were initially given 300 mg intravenously every six hours and in nine given a dose of 300 mg every four hours. Seven of eight participants who required 400 mg of cimetidine every four hours had gastric pH values below 3.5 on one or more occasions even at that dosage"

"In 37 participants treated with antacids, failure to achieve a pH of 3.5 or greater occurred in nine participants initially given 30 mL of antacid, six given 60 mL, and one given 120 mL. However, during 1259 hourly administrations of 30 mL of antacids, the gastric pH remained below 3.5 only 21 times (1.7 percent)"

"Patients in whom cimetidine "failed" (who had GI bleed, n = 7), were continued on cimetidine, and antacids were added at an initial dosage of 30 ml/hour and patients who bled with antacids would receive cimetidine also"

"The study was ended when oral feedings were begun and the nasogastric tube was removed, or the participant was discharged from the intensive care unit"

Duration of trial: January 1978 to March 1979

Duration of follow up: not mentioned in the study report. Probably until death or discharge

Outcomes

Outcomes are not categorised as primary and secondary, but from the study report, we feel GI bleeding was the primary outcome

Outcomes sought in review and reported in trial

- Incidence of GI bleeding. Gastric aspirate was checked for frank or occult blood every 4 hours with the Bench guaiac test or the Hemoccult paper test. Any participant who had frank blood in his aspirate

Priebe 1980 (Continued)

or had a 4+ positive guaiac test or a uniformly dark blue reaction with the Hemoccult paper test on 3 consecutive readings was considered to have GI bleed, and prophylaxis was considered a failure

- *Note: Participants started to bleed at 6, 8, 29, 50, 59, and 84 hours and at 8 days after initiation of treatment*

- All-cause mortality in ICU
- Number of participants who received blood transfusions
- Units of blood transfused
- Adverse events of interventions

Outcomes sought but not reported in trial

- Incidence of ventilator-associated pneumonia
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation

Outcomes reported but not used in review

- Intragastric pH status

Notes	<p>Setting: Departments of Anaesthesia and Surgery, Harvard Medical School, and the Beth Israel Hospital</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The study was approved by the Committee on Clinical Investigations, New Procedures and New Forums of Therapy of the Beth Israel Hospital"</p> <p>Informed consent: -</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: In 1 participant from the cimetidine group, GI bleeding was the cause of death</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...randomised by the table of random numbers to receive either cimetidine or antacids" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear whether outcome assessors were blinded. Definition of GI bleeding described in the study report
Blinding (detection bias)	Unclear risk	Comment: Study did not address this outcome

Priebe 1980 (Continued)

Nosocomial pneumonia

Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: All other outcomes of interest were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Source of funding is not mentioned. No additional biases were detected

Prod'hom 1994

Methods	Single-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 375 participants</p> <p>Number analysed: 244 participants</p> <p>Antacids</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 46 (17.9) • Number of participants (n): 81 • Gender (male/female; n): 55/26 <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 52.2 (18.1) • Number of participants (n): 80 • Gender (male/female; n): 54/26 <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 46.4 (17.5) • Number of participants (n): 83 • Gender (male/female; n): 56/27 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admitted to the adult medical and surgical intensive care units • Receiving mechanical ventilation • Nasogastric tube in place <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Active upper gastrointestinal bleeding • Treatment with antacids H2 blockers or sucralfate during the preceding 48 hours • Creatinine levels greater than 200 mL/L • Esogastric surgery, cardiac surgery or organ transplantations • Likely to be extubated within 24 hours

Prod'hom 1994 (Continued)

Baseline imbalances: Quote: "At randomisation, no statistically significant difference was found among the three groups in terms of age ($P = 0.058$), sex ($P > 0.2$), APACHE II scores ($P > 0.2$), Glasgow coma scores ($P > 0.2$), and other underlying characteristics such as pneumonia on admission, participants receiving antibiotic therapy or enteral nutrition"

Comment: The 3 groups were similar. Among the participants from surgical ICU, 30, 28, and 33 participants in the antacid, ranitidine, and sucralfate groups were requiring emergency surgery. Most participants from surgical ICU were diagnosed with trauma requiring some form of intervention. Among participants from the medical ICU, most had some pulmonary disease; 9, 7, and 6 participants were diagnosed with pneumonia on admission to each of the respective groups

Interventions

Antacid

- Dose (total/d): 240 mL
- Duration of treatment (days): until extubation unless interrupted earlier for any of the following pre-determined reasons: an increase in blood creatinine level to more than 200 mol/L, removal of the nasogastric tube, moribund state, discharge from intensive care units, or side effects likely to be related to the stress ulcer regimen
- Route: NG tube
- Intervention: hospital-made suspension containing 5.4% aluminium hydroxide and 1.5% magnesium hydroxide with a buffer capacity of 1.2 mEq/mL, administered every 2 hours. The standard dose of 20 mL was doubled if the gastric pH (tested with pH-indicator strips [Merck and Co., Darmstadt, Germany] before each administration) was less than 4.0. After administering, the NG tube was flushed with 10 mL of sterile water and clamped for 30 minutes
- Concomitant medications: 22 received enteral nutrition, 22 received antibiotics

Ranitidine

- Dose (total/d): 150 mg
- Duration of treatment (days): until extubation unless interrupted earlier for any of the following pre-determined reasons: an increase in blood creatinine level to more than 200/xmol/L, removal of the nasogastric tube, moribund state, discharge from intensive care units, or side effects likely to be related to the stress ulcer regimen
- Route: IV
- Intervention: administered as a continuous intravenous infusion of 150 mg/d (100 mg/d if blood creatinine level was between 150 and 200 mol/L)
- Concomitant medications: 20 received enteral nutrition, and 18 received antibiotics

Sucralfate

- Dose (total/d): 6 g
- Duration of treatment (days): until extubation unless interrupted earlier for any of the following pre-determined reasons: an increase in blood creatinine level to more than 200/xmol/L, removal of the nasogastric tube, moribund state, discharge from intensive care units, or side effects likely to be related to the stress ulcer regimen
- Route: NG tube
- Intervention: administered every 4 hours as 1 g of suspension diluted in 20 mL of sterile water. After administered, the NG tube was flushed with 10 mL of sterile water and clamped for 30 minutes.
- Concomitant medications: 23 received enteral nutrition, and 15 received antibiotics

Adherence to regimen: Quote: "375 were randomly assigned to a treatment group and 258 were eventually intubated for more than 24 hours. Fourteen were unassessable because of missing data (4, 3, and 7 patients in the antacid, ranitidine, and sucralfate groups, respectively). Thus, 244 patients could be analysed. Of these 244 patients, 81 received antacid, 80 received ranitidine, and 83 received sucralfate. The protocol had to be interrupted before extubation in 23 (28%) of the patients in the antacid group, 19 (24%) of the patients in the ranitidine group, and 17 (20%) in the sucralfate group. Renal insufficiency developed in 5, 8, and 6 patients in the antacid, ranitidine, and sucralfate groups, respectively. In the antacid group, 6 patients developed diarrhoea or ileus, which was attributed to the treatment. In the ranitidine group, one patient developed leukopenia and another patient developed a rash. Removal of the nasogastric tube, withdrawal of supportive care, or discharge from the hospi-

Prod'hom 1994 (Continued)

tal was the other reason for premature protocol interruption. Five patients in the antacid group, 5 patients in the ranitidine group, and 8 patients in the sucralfate group had these characteristics. In addition, protocol violation prompted interruption of treatment in 7 patients in the antacid group, 4 patients in the ranitidine group, and 3 patients in the sucralfate group. For patients in whom the protocol was interrupted, the total number of assessable days before interruption was not statistically different among the three groups ($P > 0.2$)"

Comment: It is also mentioned that physicians had to modify the anti-stress ulcer prophylaxis regimen in 1, 2, and 3 participants in the antacid, ranitidine, and sucralfate groups, respectively, due to GI bleed

Duration of trial: January 1989 to January 1991

Duration of follow up: not clearly mentioned in the study report. Probably until death or discharge

Outcomes

Outcomes sought in review and reported in trial

Primary outcomes

- Incidence of nosocomial pneumonia defined as: "Criteria for the diagnosis of ventilator-associated pneumonia were predetermined and derived from those of 'Salata and colleagues' as presence of a new or progressive infiltrate on the chest radiograph consistent with pneumonia, without other obvious cause, and associated with conditions A or B or both, defined as follows. Condition A refers to any of the following findings: pleural fluid or blood culture positive for an organism also isolated in the tracheal aspirate, radiographic cavitation, or histopathologic evidence of pneumonia. Condition B includes at least two of the following: tracheal aspirates with more than 25 leukocytes per low-power field (x100) on a Gram stain, new leukocytosis defined as a leukocyte count greater than $10 \times 10^9/L$ with an increase of at least 25% over baseline, or body temperature greater than 38.5°C with an increase of at least 1°C above baseline. The latter two criteria were considered only when other causes for these findings were excluded. Pneumonia was considered to be caused by a pathogen when it was cultured in high counts as the sole or predominant microorganism in the tracheal aspirate culture"
- "Using the criteria of Langer and colleagues, early-onset and late-onset pneumonia were diagnosed if they occurred during the first 4 days of or 4 days after the initiation of mechanical ventilation, respectively. Consequently, only patients observed for more than 4 days could be evaluated for the development of late-onset pneumonia. A second episode of pneumonia was diagnosed when it was clearly temporally distinct from the first episode and when it involved other areas of the lungs. Pneumonia was attributed to a given anti-stress ulcer prophylactic regimen if it developed during treatment or within 2 days after extubation or treatment interruption"
- Incidence of macroscopic GI bleeding: "Gastric aspirates were examined for the macroscopic presence of blood ('coffee ground' material or fresh blood). The severity of gastric haemorrhage was assessed by clinical criteria (physical signs, blood transfusion requirements, and outcome)
- All-cause mortality in the hospital
- Participants requiring blood transfusion
- All-cause mortality during hospitalisation
- Adverse events of interventions

Note: Early-onset pneumonia developed in 9, 8, and 7 participants in antacid, ranitidine, and sucralfate groups, respectively. Late-onset pneumonia developed in 11, 14, and 4 participants in the antacid, ranitidine, and sucralfate groups, respectively. Three of the 4 cases of late-onset pneumonia in the sucralfate group were observed on day 5

Note: In the antacid group, GI bleeding developed on third day for 2 and on day 18 for 1 participant. In the ranitidine group; it was diagnosed on the second day for 2 participants and on days 3, 4, and 6 for the remaining 3 participants. In the sucralfate group, it was detected on the second day for three and on days 3, 5, 8, 12, and 23 for the remaining participants.

Outcomes sought but not reported in trial

- All-cause mortality in ICU
- Duration of ICU stay
- Duration of intubation

Prod'hom 1994 (Continued)

Outcomes reported but not used in review

- Intragastric pH status
- Gastric colonisation
- All-cause mortality during mechanical ventilation (mortality in ICU after extubation is not clear)

Notes

Setting: Division Autonome de Medecine Preventive Hospitaliere, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne, Switzerland

Source of funding: by Merck and Co.

Conflicts of interest: -

Ethics approval: -

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Additional notes: Mortality was attributed to pneumonia in 4 participants (1 in the antacid and 3 in ranitidine groups, respectively, whereas it was attributed to GI haemorrhage in 1 participant from the sucralfate group. *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, alone or in combination, accounted for more than half of early-onset pneumonia cases (54%), whereas gram-negative bacilli were most commonly isolated in late-onset pneumonia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done using a random permutable table to generate a random treatment list" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Low risk	Quote: "Treatment regimens were included in opaque, sealed envelopes" Comment: Method adopted to obtain allocation concealment is clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: There is no clear mention of blinding outcome assessors. However, GI bleeding was an objective outcome detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Low risk	Quote: "They were interpreted by a pneumologist who had knowledge of all relevant data except for the patient's stress ulcer prophylactic regimen, gastric pH, or colonization data" Comment: VAP was detected as per the definition in the study protocol by an outcome assessor who was blinded to the above mentioned participant data
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: There is no clear mention of blinding outcome assessors. However, all other outcomes of interest were objective in nature

Prod'hom 1994 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Of the initial 375 randomised participants, only 258 were part of the analysis, as only these participants were in the trial for longer than 24 hours, as this was criterion was necessary to measure the outcomes of interest. Data on 14 participants were missing, and they seem to be well balanced across the 3 groups
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported in the study
Other bias	Low risk	Comment: The study was funded by Merck and Co. However, the role of the sponsor in the conduct and reporting of the trial is unclear. No other form of bias was detected

Reusser 1990

Methods	Open label, randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 97 participants</p> <p>Number analysed: 40 participants</p> <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 40 (19 to 63) • Number of participants (n): 19 • Gender (male/female; n): 13/6 <p>No prophylaxis</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 33 (15 to 76) • Number of participants (n): 21 • Gender (male/female; n): 17/4 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Critically ill patients • Admitted to the surgical ICU of the Basel University Hospital • Having the following risk factors: <ul style="list-style-type: none"> ◦ Severe acute intracranial lesion caused by trauma or spontaneous haemorrhage and requiring neurosurgery ◦ Respiratory failure due to impaired neurological condition and needing > 48 hours of endotracheal intubation and mechanical ventilation <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Age < 15 years • History of upper GI tract surgery • Peptic ulcer disease, with current anti ulcer treatment • Overt upper GI bleeding • Intubated for less than 48 hours • Initial endoscopy revealed gastric or duodenal ulcers • Repeat endoscopy not possible

Reusser 1990 (Continued)

Baseline imbalances: Quote: "No significant differences between treatment and control groups were detected in any of the clinical and therapeutic characteristics among both the groups. However, hypotension was more frequent in the control group (12 vs. 5)"

Comment: Both groups were comparable with respect to age and gender distribution, and risk factors such as disseminated intravascular coagulation in addition to severe intracranial lesion and respiratory failure. Severe head injury was the main primary diagnosis in both groups

Interventions
Ranitidine

- Dose (total/d): 150 mg
- Duration of treatment (days): 7 days
- Route: IV
- Intervention: 50 mg IV every 8 hours, if more than 2 gastric pH values were < 4 within the second or subsequent dosing intervals, the ranitidine dosage was increased to 50 mg every 6 hours. If thereafter still more than 1 gastric pH was < 4 within a dosing interval, an antacid was added at a dosage required to maintain gastric pH at ≥ 4
- Concomitant medications: steroids, pentobarbital, neuromuscular blockers, vasopressive drugs. Every participant had an NG tube in place. The pH was determined in aspirates of gastric fluid by indicator paper every 2 hours for the first 3 days, and thereafter every 6 hours in the control group and 3 hours after each ranitidine dose in the treatment group, because a representative ranitidine-related pH could be expected at that time

No prophylaxis

- Dose (total/d): -
- Duration of treatment (days): 7 days
- Route: -
- Intervention: -
- Concomitant medications: steroids, pentobarbital, neuromuscular blockers, vasopressive drugs. Every participant had an NG tube in place. The pH was determined in aspirates of gastric fluid by indicator paper every 2 hours for the first 3 days, and thereafter every 6 hours in the control group and 3 hours after each ranitidine dose in the treatment group, because a representative ranitidine-related pH could be expected at that time

Adherence to regimen: For treatment of the 97 eligible participants, only 40 completed the trial and were available for analysis (19 in the treatment arm and 21 in the control arm)

The remainder were excluded for the following reasons:

- Early consent was unobtainable in 12 participants
- Overlooked by house staff (n = 14)
- Not endoscoped (n = 19)
- Initial endoscopy revealed duodenal ulcer (n = 1)
- Intolerance to repeat endoscopy on day 5 (n = 1)
- Extubated within 48 hours (n = 7)
- Died within 48 hours due to neurologic deterioration (n = 3)

In the treatment group, 5 (26%) participants remained on the original ranitidine dosage of 50 mg every 8 hours throughout the study, 5 (26%) required a dosage increase to 50 mg every 6 hours, and 9 (47%) needed additional antacids

Duration of trial: August 1984 to September 1986

Duration of follow up: up to 7 days after study completion

Outcomes
Outcomes sought in review and reported in trial
Primary outcome

Reusser 1990 (Continued)

- Incidence of GI bleeding. Endoscopic bleeding signs were classified as follows: petechiae, or submucosal haematoma, traces of fresh blood or 'coffee ground' material and frank bleeding. Occult bleeding was defined as positive slide test on 3 consecutive aspirates. Overt bleeding was defined as: bright red bleeding via NG tube, melena, or decrease in Hgb level > 2 g/dL within 24 hours, associated with positive stool guaiac test or with gastric drainage of > 100 mL of 'coffee ground' material

Secondary outcomes

- All-cause mortality in hospital
- Duration of intubation
- Duration of ICU stay
- Participants requiring blood transfusion (no participant required blood transfusions)
- Units of blood transfused (no participant required blood transfusions)

Outcomes sought but not reported in trial

- Incidence of ventilator-associated pneumonia
- Adverse reactions of interventions

Outcomes reported but not used in review

- Intragastric pH values
- Risk factors for development of GI bleeding
- Incidence of stress lesions
- All-cause mortality during the study

Notes	<p>Setting: Department of Internal Medicine and Surgical Intensive Care Unit, University Hospital Basel, Switzerland</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The study was approved by the ethical committee of the Basel University Hospital"</p> <p>Informed consent: Quote: "Informed consent was obtained from each patient's legal guardian"</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: Data are provided on number of deaths during the study (n = 1 in the ranitidine group), which is not similar to all-cause mortality in ICU</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The need to monitor gastric pH to determine intensification of stress lesion prophylaxis in the treatment group prevented double-blind study design"

Reusser 1990 (Continued)

		Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "The need to monitor gastric pH to determine intensification of stress lesion prophylaxis in the treatment group prevented double-blind study design" Comment: Outcome assessors were not blinded. However, GI bleeding was an objective outcome that was detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: It is mentioned that of the 97 eligible participants, only 40 completed the trial and were available for analysis. The remaining 43 participants were excluded for reasons mentioned under "Adherence to the regimen". Therefore, a protocol analysis was done to measure the outcomes of interest, and the number of participants appears to be balanced between groups. Therefore, the likelihood of this affecting the outcomes of interest is minimal
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: The source of funding is not clearly mentioned in the study report. No additional biases were detected

Rohde 1980

Methods	Randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: -</p> <p>Number analysed: -</p> <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)):- • Number of participants (n): 14 • Gender (male/female; n): <p>Placebo</p> <ul style="list-style-type: none"> • Age (years; mean (SD)):- • Number of participants (n): 14 • Gender (male/female; n): <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Severe burns (at least 25% of the body surface area and second degree)

Rohde 1980 (Continued)

- severe cerebral injuries (unconscious for at least 72 hours)
- Severe polytrauma (at least 3 body regions)
- Respiratory insufficiency (controlled respiration for at least 8 hours)

Exclusion criteria

- Bleeding abnormalities
- History of peptic ulcer, gastric carcinoma, atrophic gastritis,
- History of gastric operations
- Age < 18 years
- Not consenting for the trial or death before the start of interventions
- Severe renal or liver insufficiency, or bone marrow disease (decision was left to the executive group)

Baseline imbalances: -

Interventions	<p>Cimetidine</p> <ul style="list-style-type: none"> • Dose (total/d): 1.2 g • Duration of treatment (days): 14 days • Route: IV and later PO • Intervention: 1.2 g/d IV for 5 days and thereafter PO for 9 days if their physical state was appropriate. Otherwise the drug was continuously applied IV until the end of treatment. The single IV dose of 200 mg (about 3 mg/kg) was given in 4-hour intervals by a 2-rain injection or infusion starting at 8 am. The oral dose was applied as 200- mg tablets at meals under surveillance of the nurses, 2 tablets at breakfast, 1 at lunch and dinner, and 2 at bedtime. In renal failure (creatinine more than 2.5 mg/dL corresponding to 221 nmol/L), the dose was reduced to 2 × 200 rag/d (8 am and 8 pm), which kept the blood level as high as 1.2 g/d in normal conditions • Concomitant medications <p>Placebo</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days): 14 days • Route: - • Intervention: - • Concomitant medications: - <p>Adherence to regimen</p> <ul style="list-style-type: none"> • In May 1977, the subgroup (strata) 1 (participants with burns) were excluded from the trial as the consultant specialising in burns left the trial centre and participants with severe burn injuries were shifted too • In September 1977, failure in trial design was detected in subgroup (strata) 2, and in February 1978, the subgroup was excluded from the trial sighting selection bias • In March 1978, subgroup (strata) 4 (participants with respiratory insufficiency) was excluded owing to "imprecise entrance criteria" • The third subgroup (strata) of polytrauma participants was included, but the trial was stopped on June 1978, much ahead of the actual date of termination for ethical reasons <p>Duration of trial: March 1977 to June 1978</p> <p>Duration of follow up: until death or discharge from hospital</p>
Outcomes	<p>Outcome sought in review and reported in trial</p> <ul style="list-style-type: none"> • Clinical manifestation of bleeding defined by detection of visible blood in the gastric aspirate (at least in 1, as diagnosed by the clinical surgeon of the executive group, on duty) or by recording haematemesis and/or melena following careful observation of participants • All-cause mortality in hospital or ICU (data given for survival)

Rohde 1980 (Continued)

Outcomes sought but not reported in trial report

- Ventilator-associated pneumonia (VAP)
- Duration of ICU stay
- Duration of intubation
- Participants requiring blood transfusion
- Units of blood transfused
- Adverse events of interventions

Outcomes reported in report but not used in review

- Acute ulceration

Notes

Setting: Department of Surgery, Marburg, Germany

Source of funding: -

Conflicts of interest: -

Ethics approval: Quote: "The definite protocol was submitted to the local ethical committee...".

Comment: Approval from the ethics committee was sought. Moreover, the trial was constantly monitored by an executive group

Informed consent: Informed consent was sought from participants, as it was a criterion for inclusion/exclusion from the trial

Clinical trials registration: -

Sample size calculation: Although the trial was planned as a double-blind trial with a fixed sample size (100 participants) of people admitted to ICU, it was executed as a sequential single-blind study only in 1 subgroup of participants (polytrauma) and was ended before the planned termination date for ethical reasons

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: Participants were randomised in blocks of 4. The method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The study was executed as a single blind sequential trial (a deviation from the planned double blind method) due to ethical reasons" Comment: unclear on who was blinded and how it was executed
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: GI bleeding was detected as per the definition in the study protocol, not blinding the outcome assessor to this objective outcome would not have caused detection or performance bias
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias)	Low risk	Comment: All other outcomes of interest were objective in nature, so the likelihood of detection bias is low

Rohde 1980 (Continued)

Adverse reactions of interventions

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Data for only 1 strata of participants (polytrauma) are available, as the strata were terminated as mentioned above in "Adherence to regimen". This appears to be an incomplete report
Selective reporting (reporting bias)	High risk	Comment: Data for only 1 strata of participants (polytrauma) are available, as the strata were terminated as mentioned above in "Adherence to regimen"
Other bias	Low risk	Comment: The source of funding is not clearly mentioned in the study report. No additional biases were detected

Ruiz-Santana 1991

Methods	Single-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 94 participants</p> <p>Number analysed: 73 participants</p> <p>Total parenteral nutrition (TNP)</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 39 (14) Number of participants (n): 30 Gender (male/female; n): 19/11 <p>TPN + sucralfate</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 37 (18) Number of participants (n): 24 Gender (male/female; n): 20/4 <p>TPN + ranitidine</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 39 (17) Number of participants (n): 19 Gender (male/female; n): 14/5 <p>Inclusion criteria</p> <ul style="list-style-type: none"> Patients having metabolic stress Stable haemodynamically Normal hepatic and renal function On total parenteral nutrition <p>Exclusion criteria</p> <ul style="list-style-type: none"> Patients with spinal cord injuries History of gastroduodenal ulcer in the 12 months preceding ICU admission Operations of the upper GI tract Active GI tract haemorrhage Hepatic or renal failure, with catabolic index ≤ 0 Patients who received antacids, H2 blockers, or sucralfate within the past 48 hours before study entry

Ruiz-Santana 1991 (Continued)

Baseline imbalances: Groups were similar with respect to age and gender. The 2 main reasons for admission were respiratory disease (n = 26) and multiple injuries (n = 14). There is no clear mention of the distribution of clinical features across study groups

Interventions

TPN

- Dose (total/d): 1500 mL
- Duration of treatment (days): min 6
- Route: -
- Intervention: 1500 mL of total parenteral nutrition (1600 kcal, 99 g protein, 150 g glucose, and 100 g fat, with electrolytes, minerals, and vitamins)
- Concomitant medications: -

TPN + sucralfate

- Dose (total/d): 6 g
- Duration of treatment (days): min. 6
- Route: NG tube
- Intervention: 1 g via NG tube every 4 hours, which is then flushed with 15 mL of water to prevent clogging + parenteral nutrition
- Concomitant medications: -

TPN + ranitidine

- Dose (total/d): 200 mg
- Duration of treatment (days): min 6
- Route: IV
- Intervention: 50 mg IV every 6 hours + parenteral nutrition
- Concomitant medications: -

Adherence to regimen: Quote: "24 participant were withdrawn from the study before the sixth day on protocol with the following reasons for withdrawal: weaned from mechanical ventilation before the sixth day (n = 10), death (n = 8), acute upper GI haemorrhage (n = 5, 2 stress induced gastroduodenal ulcers, 2 chronic duodenal ulcers, 1 stomach cancer) and early tolerance to enteral feedings (n = 1)"

Comment: The interventional arms to which these participants were initially randomised are not clearly mentioned in the study report

Duration of trial: December 1988 to January 1990

Duration of follow up: not mentioned in the study report. Probably until death or discharge

Outcomes

Outcomes sought in review and reported in trial

- Incidence of upper GI bleeding: clinical signs of haematemesis, bloody aspirate, melena, 'coffee ground' material followed by endoscopic examinations to determine the actual bleeding site
- All-cause mortality in ICU
- Duration of intubation

Outcomes sought but not reported in trial

- Incidence of ventilator-associated pneumonia
- All-cause mortality in hospital
- Participants requiring blood transfusion
- Units of blood transfused
- Adverse events of interventions

Outcomes reported but not used in review

- Catabolic index score

Ruiz-Santana 1991 (Continued)

- APACHE II score

Notes	Setting: ICU and gastroenterology service, Hospital del Pino, Las Palmas de Gran Canaria, Canary Islands, Spain	
	Source of funding: -	
	Conflicts of interest: -	
	Ethics approval: Quote: "The study was approved by the institutional review board"	
	Informed consent: -	
	Clinical trials registration: -	
	Sample size calculation: -	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comments: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comments: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "All endoscopic examinations, except a few cases performed on emergency basis was done by a single investigator uninformed as to the treatment group" Comment: Outcome assessors were mostly blinded and GI bleeding was an objective outcome that was detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear on the blinding of outcome assessors. However, all other outcomes were objective in nature
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Of the 97 participants, 24 were withdrawn from the study, as they did not complete a minimum of 6 days in the ICU as required by the protocol of this study. The interventions to which they were originally randomised were not clear from the study report. A per-protocol analysis was done for the outcomes of interest, but there appears to be an imbalance between groups with respect to the final number of participants available for analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported

Ruiz-Santana 1991 (Continued)

Other bias	Unclear risk	Comment: Source of funding is not clearly stated. Baseline characteristics (clinical) are not clearly mentioned for each group. No additional biases were detected
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Ryan 1993

Methods	Single-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 114 participants</p> <p>Numner analysed:114 participants</p> <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 65 (17-96) • Number of participants (n): 56 • Gender (male/female; n): 34/22 <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 62 (17-90) • Number of participants (n): 58 • Gender (male/female; n): 37/21 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admitted to ICU • Age > 16 years • Endotracheal intubation • Presence of nasogastric tube • Expected survival longer than 24 hours, which was based on mortality probability model (MPM), which used the following criteria: age, history of chronic renal insufficiency, admission to an ICU in the previous 6 months, cardiopulmonary resuscitation within previous 24 hours, elective and emergency ICU admission, malignancy as an active problem in the past 6 months, probable infection, level of consciousness, systolic blood pressure, heart rate, and surgical or medical care <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Admission for upper GI haemorrhage • Admission for pneumonia • Previous gastric surgery • Treatment with H2 antagonists, antacids, and sucralfate within previous 48 hours <p>Baseline imbalances: Quote: "There was no significant difference in mean age, sex ratio, or number of patients admitted to medical or surgical services"</p> <p>Comment: The 2 groups were similar with respect to their baseline characteristics</p>
Interventions	<p>Cimetidine</p> <ul style="list-style-type: none"> • Dose (total/d): varies • Duration of treatment (days): - • Route: IV • Intervention: continuous infusion, using 300-mg bolus followed by 37.5 mg/g • Concomitant medications: intragastric feeding for 25 participants, antibiotic therapy, steroid therapy

Ryan 1993 (Continued)

Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days): -
- Route: NG tube
- Intervention: administered by nasogastric tube, at a dose of 1 g every 6 hours, suspended in 20 mL of sterile water, flushed through with 10 mL of water
- Concomitant medications: intragastric feeding for 27 participants, antibiotic therapy, steroid therapy

Adherence to regimen: 114 participants who met the inclusion criteria were enrolled into the study. 25 (22%; 12 participants from cimetidine group and 13 participants from sucralfate group) participants were withdrawn from the study for the following reasons:

- Extubation within 48 hours after enrolment and discharge from ICU (n = 2)
- NG tube was removed (n = 2)
- At the request of participant or guardian (n = 3)
- Died within 48 hours (n = 8)
- Inadvertent medication change (n = 4)
- Adverse drug reaction (2 in cimetidine and 1 in sucralfate groups) (n = 3)
- Documented case of aspiration by a witness (n = 3)

The remaining 89 participants constituted the study group

Duration of trial: January 2009 to September 2009

Duration of follow-up: -

Outcomes

Outcomes sought in review and reported in trial

Primary outcomes

- Incidence of nosocomial pneumonia diagnosed based on the Center for Disease Control and Prevention Guidelines (CDC), which include rales or dullness to percussion or bronchial breath sounds on physical examination of the chest, and any of the following:
 - New onset of purulent sputum or change in the character of sputum
 - Organism isolated from blood culture
 - Isolation of pathogen from the specimen obtained from endotracheal aspirate, bronchial brushing, or biopsy

Note: Other than the CDC and prevention criteria, each participant was required to have 2 chest roentgenograms showing persistent infiltrates, with agreement by intensivist and radiologist

Secondary outcomes

- Incidence of GI haemorrhage: presence of fresh blood or 'coffee grounds' in nasogastric aspirate, which tested positive with Hemoccult test and persisted after 100 mL of saline lavage
- All-cause mortality in ICU
- Duration of intubation
- Participants requiring blood transfusion
- Adverse events of interventions

Outcomes sought but not reported in trial

- Duration of ICU stay
- All-cause mortality in hospital
- Units of blood transfused

Outcomes reported in report but not used in review

- Pathogens isolated from participants who developed pneumonia

Ryan 1993 (Continued)

Notes

Setting: Medical and Surgical Intensive Care Unit, Springfield, Mass, Tufts University

Source of funding: -

Conflicts of interest: -

Ethics approval: Quote: "The study was approved by the institutional review board"

Informed consent: Quote: "Informed consent was obtained from each patient or guardian"

Clinical trials registration: -

Sample size calculation: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised according to computer generated numbers to receive either cimetidine or sucralfate" Comment: The method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: Outcome assessors were not blinded, but GI bleeding was an objective outcome detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Low risk	Quote: "The radiologist and the intensivist who assessed the chest roentgenograms for diagnosing pneumonia were both blinded to the treatment that the participant was receiving" Comment: Nosocomial pneumonia was detected as per the definition in the study protocol by an outcome assessor who was blinded to participant data
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear on the blinding of outcome assessors. However, outcomes of interest were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "...with 10 mL of water. Twenty-five patients (22%) were withdrawn from the study for the following reasons: two because of extubation within 48 hours of enrolment and discharge from the ICU, two because the nasogastric tube was removed (the nasogastric tube was required to instil sucralfate into the stomach and monitor bleeding), three at the request of the patient or guardian, eight because they died within 48 hours, four because of inadvertent medication change, three because of documented cases of aspiration by a witness, three because of adverse reactions from medications (two patients in the cimetidine group had confusion and neutropaenia, and one patient in the sucralfate group could not tolerate the nasogastric tube clamped). The patients who were withdrawn were equally distributed between the two treatment groups. The remaining 89 patients constituted"

Ryan 1993 (Continued)

Comment: no incomplete reporting of outcomes suspected

Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Source of funding is not clearly mentioned in the study design. No other sources of bias suspected

Selvanderan 2015

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 214 participants</p> <p>Number analysed: 214 participants</p> <p>Pantoprazole</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): - (-) • Number of participants (n): - • Gender (male/female; n): - <p>Placebo</p> <ul style="list-style-type: none"> • Age (years, mean (SD)): - (-) • Number of participants (n): - • Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Anticipated to require mechanical ventilation for > 24 hours • Commence enteral nutrition within 48 hours of admission <p>Exclusion criteria: -</p> <p>Baseline imbalances: -</p>
Interventions	<p>Pantoprazole</p> <ul style="list-style-type: none"> • Dose (total/d): 40 mg • Duration of treatment (days): - • Route: IV • Intervention: - • Concomitant medications: - <p>Placebo</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days): - • Route: - • Intervention: - • Concomitant medications: - <p>Adherence to regimen: -</p> <p>Duration of trial: January 2014 to January 2015</p>

Selvanderan 2015 (Continued)

Duration of follow-up: 90 days

Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none">• Incidence of clinically important GI bleeding• Incidence of VAP• All-cause mortality in hospital <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none">• Duration of ICU stay• Duration of intubation• Adverse events of interventions <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none">• <i>Clostridium difficile</i> infection• Daily haemoglobin concentrations
Notes	<p>Setting: ICU</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: -</p> <p>Informed consent: -</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p> <p>Additional notes: -</p>
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Unclear risk Comment: not enough details reported
Allocation concealment (selection bias)	Unclear risk Comment: no details reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk <p>Quote: "double blind fashion"</p> <p>Comment: no details on blinding reported. Lack of blinding is unlikely to introduce bias to outcome measures or outcomes</p>
Blinding (detection bias) Clinically important upper GI bleeding	Low risk <p>Quote: "(haematemesis, bloody gastric aspirate, melaena or haematochezia), clinically significant bleeding (overt bleeding accompanied by a drop in mean arterial pressure > 20mmHg, or reduction in haemoglobin > 20g/L, or need for surgical intervention)"</p> <p>Comment: criteria for diagnosis of GI bleeding described.</p>
Blinding (detection bias) Nosocomial pneumonia	Unclear risk Comment: no criteria for diagnosis of VAP described

Selvanderan 2015 (Continued)

Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: no information about blinding of outcome assessors described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: not enough information reported to assess incomplete outcome data. Conference abstract
Selective reporting (reporting bias)	Low risk	Comment: no incomplete reporting of outcomes suspected. All outcomes listed in the Methods section were also reported in the Results section briefly
Other bias	Unclear risk	Comment: no other sources of bias suspected, but very little information reported overall

Selvanderan 2016

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Overall</p> <ul style="list-style-type: none"> Age (years; mean (SD)):- Number of participants at baseline (n): Total 214 Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> Anticipated to require mechanical ventilation for > 24 hours Commence enteral nutrition within 48 hours of admission <p>Exclusion criteria: -</p> <p>Baseline imbalances: -</p>
Interventions	<p>Pantoprazole</p> <ul style="list-style-type: none"> Dose (total/d): 40 mg Duration of treatment (days): - Route: IV Intervention: - Concomitant medications: - <p>Placebo</p> <ul style="list-style-type: none"> Dose (total/d): - Duration of treatment (days): - Route: - Intervention: - Concomitant medications: - <p>Adherence to regimen: -</p> <p>Duration of trial: January 2014 to January 2015</p> <p>Duration of follow-up: 90 days</p>

Selvanderan 2016 (Continued)

Outcomes

Outcomes sought in review and reported in trial

- Over GI bleeding defined as haematemesis, bloody gastric aspirate, melena, or haematochezia or clinically significant GI bleeding defined as overt bleeding accompanied by a drop in mean arterial pressure > 20 mmHg, or reduction in haemoglobin > 20 g/L, or need for surgical intervention
- Ventilator-associated pneumonia
- Mortality (adjusted hazard ratio)

Outcomes sought in review but not reported in trial

- Duration of ICU stay
- Duration of intubation
- Blood transfusions
- Adverse events of interventions

Outcomes reported in trial but not used in review

- *Clostridium difficile* infection
- Daily haemoglobin concentrations

Notes

Setting: ICU

Sponsorship source: -

Ethics approval: -

Conflicts of interest: -

Informed consent: -

Study protocol: -

Sample size calculation: -

Additional notes: conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned" Comment: not enough details reported
Allocation concealment (selection bias)	Unclear risk	Comment: no details reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind fashion" Comment: no details on blinding reported. Lack of blinding is unlikely to introduce bias to outcome measures or outcomes
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "(hematemesis, bloody gastric aspirate, melena or hematochezia), clinically significant bleeding (overt bleeding accompanied by a drop in mean arterial pressure > 20 mmHg, or reduction in haemoglobin > 20 g/L, or need for surgical intervention)" Comment: outcome measured objectively
Blinding (detection bias)	Unclear risk	Comment: no criteria for diagnosis of VAP described

Selvanderan 2016 (Continued)

Nosocomial pneumonia

Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: no information about blinding of outcome assessors described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: not enough information reported to assess incomplete outcome data. Conference abstract
Selective reporting (reporting bias)	Low risk	Comment: no incomplete reporting of outcomes suspected. All outcomes listed in the Methods section were also reported in the Results section briefly
Other bias	Unclear risk	Comment: no other sources of bias suspected, but too little information reported in this conference abstract to assess other biases

Simms 1991

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 89 participants</p> <p>Number analysed: 89 participants</p> <p>Antacids</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 37.33 (20.75) Number of participants (n): 27 Gender (male/female; n): - <p>Cimetidine</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 31.82 (16.9) Number of participants (n): 32 Gender (male/female; n): - <p>Sucralfate</p> <ul style="list-style-type: none"> Age (years; mean (SD)): 32.6 (17.1) Number of participants (n): 30 Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> All trauma patients who spent > 48 hours in surgical intensive care unit <p>Exclusion criteria</p> <ul style="list-style-type: none"> Survival not expected beyond 48 hours Intestinal tract surgery precluding the administration of the interventions in this study Pregnancy <p>Baseline imbalances: -</p>
Interventions	Antacids

Simms 1991 (Continued)

- Dose (total/d): varies
- Duration of treatment (days): min. 6
- Route: -
- Intervention: 30 to 60 mL every 2 to 4 hours
- Concomitant medications: antibiotics and antifungals; enteral feeding was received by 59.2% of participants

Cimetidine

- Dose (total/d): varies
- Duration of treatment (days): min 6
- Route: IV
- Intervention: continuous IV cimetidine 900 to 1200 mg every 2 to 4 hours
- Concomitant medications: Antibiotics and antifungals; enteral feeding was received by 62.5% of participants

Sucralfate

- Dose (total/d): 4 g
- Duration of treatment (days): min 6
- Route: NG tube or gastrotomy tubing
- Intervention: 1 g qid via nasogastric or gastrotomy tubing
- Concomitant medications: antibiotics and antifungals; enteral feeding was received by 63.3% of participants

Adherence to regimen: Quote: "Patients received cimetidine or antacids had the doses of each drug increased if the pH failed to reach 4 on any two consecutive 2- hours sampling patients receiving antacids alone at maximal doses whose intragastric pH < 4 received combination therapy to maintain intragastric pH > 4 and therefore were discontinued from the study"

"Upper GI bleeding requiring blood transfusions were seen in two patients, one receiving cimetidine and one receiving sucralfate. These two participants were eliminated from the study and were endoscopically shown to have diffuse erosive gastritis"

Duration of trial: December 1988 to January 1990

Duration of follow up: not mentioned in the study report. Probably until death or discharge

Outcomes

Outcomes were not classified as primary and secondary, but main outcomes in the study report are as follows;

Outcomes sought in review and reported in trial

- Incidence of acute upper GI bleeding
- Incidence of pneumonia diagnosis based on fever, leucocytosis, persistent new infiltrates in chest X-ray films, and sputum pathogens
- Duration of ventilation
- Participants requiring blood transfusion

Outcomes sought but not reported in trial

- All-cause mortality in ICU
- All-cause mortality in hospital
- Duration of ICU stay
- Units of blood transfused
- Adverse events of interventions

Outcomes reported but not used in review

- Duration in hospital

Simms 1991 (Continued)

- Gastric pH
- Gastric colonisation

Notes	Setting: Surgical Intensive Care Unit, Rhode Island Hospital/Brown University, Providence, USA	
	Source of funding: Smith Kline Beecham Pharmaceuticals	
	Conflicts of interest: -	
	Ethics approval: Quote: "The study was approved by the Rhode Island Hospital Human welfare protection committee"	
	Informed consent: Quote: "Informed consent was obtained from each participant before induction into the study"	
	Clinical trials registration: -	
	Sample size calculation: -	
	Additional notes: The most prevalent organisms isolated from NG tube were <i>Candida albicans</i> , <i>Enterococcus</i> organisms, and β -haemolytic streptococci; they were identical across all 3 groups	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	High risk	Comment: unclear whether outcome assessors were blinded, and definition of GI bleeding not clearly mentioned in the study report
Blinding (detection bias) Nosocomial pneumonia	High risk	Comment: unclear whether outcome assessors were blinded, and definition of pneumonia was not clearly mentioned in the study report
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature, so the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Source of funding is not clearly mentioned in the study design. No other source of bias suspected

Sirvent 1994

Methods	Randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 51 participants</p> <p>Number analysed: 51 participants</p> <p>Antacids + ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 42.6 (18.2) • Number of participants (n): 25 • Gender (male/female; n): 16/9 <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 38.1 (19.7) • Number of participants (n): 26 • Gender (male/female; n): 20/6 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admitted at ICU of Hospital de Bellvitge Princesps d'Espanya • On mechanical ventilation • Predicted intubation time of more than 72 hours <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Reasonable suspicion of airway infection at the time of admission • History of active gastro duodenal ulcers in the last six months • Gastrointestinal bleeding at the time of admission • Surgery of the digestive tract (laparotomies, gastrectomies, pancreatitis and neoplasias) • Paralytic ileus • Diffuse or localised peritoneal infection • Receiving prophylactic treatment with antacids, H2 blockers, sucralfate within 24 hours before admission to the ICU <p>Baseline imbalances: Groups were similar in demographic characteristics. Antacid + Ranitidine group had an APACHE II score of 14.7 ± 4.9, and sucralfate group had a score of 13.2 ± 5.1</p> <p>More participants in the sucralfate group were diagnosed with polytrauma (n = 16 vs 4 in the sucralfate group)</p>
Interventions	<p>Antacids + ranitidine</p> <ul style="list-style-type: none"> • Dose (total/d): antacid varies, 100 mg ranitidine • Duration of treatment (days): until extubation or when pneumonia was diagnosed • Route: NG tube IV • Intervention: antacids via nasogastric tube to maintain gastric pH superior to 4 every 4 to 6 hours and ranitidine intravenous 50 mg/12 h • Concomitant medications: 12 participants received parenteral nutrition; antibiotics; and glucocorticoids <p>Sucralfate</p> <ul style="list-style-type: none"> • Dose (total/d): 4 g • Duration of treatment (days): until extubation or when pneumonia was diagnosed • Route: NG tube • Intervention: sucralfate, nasogastric tube, 1 g every 6 hours

Sirvent 1994 (Continued)

- Concomitant medications: 11 participants received parenteral nutrition; antibiotics; and glucocorticoids

Adherence to regimen: no change in dose/regimen mentioned. No information about dropouts

Duration of trial: January 1990 to June 1991

Duration of follow-up: -

Outcomes	Outcomes sought in review and reported in trial Primary outcomes <ul style="list-style-type: none">• Incidence of nosocomial pneumonia Secondary outcomes <ul style="list-style-type: none">• Incidence of upper GI bleeding• All-cause mortality in ICU (not separately mentioned for each group)• Adverse events of interventions (nil) Outcomes sought but not reported in trial <ul style="list-style-type: none">• All-cause mortality in hospital• Duration of intubation• Duration of ICU stay• Participants requiring blood transfusion• Units of blood transfused Outcomes reported but not used in review <ul style="list-style-type: none">• Etiology of nosocomial pneumonia• Time to outbreak of nosocomial pneumonia• Differential effect on gastric pH• Gastric colonisation	
Notes	Setting: Hospital de Bellvitge-Principes d’Espanya Source of funding: grant from the health ministry Conflicts of interest: - Ethics approval: Study was approved by the clinical investigations committee at the Hospital Informed consent: - Clinical trials registration: - Sample size calculation: - Additional notes: Two episodes of mild upper GI bleeding occurred in each group; this was not of clinical significance	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report

Sirvent 1994 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: Study did not address this outcome
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: Study mentions that 2 outcome assessors were blinded
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear on blinding of assessors for other outcomes. However owing to the objective nature of the outcomes of interest, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	High risk	Comment: All-cause mortality in the ICU was not separately mentioned for each group. However, all other intended outcomes were analysed and reported
Other bias	Low risk	Comment: This study was funded by the ministry of health. The role of the sponsor in the conduct and reporting of the trial is unclear. No other sources of bias suspected

Skillman 1984

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 60 participants</p> <p>Number analysed: 46 participants</p> <p>Antacids (Mylanta II)</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 69 (-) • Number of participants (n): 22 • Gender (male/female; n): 12/10 <p>Prostaglandin ((15)-R-15-methyl prostaglandin E₂)</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 76 (-) • Number of participants (n): 24 • Gender (male/female; n): 13/11 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admission to the respiratory surgical ICU

Skillman 1984 (Continued)

Exclusion criteria

- Improper randomisation
- Less than 12 hours in the study
- Protocol not followed properly
- Repeated patient removal of the NG tube
- Uncertain Hemocult test result
- Receiving food or fluid by mouth

Baseline imbalances: no significant differences between the 2 groups in baseline characteristics such as age, sex, and risk factors. Most participants were diagnosed with intra-abdominal disease (antacids: 7 and prostaglandin: 10)

Interventions
Antacids (Mylanta II)

- Dose (total/d): varies
- Duration of treatment (hours): 64 ± 8
- Route: NG tube
- Intervention: Initial dose of 30 mL was instilled into the stomach, if gastric pH was found to be less than 3.5 after an hour; then the dose was doubled until the pH of the subsequent sample aspirated was greater than 3.5
- Concomitant medications: -

Prostaglandin ((15)-R-15-methyl prostaglandin E₂)

- Dose (total/d): 6 mL
- Duration of treatment (hours): 39 ± 6
- Route: NG tube
- Intervention: 1 mL through the NG tube washed with 10 mL of water every 4 hours
- Concomitant medications: -

Adherence to regimen: 14 patients were excluded after randomisation for reasons mentioned above under "Exclusion criteria". 11 of the 12 patients in whom prostaglandin E₂ prophylaxis failed (upper GI bleeding) were switched to antacid regimen. One of the 11 patients had "double" failure because antacid also failed

Duration of trial: October 1980 to August 1982

Duration of follow up: not clearly mentioned in the study report. Probably until death or discharge

Outcomes

Outcomes were not classified as primary or secondary in the study report; however outcomes reported were as follows.

Outcomes sought in review and reported in trial

- Incidence of upper GI bleeding defined as a positive haemocult test result
- All-cause mortality in ICU

Outcomes sought but not reported in trial

- Incidence of ventilator-associated pneumonia
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Participants requiring blood transfusion
- Units of blood transfused
- Adverse events of interventions

Outcomes reported but not used in review

Skillman 1984 (Continued)

- Relationship between underlying risk factors and development of upper GI bleed
- pH of luminal contents

Notes

Setting: Department of Surgery and Medicine Harvard Medical School and Beth Israel Hospital, Boston, Massachusetts

Source of funding: Quote: "This study was supported in part by funds from Upjohn University, Kalamazoo, Michigan and the Charls Diana Research Institures, Beth Israel Hospital, Boston"

Conflicts of interest: -

Ethics approval: Quote: "The study was approved by the Committee on Clinical Investigation, New Procedures and new Forms of Therapy of the Beth Israel Hospital"

Comment: mentioned for only 1 centre

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were selected by a table of random numbers" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: Outcome assessor was not blinded. GI bleeding was an objective outcome detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: Outcomes of interest were objective in nature, so the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 14 patients were excluded from analysis after randomisation for various reasons mentioned in "adherence to the regimen". The interventional arms to which these participants were randomised remain unclear. A per-protocol analysis was performed, and there appears to be a balance between groups in terms of the number of participants available for final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported

Skillman 1984 (Continued)

Other bias	Low risk	Comment: This study was supported in part by a research grant from Upjohn University, Kalamazoo, Michigan, and the Charls Diana Research Institures, Beth Israel Hospital. The role of the sponsor in the conduct and reporting of the trial is unclear
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Solouki 2009

Methods	Double-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 129 participants</p> <p>Number analysed: 129 participants</p> <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 49.19 (5 - 85) • Number of participants (n): 68 • Gender (male/female; n): 35/33 <p>Omeprazole</p> <ul style="list-style-type: none"> • Age (years; mean (range)): 52.41 (5 - 95) • Number of participants (n): 61 • Gender (male/female; n): 32/29 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admitted to ICU • Under mechanical ventilation for a minimum of 48 hours • Nasogastric tube in place, which would help to monitor and confirm the upper GI bleedings, if it occurred <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Individuals with • Pneumonia • Current upper GI bleeding • Previous gastrectomy • Current usage of 2 doses of prophylaxis • Transported from another ICU ward <p>Baseline imbalances: Patients' age in group A ranged from 5 to 85 years with mean age of 49.19 years. Group B patients were in the age range of 5 to 95 years with mean age of 52.41 years. In the omeprazole group. There were 32 (52.5%) males and 29 (47.5%) females. These numbers were 35 (51.5%) males and 33 (48.5%) females in the ranitidine group. The 2 groups were similar with respect to the baseline risk factors responsible for GI bleeding</p>
Interventions	<p>Ranitidine</p> <ul style="list-style-type: none"> • Dose (total/d): 100 mg • Duration of treatment (days): - • Route: IV • Intervention: Intravenous ranitidine was used with 50-mg dosage 2 times a day accompanied by placebo gavages through nasogastric tube

Solouki 2009 (Continued)

- Concomitant medications: corticosteroids and antibiotics, intermittent nasogastric feeding (300 to 400 mL, 4-hourly)

Omeprazole

- Dose (total/d): 40 mL
- Duration of treatment (days): -
- Route: NG tube
- Intervention: 20 mL of a suspension of omeprazole 2 times a day was gavaged in addition to 2 cc of a parenteral placebo drug
- Concomitant medications: corticosteroids and antibiotics, intermittent nasogastric feeding (300 to 400 mL 4-hourly)

Adherence to regimen: 128 participants were randomised to receive 2 interventions; Ranitidine + Placebo (68) and Omeprazole + Placebo (61). 12 participants died in the first group while 3 died in the second group

Duration of trial: June 2000 to January 2001

Duration of follow up: not clearly mentioned in the study report. Probably until death or discharge

Outcomes	<p>Outcomes sought in review and reported in trial</p> <p>Primary outcome</p> <ul style="list-style-type: none"> Incidence of GI bleeding: 2 types of GI bleeding including overt and clinically important bleedings were evaluated in this study. If 1 of the following happens, the situation is called "overt GI bleeding": haematemesis, 'coffee ground' in NGT, melena, or haematochezia. Overt bleeding in addition to at least 1 of the following items is called "clinically important GI bleeding": <ul style="list-style-type: none"> 20 mmHg decrease in systolic or diastolic blood pressure during the first 24 hours after bleeding 20 bpm increase in heart rate or 10 mmHg in systolic blood pressure in a standing position 2 g/dL decrease in Hb or 6% HCT during first 24 hours after bleeding Lack of increase in Hb after infusion of 2 units of packed cells <p>Secondary outcomes</p> <ul style="list-style-type: none"> Incidence of ventilator-associated pneumonia defined as new infiltration in chest X-ray along with 2 of the 3 following criteria: fever $\geq 38.3^{\circ}\text{C}$, leucocytosis $\geq 10,000$, and pus in tracheal tube suction. Ultimate diagnosis was achieved by a positive culture of tracheal secretions. Existence of at least 105 colonies of pathogenic micro-organisms was considered positive All-cause mortality in ICU Duration of intubation <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> All-cause mortality in hospital Adverse drug reactions Participants requiring blood transfusions Units of blood transfused <p>Outcomes reported but not used in review</p> <ul style="list-style-type: none"> Nil
Notes	<p>Setting: Department of Internal Medicine and Intensive Care Unit, Imam Hossein Hospital, Shahid Beheshti University, M.C., Tehran, Iran</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The study was approved by the institutional ethics committee..."</p>

Solouki 2009 (Continued)

Informed consent: Quote: "Written consents signed by the patients or their family members were obtained for participation in the study"

Clinical trials registration: -

Sample size calculation: -

Additional notes: In the ranitidine group, 4 in 14 participants who had overt bleeding had clinically important GI bleeding. This was 1 in 3 participants from omeprazole group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using the table numbers randomly, all ICU beds were divided into two groups of A and B" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: This was a randomised double-blind placebo-controlled trial, and outcome assessors appeared to be blinded. GI bleeding was an objective outcome detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: This was a randomised double-blind placebo-controlled trial, and outcome assessors appeared to be blinded. VAP was an objective outcome detected as per the definition in the study protocol
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: This was a randomised double-blind controlled trial, and outcome assessors seem to be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Source of funding not known. No other known source of bias

Somberg 2008

Methods	Multi-centre open-label randomised controlled trial
Participants	Baseline characteristics
	Number randomised: 202 participants
	Number analysed: 202 participants

Somberg 2008 (Continued)

Pantoprazole (40 mg per 24 hours)

- Age (years; mean (SD)): 42.3 (21.8)
- Number of participants (n): 32
- Gender (male/female; n): 22/10

Pantoprazole (40 mg per 12 hours)

- Age (years; mean (SD)): 38.7 (18)
- Number of participants (n): 38
- Gender (male/female; n): 24/14

Pantoprazole (80 mg per 24 hours)

- Age (years; mean (SD)): 33.5 (15.5)
- Number of participants (n): 23
- Gender (male/female; n): 15/8

Pantoprazole (80 mg per 12 hours)

- Age (years; mean (SD)): 42.3 (19.2)
- Number of participants (n): 39
- Gender (male/female; n): 29/10

Pantoprazole (80 mg per 8 hours)

- Age (years; mean (SD)): 41.3 (16.4)
- Number of participants (n): 35
- Gender (male/female; n): 28/7

Cimetidine

- Age (years; mean (SD)): 44.5 (17.5)
- Number of participants (n): 35
- Gender (male/female; n): 27/8

Inclusion criteria

- Written informed consent obtained
- Unique patient ID assigned
- Male or non-pregnant female
- Age ≥ 18 years
- One of the risk factors for stress-related upper GI bleeding
- Postoperative major surgery
- Major trauma (head, chest, abdomen, or limbs)
- Hypovolumic shock defined clinically as a syndrome of inadequate tissue perfusion characterised by systolic blood pressure < 90 mmHg (or a decrease of 30 mmHg in previously hypertensive patients) and metabolic acidosis
- Sepsis, including peritonitis, confirmed or suspected bacteraemia, complex of fever, increased leucocyte count
- Acute respiratory failure, defined as 1 of the following:
 - Need for mechanically assisted ventilation
 - Severe hypoxaemia with an oxygen deficit great enough to require a fraction of inspired oxygen (FiO_2) of 0.31 by mask or at least 2 L/min of oxygen by nasal prongs to maintain 90% oxygen saturation
 - Acute hypoventilation resulting in an arterial blood pH < 7.34
- Burns involving $\geq 30\%$ of body surface area
- Coagulopathy defined as a platelet count $< 50,000 \text{ mm}^3$ or increased international normalised ratio or partial thromboplastin time > 1.5 times upper normal limit

Somberg 2008 (Continued)

- Baseline gastric aspirate that was clear (defined as no particulate matter, clots, or 'coffee grounds' and no red or brown colour, bile-tinged fluid was allowed) with no more than moderate positivity for occult blood on Gastrocult testing

Exclusion criteria

- Known hypersensitivity to PPIs
- Pregnancy
- Any condition known to compromise patient safety, according to the investigator
- Intubated for more than 24 hours at the time of drug administration
- ICU admission following oesophageal, gastric, or duodenal surgery or acute illicit drug overdose
- History of gastrectomy or UGI lesion with the potential for haemorrhage
- History of hypersecretory conditions like Zollinger-Ellison Syndrome
- Existence of peptic ulcer diseases within 1 year of study entry (on any of the study drugs immediately before or during the study)
- Inability to tolerate NG tube
- Previous participation in the study
- Clinical signs and symptoms/documentation of aspiration (or documentation of aspiration on the screening chest X-ray)
- Suspected/documented pneumonia

Baseline characteristics: Groups were similar with respect to age, gender, and race. Trauma was the main cause for admission, and coagulopathy was present in 2 participants from the pantoprazole group

Interventions

Pantoprazole

- Dose (total/d): 200 mg
- Duration of treatment (days): 2 to 7
- Route: -
- Intervention: 40 mg per 24 hours, 40 mg per 12 hours, 80 mg per 24 hours, 80 mg per 12 hours, 80 mg per 8 hours
- Concomitant medications: Enteral feeding was given to 50 participants

Cimetidine

- Dose (total/d): (300mg bolus +) 120 mg
- Duration of treatment (days): 2 to 7
- Route: IV
- Intervention: continuous infusion of cimetidine (300-mg bolus followed by 5-mg/h infusion) simultaneous intervention of external feeding for selected patients based on physician's opinion
- Concomitant medications: Enteral feeding was given to 4 participants

Adherence to regimen: Quote: "Subjects received study medication within 24 hours of the precipitating stress event and treatment was to be continued for at least 48 hours and up to 7 days. Patients were considered as completers if they received the study medication as described and participated in the study for at least 48 hours"

Of 202 participants, 144 remained NPO, while 58 participants were switched over to enterally feed, mainly on day 2 (48 participants)

"32 patients (16%) prematurely discontinued from the study. The most frequent reason for premature discontinuation was removal or inability to maintain tolerate NG/OG tube. Other reasons for premature discontinuation from the study included adverse events (3 in total, 2 in pantoprazole and 1 in cimetidine) or legal guardian request"

Duration of trial: June 2000 to September 2001

Duration of follow up: up to 30 days

Somberg 2008 (Continued)

Outcomes

Outcomes sought in review and reported in trial (none of these were primary outcomes of interest for this study)

- Incidence of upper GI bleeding occurring anytime during the study up to the last dose of study medication. Defined mainly as presence of haematemesis or bright red blood in gastric aspirate that did not clear after adjustment of nasogastric or orogastric tube and a 5 to 10 minute lavage with iced water or saline. Persistent 'coffee ground' material for 8 consecutive hours that did not clear with 100 mL of lavage, or was accompanied by 5% decrease in haematocrit. A decrease in haematocrit requiring one or more transfusions that occurred in the absence of any obvious source and required further diagnostic studies. Malena or frank bloody stools from upper gastrointestinal sources
- Incidence of ventilator-associated pneumonia defined as radiographic findings of a new or evolving infiltrate in the chest X ray, fever, elevated white blood cell count > 15% immature neutrophils (band) or leucopaenia, presence of at least 3 of the following: new or increased cough, new onset of purulent sputum production or a change in the character of the sputum, auscultatory findings on pulmonary examination of rales or evidence of pulmonary consolidation
- Dyspnoea, tachypnoea, or respiratory rates ≥ 20 breaths/min
- Hypoxaemia with $\text{PaO}_2 < 60$ mmHg or oxygen saturation < 90%, while the patient was breathing room air, or respiratory failure requiring mechanical ventilation, tachycardia, pleuritic chest pain, new or worsened confusion
- All-cause mortality in ICU
- Adverse events of interventions

Outcomes sought but not reported in trial

- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Participants requiring blood transfusions
- Units of blood transfused

Outcomes reported but not used in review

- Intragastric pH status (with and without enteral nutrition)
- Incidence of diarrhoea

Notes

Setting: 14 ICU centres across the United States

Source of funding: Quote: "Supported by Wyeth Pharmaceuticals, Collegeville, PA"

Ethics approval: Quote: "The study conducted according to declaration of Helsinki and its amendments. and was approved by the independent ethics committee or institutional review board at each ICU centre"

Informed consent: Quote: "Written informed consent was obtained from all patients or their legal representatives before enrolment"

Clinical trials registration: -

Sample size calculation: The sample size of 30 patients per group was chosen based on a common standard deviation of 24% for the primary end point (pH response associated with each treatment group), and there was approximately 80% power to detect a mean difference of 18% for treatment group comparisons

Additional notes: *H influenzae* was one of the most common bacterial isolates among participants who developed pneumonia. The pantoprazole arms were combined to form a common interventional arm vs the H2 receptor antagonist as the review did not aim to investigate efficacy on the basis of dose or mode of administration in the same drug

Risk of bias

Somberg 2008 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...the study centre called the central randomisation centre to obtain the treatment assignment..." Comment: Sequence generation was probably done
Allocation concealment (selection bias)	Low risk	Quote: "...the study centre called the central randomisation centre to obtain the treatment assignment..." Comment: Allocation was probably concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "One physician per patient remained blinded to the patients treatment assignment and pH data to assess patient's safety" Comment: Each patient had a physician in charge, who was blinded. Unclear on how this was possible, as it is not a placebo-controlled trial, and all other personnel were aware of the intervention
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear on blinding of outcome assessors. GI bleeding was an objective outcome detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: unclear on blinding of outcome assessors. VAP was detected as per the definition in the study protocol
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear on blinding of outcome assessors. However, owing to the objective nature of the outcomes of interest, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants completed the trial and were included in the final analysis. There were no treatment withdrawals and no trial group changes
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Study was supported by Wyeth Pharmaceuticals, Collegeville, PA. The role of the sponsor in the conduct and reporting of the trial is unclear

Stoehr 2006

Methods	Randomised controlled trial
Participants	Baseline characteristics Number randomised: 30 participants Number analysed: 30 participants Sucralfate <ul style="list-style-type: none"> Age (years; mean (SD)): - (-) Number of participants (n): 15 Gender (male/female; n): 7/8 Ranitidine

Stoehr 2006 (Continued)

- Age (years; mean (SD)): - (-)
- Number of participants (n): 15
- Gender (male/female; n): 8/6

Inclusion criteria

- Intact renal function
- Requiring intensive care management and mechanical ventilation
- Showing significantly increased risk of stress ulcer complications

Exclusion criteria

- Age < 18 years
- Pregnancy
- Previous duodenal or gastric surgery
- History of gastric ulcers, active upper gastrointestinal bleeding, or pneumonia; therapy with H2 receptor antagonists, antacids, omeprazole, pirenzepine, or sucralfate within the last year
- Treatment with non-steroidal anti-inflammatory drugs or coumarin within the last 7 days
- Primary coagulation disorders
- Ventilation expected to last less than 3 days

Baseline characteristics: Quote: "The study sample was homogeneous in terms of age and sex distribution, duration of treatment, severity of illness, inclusion criteria, and basic intensive care regimens"

Interventions
Sucralfate

- Dose (total/d): 6 g
- Duration of treatment (days): -
- Route: IG tube
- Intervention: 1 g 6 times daily by stomach tube
- Concomitant medications: Enteral feeding was given to 50 participants

Ranitidine

- Dose (total/d): 200 mg
- Duration of treatment (days): -
- Route: IV
- Intervention: ranitidine (200 mg/d) by continuous intravenous infusion

Adherence to regimen: -

Duration of trial: -

Duration of follow-up: -

Outcomes
Outcomes sought in review and reported in trial

-

Outcomes sought but not reported in trial

- Upper GI bleeding
- VAP
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Participants requiring blood transfusions
- Units of blood transfused

Stoehr 2006 (Continued)

Outcomes reported but not used in review

- Aluminium content in nutrition solution
- Aluminium intake
- Serum aluminium levels
- Renal aluminium excretion

Notes

Setting: Surgical ICUs at a university hospital in Germany

Source of funding: -

Ethics approval: Quote: "The study was approved by the Ethics Committee of the University of Düsseldorf"

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Additonal notes: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information reported
Allocation concealment (selection bias)	Unclear risk	Comment: no information reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information reported
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: no information reported
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: This was not an outcome of the study
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: This was not an outcome of the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All participants randomised were included in the analysis
Selective reporting (reporting bias)	Low risk	Comment: All outcomes described in the Methods section were included in the Results section
Other bias	Low risk	Comment: no other source of bias suspected. Source of funding unclear

Stothert 1980

Methods	Single-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 144 participants</p> <p>Number analysed: 123 participants</p> <p>Antacids</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 47 (-) • Number of participants (n): 58 • Gender (male/female; n): 41/17 <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 43 (-) • Number of participants (n): 65 • Gender (male/female; n): 48/17 <p>Inclusion criteria</p> <p>-</p> <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Diagnosis of gastric haemorrhage • Failure to follow the outlined protocol <p>Baseline imbalances: Quote: "No significant difference exists between the groups in relation to the risk factors such as abdominal trauma, cardiovascular disease, respiratory failure, sepsis, neurologic injury, orthopedic injury, vascular injury, renal failure, hepatic failure, alcohol or drug abuse, metastatic carcinoma, hypotension and history of peptic ulcer. Similarly, the two groups are quite comparable in age and sex ratio"</p> <p>Comment: There was no significant difference between the 2 groups with respect to demographic and baseline risk factors. Nine and 6 participants in both groups had a history of ulcers</p>
Interventions	<p>Antacids</p> <ul style="list-style-type: none"> • Dose (total/d): 720 cc • Duration of treatment (days): until the patient no longer required gastric decompression or was discharged from the intensive care unit as a result of improvement or death • Route: NG or gastrostomy tube • Intervention: 30 cc of Mylanta II every hour via the nasogastric or gastrostomy tube. The tube was subsequently clamped for 30 minutes and then placed on suction for 30 minutes. If the pH < 4 at the end of 3 of 6 consecutive hourly time periods, the amount of Mylanta II was increased to 60 cc/h. Similarly, if pH control failed at this level, the amount of antacid was increased to 90 cc/h and finally to 120 cc/h if required. Any patient who required more than 120 cc/h of antacid then had cimetidine added to the protocol. Any patient developing severe diarrhoea (defined as greater than 4 loose stools per day) while on Mylanta II underwent substitution of the antacid with Alternagel • Concomitant medications: Each participant remained NPO for the duration of the study <p>Cimetidine</p> <ul style="list-style-type: none"> • Dose (total/d): 1200 mg • Duration of treatment (days): until the patient no longer required gastric decompression or was discharged from the intensive care unit as a result of improvement or death • Route: IV

Stohtert 1980 (Continued)

- Intervention: Cimetidine was administered using an initial dosage level of 300 mg every 6 hours and was continued at this rate if the intragastric pH > 4. If this pH was not achieved, the frequency of drug administration was increased to every 4 hours, and then to every 3 hours. Criteria for failure at a given dose included a pH < 4 for 3 out of 6 consecutive hourly measurements. Maximum dose was 2400 mg per 24 hours. Any patient who failed all 3 dosage levels then had antacid added to the cimetidine regimen according to the antacid protocol
- Concomitant medications: Each participant remained NPO for the duration of the study

Adherence to regimen: Quote: "One hundred forty-four patients were included in this study. Fifty-eight patients were randomised to the antacid treatment group and 65 patients were randomised to the cimetidine therapy group. Forty-six patients were not included in these results because they met protocol criteria for less than 24 hours. Twenty-one patients required no therapy because of persistent pH ≥ 4. Forty-eight (74%) cimetidine recipients had the expected elevation of pH ≥ 4. Seventeen (26%) failed despite maximum dosage of cimetidine. All failures with cimetidine had antacids added and responded successfully. No failure of antacid therapy was seen in this study and therefore no patients crossed over from the antacid therapy group into the cimetidine therapy group. The twenty-one patients who maintained a gastric pH ≥ 4 required no prophylaxis and were not further dealt with further in this paper. All studies continued until the patient no longer required gastric decompression or was discharged from the intensive care unit as a result of improvement or death"

Comment: also stated that all patients responded to antacid therapy

"Forty participants responded to 30 cc every hour to maintain gastric pH at the desired level. Only three patients required 120 cc per hour to maintain this level. In the group receiving cimetidine, 34% responded to 300 mg every six hours. An additional 40% of the participants responded to administration at a dosage level of every four or every three hours"

Duration of trial: October 1978 to July 1979

Duration of follow up: not clearly mentioned in the study report. Probably until death or discharge

Outcomes	<p>Outcomes sought in review and reported in trial (none of these were primary outcomes of the study)</p> <ul style="list-style-type: none"> • Incidence of GI bleeding defined as occurrence of melena or bright red bleeding from NG tube that would not clear with iced saline lavage • All-cause mortality in ICU • Participants requiring blood transfusions • Adverse events of interventions <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • Incidence of ventilator-associated pneumonia • Duration of ICU stay • Duration of intubation • All-cause mortality in hospital • Units of blood transfused <p>Outcomes reported but not used in review</p> <ul style="list-style-type: none"> • Intragastric pH status
Notes	<p>Setting: Harborview Medical Center Surgical Intensive Care Unit (SICU), 325 Ninth Avenue, Seattle, WA 98104</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: -</p> <p>Informed consent: -</p>

Stohtert 1980 (Continued)

Clinical trials registration: -

Sample size calculation: -

Additional notes: It is mentioned that diarrhoea occurred in 5 of the 75 participants treated with antacids. This included 58 antacid-treated participants and 17 participants in whom cimetidine "failed" as per the study protocol. These data are unclear on the incidence in the original denominator, so could not be analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation process was based on a random number table in a blinded fashion" Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: Not clearly mentioned in the study report. However, the baseline there is no imbalance in baseline characteristics, indicating low risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Day-to-day clinical management was performed by an attending physician independent of the study protocol" Comment: Personnel were blinded
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: no clear mention of blinding of outcome assessors. GI bleeding was an objective outcome detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: A per-protocol analysis was performed to measure the outcomes of interest. Only 123 of 144 participants were accounted for in the analysis. Groups to which these 67 participants were randomised remains unclear. However, there is no imbalance between groups with respect to the number of participants available for final analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes stated were analysed and reported
Other bias	Low risk	Comment: source of funding not clear. No other known form of bias detected

Tabeeefar 2012

Methods	Parallel-group randomised controlled trial
Participants	Baseline characteristics Number randomised: 27 participants

Tabeefar 2012 (Continued)

Number analysed: 27 participants

Pantoprazole I

- Age (years; mean (SD)): 47.0 (11.0)
- Number of participants (n): 11
- Gender (male/female; n): 9/2

Pantoprazole II

- Age (years, mean (SD)): 39.7 (8.0)
- Number of participants (n): 8
- Gender (male/female; n): 6/2

Ranitidine

- Age (years, mean (SD)): 50.4 (8.0)
- Number of participants (n): 8
- Gender (male/female; n): 6/2

Inclusion criteria

- Non per oral patients
- Need of mechanical ventilation
- Presence of a nasogastric tube with a gastric position confirmed on abdominal radiography
- Baseline gastric juice with pH equal to or lower than 3.0
- Presence of at least 1 risk factor other than ventilation for a gastroduodenal stress ulcer that would commonly indicate the SRMD prophylaxis
- Not receiving any H2-blocker, proton pump inhibitor, or antacids for the last 2 days
- No enteral feeding during the study period

Exclusion criteria

- Age < 18 years
- Patients with renal or hepatic failure

Baseline imbalances: No statistical differences in age, sex, and basal pH and SOFA were found between treatment groups

Interventions
Pantoprazole I

- Dose (total/d): 80 mg
- Duration of treatment (days): 2
- Route: IV
- Intervention: 40 mg every 12 hours for 48 hours (four doses)
- Concomitant medications: none

Pantoprazole II

- Dose (total/d): 80 mg
- Duration of treatment (days): 2
- Route: IV
- Intervention: 80 mg/day pantoprazole as continuous infusion for 48 hours
- Concomitant medications: none

Ranitidine

- Dose (total/d): 150 mg
- Duration of treatment (days): 2
- Route: IV

Tabeefar 2012 (Continued)

- Intervention: 150 mg ranitidine as 24 h continuous infusion for 48 hours
- Concomitant medications: none

Adherence to regimen: -

Duration of trial: April 2010 to August 2011

Duration of follow-up: 2 days

Outcomes	<p>Outcomes sought in review and reported in trial</p> <p>-</p> <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • Incidence of clinically important GI bleedingIncidence of VAP • Duration of ICU stay • All-cause mortality in hospital • Duration of intubation • Adverse events of interventions <p>Outcomes reported in trial but not used in review</p> <ul style="list-style-type: none"> • Plasma IL-1 β concentration • Intragastric pH
Notes	<p>Setting: ICU, Department of Pharmacotherapy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Study protocol was approved by our institutional ethics committee</p> <p>Informed consent: Written consent form was obtained from each patient's closest family member</p> <p>Clinical trials registration: This trial is registered in www.anzctr.org.au</p> <p>Sample size calculation: -</p> <p>Additional notes:</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to 3 study groups according to a computer-generated table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: not enough information reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: insufficient information to allow judgement, but the outcome is unlikely to be influenced by performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: Study did not address this outcome

Tabeeifar 2012 (Continued)

Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: insufficient information to allow judgement, but the outcome is unlikely to be influenced by detection bias, provided it was a laboratory measurement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no incomplete outcome data suspected. All patients randomised at baseline were also included in the analyses
Selective reporting (reporting bias)	Low risk	Comment: All outcomes listed in the Methods section were also reported in the Results
Other bias	Low risk	Comment: no other sources of bias suspected

Terzi 2009

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 24 participants</p> <p>Number analysed: 20 participants</p> <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 44 (20) • Number of participants (n): 10 • Gender (male/female; n): 5/5 <p>Pantoprazole</p> <ul style="list-style-type: none"> • Age (years; mean (SD)): 45 (15) • Number of participants (n): 10 • Gender (male/female; n): 7/3 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Written consent from a first-degree relative of each patient • Mechanically ventilated for more than 48 hours • Sepsis as defined by evidence of infection and exhibited 2 or more of the criteria defined by the ACCP/SCCM Consensus Conference <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Age < 18 years • Pregnancy or breast-feeding • Admitted to the ICU after oesophageal, gastric, or duodenal surgery • History of gastrectomy or known upper GI lesion • Potential for haemorrhage • History or existence of a hypersecretory condition such as Zollinger- Ellison syndrome • History or existence of peptic ulcer disease within 1 year before the study commencing • Coagulation disorders

Terzi 2009 (Continued)

Baseline imbalances: Participants were comparable with respect to age, gender, and other clinical characteristics including the presence of *H pylori*, APACHE II score was 12 +/- 7 and 16 +/- 4 for ranitidine and pantoprazole groups

Interventions	<p>Ranitidine</p> <ul style="list-style-type: none"> • Dose (total/d): 150 mg • Duration of treatment (days): - • Route: IV • Intervention: 50 mg of the drug every 8 hours, diluted in 20 mL of 0.9% saline solution and administered by slow intravenous infusion (2 to 3 minutes) • Concomitant medications: conventional treatment of sepsis, including antibiotic therapy, fluid replacement, glucose control, treatment with vasoactive drugs, and dialysis when required, in addition to routine supplementary tests. Patients remained fasting <p>Pantoprazole</p> <ul style="list-style-type: none"> • Dose (total/d): 80 mg • Duration of treatment (days): - • Route: IV • Intervention: 40 mg of drug diluted in 10 mL of 0.9% saline solution and administered intravenously (2 minutes), every 12 hours at standardised times • Concomitant medications: conventional treatment of sepsis, including antibiotic therapy, fluid replacement, glucose control, treatment with vasoactive drugs, and dialysis when required, in addition to routine supplementary tests. Patients remained fasting <p>Adherence to regimen: Quote: "Four patients, 3 from ranitidine group, were excluded for technical reasons"</p> <p>Duration of trial: -</p> <p>Duration of treatment: -</p> <p>Duration of follow-up: not clearly mentioned in the trial report. Probably until discharge or an untimely event of death</p>
Outcomes	<p>Outcomes sought in review and reported in trial (none of these were the primary outcomes of the trial)</p> <ul style="list-style-type: none"> • GI bleeding defined as a decrease in haemoglobin levels greater than 2 g/dL, a decrease in systolic arterial pressure greater than 20 mmHg, the need for a transfusion of 2 or more units of concentrated red blood cells, all within a period of 2 hours, gastric bleeding requiring surgery (No gastric bleeding was detected) • All-cause mortality in ICU <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • Incidence of ventilator-associated pneumonia • All-cause mortality in hospital • Duration of ICU stay • Duration of intubation • Participants requiring blood transfusions • Units of blood transfused • Adverse reactions of interventions <p>Outcomes reported but not used in review</p> <ul style="list-style-type: none"> • Gastric pH levels • Investigation for <i>H pylori</i>

Terzi 2009 (Continued)

Notes

Setting: State University of Campinas (UNICAMP), Campinas, São Paulo, Brazil

Source of funding: Quote: "Support funds for research and development were provided by FAEPEX. Fundação de Apoio ao Ensino, à Pesquisa e à Extensão"

Conflicts of interest: -

Ethics approval: Quote: "The present study was approved by the ethics committee of the State University of Campinas, Brazil (no. 035/2003, dated February 18, 2003)"

Informed consent: Quote: "The informed consent form was signed by a relative of each patient included in the study, as required by Resolution no. 196/96 of the National Health Council, Brazilian Ministry of Health, concerning research involving human beings"

Clinical trials registration: -

Sample size calculation: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and different modes of administering the study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: This was an open-label trial, and outcome assessors were not blinded. However GI bleeding was an objective outcome that had to be detected as per the study protocol
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: This was an open-label trial, and outcome assessors were not blinded. However the outcome of interest was an objective outcome, so the likelihood of detection bias is low.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote "Four patients, 3 from ranitidine group, were excluded for technical reasons" Comment: Nearly 16% of randomised participants were excluded from analysis. An intention to treat analysis was not performed. This would have contributed to attrition bias
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes have been reported
Other bias	Low risk	Comment: Funding was provided by FAEPEX. Fundação de Apoio ao Ensino, à Pesquisa e à Extensão. However, the role of the sponsor in the conduct and reporting of the trial is unclear

Thomason 1996

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 424 participants</p> <p>Number analysed: 242 participants</p> <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; median (SD)): 27.7 (-) • Number of participants (n): 80 • Gender (male/female; n): 53/27 <p>Antacids</p> <ul style="list-style-type: none"> • Age (years; median (SD)): 32.9 (-) • Number of participants (n): 82 • Gender (male/female; n): 53/29 <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; median (SD)): 31.0 (-) • Number of participants (n): 80 • Gender (male/female; n): 52/28 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age $\geq$ 18 years old • Admitted to the trauma, surgical, or neurosurgical intensive care unit (ICU) • Mechanically ventilated via an endotracheal tube • Nasogastric (NG) tube in place <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Anticipated to require mechanical ventilation for < 24 hours • Pregnancy • Having received sucralfate, antacids, or an H₂ antagonist within the previous 24 hours • Recent oesophageal or gastric injury, disease, or operation • Taking steroids • Known to have acquired immunodeficiency syndrome (AIDS) • Participation in a conflicting clinical study • Having an infiltrate on the initial chest roentgenogram or developed pneumonia within 24 hours of admission • Initial chest roentgenogram could not be evaluated <p>Baseline imbalances: Participants were similar in the different groups with respect to age, gender, race, median Injury Severity Score (ISS), Trauma Score (TS), Glasgow Coma Scale Score, and APACHE II (Acute Physiology and Chronic Health Evaluation) Score and Habits (Tobacco and Caffeine consumption). The only significant baseline difference observed in the 11 variables recorded for participants in the 3 drug treatment groups were median alcohol level on admission ($P = 0.045$) and self-reported use of alcohol ($P = 0.007$)</p>
Interventions	<p>Sucralfate</p> <ul style="list-style-type: none"> • Dose (total/d): • Duration of treatment (days): 7

Thomason 1996 (Continued)

- Route: NG tube
- Intervention: sucralfate slurry administered orally 1 g in 30 mL of normal saline, then flushing the NG tube with 30 mL of normal saline every 6 hours
- Concomitant medications: -

Antacids

- Dose (total/d):
- Duration of treatment (days): 7
- Route: NG tube
- Intervention: antacid (1350 mg of aluminium hydroxide and 1200 mg of magnesium hydroxide per dose) administered 30 mL per NG tube, then flushing with 30 mL of normal saline every 4 hours as needed to maintain gastric pH ≥ 4.0 . Gastric pH was measured before each dose of study drug by pH-indicator strips (Hydrinon Papers, Improved Papers, Micro Essential Laboratory, Brooklyn, NY). If the gastric pH was < 4.0 , the patient was given 30 mL of antacid every 2 hours until the pH ≥ 4.0 . If the gastric pH ≥ 4.0 , the antacid was withheld
- Concomitant medications: -

Ranitidine

- Dose (total/d):
- Duration of treatment (days): 7
- Route: IV
- Intervention: ranitidine administered as 150 mg/250 mL D₅W continuous infusion at 10 mL/h (6.25 mg/h) and titrating to maintain gastric pH ≥ 4.0 . If pH was < 4.0 , the infusion rate was increased in 10-mL increments every 2 hours until gastric pH ≥ 4.0
- Concomitant medications: -

Adherence to regimen: Between November 1990 and May 1994, 424 patients were randomised to 1 of 3 treatment regimens. One hundred eighty-two patients were discontinued from study participation, mainly because of the following occurring within 24 hours of study entry:

- Extubated < 24 hours after study entry (n = 71)
- Pneumonia < 24 hours after study entry (n = 43)
- Death < 24 hours after study entry (n = 38)
- Received a study medication during the previous 24 hours (n = 17)
- Recent oesophageal/gastric injury, disease, and/or surgery (n = 15)
- Consent not signed (n = 10)
- Other (n = 10)
- Initial chest roentgenogram could not be evaluated (n = 3)
- Steroid use (n = 1)
- Total n = 182

A patient was considered to have discontinued the study if gastrointestinal haemorrhage occurred before study day 7, if diet by mouth or by gastric feeding was begun before day 7, or if the study drug was discontinued or changed. A patient was considered to have completed the study if the patient developed pneumonia > 24 hours after study entry, completed study day 7, was extubated for 48 hours before study day 7, or died. Data from patients who died before study day 7 but who completed at least 24 hours on the study were included in the analysis. All patients randomised to the study were followed-up until hospital discharge for the outcome variables of laboratory, roentgenogram, and clinical signs of pneumonia, GI bleeding, or death. Forty of the 242 patients completed all 7 study days without getting pneumonia > 24 hours after study entry or dropping out of the study

Duration of trial: November 1990 to May 1994

Duration of follow up: Quote: "Mean follow up for intention to treat was 24.3 days (median, 16 days)"

"The mean follow-up time for patients in the drug treatment groups was 27.3 days, with a range of 1 to 257 days (median, 19 days)"

Thomason 1996 (Continued)

Participants were followed up until death or discharge

Outcomes
Outcomes sought in review and reported in trial

Outcomes are not categorised as primary and secondary

- Incidence of nosocomial pneumonia defined as an infiltrate on chest roentgenogram plus 3 of the following criteria: (1) leucocytosis > 10,000 cells, (2) gram-negative organisms on a tracheal or blood culture, (3) tracheal Gram stain demonstrating moderate to heavy bacteria or polymorphoneutrophils (> 25/HPF), (4) pathogens isolated from a tracheal culture, and (5) temperature > 38°C. This definition was derived from the Centers for Disease Control definition for nosocomial pneumonia. Early pneumonia was defined as occurring on study days 2 through 7. Late pneumonia was defined as occurring after study day 7
- Incidence of GI bleeding defined as any of the following: haematemesis, melena, haematochezia, red blood per NG tube that did not clear with 500 mL of saline lavage, or a drop in haemoglobin greater than or equal to 2 g/mL associated with any of the above. GI bleeding thought to be the result of injury was excluded from analysis
- All-cause mortality in ICU
- Number of participants requiring blood transfusions (none required)
- Number of units of blood transfused (none required)

Note: Greatest incidence of pneumonia developed within 7 days into the study

Outcomes sought but not reported in trial

- All-cause mortality in the hospital
- Duration of ICU stay
- Duration of intubation
- Adverse reactions of interventions

Outcomes reported but not used in review

- Intragastric pH status (with and without enteral nutrition)
- Bacterial colonisation

Notes

Setting: Carolinas Medical Center, Charlotte, North Carolina , USA

Source of funding: Quote: "This project was supported by the Health Services Foundation of Carolinas Medical Center"

Conflicts of interest: -

Ethics approval: Quote: "The study protocol was reviewed and approved by the institutional review board at Carolinas Medical Center"

Informed consent: Quote: "10 participants were excluded because consent was not signed"

Clinical trials registration: -

Sample size calculation: Sample size analysis showed that 80 participants were needed in each treatment arm (assuming an alpha level of 0.05 and a power of 80%). This assumes a pneumonia rate of 40%, which is supported by previous studies in intensive care unit patients, and also assumes that one of the treatments would reduce the rate to 20%, enough to be meaningful clinically; therefore, our goal was to recruit 240 assessable patients

Additional notes: Gram-negative micro-organisms were the most common tracheal isolates both in participants with and without pneumonia, and 13% of participants who developed pneumonia had retrograde colonisation from stomach or trachea

Risk of bias

Thomason 1996 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised using a computer-generated random number table to one of the following stress ulcer prophylaxis regimens..." Comment: Method adopted to obtain random sequence generation is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear whether outcome assessors were blinded. GI bleeding was an objective outcome that was detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: unclear whether outcome assessors were blinded. Pneumonia was an objective outcome that was detected as per the definition in the study protocol
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature, so the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 424 patients were randomised to 1 of 3 treatment regimens. One hundred eighty-two patients were discontinued from study participation for reasons mentioned under 'adherence of regimens'. Intention to treat was done for the outcomes of pneumonia and mortality only. All participants who were randomised to the 2 groups were not analysed for all outcomes, and a per-protocol analysis was done. The number of participants available for analysis appears to be balanced between groups. Therefore, the likelihood of bias due to attrition is low
Selective reporting (reporting bias)	High risk	Comment: All intended outcomes were analysed and reported, but intention to treat was done for the outcomes of pneumonia and mortality only
Other bias	Low risk	Comment: Source of funding was Health Services Foundation of Carolinas Medical Center. The role of the sponsor in the conduct and reporting of the trial is unclear. No other known source of bias

Tryba 1985

Methods	Open-label randomised controlled trial
Participants	Baseline characteristics Number randomised:100 Number analysed: 100 Cimetidine

Tryba 1985 (Continued)

- Age (years; median (SD)): 55.8 (17.6)
- Number of participants (n): 33
- Gender (male/female; n): 16/17

Antacids

- Age (years; median (SD)): 55.6 (14.7)
- Number of participants (n): 33
- Gender (male/female; n): 8/25

Sucralfate

- Age (years; median (SD)): 57.1 (12.8)
- Number of participants (n): 34
- Gender (male/female; n): 12/22

Inclusion criteria

- Total risk score of above 10 as devised by Tryba et al
- Being in the intensive care unit for at least 2 days

Exclusion criteria

- Admission because of acute GI haemorrhage
- Gastric or duodenal ulcer in the preceding 12 months

Baseline imbalances: Quote: "There were no statically significant differences among the three treatment groups on basic or laboratory parameters"

Comment: The 3 groups were similar with respect to demographic data

Interventions

Cimetidine

- Dose (total/d): 2 g
- Duration of treatment (days): as long as the participant was in the ICU
- Route: IV
- Intervention: 2 g every 24 hours by continuous IV infusion
- Concomitant medications: All participants received 50 mg of pirenzepine daily. Enteral feeding was administered to all stable participants. Potassium phosphate was given routinely (0 to 140 mmol daily)

Antacids

- Dose (total/d): 120 mL
- Duration of treatment (days): as long as the participant was in the ICU
- Route: -
- Intervention: 10 mL antacid containing aluminium hydroxide and calcium carbonate every 2 hours
- Concomitant medications: All participants received 50 mg of pirenzepine daily. Enteral feeding was administered to all stable participants. Potassium phosphate was given routinely (0 to 140 mmol daily)

Sucralfate

- Dose (total/d): 6 g
- Duration of treatment (days): as long as the participant was in the ICU
- Route: -
- Intervention: 1 g of sucralfate was given every 4 hours
- Concomitant medications: All participants received 50 mg of pirenzepine daily. Enteral feeding was administered to all stable participants. Potassium phosphate was given routinely (0 to 140 mmol daily)

Tryba 1985 (Continued)

Adherence to regimen: Quote: "... nausea and vomiting led to the discontinuation of antacid in four patients. The interval between administration of antacid doses had to be extended to four hours in 18 patients following the removal of their stomach tubes because they refused more frequent doses. Moreover, antacids could not be administered every two hours during the night in patients without a stomach tube since it was unreasonable to awaken them repeatedly for this purpose. Nausea or vomiting occurred in nine patients receiving sucralfate following the removal of the stomach tubes. This necessitated discontinuing the drug in one patient and changing the dosage interval to eight hours in four patients"

Duration of trial: September 1982 to December 1983

Duration of follow up: not clearly mentioned in the study report. Probably until death or discharge

Outcomes	<p>Outcomes sought in review and reported in trial</p> <p>Primary outcomes</p> <ul style="list-style-type: none"> Acute upper GI haemorrhage: macroscopically visible bleeding (haematemesis, bloody aspirate, or melena) as the criteria for acute upper GI bleeding <p>Secondary outcomes</p> <ul style="list-style-type: none"> All-cause mortality in ICU Adverse events due to interventions <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> Incidence of ventilator-associated pneumonia All-cause mortality in hospital Duration of ICU stay Duration of intubation Number of participants requiring blood transfusion Units of blood transfused <p>Outcomes reported but not used in review</p> <ul style="list-style-type: none"> Gastric pH values
Notes	<p>Setting: Department of Anaesthesiology and Biometry Hannover School of Medicine, Hannover, Federal Republic of Germany</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The study was carried out from September 1982 to December 1983 with institutional approval and in accordance with the guidelines of the German Drug Law"</p> <p>Informed consent: -</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p>
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Unclear risk Comment: not clearly mentioned in the study report

Tryba 1985 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear whether outcome assessors were blinded. However, GI bleeding was an objective outcome that was detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: All other outcomes of interest were objective in nature
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: unclear on the source of funding. No other form of bias detected

Tryba 1987

Methods	Single-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 100 participants</p> <p>Number analysed: 100 (for all outcomes except for pneumonia, reasons mentioned below)</p> <p>Antacid</p> <ul style="list-style-type: none"> • Age (years; median (SD)): 43.7 (20.1) • Number of participants (n): 50 • Gender (male/female; n): 28/22 <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (years; median (SD)): 44.9 (20.6) • Number of participants (n): 50 • Gender (male/female; n): 31/19 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Total risk score of at least 10 as devised by Tybra et.al • Undergone mechanical ventilation for at least 1 day • Has not undergone surgery of the upper GI tract

Tryba 1987 (Continued)

Exclusion criteria

- Admitted to the unit because of acute GI haemorrhage
- Gastric or duodenal ulcer in the preceding 12 months

Baseline imbalances: Quote: "Both the groups were comparable on basic clinical or laboratory parameters"

Comment: Both groups were comparable with respect to the distribution of demographic characteristics and risk factors

Interventions
Antacids

- Dose (total/d): 120 mL
- Duration of treatment (days, mean (SD)): 5.6 (4.0)
- Route: gastric tube
- Intervention: antacid containing aluminium hydroxide, magnesium hydroxide, or calcium carbonate with a high neutralizing capacity given as 10 mL every 2 hours
- Concomitant medications: Routine potassium phosphate was given to all participants. Details on antibiotic therapy are not clearly mentioned in the study report. Treatment was started within the first 12 hours of admission of participants to the unit

Sucralfate

- Dose (total/d): 25 mL
- Duration of treatment (days, mean (SD)): 6.2 (4.6)
- Route: gastric tube
- Intervention: 5 mL sucralfate suspension was given every 4 hours through the stomach tube, which was then rinsed with 10 to 15 mL of water
- Concomitant medications: Routine potassium phosphate was given to all participants. Details on antibiotic therapy are not clearly mentioned in the study report. Treatment was started within the first 12 hours of admission of participants to the unit

Adherence to regimen: Antacid therapy was discontinued in 3 participants (vomiting after extubation (n = 2) and alkalosis on the second day (n = 1))

Duration of trial: July 1984 to November 1986

Duration of follow-up: -

Outcomes
Outcomes sought in review and reported in trial
Primary outcomes

- Significant upper GI bleeding: Evidence of occult bleed in gastric juice aspirate was disregarded, therefore, macroscopically visible bleeding was taken into consideration (haematemesis, bloody aspirate, or melena) as the criteria for acute GI haemorrhage
- Diagnosis of pneumonia: radiographic evidence of pulmonary changes, temperature above 38.5°C, leucocytosis, bacteria in the tracheal smear, and suggestive changes in arterial blood gases. A diagnosis of pneumonia was established; only radiologic changes were present along with 3 further criteria. Only participants who showed no pathologic pulmonary changes were included in the analysis (participants showing signs of pneumonia on admission to ICU or those who had undergone thoracic trauma were excluded from analysis)

Secondary outcomes

- Adverse drug reactions
- Duration of ventilation
- All-cause mortality in ICU
- Participants requiring blood transfusions
- Duration of intubation

Tryba 1987 (Continued)

Outcomes sought but not reported in trial

- All-cause mortality in hospital
- Duration of ICU stay

Outcomes reported but not used in review

- Gastric pH values

Notes

Setting: Department of Anaesthesiology, Hannover School of Medicine, Hannover, Federal Republic of Germany

Source of funding: Quote: "This study was supported by a grant from E. Merck"

Ethics approval: Quote: "...with the approval of the local ethical committee and in accordance with the guidelines of the German Drug Law"

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear whether outcome assessors were blinded. GI bleeding was detected as per the definition in the study protocol. Therefore, the likelihood of detection bias is low
Blinding (detection bias) Nosocomial pneumonia	Low risk	Quote: "The diagnosis of pneumonia was done by a physician who was unaware of the object of the study" Comment: There was clear definition for diagnosing pneumonia, and the outcome assessor was blinded to the interventions. Therefore, the likelihood of detection bias is low
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear on blinding of outcome assessors. However, outcomes of interest were objective in nature, so the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "For analysis of pulmonary infections, 39 participants were withdrawn from the study because of thoracic trauma or pneumonia at the time of admission to ICU (18 from antacid arm and 21 from sucralfate arm)" For all other outcomes, all 100 randomised participants were part of the analysis

Tryba 1987 (Continued)

		Comment: Excluding these participants is justified as it could not have led to the true estimate of the outcome (incidence of nosocomial pneumonia) due to the intervention
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Study was supported by a grant from E. Merck. The role of the sponsor in the conduct and reporting of the trial is unclear. No other form of bias detected

Tryba 1988

Methods	Randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 400 participants</p> <p>Number analysed: 400 participants</p> <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (years; median (SD)): 56.8 (16.7) • Number of participants (n): 200 • Gender (female; %): 72.5 <p>Pirenzepine</p> <ul style="list-style-type: none"> • Age (years; median (SD)): 57.7 (16.8) • Number of participants (n): 200 • Gender (female; %): 78.5 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Participants on general surgical ICU unit or anaesthesiological ICU unit • Expected duration of stay at ICU > 36 hours <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Surgery of upper gastrointestinal tract • History of ulcer disease in the last 12 months • Expected long-term respiratory support <p>Baseline imbalances: no significant differences</p>
Interventions	<p>Ranitidine</p> <ul style="list-style-type: none"> • Dose (total/d): 200 mg • Duration of treatment (days, mean (SD)): 3.8 (2.3) • Route: IV • Intervention: 200 mg ranitidine continuous IV infusion (started within 12 hours after admission to ICU) • Concomitant medications: - <p>Pirenzepine</p> <ul style="list-style-type: none"> • Dose (total/d): 50 mg • Duration of treatment (days, mean (SD)): 4.1 (3.0)

Tryba 1988 (Continued)

- Route: IV
- Intervention: 50 mg pirenzepine continuous IV infusion (started within 12 hours after admission to ICU)
- Concomitant medications: -

Adherence to regimen: -

Duration of trial: October 1984 to November 1986

Duration of follow-up: unclear, but might be until discharge from ICU

Outcomes	<p>Outcomes sought in review and reported in trial</p> <p>Primary outcomes</p> <ul style="list-style-type: none">• Gastrointestinal bleeding defined as microscopically detectable bleeding (melena, bloody aspirate, haematemesis) <p>Secondary outcomes</p> <ul style="list-style-type: none">• Ventilator-associated pneumonia defined as changes in lungs as seen on X-ray films and 3 of the following: fever > 38.5°C, leucocytosis, pathogens isolated from a tracheal culture, change in arterial gas balance• Gastric pH• Adverse events of interventions• All-cause mortality in ICU• Duration of intubation: not mentioned. <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none">• All-cause mortality in hospital• Duration of ICU stay (not absolutely clear, but likely 3.8 days ± 2.3 in ranitidin group and 4.1 ± 3.0 in pirenzepine group)• Participants requiring blood transfusion <p>Outcomes reported but not used in review</p> <ul style="list-style-type: none">• Gastric pH values	
Notes	<p>Setting: Anaesthesiology Department, Hannover and Bochum, Germany</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics Approval: Study was conducted according to the drug law. No further information</p> <p>Informed Consent: -</p> <p>Clinical Trials Registration: -</p> <p>Sample Size Calculation: -</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report

Tryba 1988 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear whether outcome assessors were blinded. GI bleeding was an objective outcome that was detected as per the definition in the study protocol
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: unclear whether outcome assessors were blinded. Pneumonia was an objective outcome that was detected as per the definition in the study protocol. Outcome assessor was blinded to study aims
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: Outcome assessor was blinded to study aims. Therefore, low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were part of the analysis
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes have been reported
Other bias	Low risk	Comment: No additional biases were detected

van den Berg 1985

Methods	Double-blind randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 34 participants</p> <p>Number analysed: 28 participants</p> <p>Cimetidine</p> <ul style="list-style-type: none"> • Age (years; median (SD)): 43.9 (-) • Number of participants (n): 14 • Gender (male/female; n): 9/5 <p>Placebo</p> <ul style="list-style-type: none"> • Age (years; median (SD)): 48.4 (-) • Number of participants (n): 14 • Gender (male/female; n): 9/5 <p>Inclusion criteria</p> <ul style="list-style-type: none"> • On assisted ventilation in either medical or surgical ICU <p>Exclusion criteria</p>

van den Berg 1985 (Continued)

- Previous oesophageal or gastric operations
- Upper gastrointestinal bleeding on admission
- Period of assisted ventilation was expected to be less than 3 days

Baseline imbalances: Quote "All the factors including the distribution of patients according to sex, age, nature of intensive care unit were almost same within the two groups except for the mean risk factors (it was 2.6 per person in the cimetidine group and 1.9 in the placebo group)"

Comment: More people in the cimetidine group had 3 or more risk factors when compared with the placebo group

Interventions
Cimetidine

- Dose (total/d): varies
- Duration of treatment (days, mean (SD)): Treatment was given for at least 3 days and ended on extubation of the patient after 14 days in case of assisted mechanical ventilation
- Route: IV
- Intervention: cimetidine 20 mg/kg weight per 24 hours by continuous infusion. In participants with renal insufficiency or anuria, no more than 400 mg of cimetidine per 24 hours was given
- Concomitant medications: Sour skimmed milk mixture (pH 6.5 at 600 mL per 24 hours) was used as supportive treatment in participants with a relatively good condition (6 participants in cimetidine and 11 participants in the placebo group)

Placebo

- Dose (total/d): -
- Duration of treatment (days, mean (SD)): Treatment was given for at least 3 days and ended on extubation of the patient after 14 days in case of assisted mechanical ventilation
- Route: IV
- Intervention: placebo normal saline by continuous infusion
- Concomitant medications: Sour skimmed milk mixture (pH 6.5 at 600 mL per 24 hours) was used as supportive treatment in participants with a relatively good condition (6 participants in the cimetidine and 11 participants in the placebo group)

Adherence to regimen: 34 participants entered the study. While 28 completed the trial, 6 people dropped out for the following reasons: 1 participant died on the second day of the study from sepsis, 1 participant developed exanthema on the second day after which all medication was stopped, 1 participant was inadvertently given open cimetidine, 1 participant had bleeding duodenal ulcer proven endoscopically at the end of the study, 1 participant developed anuria, and 1 participant proved to have previous gastric surgery

Duration of trial: -

Duration of follow-up: not clearly mentioned in the study report. Probably until death or discharge

Outcomes
Outcomes sought in review and reported in trial
Primary outcomes

- Stress induced upper gastrointestinal bleeding: blood loss from the upper GI tract was measured by labelling the erythrocytes in 10 mL of autologous blood with 25 μ Ci of chromium chloride. These labelled erythrocytes were re-injected intravenously at the beginning of the treatment period. The gastric contents were aspirated either continuously or hourly, starting from the first day of treatment. Blood loss was calculated from the radioactivity of the gastric contents. Previous experience has shown that participants lost around 1 to 7 mL of blood every 25 hours. Blood loss more than double the higher figure of 15 mL per 24 hours was considered to be suggestive of mucosal damage

Secondary outcomes

- All-cause mortality in ICU (not clearly mentioned for each intervention)

van den Berg 1985 (Continued)

Outcomes sought but not reported in trial

- Incidence of ventilator-associated pneumonia
- All-cause mortality in hospital
- Duration of ICU stay
- Duration of intubation
- Number of participants requiring blood transfusions
- Units of blood transfused
- Adverse reactions due to interventions

Outcomes reported in trial but not used in review

- Gastric pH values
- Blood loss (measured by Cr-labelled erythrocytes)

Notes	Setting: Rotterdam University Hospital, Netherlands Source of funding: - Conflicts of interest: - Ethics approval: - Informed consent: - Clinical trials registration: - Sample size calculation: -
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study was performed double blind. The investigators were not involved in the treatment of the patients" Comment: This was a placebo-controlled trial, and study personnel and investigators were blinded. Therefore, the likelihood of performance bias is low
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Quote: "The study was performed double blind. The investigators were not involved in the treatment of the patients" Comment: GI bleeding was detected as per the definition in the study protocol and the investigators were blinded. Therefore, the likelihood of detection or performance bias is low
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Quote: "The study was performed double blind. The investigators were not involved in the treatment of the patients"

van den Berg 1985 (Continued)

		Comment: Study was performed as a double-blinded randomised controlled trial, and the outcomes of interest were objective in nature. Therefore, the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Not all randomised participants were part of the final analysed. 6 participants were excluded for reasons mentioned under "Adherence to the regimen". Moreover, it is unclear to which group these participants belonged, and an intention-to-treat analysis was not done. A per-protocol analysis was performed for the outcomes of interest, and the number of participants available for analysis appears to be balanced between groups. Therefore, the likelihood of attrition bias is low
Selective reporting (reporting bias)	High risk	Comment: All intended outcomes were analysed and reported. All-cause mortality in ICU was not specifically reported for each group
Other bias	Low risk	Comment: unclear on the source of funding. No additional biases were detected

van Essen 1985

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 90 participants</p> <p>Number analysed: 58 participants</p> <p>Prostaglandin</p> <ul style="list-style-type: none"> • Age (years; median (SD)): - (-) • Number of participants (n): 29 • Gender (n, male/female): - <p>Placebo</p> <ul style="list-style-type: none"> • Age (years; median (SD)): - (-) • Number of participants (n): 29 • Gender (n, male/female): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admitted to surgical or medical ICU <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Previous oesophageal or gastric surgery • Presence of oesophageal varices or extensive burns • Evidence of GI bleeding on ICU admission • Expected discharge or expected oral feeding in 3 days <p>Baseline imbalances: Quote: "29 participants in both the groups were similar with regard to sex distribution, age and number and nature of risk factors"</p> <p>Comment: no significant difference between the 2 groups with respect to demographic and baseline risk factors</p>
Interventions	Prostaglandin

van Essen 1985 (Continued)

- Dose (total/d): -
- Duration of treatment (days, mean (SD)): 3 - 7 (-)
- Route: gastric tube
- Intervention: intragastric prostaglandin E₂PGE₂; 0.5 mg dissolved in 20 mL of water + flushed with 20 mL water, administered every 4 hours via gastric tube
- Concomitant medications:

Placebo

- Dose (total/d): -
- Duration of treatment (days, mean (SD)): 3 - 7 (-)
- Route: gastric tube
- Intervention: only water, flushed with 20 mL of water, administered every 4 hours via gastric tube
- Concomitant medications: -

Adherence to regimen: Quote: "The study lasted 3 - 7 days. Treatment was discontinued if enteral feeding was given within the first three days, if gastric tube was removed or participant underwent surgery or had GI bleeding"

Of 32 participants, 8 participants had gastrectomy performed within first 3 days; in 1 participant, no chromium labelling was performed, 6 participants were discharged within first 3 days from ICU

3 participants showed non-compliance with entry criteria, 12 participants received enteral feeds or underwent gastric tube removal within first 3 days, and 9 participants died within the first 3 days

Duration of trial: November 1981 to September 1983

Duration of follow-up: -

Outcomes	Outcomes sought in review and reported in trial
	<p>Primary outcomes</p> <ul style="list-style-type: none"> • GI haemorrhage measured every 3.5 hours by inspection for manifest haemorrhage and by peroxidise test based on orthotolidine reaction and qualitatively measured every 24 hours by Cr-chromate labelling for erythrocytes. More than 15 mL blood loss from the upper GI tract was considered to be evidence of mucosal damage in the stomach <p>Secondary outcomes</p> <ul style="list-style-type: none"> • All-cause mortality in ICU <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • Participants requiring blood transfusion • Units of blood transfused • Nosocomial pneumonia • All-cause mortality in hospital • Length of stay in ICU • Length of stay on ventilator • Adverse events <p>Outcomes reported but not used in review</p> <ul style="list-style-type: none"> • Nil
Notes	
	<p>Setting: Departments of Internal Medicine and Surgery, University Hospital, Dijkzigt, Rotterdam, The Netherlands</p> <p>Source of funding: Quote: "The study was supported, in part, by a grant-in-aid from Upjohn Inc., Kalamazoo, MI"</p>

van Essen 1985 (Continued)

Conflicts of interest: -

Ethics approval: -

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients were randomly assigned to receive placebo or prostaglandin therapy in a double blind fashion" Comment: This was a placebo-controlled trial where most likely participants and study personnel were blinded to the interventions. Therefore, the likelihood of performance bias is low
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear on blinding of outcome assessors. However, GI bleeding was an objective outcome that was detected as per the definition in the study protocol. Therefore the likelihood of detection bias is low
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: unclear on blinding of outcome assessors. However, the outcome of interest was objective in nature, so the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Not all randomised participants were part of the final analysis. 90 were randomised, and only 58 were part of the study. However, this was a per-protocol analysis, and the numbers were well balanced between groups. Therefore there is no serious attrition bias
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported in the study
Other bias	Low risk	Comment: Upjohn Inc., Kalamazoo, MI, partially funded the study. The role of the sponsor in the conduct and reporting of the trial is unclear. No other sources of bias are suspected

Wang 2015

Methods	Parallel-group randomised controlled trial
Participants	Baseline characteristics Number randomised: 100

Wang 2015 (Continued)

Number analysed: 100

Bowel stimulation protocol

- Age (median for both groups; years): 40.7 (4.9)
- Number of participants at baseline (n): 50
- Gender (male/female; n): 27/23

No prophylaxis

- Age (median for both groups; years): 41.6 (5.3)
- Number of participants at baseline (n): 50
- Gender (male/female; n): 32/18

Inclusion criteria

- Mechanical ventilation for 3 or more days
- Free of GI dysfunction or multiple organ failure
- Patient's relatives were well aware of the study and signed the informed consent

Exclusion criteria

- GI tract trauma or surgical patients
- Patients with diarrhoea, abdominal trauma or unhealed wound, or any condition that was contraindicated for abdominal massage
- Patients with contraindications for enema, or those with high-pitched bowel sound and patients with acute abdomen
- Pregnancy
- Unstable vital signs

Baseline imbalances: none

Interventions	<p>Bowel stimulation protocol</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days, mean (range)): at least 5 days • Route: - • Intervention: abdominal massage for 15 to 20 minutes, 3 to 4 cm in depth, rectal digital stimulation, enema on day 2 if patients failed to pass the stool • Concomitant medications: continuous feeding, mosapride, bifidobacterial <p>No prophylaxis</p> <ul style="list-style-type: none"> • Dose (total/d): - • Duration of treatment (days, mean (range)): at least 5 days • Route: - • Intervention: observation • Concomitant medications: continuous feeding, mosapride, bifidobacterial
Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • Clinically important GI bleeding <p>Outcomes sought in review and not reported in trial</p> <ul style="list-style-type: none"> • Ventilator-associated pneumonia • Duration of ICU stay • Duration of hospital stay • Mortality • Duration of intubation

Wang 2015 (Continued)

- Participants requiring blood transfusions
- Units of blood transfused
- Adverse events of interventions

Outcomes reported in trial and not used in review

- Nil

Notes	<p>Setting: Department of ICU, the Second Hospital Affiliated to Tianjin Medical University, Tianjin, China</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Comment: mentioned in the study report that study authors sought ethics approval</p> <p>Informed consent: Comment: mentioned in the study report that study authors sought for informed consent</p> <p>Clinical trials registration: -</p> <p>Sample size calculation: -</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Patients were randomly divided into an intervention group and a control group, with 50 patients in each group, but the detailed methods were not mentioned
Allocation concealment (selection bias)	Unclear risk	Comment: no information reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: lack of blinding of participants and healthcare providers, but outcomes were measured objectively
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: Outcome was measured objectively, and no detection bias is suspected
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: no information reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing data detected
Selective reporting (reporting bias)	Low risk	Comment: All outcomes described in Methods were reported in Table 2
Other bias	Unclear risk	Comment: Detailed diagnosis of GI dysfunction was not reported - probably differential diagnostic activity between intervention group and control group

Wee 2013

Methods	Parallel-group randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: -</p> <p>Number analysed: -</p> <p>Famotidine</p> <ul style="list-style-type: none"> • Age (median for both groups; years): 72 • Number of participants at baseline (n): 61 • Gender (male/female; n): - <p>Pantoprazole</p> <ul style="list-style-type: none"> • Age (median for both groups; years): 72 • Number of participants at baseline (n): 68 • Gender (male/female; n): - <p>Inclusion criteria: each patient admitted to ICU/CCM</p> <p>Exclusion criteria: -</p> <p>Baseline imbalances: Both groups had similar baseline characteristics including risk factors for SRMB (2.7 vs 2.7, $P = 0.50$); however, the pantoprazole group had higher APACHE-II scores (23.9 vs 20.1; $P < 0.01$)</p>
Interventions	<p>Famotidine</p> <ul style="list-style-type: none"> • Dose (total/d): 40 mg • Duration of treatment (days): - • Route: IV • Intervention: famotidine 20 mg IVPB Q12H • Concomitant medications: - <p>Pantoprazole</p> <ul style="list-style-type: none"> • Dose (total/d): 40 mg • Duration of treatment (days): - • Route: IV • Intervention: pantoprazole 40 mg IVPB QAM • Concomitant medications: - <p>Adherence to regimen: -</p> <p>Duration of trial: December 2012 to April 2013</p> <p>Duration of follow-up: until discharge</p>
Outcomes	<p>Outcomes sought in review and reported in trial</p> <ul style="list-style-type: none"> • GI bleeding • Duration of ICU stay • Duration of mechanical ventilation • Any other adverse events <p>Outcomes sought in review and not reported in trial</p>

Wee 2013 (Continued)

- Ventilator-associated pneumonia
- Mortality
- Blood transfusion

Outcomes reported in trial, but not used in review

-

Notes

Setting: ICU/CCU, Kingsbrook Jewish Medical Center, Brooklyn, NY 11203, USA, Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Brooklyn, NY 11201, USA

Sponsorship source: -

Conflicts of interest: -

Comments: 2 conference abstracts reporting on 1 study

Ethical approval: Quote: "Expedited IRB approval was granted"

Informed consent: Quote: "Informed consent was not required"

Sample size calculation: -

Clinical trials registration: -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomized" Comment: not enough details reported
Allocation concealment (selection bias)	Unclear risk	Comment: no information reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: no information on blinding reported. Lack of blinding is unlikely to introduce bias to outcome measures and outcomes
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: not enough details described
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Unclear risk	Comment: no information on blinding of outcome assessors reported. Lack of blinding might potentially introduce bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: conference abstracts. Not enough information reported to assess incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Comment: Secondary outcomes listed in the Methods sections of the two abstracts differ slightly. Not enough information reported to assess selective outcome reporting

Wee 2013 (Continued)

Other bias	Unclear risk	Comment: not enough information reported to assess other sources of bias
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Weigelt 1981

Methods	Quasi-randomised trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 77 participants</p> <p>Number analysed: 77 participants</p> <p>Antacid</p> <ul style="list-style-type: none"> Age (years; mean (range)): overall. 40.5 (16 to 88) Number of participants (n): 16 Gender (male/female; n): - <p>Cimetidine (300 mg every 4 hours)</p> <ul style="list-style-type: none"> Age (years; mean (SD)):- Number of participants (n): 19 Gender (male/female; n): - <p>Cimetidine (300 mg every 6 hours)</p> <ul style="list-style-type: none"> Age (years; mean (SD)):- Number of participants (n): 19 Gender (male/female; n): - <p>Cimetidine (400 mg every 4 hours)</p> <ul style="list-style-type: none"> Age (years; mean (SD)):- Number of participants (n): 23 Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> Admission to the surgical intensive care unit Presence of nasogastric or gastrostomy tube Definition of illness severity by a therapeutic intervention scoring system (TISS) (classification of II or greater) <p>Exclusion criteria</p> <ul style="list-style-type: none"> Active peptic ulcer diseases Previous operative procedure designed to alter gastric acid secretion Compromised renal function Institution of stress ulcer prophylaxis prior to notification of investigators <p>Baseline imbalances: Quote: "A modification of Therapeutic intervention scoring system (TISS) was used to grade severity of illness for patient selection and group comparison"</p> <p>Comment: Average TISS score was 3 for antacids and 3.16 for combined cimetidine groups</p>
Interventions	<p>Antacids</p> <ul style="list-style-type: none"> Dose (total/d): 30 mL

Weigelt 1981 (Continued)

- Duration of treatment (days, mean (range)): 8.5 (1 to 28)
- Route: -
- Intervention: antacid, a combination of aluminium hydroxide and magnesium hydroxide (Maalox) to maintain gastric pH of 6. The initial dose of antacid was 30 mL. This dose was increased in 30-mL increments if gastric pH was not controlled
- Concomitant medications: -

Cimetidine

- Dose (total/d): 50 mg
- Duration of treatment (days, mean (range)): 2.6 (1 to 11)
- Route: IV
- Intervention: cimetidine (300 mg) intravenously every 6 hours or cimetidine (300 mg) intravenously every 4 hours or cimetidine (400 mg) intravenously every 4 hours
- Concomitant medications: -

Adherence to regimen: Quote: "The pH control in the antacid group was achieved with an average dose of 30 mL of antacid every two hours (range 15 to 120 mL/hour). Only one patient required more than 60 mL/hour for pH control. The duration of cimetidine treatment was similar in the three groups regardless of the efficacy of pH control"

Comment: According to the study report, pH was controlled in 14 cimetidine participants. The rest might have switched over to antacids according to the study protocol (but this is not clearly mentioned in the study report)

Duration of trial: February 1979 to August 1979

Duration of follow up: Quote: "All patients were followed up until death, discharge from ICU or institution of enteral feedings"

Outcomes	Outcomes sought in review and reported in trial
	Primary outcomes <ul style="list-style-type: none"> • Incidence of upper GI bleeding defined as blood per nasogastric tube (guaiac-positive nasogastric aspirate, unaccompanied by a fall in haematocrit value or obvious GI tract bleeding not considered to be clinically important)
	Secondary outcomes <ul style="list-style-type: none"> • All-cause mortality in ICU • Adverse events of interventions
	Outcomes sought but not reported in trial <ul style="list-style-type: none"> • Incidence of ventilator-associated pneumonia • All-cause mortality in hospital • Duration of ICU stay • Duration of intubation • Units of blood transfused
	Outcomes reported but not used in review <ul style="list-style-type: none"> • Intragastric pH status • Participants (with GI bleeding) requiring blood transfusion
Notes	Setting: Departments of Surgery, South-Western Medical School, University of Texas Health Science Centre, Dallas Source of funding: -

Weigelt 1981 (Continued)

Conflicts of interest: -

Ethics approval: -

Informed consent: -

Clinical trials registration: -

Sample size calculation: -

Additional notes: Cimetidine groups were combined to form a common interventional arm vs antacids, as the review did not aim to investigate efficacy among different routes of administration of the same intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Patients entering the study were randomised by hospital unit number into one of the four groups..." Comment: This was a quasi-randomised trial, and sequence was not generated
Allocation concealment (selection bias)	High risk	Quote: "Patients entering the study were randomised by hospital unit number into one of the four groups..." Comment: This was a quasi-randomised trial, and allocation was not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: unclear on the blinding of outcome assessors. However, GI bleeding was an objective outcome that was detected as per the study definition, so the likelihood of performance or detection bias is low
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: Outcomes of interest were objective in nature, so the likelihood of performance or detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All quasi-randomised participants were part of the final analysis, so there is no attrition bias
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: unclear on source of funding. No other form of bias detected

Yildizdas 2002

Methods	Open-label randomised controlled trial
Participants	<p>Baseline characteristics</p> <p>Number randomised: 200 participants</p> <p>Number analysed: 160 participants</p> <p>Sucralfate</p> <ul style="list-style-type: none"> • Age (months; mean (SD)): 58 (50) • Number of participants (n): 38 • Gender (male/female; n): - <p>Ranitidine</p> <ul style="list-style-type: none"> • Age (months; mean (SD)): 59 (49) • Number of participants (n): 42 • Gender (male/female; n): - <p>Omeprazole</p> <ul style="list-style-type: none"> • Age (months; mean (SD)): 59 (47) • Number of participants (n): 38 • Gender (male/female; n): - <p>No prophylaxis</p> <ul style="list-style-type: none"> • Age (months; mean (SD)): 60 (50) • Number of participants (n): 42 • Gender (male/female; n): - <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Admitted to paediatric ICU <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Extubation, death, pneumonia in the first 48 hours after enrolment • Any study medication in the last 48 hours before admission <p>Baseline imbalances: no significant difference between groups with respect to age, gender, or primary disease (sepsis and bronchitis were the most common primary diseases among participants)</p>
Interventions	<p>Sucralfate</p> <ul style="list-style-type: none"> • Dose (total/day): varies • Duration of treatment (days, mean (SD)): 11.3 (4.0) (duration at PICU) • Route: NG tube • Intervention: 60 mg/kg bw/d in 4 doses via NG tube + 10 mL of sterile water to flush • Concomitant medications: - <p>Ranitidine</p> <ul style="list-style-type: none"> • Dose (total/d): varies • Duration of treatment (days, mean (SD)): 11.6 (4.3) (duration at PICU) • Route: IV • Intervention: 2 mg/kg bw/d intravenously in 4 doses • Concomitant medications: - <p>Omeprazole</p>

Yildizdas 2002 (Continued)

- Dose (total/d): varies
- Duration of treatment (days, mean (SD)): 11.4 (4.1) (duration at PICU)
- Route: IV
- Intervention: 1 mg/kg bw/d intravenously in 2 doses
- Concomitant medications: -

No prophylaxis

- Dose (total/d): -
- Duration of treatment (days, mean (SD)): 11.1 (4.5) (duration at PICU)
- Route: -
- Intervention: -
- Concomitant medications: -

Adherence to regimen: Quote: "Administration of the drugs were unblinded and were begun within 6 hours of PICU admission"

"40 patients were excluded from study according to the exclusion criteria"

Duration of trial: August 2000 to February 2002

Duration of follow-up: -

Outcomes
Outcomes sought in review and reported in trial
Primary outcome

- Incidence of ventilator-associated pneumonia definition as modified to the American College of Chest Physicians: new or persistent radiographic infiltrate in the conjugation with the same organism recovered in the tracheal aspirate or sputum, radiographic cavitation, histopathologic evidence of pneumonia, or at least 2 of the following: fever, leucocytosis, and purulent tracheal aspirate or sputum. Pneumonia was considered as ventilator-associated if occurring after a minimum of 48 hours after mechanical ventilation

Secondary outcomes

- Incidence of GI bleeding
- All-cause mortality in the ICU
- Duration of intubation
- Duration of ICU stay

Outcomes sought but not reported in trial report

- All-cause mortality in hospital (other than those occurring in PICU)
- Number of participants requiring blood transfusion
- Units of blood transfused
- Adverse events of interventions

Outcomes reported in report but not used in review

- Pathogens cultured in participants with VAP

Notes

Setting: PICU of Faculty of Medicine, Cukurova University, Adana, Turkey

Source of funding: -

Conflicts of interest: -

Ethics approval: -

Clinical trials registration: -

Yildizdas 2002 (Continued)

Sample size calculation: -

Additional notes: According to the study, hospital mortality was defined as deaths occurring in the PICU, and hospital stay was defined as days spent in the PICU. *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were the most common organisms cultured in participants with the diagnosis of ventilator-associated pneumonia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised to one of the following stress ulcer prophylaxis regimens by using a computer generated random number table" Comment: The method adopted to generate a random sequence is clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Administration of drugs were unblinded..." Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Unclear risk	Comment: not clear whether outcome assessors were blinded. Moreover, the definition for diagnosing GI bleeding, which is an objective outcome, is not clearly mentioned in the study report. Not clear whether this would have caused any detection bias
Blinding (detection bias) Nosocomial pneumonia	Low risk	Comment: not clear whether outcome assessors were blinded. But ventilator-associated pneumonia was assessed as per the definition in the study report. Therefore, the likelihood of performance or detection bias is low
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: not clear whether outcome assessors were blinded. However, the other outcomes of interest were objective in nature, so the likelihood of performance or detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "...200 patients were randomised to one of the 4 treatment regimens. 40 patients were excluded from study according to the exclusion criteria" Comment: A per-protocol analysis was done, and only those participants who completed ≥ 48 hours in the study were part of the final analysis. There is also a balance between groups with respect to the number of participants analysed. Therefore, the likelihood of attrition bias is low
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes have been analysed and reported
Other bias	Low risk	Comment: unclear on the source of funding. No additional biases were detected

Zinner 1981

Methods Open-label randomised controlled trial

Zinner 1981 (Continued)

Participants

Baseline characteristics

Number randomised: 300 participants (the report says that 40 additional participants were entered in- to the randomised trial, not sure if they were randomised)

Number analysed: 300 participants

Cimetidine

- Age (years; mean (SD)): 56.7 (-)
- Number of participants (n): 100
- Gender (male/female; n): 63/37

Antacids

- Age (years; mean (SD)): 58.7 (-)
- Number of participants (n): 100
- Gender (male/female; n): 59/41

No prophylaxis

- Age (years; mean (SD)): 55.5 (-)
- Number of participants (n): 100
- Gender (male/female; n): 63/37

Inclusion criteria

- Admitted for at least 48 hours to the surgical intensive care unit

Exclusion criteria

- Upper GI bleeding
- Recent peptic ulcer diseases
- Having undergone an operation on the oesophagus or the stomach

Baseline imbalances: The 3 groups were similar with respect to age, gender, and medical conditions. Most participants were admitted for cardiac or general surgery

Interventions

Cimetidine

- Dose (total/d): 1200 mg
- Duration of treatment (days, mean (range)): -
- Route: IV
- Intervention: 300 mg of cimetidine intravenously every 6 hours
- Concomitant medications: It is mentioned that participants received additional medications, but the names of the medications are not clearly mentioned

Antacids

- Dose (total/day): 240 mL
- Duration of treatment (days, mean (range)): -
- Route: -
- Intervention: 10 mL of magnesium aluminium hydroxide antacid (Maalox) + water to maintain a gastric pH ≥ 4 at the end of every hour. If pH was < 4 , the dose was doubled along with water. None of the participants required more than 80 mL of Maalox therapeutic concentrate every 2 hours, and 20 mL every 2 hours was sufficient in approximately 85% of participants
- Concomitant medications: It is mentioned that participants received additional medications, but the names of the medications are not clearly mentioned

No prophylaxis

Zinner 1981 (Continued)

- Dose (total/d): -
- Duration of treatment (days, mean (range)): -
- Route: -
- Intervention: no prophylaxis
- Concomitant medications: It is mentioned that participants received additional medications, but the name of the medications are not clearly mentioned

Adherence to regimen: 33 participants who met the inclusion criteria were randomised (100 in each treatment arm). 40 additional participants entered into the study but were removed for the following reasons: protocol errors or request from physician (n = 31), no reason mentioned (n = 9)

Duration of trial: December 1977 to December 1979

Duration of follow-up: not clearly mentioned in the study report. Probably until death or discharge

Outcomes	<p>Outcomes sought in review and reported in trial</p> <p>Primary outcome</p> <ul style="list-style-type: none"> • Incidence of upper GI bleeding defined as persistent guaiac 4+ positive nasogastric aspirate, continuous for greater than 16 hours (2 consecutive nursing shifts) even after nasogastric lavage, bright red bleeding per nasogastric tube or by emesis, and guaiac-positive stools and documented fall in haematocrit value <p>Secondary outcomes</p> <ul style="list-style-type: none"> • All-cause mortality in ICU • Participants requiring blood transfusion (according to the study, it was not clear if weather transfusions were performed solely because of GI bleeding, as these participants had multiple sites of bleeding) • Adverse reactions of interventions <p>Outcomes sought but not reported in trial</p> <ul style="list-style-type: none"> • Incidence of ventilator-associated pneumonia • Duration of ICU stay • Duration of intubation • All-cause mortality in hospital <p>Outcomes reported but not used in review</p> <ul style="list-style-type: none"> • Intragastric pH status with respect to Zinner Index score • Total time needed for gastric pH to reach ≥ 4 with respect to Zinner Index score • Duration of ICU stay (only median values are reported)
Notes	<p>Setting: surgical intensive care unit of the Johns Hopkins Hospital and the intensive care unit of the Baltimore City Hospitals</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: study approved by the joint committee on clinical investigation of John Hopkins Medical Institutions</p> <p>Informed consent: Quote: "Informed consent was obtained from all participants"</p> <p>clinical trials registration: -</p> <p>Sample size calculation: -</p>

Zinner 1981 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This was not a placebo-controlled trial, and the different modes of administering study interventions would not have made it possible to blind study personnel and participants. Moreover, 2 arm received no prophylaxis. Therefore, high risk of performance bias
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: It is unclear whether outcome assessors were blinded. GI bleeding was an objective outcome detected as per the definition in the study protocol. Therefore, the likelihood of detection bias is low
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: It is unclear whether outcome assessors were blinded. Moreover, outcomes of interest were objective in nature. Therefore the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: "Three hundred participants entered the inclusion criteria and were randomised to three treatment groups. Forty additional participants were entered into RCT but were removed from the protocol. Thirty one of these participants were excluded because of protocol errors or because of request by physician. These were evenly distributed between the treatment groups"</p> <p>Comment: The reason for exclusion of the remaining 9 participants is not clear. The study arms of these 40 participants are also not clearly mentioned in the study report. However, there appears to be no imbalance between study groups with respect to the number of participants available for analysis. Therefore the likelihood of bias due to attrition is low</p>
Selective reporting (reporting bias)	Low risk	Comment: All intended outcomes were analysed and reported
Other bias	Low risk	Comment: Source of funding is unclear. No other known source of bias

Zinner 1989

Methods	Single-blind randomised controlled trial
Participants	Baseline characteristics Number randomised: 371 Number analysed: 281 (for primary outcome) Misoprostol <ul style="list-style-type: none"> Age (years; mean (SD)):-

Zinner 1989 (Continued)

- Number of participants (n): 187
- Gender (male/female; n): 152/35

Antacid

- Age (years; mean (SD)): -
- Number of participants (n): 181
- Gender (male/female; n): 153/24

Inclusion criteria

- Participants scheduled to undergo major surgical procedures
- Expected to require at least 48 hours of postoperative monitoring in an ICU
- Participants with risk factors such as sepsis, trauma, electrolyte imbalance, diabetes, major burns, respiratory failure requiring ventilator assistance, congestive heart failure, arrhythmias requiring medication, or need for steroids

Exclusion criteria

- Active peptic ulcer disease
- Oesophageal, gastric, or duodenal malignancies
- Oesophageal varices
- Gastric outlet obstruction
- Acute renal failure
- Concurrent therapy with salicylates, non-steroidal anti-inflammatory drugs, antiulcer therapy, or antineoplastic agents

Baseline imbalances: Quote: "There were no statistical differences between the two treatment groups with respect to age, sex, or race. They were also comparable in mean height, weight, and vital signs on admission, and these did not differ with respect to study site. Initial gastric lesion scores were 0 or 1 in 88% of the patients, and initial duodenal lesion scores were 0 or 1 in 96% of the patients, with no significant differences between the two treatment groups ($p = 0.141$ and 0.848 , respectively)"

Comment: The 2 groups were similar with respect to demographic and baseline risk factors

Interventions

Misoprostol

- Dose (total/d): 1200 mcg
- Duration of treatment (days, mean (range)): max. 14
- Route: NG tube or PO
- Intervention: misoprostol tablets containing 200 mcg of misoprostol (Searle Inc., Skokie, IL) every 4 hours plus placebo liquid antacid every 2 hours. Tablets were dissolved in 20 mL of water and were administered 6 times daily through a nasogastric tube, or were given orally if no tube was in place
- Concomitant medications: -

Antacid

- Dose (total/d): -
- Duration of treatment (days, mean (range)): max 14
- Route: NG tube or PO
- Intervention: antacid: placebo tablets every 4 hours plus magnesium-aluminium hydroxide liquid antacid (Maalox TC, Rohrer Pharmaceuticals, Fort Washington, PA) every 2 hours. Tablets were dissolved in 20 mL of water and were administered 6 times daily through a nasogastric tube, or were given orally if no tube was in place. Antacid or placebo liquid was administered every 2 hours at a dose of 10, 20, 40, or 80 mL, increasing the dose upward as necessary during the first 72 hours to maintain gastric pH at 4.0 or higher. Samples were aspirated through the nasogastric tube every 2 hours and gastric pH was measured using litmus paper. After 72 hours, repeat endoscopic examinations were done and the liquid antacid or placebo was titrated downward to 20 mL every 4 hours
- Concomitant medications: -

Zinner 1989 (Continued)

Adherence to regimen: Quote: "Comparable numbers of patients completed the 14 days of treatment or were released earlier, having met the dietary requirement. By the eighth day, only 16% of the misoprostol group and 21% of the antacid group remained in the ICU ($p =$ not significant). Total time of nasogastric medication administration was also somewhat shorter in the misoprostol group (655 patient days vs. 731 patient days in the antacid group), but again these differences were not statistically significant.", "141 in Misoprostol and 140 in Antacid were only analysed as they met the following four criteria for other evaluations 1. completed at least three days in the study, 2. took at least 80% of the assigned medication, 3. did not withdraw from the study except for side effects of the medication, 4. had sufficient follow up endoscopy information to permit outcome evaluation"

Comment: 46 participants on misoprostol and 44 participants on antacid regimens were not unavailable for analysis of the primary outcome of GI bleeding

Duration of trial: -

Duration of follow-up: -

Outcomes	Outcomes sought in review and reported in trial
	<p>Primary outcomes</p> <ul style="list-style-type: none"> Clinically significant GI bleeding defined as persistent guaiac 4+ positive nasogastric aspirate, continuous for greater than 16 hours (2 consecutive nursing shifts) even after nasogastric lavage, bright red bleeding per nasogastric tube or by emesis, and guaiac-positive stools and documented fall in haematocrit value (no participant had the event) <p>Secondary outcomes</p> <ul style="list-style-type: none"> Adverse events of interventions All-cause mortality in ICU <p>Outcomes sought but not reported in trial report</p> <ul style="list-style-type: none"> Incidence of ventilator-associated pneumonia All-cause mortality in hospital Participants requiring blood transfusion Units of blood transfused Duration of ICU stay Duration of intubation <p>Outcomes reported in report but not used in review</p> <ul style="list-style-type: none"> Gastric pH Endoscopically confirmed upper GI lesions
Notes	<p>Setting: 16 university-associated medical centres: King/Drew Medical Center, Los Angeles, University of Minnesota Hospitals, Minneapolis, MN, Georgetown University Hospital, Washington, DC, Denver General Hospital, Denver, Health Science Center, Brooklyn, NY: Cook County Hospital, Chicago, IL, Minneapolis VA Medical Center, Minneapolis, Hines VA Hospital, Milton S. Hershey Medical Center, VA Medical Center, Fresno, CA, W.P. Temple University Hospital, Philadelphia, PA, University of California, Irvine, CA, VA Medical Center, San Francisco, CA, University Texas Health Science Center, Dallas, TX, Johns Hopkins Medical Institutions, Baltimore</p> <p>Source of funding: -</p> <p>Conflicts of interest: -</p> <p>Ethics approval: Quote: "The Institutional Review Board at each of the study sites approved the protocol"</p> <p>Informed consent: Quote: "Each patient gave written informed consent"</p> <p>Clinical trials registration: -</p>

Zinner 1989 (Continued)

Sample size calculation: Quote: "The protocol was designed to require a minimum of 270 fully evaluable patients to complete the study (135 in each group). This sample size is sufficient to detect differences of 20% or more between two treatment groups ($p = 0.05$; power = 0.90) with two-sided tests of significance. That is, this study size should detect a clinically significant difference between misoprostol and antacid that is greater than 20%"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not clearly mentioned in the study report
Allocation concealment (selection bias)	Unclear risk	Comment: nNot clearly mentioned in the study report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Acceptable candidates were randomly assigned to each group and they received either tablets containing 200 mcg of misoprostol every four hours plus placebo liquid antacid every two hours, or placebo tablets every four hours plus magnesium-aluminum hydroxide liquid antacid every two hours. Tablets were dissolved in 20 mL of water and administered six times daily through a nasogastric tube, or were given orally if no tube was in place" Comment: This was a 'double-dummy' placebo-controlled trial, and participants and study personnel appear to be blinded. Therefore, the likelihood of performance bias is low
Blinding (detection bias) Clinically important upper GI bleeding	Low risk	Comment: This was a 'double-dummy' placebo-controlled trial. Moreover, GI bleeding was an objective outcome that was detected as per the definition in the study protocol. Therefore, there is no likelihood of performance bias in this study
Blinding (detection bias) Nosocomial pneumonia	Unclear risk	Comment: Study did not address this outcome
Blinding of outcome assessment (detection bias) Adverse reactions of interventions	Low risk	Comment: This was a 'double-dummy' placebo-controlled trial. However, outcomes of interest were objective in nature, so the likelihood of detection bias is low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Not all 371 randomised participants were part of the final analysis. The study was designed in such a way that only those participants who met certain criteria for evaluation of the primary outcome (as described under 'adherence to the regimen') were included in the study report (141 participants in misoprostol and 140 participants in antacid groups). A per-protocol analysis was done. However, the participants for whom outcomes were reported were well balanced between groups. Therefore, the likelihood of bias due to attrition is low
Selective reporting (reporting bias)	High risk	Comment: Study says that all randomised participants were analysed for safety of the drug, but this was true only for the adverse event of diarrhoea and not for other adverse events. The reasons for excluding some of the participants is not clearly mentioned in the study report
Other bias	Low risk	Comment: unclear on the source of funding. No other form of bias detected

ADH: antidiuretic hormone.

APACHE: Acute Physiologic Assessment and Chronic Health Evaluation.

APS: acute physiology score.

BAL: bronchoalveolar lavage.
 BMI: body mass index.
 bw: body weight.
 CABG: coronary artery bypass graft.
 CNS: central nervous system.
 CXR: chest X-ray.
 GCS: Glasgow Coma Scale.
 GD: gastroduodenal.
 GI: gastrointestinal.
 ICU: intensive care unit.
 IMED: infusion pump.
 IQR: interquartile ratio.
 ITT: intention-to-treat.
 IV: intravenous.
 IVAC: infusion pump.
 NG: nasogastric.
 NPO: nothing by mouth.
 NSAID: non-steroidal anti-inflammatory drug.
 OR: odds ratio.
 PaO₂: partial pressure of oxygen in arterial blood.
 PCT: procalcitonin
 PICU: paediatric intensive care unit.
 PSB: protected specimen brush.
 SD: standard deviation.
 SE: standard error.
 SICU: surgical intensive care unit.
 SOFA: sepsis-related organ failure assessment score.
 SRMD: stress-related mucosal disease.
 SUP: stress- ulcer prophylaxis
 TISS: therapeutic intervention scoring system.
 VAP: ventilator-associated pneumonia.
 WBC: white blood cell.

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

Study	Reason for exclusion
Aanpreung 1998	The review does not deal with comparing different drugs in the same class (H ₂ receptor antagonists)
Abe 2004	Wrong study population
Al-Quorain 1994	The review does not deal with comparing different drugs in the same class (H ₂ blocker antagonists)
Alaniz 2014	Wrong study design
Anonymous 2013	Wrong study design
Anonymous 2015	Wrong study design
Arora 1991	Wrong study population
Baccino 1987	Wrong study population
Baghaie 1995	The review does not deal with comparing different drugs in the same class (H ₂ receptor antagonists)
Barth 1984	The review does not deal with comparing different drugs in the same class (H ₂ blocker antagonists)

Study	Reason for exclusion
Bauer 1977	Wrong study design
Bergmans 2001	Wrong indication
Bhatt 2010	Wrong setting, no ICU setting
Cheadle 1985	Wrong setting
Chernov 1971	Wrong study design
Cloud 1994	Wrong indication/study aim (prevention of gastritis) (conference abstract)
Critchlow 1987	Wrong study design
Dabiri 2015	The review does not deal with comparing different drugs in the same class (proton pump inhibitors)
Driscoll 1993	Wrong intervention and comparison
Duma 1986	The review does not deal with comparing different drugs in the same class (H2 receptor antagonists)
Estruch 1991	Wrong population
Fiorucci 1989	Wrong study design
Forestier 2008	Wrong intervention and study aim
Friedl 1985	The review does not deal with comparing different drugs in the same class (H2 receptor antagonists)
Geus 1993	The review does not deal with comparing different drugs in the same class (H2 receptor antagonists)
Hauer 1996	Wrong study design
Heiselman 1995	The review does not deal with comparing different drugs in the same class (H2 receptor antagonists)
Herrmann 1979	Wrong study design
Hollander 1973	Wrong population
Huang 2017	Wrong setting
Kalfarentzos 1997	The review does not deal with comparing different drugs in the same class (nutrition regimen)
Karlstadt 1993	Wrong population
Ketterl 1984	The review does not deal with comparing different drugs in the same class (H2 receptor antagonists)
Khan 1981	Wrong study design
Klarin 2008	Wrong intervention and comparison

Study	Reason for exclusion
Krag 2015	Wrong study design
Krier 1990	Wrong study design
Krueger 2002	Wrong intervention and comparison
Kuusela 1998	The review does not deal with comparing different drugs in the same class (H2 receptor antagonists)
Laterre 2001	The review does not deal with comparing different drugs in the same class (proton pump inhibitors)
Levine 1994	The review does not deal with comparing different drugs in the same class (H2 receptor antagonist)
Liu 2013	Wrong study population
Madani 2014	Wrong indication/study aim (prevention of gastritis)
McAlhany 1976	Wrong study population
McElwee 1979	Wrong study population
Metz 2010	Wrong study design
Misra 2005	Wrong study population
Mojtahedzadeh 2002	The review does not deal with comparing different drugs in the same class (H2 receptor antagonist)
More 1985	The review does not deal with comparing different drugs in the same class (H2 receptor antagonists)
Mulla 2001	Wrong population (patients on continuous venovenous hemofiltration)
Olsen 1995	The review does not deal with comparing different drugs in the same class (H2 receptor antagonists)
Olsen 2008	The review does not deal with comparing different drugs in the same class (proton pump inhibitor)
Osteyee 1994	The review does not deal with comparing different drugs in the same class (H2 receptor antagonist)
Pelfrene 1996	The review does not deal with comparing different drugs in the same class (H2 receptor antagonist)
Phillips 2001	The review does not deal with comparing different drugs in the same class (nutrition regimen)
Reid 1986	The review does not deal with comparing different drugs in the same class (H2 receptor antagonist)
Ren 2015	Wrong indication (management of gastrointestinal bleeding)
Schentag 1989	The review does not deal with comparing different drugs in the same class (H2 receptor antagonist)
Simon 1984	The review does not deal with comparing different drugs in the same class (H2 receptor antagonist)
Solana 2013	The review does not deal with comparing different drugs in the same class (omeprazole)
Sung 2003	Wrong study design

Study	Reason for exclusion
Taha 1996	Wrong study population
Tofil 2008	Wrong study design
Toyota 1998	Wrong study population
Udd 2005	The review does not deal with comparing different drugs in the same class (omeprazole)
Vaduganathan 2016	Wrong setting
Vargas 1993	The review does not deal with comparing different drugs in the same class (H2 receptor antagonist)
Wang 1995	The review does not deal with comparing different drugs in the same class (H2 receptor antagonist)
Yao 2015	Wrong setting, no ICU setting
Zhou 2002	Wrong study population

ICU: intensive care unit.

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

[Labattut 1992](#)

Methods	Randomised controlled trial
Participants	People admitted to surgical ICU
Interventions	-
Outcomes	-
Notes	Full text could not be obtained

[Morris 2001](#)

Methods	Randomised controlled trial
Participants	People admitted to surgical ICU
Interventions	-
Outcomes	-
Notes	Full text could not be obtained

ICU: intensive care unit.

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

ACTRN12616000481471

Trial name or title	Proton pump inhibitors vs histamine-2 receptor blockers for ulcer prophylaxis therapy in the intensive care unit
Methods	Multi-centre open-label cluster-randomised cross-over study
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age $\geq$ 18 years • Mechanically ventilated within 24 hours of ICU admission <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Admitted to ICU with upper GI bleeding (APACHE III admission diagnostic codes 303, 305, and 1403)
Interventions	<p>Intervention: proton pump inhibitors</p> <p>Control: H2 receptor antagonists</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • All-cause mortality in hospital <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Upper GI bleeding (new clinically significant upper GI bleeding developing as a complication in ICU) defined as overt GI bleeding (e.g. haematemesis, melena, or frank blood in the nasogastric tube or upper GI endoscopy) AND 1 or more of the following features within 24 hours of GI bleeding: <ul style="list-style-type: none"> ◦ Spontaneous drop of systolic mean arterial pressure or diastolic blood pressure of 20 mmHg or more ◦ Start of vasopressor or 20% increase in vasopressor dose ◦ Decrease in haemoglobin $\geq$ 20 g/L or ◦ Transfusion of 2 units of packed red blood • <i>Clostridium difficile</i> infection rates defined as toxin-positive or culture-positive stool samples collected during an ICU admission (excluding any patients who had positive tests from specimens collected before ICU admission) • Duration of mechanical ventilation • Duration of ICU stay • Duration of hospital stay
Starting date	April 2016
Contact information	Dr. Paul Young, Wellington Hospital, Riddiford Street, Newtown, Wellington 6021, New Zealand; paul.young@ccdhb.org.nz
Notes	anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370438

EUCTR2015-000318-24-DK

Trial name or title	Stress ulcer prophylaxis in the intensive care unit
Methods	Parallel-group double-blind randomised controlled study
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Acute admission to the ICU AND

EUCTR2015-000318-24-DK (Continued)

- Aged ≥ 18 years AND
- One or more of the following risk factors:
 - Shock (continuous infusion with vasopressors or inotropes, systolic blood pressure < 90 mmHg, mean arterial blood pressure < 70 mmHg, or lactate > 4 mmol/L)
 - Acute or chronic intermittent or continuous renal replacement therapy
 - Invasive mechanical ventilation, which is expected to last > 24 hours. When in doubt of the forecast, the patient should be enrolled
 - Coagulopathy (platelets $< 50 \times 10^9/L$ or international normalized ratio (INR) > 1.5 or prothrombin time (PT) > 20 seconds) documented within the last 24 hours
 - Ongoing treatment with anticoagulant drugs (prophylaxis doses excluded)
 - History of coagulopathy (platelets $< 50 \times 10^9/L$ or INR > 1.5 or PT > 20 seconds within 6 months before hospital admission)
 - History of chronic liver disease (portal hypertension, cirrhosis proven by biopsy, computed tomography (CT) scan or ultrasound, history of variceal bleeding or hepatic encephalopathy in the past medical history)

Exclusion criteria

- Contraindications to PPI
- Ongoing treatment with PPI and/or H2RA on a daily basis
- GI bleeding of any origin during current hospital admission
- Peptic ulcer diagnosed during current hospital admission
- Organ transplant during current hospital admission
- Withdrawal from active therapy or brain death
- Fertile woman with positive urine human chorionic gonadotropin (hCG) or plasma-hCG
- Consent according to national regulations not obtainable

Interventions	Intervention: 4 mL pantoprazole IV Control: placebo
Outcomes	Primary outcomes <ul style="list-style-type: none"> • Mortality Secondary outcomes <ul style="list-style-type: none"> • Adverse events: clinically important gastrointestinal bleeding, pneumonia, <i>Clostridium difficile</i> infection, or acute myocardial ischaemia in the ICU • Clinically significant GI bleeding in the ICU • One or more infectious adverse events (pneumonia or <i>Clostridium difficile</i> infection) in the ICU • 1-Year “landmark” mortality post randomisation • Days alive without use of mechanical ventilation, renal replacement therapy, or circulatory support in the 90-day period • Number of SARs • Health economic analysis. Analytical details will be based on results of the study and will be specified (cost-benefit vs cost-minimisation analyses)
Starting date	August 2016
Contact information	Morten Hylander; mortenhylander@gmail.com
Notes	clinicaltrialsregister.eu/ctr-search/search?query=EUCTR2015-000318-24-DK

EudraCT 2007-006102-19

Trial name or title	Omeprazole treatment for prophylaxis of gastrointestinal bleeding and gastro-oesophageal reflux in critically ill children [Tratamiento con omeprazole para la profilaxis de la hemorragia digestiva y el reflujo gastroesofágico en niños críticos]
Methods	-
Participants	Infants and toddlers, children, adolescents, under 18
Interventions	Intervention: 0.4 mL omeprazole IV Control: 10 mL ranitidine IV
Outcomes	Primary outcomes: <ul style="list-style-type: none"> • Gastric pH • Percentage of time with gastric pH > 4 • Presence and intensity of gastric haemorrhage • Number and duration of gastric reflux • Bacterial count of gastric juice and tracheal aspirate • Incidence of nosocomial pneumonia • Heart rate, blood pressure, central venous pressure • Side effects Secondary outcomes: -
Starting date	February 2008
Contact information	-
Notes	clinicaltrialsregister.eu/ctr-search/search?query=EUCTR2007-006102-19-ES

IRCT201104134578N2

Trial name or title	Ranitidine and pantoprazole in prevention of stress ulcer
Methods	Not stated
Participants	Inclusion criteria <ul style="list-style-type: none"> • Requiring mechanical ventilation • Age > 18 years • Admission to the ICU • APACHE score II < 25 • Admission at least 24 hours in ICU • Patients with suctionable secretion • No GI bleeding at beginning of study Exclusion criteria <ul style="list-style-type: none"> • History of GI bleeding • Liver or kidney insufficiency • History of corticosteroids or NSAID usage

IRCT201104134578N2 (Continued)

	<ul style="list-style-type: none"> Gastric pH > 4 before beginning of prophylaxis
Interventions	Intervention: pantoprazole 40 mg infusion once a day until end of patient admission Control: ranitidine 50 mg infusion twice a day until end of patient admission
Outcomes	Primary outcome <ul style="list-style-type: none"> Gastric pH (before intervention, every 8 hours after intervention for next 2 days), measured by AZ8685 pH metery instrument Secondary outcome <ul style="list-style-type: none"> GI bleeding, measured by evaluating the secretion that lavaged from the patient NG tube to the end of admission in the ICU
Starting date	20 February 2011
Contact information	Farshid Rahimi Bashar, Mahdiye Street, Hamedan University Of Medical Sciences, Hamedan Iran, Islamic Republic of Telephone: 00988118276295; fr_rahimibashar@yahoo.com
Notes	-

ISRCTN12845429

Trial name or title	A placebo-controlled double-blind randomised feasibility trial of desmopressin (DDAVP) in critical illness prior to procedures
Methods	Placebo-controlled double-blind randomised study
Participants	Inclusion criteria <ul style="list-style-type: none"> Adult patients (age ≥ 18 years) Platelet count $\leq 100 \times 10^9/L$ Inpatient on a critical care ward Due to undergo an interventional procedure Exclusion criteria <ul style="list-style-type: none"> Active bleeding History of ischaemic heart disease (myocardial infarction or angina), stroke, or transient ischaemic attack (TIA) Admission to ICU with traumatic brain injury or seizures Congenital bleeding disorder Pregnant or breastfeeding History of anaphylaxis to desmopressin
Interventions	Intervention: desmopressin Control: -
Outcomes	Primary outcome <ul style="list-style-type: none"> Proportion of eligible patients randomised into study and receiving OCTIM Injection Secondary outcome

ISRCTN12845429 (Continued)

Starting date	November 2016
Contact information	-
Notes	clinicaltrialsregister.eu/ctr-search/search?query=EUCTR2016-001126-33-GB

Krag 2016

Trial name or title	Stress ulcer prophylaxis with a proton pump inhibitor vs placebo in critically ill patients (SUP-ICU trial): study protocol for a randomised controlled trial
Methods	Investigator-initiated pragmatic international multi-centre randomised blinded parallel-group study
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • All adults (≥ 18 years) • Acutely admitted to the ICU with 1 or more risk factors for GI bleeding: <ul style="list-style-type: none"> ◦ Shock (continuous infusion with vasopressors or inotropes, systolic blood pressure < 90 mmHg, mean arterial blood pressure < 70 mmHg, or plasma lactate level ≥ 4 mmol/L) ◦ Acute or chronic intermittent or continuous renal replacement therapy (RRT) ◦ Invasive mechanical ventilation that is expected to last more than 24 hours ◦ Coagulopathy (platelets $< 50 \times 10^9/L$ or international normalised ratio (INR) > 1.5, or prothrombin time (PT) > 20 s) documented within the last 24 hours ◦ Ongoing treatment with anticoagulant drugs (prophylactic doses excluded) ◦ History of coagulopathy (platelets $< 50 \times 10^9/L$ or INR > 1.5 or PT > 20 s within the 6 months before hospital admission) ◦ History of chronic liver disease (portal hypertension; cirrhosis proven by biopsy, computed tomography (CT) scan, or ultrasound; or history of variceal bleeding or hepatic encephalopathy) <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Contraindications to PPIs (including intolerance of PPIs and treatment with atazanavir (anti-human immunodeficiency virus (HIV) medication)) • Current daily treatment with a PPI and/or a H2RA • GI bleeding of any origin during current hospital admission • Diagnosis of peptic ulcer during current hospital admission • Organ transplant during current hospital admission • Withdrawal from active therapy or brain death • Fertile woman with positive test for urinary or plasma human chorionic gonadotropin (hCG) • Consent according to national regulations not obtainable
Interventions	<p>Intervention: pantoprazole 40 mg IV (pantoprazole; Actavis, Gentofte, Denmark)</p> <p>Control: placebo, given once daily IV, from randomisation until ICU discharge or death for a maximum of 90 days</p>
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> • All-cause mortality 90 days after randomisation <p>Secondary outcomes</p>

Krag 2016 (Continued)

- Adverse events during ICU stay: clinically important GI bleeding, pneumonia, CDI, or acute myocardial ischaemia
- Clinically important GI bleeding during ICU stay
- Infectious adverse events (pneumonia or CDI) during ICU stay
- Days alive without use of mechanical ventilation, RRT, or circulatory support in the 90-day trial period
- Number of serious adverse reactions (SARs) during ICU stay
- Mortality 1 year after randomisation
- A health economic analysis will be performed. Analytical details will be based on results of the study and will be specified at that time (cost-benefit vs cost-minimisation analyses)

Starting date	January 2016
Contact information	Mette Krag, Department of Intensive Care 4131, Copenhagen University Hospital, Rigshospitalet; mette.krag.01@regionh.dk
Notes	-

NCT00590928

Trial name or title	Gastric pH in critically ill patients
Methods	Double-blind parallel-group randomised controlled study
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Critically ill patients • Indication for stress ulcer prophylaxis • Gastric pH < 4 <p>Exclusion criteria</p> <ul style="list-style-type: none"> • GI bleeding • Gastric pH > 4
Interventions	<p>Intervention: esomeprazole 40 mg once daily</p> <p>Control: ranitidine 50 mg every hour</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Percentage of time with gastric pH > 4 <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Median gastric pH • Incidence of gastrointestinal bleeding • Incidence of ventilator-associated pneumonia • Percentage of time with gastric pH > 5
Starting date	July 2004
Contact information	Christian Madl, MD, Medical University of Vienna
Notes	clinicaltrials.gov/ct2/show/record/ NCT00590928

NCT00702871

Trial name or title	A clinico-bacteriological study and effect of stress ulcer prophylaxis on occurrence of ventilator associated pneumonia
Methods	Parallel-group open-label randomised controlled study
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age > 12 years • Those on mechanical ventilation longer than 48 hours <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Pre-existing pneumonia at beginning of ventilation • Developing pneumonia within 48 hours of ventilation • Patients taking oral antibiotics
Interventions	<p>Intervention: ranitidine 50 mg IV 8-hourly for entire duration of ICU stay</p> <p>Control: sucralfate 1 g via NG tube 6-hourly for entire duration of ICU stay</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Occurrence of ventilator-associated pneumonia <p>Secondary outcome</p> <p>-</p>
Starting date	March 2005
Contact information	Rajiv Singla, MD, Maulana Azad Medical College and Lok Nayak Hospital, Delhi, India
Notes	clinicaltrials.gov/ct2/show/record/NCT00702871

NCT02157376

Trial name or title	Stress ulcer prophylaxis of intravenous esomeprazole in Chinese seriously ill patients (SUP)
Methods	Double-blind parallel-group randomised controlled study
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Critically ill patients • Requirement for mechanical ventilation • ≥ 1 major risk factor for stress ulcer-related bleeding <p>Exclusion criteria</p> <ul style="list-style-type: none"> • History of gastric or oesophageal surgery • Evidence of active GI bleeding • Advanced renal disease • Treatment with any proton pump Inhibitors
Interventions	Intervention: IV esomeprazole 30 min intermittent infusions given for maximum 14 days

NCT02157376 (Continued)

Control: IV cimetidine 30 min bolus infusion followed by IV cimetidine continuous infusion given for maximum 14 days

Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> Percentage of patients with clinically significant upper GI bleeding during treatment evaluation phase defined as: <ul style="list-style-type: none"> Bright red blood per NG or OG tube that did not clear after NG or OG tube adjustment and 5 to 10 minutes of ≥ 100 mL lavage with room temperature normal saline Persistent Gastrocult-positive 'coffee ground' material During IMP treatment days 1 and 2: persistent Gastrocult-positive 'coffee ground' material for ≥ 8 consecutive hours that did not clear with ≥ 100 mL of lavage with room temperature normal saline During IMP treatment days 3 to 14: persistent Gastrocult-positive 'coffee ground' material in ≥ 3 consecutive gastric aspirates within 2 to 4 hours ($\geq 60 \pm 20$ minutes apart) that did not clear with ≥ 100 mL of lavage with room temperature normal saline <p>Secondary outcomes</p> <ul style="list-style-type: none"> Any overt upper GI bleeding (significant and non-significant) during treatment evaluation phase defined as in criteria for a significant upper GI bleeding as described in primary outcome measure or <ul style="list-style-type: none"> Bright red blood per NG or OG tube that clears after NG or OG tube adjustment and 5 to 10 minutes of lavage with room temperature normal saline Persistent Gastrocult-positive 'coffee ground' material During IMP treatment days 1 to 2: persistent Gastrocult-positive 'coffee ground' material for < 8 consecutive hours or that clears with ≥ 100 mL of lavage with room temperature normal saline During IMP treatment days 3 to 14: persistent Gastrocult-positive 'coffee ground' material in < 3 consecutive gastric aspirates within 2 to 4 hours ($\geq 60 \pm 20$ minutes apart) or that clear with ≥ 100 mL of lavage with room temperature normal saline Any clinical signs of haematemesis or melena or haematochezia judged (by the investigator) to be from an upper GI source
Starting date	July 2014
Contact information	Xinyu Qin, Professor and Chairman, Department of General Surgery, Zhongshan, Hospital, Fudan University
Notes	clinicaltrials.gov/ct2/show/record/NCT02157376

NCT02290327

Trial name or title	Re-evaluating the inhibition of stress erosions: gastrointestinal bleeding prophylaxis In ICU (REVISE)
Methods	Quadruple blind parallel-group randomised controlled study
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Adults ≥ 18 years Anticipated invasive mechanical ventilation ≥ 48 hours, as determined by the intensivist <p>Exclusion criteria</p> <ul style="list-style-type: none"> Invasive mechanical ventilation > 72 hours before randomisation Must receive PPI owing to active bleeding or increased bleeding risk (e.g. patients with acute GI bleeding, recent severe oesophagitis, Zollinger-Ellison syndrome, Barrett's oesophagus, peptic

NCT02290327 (Continued)

	<p>ulcer bleeding within 8 weeks (mild dyspepsia or mild gastro-oesophageal reflux disease will not be excluded))</p> <ul style="list-style-type: none"> Receiving dual antiplatelet therapy aspirin and clopidogrel before randomisation Palliative care or decision to withdraw advanced life support (decision to forego cardiopulmonary resuscitation will not be excluded) Previous enrolment in this or a related study Pregnancy Physician, patient, or substitute decision-maker (SDM) declines Two or more "daily doses" of prophylaxis with H2RA or PPI (1 day of a single PPI dose is not an exclusion criterion if once-daily dosing of PPI prophylaxis was administered; 1 day of bid (twice-daily) dosing of an H2RA is not an exclusion criterion if twice-daily H2RA prophylaxis was administered; 1 day of 3 times daily dosing of an H2RA is not an exclusion criterion if thrice-daily H2RA prophylaxis was administered)
Interventions	<p>Intervention: pantoprazole 40 mg in 50 mL 0.9% normal saline intravenously once daily</p> <p>Control: placebo 50 mL of 0.9% normal saline intravenously once daily</p>
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> Consent rate [time frame: 12 months]. This will be calculated as the overall proportion of consented patients of those substitute decision-makers (SDMs) approached (with 95% CI). A successful consent rate will be defined as $\geq 70\%$ of SDMs approached to consent Recruitment rate [time frame: 12 months]. A successful recruitment rate will be defined as achieving enrolment of 60 patients, conventionally expressed as 2 patients per center per month over 12 months Protocol adherence [time frame: 12 months]. This will be calculated as doses of study drug administered as a proportion of doses prescribed and associated 95% confidence intervals. Successful adherence will be defined as $\geq 80\%$ of prescribed drugs being administered <p>Secondary outcomes</p> <ul style="list-style-type: none"> Clinically important upper gastrointestinal bleeding [time frame: during ICU stay (expected average is 10 days)] Ventilator-associated pneumonia [time frame: during ICU stay (expected average is 10 days)] Mortality [time frame: during ICU and hospital stay (expected average ICU stay is 10 days, expected average hospital stay is 30 days)] <i>Clostridium difficile</i> infection [time frame: during ICU stay (expected average ICU stay is 10 days)]
Starting date	May 2015
Contact information	-
Notes	clinicaltrials.gov/ct2/show/record/NCT02290327

NCT02718261

Trial name or title	Sup-Icu RENal (SIREN) - a subanalysis of the prospective SUP (stress ulcer prophylaxis)-ICU trial on the risk of GI bleeding in ICU patients receiving renal replacement therapy
Methods	Parallel-group triple-blind randomised controlled study
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Acute admission to ICU Age ≥ 18 years

NCT02718261 (Continued)

- ≥ 1 of the following risk factors:
 - Shock (continuous infusion with vasopressors or inotropes, systolic blood pressure < 90 mmHg, mean arterial blood pressure < 70 mmHg, or lactate > 4 mmol/L)
 - Acute or chronic intermittent or continuous renal replacement therapy
 - Invasive mechanical ventilation that is expected to last > 24 hours
 - Coagulopathy (platelets $< 50 \times 10^9/L$ or international normalized ratio (INR) > 1.5 or prothrombin time (PT) > 20 seconds) documented within the last 24 hours
 - Ongoing treatment with anticoagulant drugs (prophylaxis doses excluded)
 - History of coagulopathy (platelets $< 50 \times 10^9/L$ or INR > 1.5 or PT > 20 seconds) within 6 months before hospital admission
 - History of chronic liver disease (portal hypertension, cirrhosis proven by biopsy, computed tomography (CT) scan or ultrasound, history of variceal bleeding or hepatic encephalopathy in the past medical history)

Exclusion criteria

- Contraindications to PPI
- Ongoing treatment with PPI and/or H2RA on a daily basis
- GI bleeding of any origin during current hospital admission
- Diagnosis of peptic ulcer during current hospital admission
- Organ transplant during current hospital admission
- Withdrawal from active therapy or brain death
- Fertile woman with positive urine human chorionic gonadotropin (hCG) or plasma hCG
- Consent according to national regulations not obtainable

Interventions	Intervention: pantoprazole IV Control: 0.9% saline IV
Outcomes	Primary outcome <ul style="list-style-type: none"> • Clinical GI bleeding episodes undergoing RRT within first 3 days following ICU admission ("RRT group") vs in patients without the need for RRT during ICU stay ("control group") Secondary outcomes <ul style="list-style-type: none"> • Adverse events: clinically important GI bleeding, pneumonia, <i>Clostridium difficile</i> infection, or acute myocardial ischaemia in the ICU • Serious adverse reactions • Infectious adverse events (pneumonia or CDI) in the ICU [time frame: 90 days or length of ICU stay, as applicable] • Days alive without use of mechanical ventilation, renal replacement therapy, or circulatory support in the 90-day period • 90-Day and 1-year (365 days) mortality post randomisation • Proportion of patients receiving treatment (interventions) to stop GI bleeding (i.e. endoscopy/open or laparoscopic surgery/coiling) • Number of units of packed red blood cells (RBCs) transfused • 90-Day/360-day ICU mortality rate in "RRT group" vs "ESRD group" vs "RRT at any time on the ICU" vs "control group" incl analysis of verum/placebo subgroups
Starting date	February 2016
Contact information	Joerg Schefold; joerg.schefold@insel.ch
Notes	clinicaltrials.gov/ct2/show/record/NCT02718261

NCT03098537

Trial name or title	Effects of enteral nutrition on stress ulcer haemorrhage - multi-center randomised controlled trial
Methods	Open-label parallel-group randomised controlled study
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age ≥ 18 years • Admission to ICU • Expected to stay in ICU > 24 hours • No contraindications to EN within first 24 hours after admission to intensive care unit <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Evidence of active GI bleeding during current hospitalisation before study entry • Coagulopathy (PLT < 50.000, INR > 1.5, aPTT > 2 × control) • Patients receiving acid-suppressing drugs before admission • Pregnancy or lactation • History/documentated gastric ulcer • Burn > 30% body surface area • Head injury or increased intracranial pressure • Partial or complete gastrectomy • Shock • Multi-system trauma • Exposure to gastric irritant drugs • Patients not giving informed consent
Interventions	<p>Intervention: enteral nutrition + proton pump inhibitor</p> <p>Control: enteral nutrition only</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • GI bleeding (until discharge from ICU or cessation of enteral nutrition up to 4 weeks) <ul style="list-style-type: none"> ◦ Overt GI bleeding (presence of 'coffee ground' emesis haematemesis, melena, or haematochezia) ◦ Significant GI bleeding, defined by 3-point decrease in haematocrit within 24 hours accompanied by overt GI bleeding or by an unexplained 6-point decrease in haematocrit during any 48-hour period <p>Secondary outcome</p> <p>-</p>
Starting date	August 2016
Contact information	kgundogan@erciyes.edu.tr
Notes	clinicaltrials.gov/ct2/show/record/NCT03098537

APACHE: Acute Physiologic Assessment and Chronic Health Evaluation.

aPTT: activated partial thromboplastin time.

CDI: *Clostridium difficile* infection.

CT: computed tomography.

DDAVP: desmopressin.

EN: enteral nutrition.

ESRD: end-stage renal disease.

GI: gastrointestinal.
H2RA: histamine receptor-2 antagonist.
hCG: human chorionic gonadotropin.
HIV: human immunodeficiency virus.
ICU: intensive care unit.
INR: international normalised ratio.
IV: intravenous.
NG: nasogastric.
NSAIDs: non-steroidal anti-inflammatory drugs.
OG: orogastric.
PLT: platelet blood test.
PPI: proton pump inhibitor.
PT: prothrombin time.
RBC: red blood cell.
RRT: rapid resolution therapy.
SAR: serious adverse reaction.
SDM: substitute decision-maker.
TIA: transient ischaemic attack.

DATA AND ANALYSES

Comparison 1. Interventions versus placebo or no prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	30	3132	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.39, 0.57]
1.1 H2 receptor antagonists vs placebo or no prophylaxis	24	1844	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.37, 0.59]
1.2 Proton pump inhibitors vs placebo or no prophylaxis	3	159	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.13, 2.59]
1.3 Prostaglandin analogues vs placebo or no prophylaxis	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.22, 4.55]
1.4 Anticholinergics vs placebo or no prophylaxis	2	103	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.30, 2.49]
1.5 Antacids vs placebo or no prophylaxis	7	515	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.23, 0.63]
1.6 Sucralfate vs placebo or no prophylaxis	7	453	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.25, 0.87]
2 Nosocomial pneumonia	9	1331	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.90, 1.48]
2.1 H2 receptor antagonists vs placebo or no prophylaxis	8	788	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.77, 1.46]
2.2 Proton pump inhibitors vs placebo or no prophylaxis	2	149	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.59, 2.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Anticholinergics vs placebo or no prophylaxis	1	72	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.43, 2.59]
2.4 Sucralfate vs placebo or no prophylaxis	4	322	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.84, 3.01]
3 All-cause mortality in ICU	19	2159	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.90, 1.34]
3.1 H2 receptor antagonists vs placebo or no prophylaxis	14	1209	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.89, 1.53]
3.2 Proton pump inhibitors vs placebo or no prophylaxis	3	180	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.46, 2.38]
3.3 Prostaglandin analogues vs placebo or no prophylaxis	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.48, 2.74]
3.4 Anticholinergics vs placebo or no prophylaxis	2	103	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.59, 2.56]
3.5 Antacids vs placebo or no prophylaxis	2	250	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.58, 1.79]
3.6 Sucralfate vs placebo or no prophylaxis	5	359	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.58, 1.51]
4 All-cause mortality in hospital	5	857	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.85, 1.55]
4.1 H2 receptor antagonists vs placebo or no prophylaxis	4	387	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.71, 1.83]
4.2 Proton pump inhibitors vs placebo or no prophylaxis	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.42, 3.22]
4.3 Antacids vs placebo or no prophylaxis	1	126	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.79, 2.64]
4.4 Sucralfate vs placebo or no prophylaxis	2	244	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.53, 1.68]
5 Duration of ICU stay	2	447	Mean Difference (IV, Fixed, 95% CI)	0.24 [-1.13, 1.61]
5.1 H2 receptor antagonists vs placebo or no prophylaxis	2	152	Mean Difference (IV, Fixed, 95% CI)	0.73 [-1.64, 3.09]
5.2 Proton pump inhibitors vs placebo or no prophylaxis	2	149	Mean Difference (IV, Fixed, 95% CI)	0.01 [-2.33, 2.35]
5.3 Sucralfate vs placebo or no prophylaxis	2	146	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-2.40, 2.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Duration of intubation	2	447	Mean Difference (IV, Fixed, 95% CI)	0.87 [-0.58, 2.31]
6.1 H2 receptor antagonists vs placebo or no prophylaxis	2	152	Mean Difference (IV, Fixed, 95% CI)	0.78 [-1.72, 3.29]
6.2 Proton pump inhibitors vs placebo or no prophylaxis	2	149	Mean Difference (IV, Fixed, 95% CI)	0.36 [-2.18, 2.90]
6.3 Sucralfate vs placebo or no prophylaxis	2	146	Mean Difference (IV, Fixed, 95% CI)	1.43 [-1.04, 3.89]
7 Number of participants requiring blood transfusions	9	981	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.41, 0.97]
7.1 H2 receptor antagonists vs placebo or no prophylaxis	7	605	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.35, 0.94]
7.2 Antacids vs placebo or no prophylaxis	2	226	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.30, 2.96]
7.3 Sucralfate vs placebo or no prophylaxis	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.13, 4.34]
8 Units of blood transfused	2	309	Mean Difference (IV, Random, 95% CI)	0.09 [-0.99, 1.17]
8.1 H2 receptor antagonists vs placebo or no prophylaxis	2	159	Mean Difference (IV, Random, 95% CI)	-1.73 [-6.37, 2.90]
8.2 Sucralfate vs placebo or no prophylaxis	1	150	Mean Difference (IV, Random, 95% CI)	0.80 [0.25, 1.35]

Analysis 1.1. Comparison 1 Interventions versus placebo or no prophylaxis, Outcome 1 Clinically important upper GI bleeding.

Analysis 1.2. Comparison 1 Interventions versus placebo or no prophylaxis, Outcome 2 Nosocomial pneumonia.

Analysis 1.3. Comparison 1 Interventions versus placebo or no prophylaxis, Outcome 3 All-cause mortality in ICU.

Study or subgroup	Intervention n/N	Placebo / no prophylaxis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for subgroup differences: $\chi^2=0.81$, $df=1$ ($P=0.98$), $I^2=0\%$					
			Favours intervention		Favours placebo/no proph.

Analysis 1.4. Comparison 1 Interventions versus placebo or no prophylaxis, Outcome 4 All-cause mortality in hospital.

Study or subgroup	Intervention n/N	Placebo/no prophylaxis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 H2 receptor antagonists vs placebo or no prophylaxis					
Ben-Menachem 1994	28/100	10/50		20.46%	1.4[0.74,2.65]
Chan 1995	0/49	1/52		2.23%	0.35[0.01,8.47]
Kantorova 2004	11/71	4/25		9.08%	0.97[0.34,2.77]
Reusser 1990	5/19	6/21		8.75%	0.92[0.33,2.53]
Subtotal (95% CI)	239	148		40.53%	1.14[0.71,1.83]
Total events: 44 (Intervention), 21 (Placebo/no prophylaxis)					
Heterogeneity: $\tau^2=0$; $\chi^2=1.18$, $df=3$ ($P=0.76$); $I^2=0\%$					
Test for overall effect: $Z=0.55$ ($P=0.58$)					
1.4.2 Proton pump inhibitors vs placebo or no prophylaxis					
Kantorova 2004	14/75	4/25		9.21%	1.17[0.42,3.22]
Subtotal (95% CI)	75	25		9.21%	1.17[0.42,3.22]
Total events: 14 (Intervention), 4 (Placebo/no prophylaxis)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.3$ ($P=0.77$)					
1.4.3 Antacids vs placebo or no prophylaxis					
Pinilla 1985	20/65	13/61		20.58%	1.44[0.79,2.64]
Subtotal (95% CI)	65	61		20.58%	1.44[0.79,2.64]
Total events: 20 (Intervention), 13 (Placebo/no prophylaxis)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=1.19$ ($P=0.23$)					
1.4.4 Sucralfate vs placebo or no prophylaxis					
Ben-Menachem 1994	17/100	9/50		18.42%	0.94[0.45,1.97]
Kantorova 2004	13/69	5/25		11.27%	0.94[0.37,2.37]
Subtotal (95% CI)	169	75		29.68%	0.94[0.53,1.68]
Total events: 30 (Intervention), 14 (Placebo/no prophylaxis)					
Heterogeneity: $\tau^2=0$; $\chi^2=0$, $df=1$ ($P=1$); $I^2=0\%$					
Test for overall effect: $Z=0.2$ ($P=0.84$)					
Total (95% CI)	548	309		100%	1.15[0.85,1.55]
Total events: 108 (Intervention), 52 (Placebo/no prophylaxis)					
Heterogeneity: $\tau^2=0$; $\chi^2=2.19$, $df=7$ ($P=0.95$); $I^2=0\%$					
Test for overall effect: $Z=0.91$ ($P=0.36$)					
Test for subgroup differences: $\chi^2=1$, $df=1$ ($P=0.8$), $I^2=0\%$					
			Favours intervention		Favours placebo/no proph.

Analysis 1.5. Comparison 1 Interventions versus placebo or no prophylaxis, Outcome 5 Duration of ICU stay.

Analysis 1.6. Comparison 1 Interventions versus placebo or no prophylaxis, Outcome 6 Duration of intubation.

Analysis 1.7. Comparison 1 Interventions versus placebo or no prophylaxis, Outcome 7 Number of participants requiring blood transfusions.

Analysis 1.8. Comparison 1 Interventions versus placebo or no prophylaxis, Outcome 8 Units of blood transfused.

Comparison 2. H2 receptor antagonists versus placebo or no prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	24	2149	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.36, 0.70]
1.1 Cimetidine vs placebo	10	772	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.28, 1.02]
1.2 Famotidine vs placebo	1	146	Risk Ratio (M-H, Random, 95% CI)	2.11 [0.20, 22.79]
1.3 Ranitidine vs placebo	5	446	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.17, 0.77]
1.4 Cimetidine vs no prophylaxis	3	516	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.23, 1.48]
1.5 Famotidine vs no prophylaxis	1	50	Risk Ratio (M-H, Random, 95% CI)	0.3 [0.09, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Ranitidine vs no prophylaxis	4	219	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.26, 1.00]
2 Nosocomial pneumonia	8	945	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.85, 1.48]
2.1 Cimetidine vs placebo	2	204	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.06, 2.00]
2.2 Famotidine vs placebo	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.49, 4.45]
2.3 Ranitidine vs placebo	2	277	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.47, 1.31]
2.4 Cimetidine vs no prophylaxis	1	200	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [0.86, 5.47]
2.5 Ranitidine vs no prophylaxis	2	118	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.93, 1.90]
3 All-cause mortality in ICU	14	1428	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.88, 1.42]
3.1 Cimetidine vs placebo	4	478	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.66, 1.68]
3.2 Famotidine vs placebo	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.55, 3.16]
3.3 Ranitidine vs placebo	2	148	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.31, 1.54]
3.4 Cimetidine vs no prophylaxis	2	400	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.61, 1.63]
3.5 Famotidine vs no prophylaxis	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.59, 2.64]
3.6 Ranitidine vs no prophylaxis	4	206	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.97, 2.58]
4 All-cause mortality in hospital	4	487	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.79, 1.70]
4.1 Famotidine vs placebo	1	146	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.43, 1.86]
4.2 Ranitidine vs placebo	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.47]
4.3 Cimetidine vs no prophylaxis	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.88, 2.46]
4.4 Ranitidine vs no prophylaxis	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.33, 2.53]
5 Duration of ICU stay	2	230	Mean Difference (IV, Fixed, 95% CI)	0.73 [-0.92, 2.38]
5.1 Famotidine vs placebo	1	146	Mean Difference (IV, Fixed, 95% CI)	1.5 [-1.93, 4.93]
5.2 Ranitidine vs no prophylaxis	1	84	Mean Difference (IV, Fixed, 95% CI)	0.5 [-1.38, 2.38]
6 Duration of intubation	2	230	Mean Difference (IV, Fixed, 95% CI)	0.79 [-0.95, 2.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Famotidine vs placebo	1	146	Mean Difference (IV, Fixed, 95% CI)	1.20 [-1.86, 4.26]
6.2 Ranitidine vs no prophylaxis	1	84	Mean Difference (IV, Fixed, 95% CI)	0.60 [-1.52, 2.72]
7 Number of participants requiring blood transfusions	7	655	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.36, 0.95]
7.1 Cimetidine vs placebo	3	107	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.19, 0.79]
7.2 Ranitidine vs placebo	2	148	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.24, 4.60]
7.3 Cimetidine vs no prophylaxis	2	400	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.35, 1.71]
8 Units of blood transfused	2	209	Mean Difference (IV, Fixed, 95% CI)	0.33 [-0.04, 0.70]
8.1 Cimetidine vs placebo	1	9	Mean Difference (IV, Fixed, 95% CI)	-4.35 [-7.35, -1.35]
8.2 Cimetidine vs no prophylaxis	1	200	Mean Difference (IV, Fixed, 95% CI)	0.40 [0.03, 0.77]
9 Adverse events of interventions	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Diarrhoea	2	225	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.57, 2.96]
9.2 Thrombocytopenia	1	200	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.77]
9.3 Hypophosphatemia	1	25	Risk Ratio (M-H, Fixed, 95% CI)	3.75 [0.17, 84.02]
9.4 Mental confusion	5	657	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [1.10, 3.65]
9.5 Nausea and vomiting	2	287	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.09, 2.35]
9.6 Increased creatinine levels	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.64, 1.69]
9.7 Erythema	1	70	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.22]
9.8 Pancreatitis	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.01, 6.66]
9.9 Chest infection	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [0.92, 3.30]
9.10 Delirium	1	39	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [0.11, 59.93]
9.11 Hallucinations	1	39	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [0.11, 59.93]
9.12 Severe bleeding	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.47]

Analysis 2.1. Comparison 2 H2 receptor antagonists versus placebo or no prophylaxis, Outcome 1 Clinically important upper GI bleeding.

Analysis 2.2. Comparison 2 H2 receptor antagonists versus placebo or no prophylaxis, Outcome 2 Nosocomial pneumonia.

Analysis 2.3. Comparison 2 H2 receptor antagonists versus placebo or no prophylaxis, Outcome 3 All-cause mortality in ICU.

Analysis 2.4. Comparison 2 H2 receptor antagonists versus placebo or no prophylaxis, Outcome 4 All-cause mortality in hospital.

Analysis 2.5. Comparison 2 H2 receptor antagonists versus placebo or no prophylaxis, Outcome 5 Duration of ICU stay.

Analysis 2.6. Comparison 2 H2 receptor antagonists versus placebo or no prophylaxis, Outcome 6 Duration of intubation.

Analysis 2.7. Comparison 2 H2 receptor antagonists versus placebo or no prophylaxis, Outcome 7 Number of participants requiring blood transfusions.

Analysis 2.8. Comparison 2 H2 receptor antagonists versus placebo or no prophylaxis, Outcome 8 Units of blood transfused.

Analysis 2.9. Comparison 2 H2 receptor antagonists versus placebo or no prophylaxis, Outcome 9 Adverse events of interventions.

Comparison 3. Proton pump inhibitors versus placebo or no prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	3	237	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.18, 2.22]
1.1 Omeprazole vs placebo	1	147	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.07, 16.34]
1.2 Omeprazole vs no prophylaxis	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.13, 4.18]
1.3 Pantoprazole vs placebo	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.02, 4.66]
2 Nosocomial pneumonia	2	227	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.77, 1.98]
2.1 Omeprazole vs placebo	1	147	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.57, 4.86]
2.2 Omeprazole vs no prophylaxis	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.66, 1.84]
3 All-cause mortality in ICU	3	258	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.60, 1.99]
3.1 Omeprazole vs placebo	2	178	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.51, 2.83]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Omeprazole vs no prophylaxis	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.42, 2.29]
4 All-cause mortality in hospital	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.54, 2.13]
4.1 Omeprazole vs placebo	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.54, 2.13]
5 Duration of ICU stay	2	227	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-1.63, 1.58]
5.1 Omeprazole vs placebo	1	147	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-3.96, 2.16]
5.2 Omeprazole vs no prophylaxis	1	80	Mean Difference (IV, Fixed, 95% CI)	0.30 [-1.58, 2.18]
6 Duration of intubation	2	227	Mean Difference (IV, Fixed, 95% CI)	0.36 [-1.43, 2.15]
6.1 Omeprazole vs placebo	1	147	Mean Difference (IV, Fixed, 95% CI)	0.5 [-2.72, 3.72]
6.2 Omeprazole vs no prophylaxis	1	80	Mean Difference (IV, Fixed, 95% CI)	0.30 [-1.85, 2.45]

Analysis 3.1. Comparison 3 Proton pump inhibitors versus placebo or no prophylaxis, Outcome 1 Clinically important upper GI bleeding.

Analysis 3.2. Comparison 3 Proton pump inhibitors versus placebo or no prophylaxis, Outcome 2 Nosocomial pneumonia.

Analysis 3.3. Comparison 3 Proton pump inhibitors versus placebo or no prophylaxis, Outcome 3 All-cause mortality in ICU.

Analysis 3.4. Comparison 3 Proton pump inhibitors versus placebo or no prophylaxis, Outcome 4 All-cause mortality in hospital.

Analysis 3.5. Comparison 3 Proton pump inhibitors versus placebo or no prophylaxis, Outcome 5 Duration of ICU stay.

Analysis 3.6. Comparison 3 Proton pump inhibitors versus placebo or no prophylaxis, Outcome 6 Duration of intubation.

Comparison 4. Proton pump inhibitors + sucralfate versus no prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Proton pump inhibitors + sucralfate versus no prophylaxis, Outcome 1 Clinically important upper GI bleeding.

Comparison 5. Prostaglandin analogues versus placebo or no prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Prostaglandin analogues vs placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 All-cause mortality in ICU	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Prostaglandin analogues versus placebo or no prophylaxis, Outcome 1 Clinically important upper GI bleeding.

Analysis 5.2. Comparison 5 Prostaglandin analogues versus placebo or no prophylaxis, Outcome 2 All-cause mortality in ICU.

Comparison 6. Anticholinergics versus placebo or no prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	2	131	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.36, 2.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Pirenzepine vs placebo	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [0.34, 11.13]
1.2 Pirenzepin + ranitidine vs placebo + ranitidine	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.17, 2.07]
2 Nosocomial pneumonia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Pirenzepine vs placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 All-cause mortality in ICU	2	131	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.66, 2.30]
3.1 Pirenzepine vs placebo	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.65, 2.60]
3.2 Pirenzepine + ranitidine vs placebo + ranitidine	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.24, 4.18]

Analysis 6.1. Comparison 6 Anticholinergics versus placebo or no prophylaxis, Outcome 1 Clinically important upper GI bleeding.

Analysis 6.2. Comparison 6 Anticholinergics versus placebo or no prophylaxis, Outcome 2 Nosocomial pneumonia.

Analysis 6.3. Comparison 6 Anticholinergics versus placebo or no prophylaxis, Outcome 3 All-cause mortality in ICU.

Comparison 7. Antacids versus placebo or no prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	8	774	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.25, 0.99]
1.1 Antacids vs placebo	2	145	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.72, 5.79]
1.2 Antacids vs no prophylaxis	6	629	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.20, 0.60]
2 All-cause mortality in ICU	2	300	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.53, 1.96]
2.1 Antacids vs no prophylaxis	2	300	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.53, 1.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 All-cause mortality in hospital	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Antacids vs no prophylaxis	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Number of participants requiring blood transfusions	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Antacids vs no prophylaxis	2	226	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.30, 2.96]
5 Adverse events of interventions	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Diarrhoea	4	395	Risk Ratio (M-H, Fixed, 95% CI)	3.56 [1.83, 6.94]
5.2 Hypomagnesaemia	1	25	Risk Ratio (M-H, Fixed, 95% CI)	3.75 [0.17, 84.02]
5.3 Hypophosphataemia	2	225	Risk Ratio (M-H, Fixed, 95% CI)	5.48 [1.81, 16.61]
5.4 Hypermagnesaemia	1	100	Risk Ratio (M-H, Fixed, 95% CI)	6.73 [0.36, 127.02]
5.5 Nausea and vomiting	3	370	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [0.86, 6.64]
5.6 Mental confusion	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.61, 2.67]
5.7 Creatinine increase	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.73, 1.87]

Analysis 7.1. Comparison 7 Antacids versus placebo or no prophylaxis, Outcome 1 Clinically important upper GI bleeding.

Analysis 7.2. Comparison 7 Antacids versus placebo or no prophylaxis, Outcome 2 All-cause mortality in ICU.

Analysis 7.3. Comparison 7 Antacids versus placebo or no prophylaxis, Outcome 3 All-cause mortality in hospital.

Analysis 7.4. Comparison 7 Antacids versus placebo or no prophylaxis, Outcome 4 Number of participants requiring blood transfusions.

Analysis 7.5. Comparison 7 Antacids versus placebo or no prophylaxis, Outcome 5 Adverse events of interventions.

Comparison 8. Sucralfate versus placebo or no prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	7	598	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.32, 0.88]
1.1 Sucralfate vs placebo	2	170	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.30, 6.62]
1.2 Sucralfate vs no prophylaxis	5	428	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.26, 0.80]
2 Nosocomial pneumonia	4	450	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.86, 2.04]
2.1 Sucralfate vs placebo	2	170	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.49, 4.16]
2.2 Sucralfate vs no prophylaxis	2	280	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.82, 2.07]
3 All-cause mortality in ICU	5	500	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.66, 1.43]
3.1 Sucralfate vs placebo	2	170	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.48, 1.80]
3.2 Sucralfate vs no prophylaxis	3	330	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.62, 1.60]
4 All-cause mortality in hospital	2	344	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.62, 1.52]
4.1 Sucralfate vs placebo	1	144	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.54, 2.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Sucralfate vs no prophylaxis	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.49, 1.62]
5 Duration of ICU stay	2	224	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-1.70, 1.65]
5.1 Sucralfate vs placebo	1	144	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-4.07, 2.67]
5.2 Sucralfate vs no prophylaxis	1	80	Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.73, 2.13]
6 Duration of intubation	2	224	Mean Difference (IV, Fixed, 95% CI)	1.42 [-0.27, 3.10]
6.1 Sucralfate vs placebo	1	144	Mean Difference (IV, Fixed, 95% CI)	0.80 [-2.20, 3.80]
6.2 Sucralfate vs no prophylaxis	1	80	Mean Difference (IV, Fixed, 95% CI)	1.70 [-0.34, 3.74]
7 Number of participants requiring blood transfusions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Sucralfate vs no prophylaxis	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Units of blood transfused	1	200	Mean Difference (IV, Fixed, 95% CI)	0.8 [0.32, 1.28]
8.1 Sucralfate vs no prophylaxis	1	200	Mean Difference (IV, Fixed, 95% CI)	0.8 [0.32, 1.28]
9 Adverse events of interventions	1	70	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.50, 161.13]
9.1 Nausea / Vomiting	1	70	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.50, 161.13]

Analysis 8.1. Comparison 8 Sucralfate versus placebo or no prophylaxis, Outcome 1 Clinically important upper GI bleeding.

Analysis 8.2. Comparison 8 Sucralfate versus placebo or no prophylaxis, Outcome 2 Nosocomial pneumonia.

Analysis 8.3. Comparison 8 Sucralfate versus placebo or no prophylaxis, Outcome 3 All-cause mortality in ICU.

Analysis 8.4. Comparison 8 Sucralfate versus placebo or no prophylaxis, Outcome 4 All-cause mortality in hospital.

Study or subgroup	Sucralfate n/N	Placebo or no prophylaxis n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for subgroup differences: $\chi^2=0.17$, $df=1$ ($P=0.68$), $I^2=0\%$					
			Favours sucralfate		Favours placebo/no proph.

Analysis 8.5. Comparison 8 Sucralfate versus placebo or no prophylaxis, Outcome 5 Duration of ICU stay.

Study or subgroup	Sucralfate		Placebo or no prophylaxis		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
8.5.1 Sucralfate vs placebo							
Kantorova 2004	69	7.9 (9.3)	75	8.6 (11.3)		24.68%	-0.7[-4.07,2.67]
Subtotal ***	69		75			24.68%	-0.7[-4.07,2.67]
Heterogeneity: Not applicable Test for overall effect: $Z=0.41$ ($P=0.68$)							
8.5.2 Sucralfate vs no prophylaxis							
Yildizdas 2002	38	11.3 (4.3)	42	11.1 (4.5)		75.32%	0.2[-1.73,2.13]
Subtotal ***	38		42			75.32%	0.2[-1.73,2.13]
Heterogeneity: Not applicable Test for overall effect: $Z=0.2$ ($P=0.84$)							
Total ***	107		117			100%	-0.02[-1.7,1.65]
Heterogeneity: $\tau^2=0$; $\chi^2=0.21$, $df=1$ ($P=0.65$); $I^2=0\%$ Test for overall effect: $Z=0.03$ ($P=0.98$) Test for subgroup differences: $\chi^2=0.21$, $df=1$ ($P=0.65$), $I^2=0\%$							
					Favours sucralfate		Favours placebo/no proph.

Analysis 8.6. Comparison 8 Sucralfate versus placebo or no prophylaxis, Outcome 6 Duration of intubation.

Study or subgroup	Sucralfate		Placebo or no prophylaxis		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
8.6.1 Sucralfate vs placebo							
Kantorova 2004	69	6.9 (7.9)	75	6.1 (10.4)		31.55%	0.8[-2.2,3.8]
Subtotal ***	69		75			31.55%	0.8[-2.2,3.8]
Heterogeneity: Not applicable Test for overall effect: $Z=0.52$ ($P=0.6$)							
8.6.2 Sucralfate vs no prophylaxis							
Yildizdas 2002	38	11.3 (4.3)	42	9.6 (5)		68.45%	1.7[-0.34,3.74]
Subtotal ***	38		42			68.45%	1.7[-0.34,3.74]
Heterogeneity: $\tau^2=0$; $\chi^2=0$, $df=0$ ($P<0.0001$); $I^2=100\%$ Test for overall effect: $Z=1.63$ ($P=0.1$)							
Total ***	107		117			100%	1.42[-0.27,3.1]
Heterogeneity: $\tau^2=0$; $\chi^2=0.24$, $df=1$ ($P=0.63$); $I^2=0\%$ Test for overall effect: $Z=1.65$ ($P=0.1$)							
					Favours sucralfate		Favours placebo/no proph.

Study or subgroup	Sucralfate		Placebo or no prophylaxis		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Test for subgroup differences: $\chi^2=0.24$, $df=1$ ($P=0.63$), $I^2=0\%$							
					Favours sucralfate		Favours placebo/no proph.

Analysis 8.7. Comparison 8 Sucralfate versus placebo or no prophylaxis, Outcome 7 Number of participants requiring blood transfusions.

Study or subgroup	Sucralfate		No prophylaxis		Risk Ratio	Risk Ratio
	n/N		n/N		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
8.7.1 Sucralfate vs no prophylaxis						
Ben-Menachem 1994	3/100		5/100			0.6[0.15,2.44]
					Favours sucralfate	Favours no prophylaxis

Analysis 8.8. Comparison 8 Sucralfate versus placebo or no prophylaxis, Outcome 8 Units of blood transfused.

Study or subgroup	Sucralfate		No Prophylaxis		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
8.8.1 Sucralfate vs no prophylaxis							
Ben-Menachem 1994	100	2 (2)	100	1.2 (1.4)		100%	0.8[0.32,1.28]
Subtotal ***	100		100			100%	0.8[0.32,1.28]
Heterogeneity: Not applicable Test for overall effect: $Z=3.28(P=0)$							
Total ***	100		100			100%	0.8[0.32,1.28]
Heterogeneity: Not applicable Test for overall effect: $Z=3.28(P=0)$							
					Favours sucralfate		Favours no prophylaxis

Analysis 8.9. Comparison 8 Sucralfate versus placebo or no prophylaxis, Outcome 9 Adverse events of interventions.

Study or subgroup	Sucralfate		Placebo or no prophylaxis		Risk Ratio	Weight	Risk Ratio
	n/N		n/N		M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
8.9.1 Nausea / Vomiting							
Lopez-Herce 1992	4/35		0/35			100%	9[0.5,161.13]
Subtotal (95% CI)	35		35			100%	9[0.5,161.13]
Total events: 4 (Sucralfate), 0 (Placebo or no prophylaxis) Heterogeneity: Not applicable Test for overall effect: $Z=1.49(P=0.14)$							
Total (95% CI)	35		35			100%	9[0.5,161.13]
Total events: 4 (Sucralfate), 0 (Placebo or no prophylaxis) Heterogeneity: Not applicable Test for overall effect: $Z=1.49(P=0.14)$							
					Favours sucralfate		Favours placebo/no proph.

Comparison 9. H2 receptor antagonists versus proton pump inhibitors

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	13	1636	Risk Ratio (M-H, Fixed, 95% CI)	2.90 [1.83, 4.58]
1.1 Cimetidine vs omeprazole	1	359	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.55, 3.61]
1.2 Famotidine vs lansoprazole	1	51	Risk Ratio (M-H, Fixed, 95% CI)	3.63 [0.15, 84.98]
1.3 Famotidine vs omeprazole	1	143	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.19, 21.87]
1.4 Famotidine vs pantoprazole	2	159	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.18, 3.04]
1.5 Famotidine vs esomeprazole	2	371	Risk Ratio (M-H, Fixed, 95% CI)	7.53 [1.39, 40.85]
1.6 Ranitidine vs omeprazole	5	413	Risk Ratio (M-H, Fixed, 95% CI)	4.08 [1.99, 8.36]
1.7 Ranitidine vs rabeprazole	1	140	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.49, 164.09]
2 Nosocomial pneumonia	10	1256	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.77, 1.35]
2.1 Cimetidine vs omeprazole	1	359	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.45, 1.54]
2.2 Cimetidine vs pantoprazole	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.28, 2.91]
2.3 Famotidine vs esomeprazole	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.26]
2.4 Famotidine vs omeprazole	1	143	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.34, 2.32]
2.5 Ranitidine vs omeprazole	5	413	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.80, 1.75]
2.6 H2 receptor antagonists (not defined) vs proton pump inhibitors (not defined)	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.47, 2.26]
3 All-cause mortality in ICU	12	1564	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.78, 1.19]
3.1 Cimetidine vs omeprazole	1	359	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.45, 1.30]
3.2 Cimetidine vs pantoprazole	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.25, 2.55]
3.3 Famotidine vs omeprazole	1	143	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.49, 2.61]
3.4 Ranitidine vs omeprazole	5	387	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.86, 1.40]
3.5 Ranitidine vs pantoprazole	3	333	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.31, 1.43]
3.6 Ranitidine vs rabeprazole	1	140	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 All-cause mortality in hospital	2	454	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.37, 1.43]
4.1 Famotidine vs esomeprazole	1	311	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.04, 3.49]
4.2 Famotidine vs omeprazole	1	143	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.39, 1.63]
5 Duration of ICU stay	5	482	Mean Difference (IV, Fixed, 95% CI)	0.14 [-1.14, 1.41]
5.1 Famotidine vs esomeprazole	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-6.51, 5.91]
5.2 Famotidine vs omeprazole	1	143	Mean Difference (IV, Fixed, 95% CI)	2.40 [-0.44, 5.24]
5.3 Ranitidine vs omeprazole	3	279	Mean Difference (IV, Fixed, 95% CI)	-0.44 [-1.90, 1.02]
6 Duration of intubation	5	542	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-1.48, 0.78]
6.1 Famotidine vs omeprazole	1	143	Mean Difference (IV, Fixed, 95% CI)	0.70 [-2.24, 3.64]
6.2 Ranitidine vs omeprazole	3	279	Mean Difference (IV, Fixed, 95% CI)	-0.78 [-2.24, 0.67]
6.3 Ranitidine vs pantoprazole	1	120	Mean Difference (IV, Fixed, 95% CI)	0.07 [-2.18, 2.32]
7 Number of participants requiring blood transfusions	3	575	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [0.75, 5.21]
7.1 Cimetidine vs omeprazole	1	359	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.29, 3.34]
7.2 Ranitidine vs omeprazole	1	76	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 100.80]
7.3 Ranitidine vs rabeprazole	1	140	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.49, 164.09]
8 Adverse events of interventions	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Pyrexia	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.05, 19.03]
8.2 Thrombocytopaenia	2	253	Risk Ratio (M-H, Fixed, 95% CI)	3.64 [0.65, 20.46]
8.3 Neuroleptic malignant syndrome	1	202	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.06, 37.42]
8.4 Cholestatic jaundice	1	202	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.06, 37.42]
8.5 Abnormal liver function test	1	202	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.06, 37.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.6 Pruritus	1	202	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.06, 37.42]
8.7 Phlebitis	1	202	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.06, 37.42]
8.8 Major CV events	1	311	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.26, 2.43]
8.9 Abdominal distension and vomiting	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.62, 2.14]
8.10 Hypomagnesaemia	1	129	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.16, 1.13]
8.11 Nausea and vomiting	1	129	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.13, 1.77]
8.12 Diarrhoea	1	129	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.16, 7.67]

Analysis 9.1. Comparison 9 H2 receptor antagonists versus proton pump inhibitors, Outcome 1 Clinically important upper GI bleeding.

Analysis 9.2. Comparison 9 H2 receptor antagonists versus proton pump inhibitors, Outcome 2 Nosocomial pneumonia.

Analysis 9.3. Comparison 9 H2 receptor antagonists versus proton pump inhibitors, Outcome 3 All-cause mortality in ICU.

Analysis 9.4. Comparison 9 H2 receptor antagonists versus proton pump inhibitors, Outcome 4 All-cause mortality in hospital.

Analysis 9.5. Comparison 9 H2 receptor antagonists versus proton pump inhibitors, Outcome 5 Duration of ICU stay.

Analysis 9.6. Comparison 9 H2 receptor antagonists versus proton pump inhibitors, Outcome 6 Duration of intubation.

Analysis 9.7. Comparison 9 H2 receptor antagonists versus proton pump inhibitors, Outcome 7 Number of participants requiring blood transfusions. **Analysis 9.8. Comparison 9 H2 receptor antagonists versus proton pump inhibitors, Outcome 8 Adverse events of interventions.**

Comparison 10. H2 receptor antagonists versus antacids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	16	1700	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.67, 1.36]
1.1 Cimetidine vs antacids	11	1155	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.65, 1.78]
1.2 Cimetidine + pirenzepine vs antacid + pirenzepine	1	66	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.15, 6.68]
1.3 Ranitidine vs antacids	4	479	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.42, 1.23]
2 Nosocomial pneumonia	4	581	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.81, 1.36]
2.1 Cimetidine vs antacids	2	136	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.70, 2.19]
2.2 Ranitidine vs antacids	2	445	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.34]
3 All-cause mortality in ICU	11	1321	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.66, 1.55]
3.1 Cimetidine vs antacids	8	885	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.69, 1.59]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Cimetidine + pirenzepine vs antacid + pirenzepine	1	66	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.37, 4.25]
3.3 Ranitidine vs antacids	2	370	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.14, 8.97]
4 All-cause mortality in hospital	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Ranitidine vs antacids	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Duration of intubation	3	121	Mean Difference (IV, Random, 95% CI)	-0.81 [-3.85, 2.23]
5.1 Cimetidine vs antacids	3	121	Mean Difference (IV, Random, 95% CI)	-0.81 [-3.85, 2.23]
6 Number of participants requiring blood transfusions	6	744	Risk Ratio (M-H, Fixed, 95% CI)	2.49 [1.35, 4.62]
6.1 Cimetidine vs antacids	5	583	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [1.32, 4.63]
6.2 Ranitidine vs antacids	1	161	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.13, 73.46]
7 Adverse events of interventions	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Diarrhoea	6	777	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.13, 0.43]
7.2 Thrombocytopenia	4	452	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.93, 2.09]
7.3 Nausea and vomiting	4	380	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.19, 1.10]
7.4 Hypophosphataemia	2	108	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.04, 1.30]
7.5 Hypomagnesaemia	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.39]
7.6 Increase in creatinine	2	286	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.56, 1.28]
7.7 Mental confusion	4	476	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.77, 2.07]
7.8 Hypermagnesaemia	2	115	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.17, 2.03]
7.9 Rash/Erythema	2	231	Risk Ratio (M-H, Fixed, 95% CI)	3.02 [0.32, 28.53]
7.10 Alkalosis	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.73]
7.11 Dryness of mouth	1	67	Risk Ratio (M-H, Fixed, 95% CI)	5.15 [0.26, 103.33]
7.12 Leucopenia	1	161	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.13, 73.46]

Analysis 10.1. Comparison 10 H2 receptor antagonists versus antacids, Outcome 1 Clinically important upper GI bleeding.

Analysis 10.2. Comparison 10 H2 receptor antagonists versus antacids, Outcome 2 Nosocomial pneumonia.

Analysis 10.3. Comparison 10 H2 receptor antagonists versus antacids, Outcome 3 All-cause mortality in ICU.

Analysis 10.4. Comparison 10 H2 receptor antagonists versus antacids, Outcome 4 All-cause mortality in hospital.

Analysis 10.5. Comparison 10 H2 receptor antagonists versus antacids, Outcome 5 Duration of intubation.

Analysis 10.6. Comparison 10 H2 receptor antagonists versus antacids, Outcome 6 Number of participants requiring blood transfusions.

Analysis 10.7. Comparison 10 H2 receptor antagonists versus antacids, Outcome 7 Adverse events of interventions.

Comparison 11. H2 receptor antagonists versus sucralfate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	24	3316	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.87, 1.41]
1.1 Cimetidine vs sucralfate	7	873	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.87, 2.14]
1.2 Famotidine vs sucralfate	2	190	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.21, 1.78]
1.3 Ranitidine vs sucralfate	14	2186	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.76, 1.39]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Cimetidine + pirenzepine vs sucralfate + pirenzepine	1	67	Risk Ratio (M-H, Fixed, 95% CI)	5.15 [0.26, 103.33]
2 Nosocomial pneumonia	17	3041	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.07, 1.40]
2.1 Cimetidine vs sucralfate	5	758	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.87, 1.47]
2.2 Famotidine vs sucralfate	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.40, 3.20]
2.3 Ranitidine vs sucralfate	11	2143	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.07, 1.48]
3 All-cause mortality in ICU	21	3178	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.95, 1.24]
3.1 Cimetidine vs sucralfate	6	814	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.91, 1.54]
3.2 Famotidine vs sucralfate	2	190	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.69, 2.19]
3.3 Ranitidine vs sucralfate	12	2107	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.88, 1.22]
3.4 Cimetidine + pirenzepine vs sucralfate + pirenzepine	1	67	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.38, 4.38]
4 All-cause mortality in hospital	4	717	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.86, 1.50]
4.1 Cimetidine vs sucralfate	2	413	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.86, 1.92]
4.2 Ranitidine vs sucralfate	1	164	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.71, 1.74]
4.3 Famotidine vs sucralfate	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.40, 1.71]
5 Duration of intubation	10	1751	Mean Difference (IV, Random, 95% CI)	0.22 [-1.55, 2.00]
5.1 Cimetidine vs sucralfate	2	97	Mean Difference (IV, Random, 95% CI)	0.58 [-1.71, 2.87]
5.2 Famotidine vs sucralfate	1	140	Mean Difference (IV, Random, 95% CI)	0.40 [-2.30, 3.10]
5.3 Ranitidine vs sucralfate	7	1514	Mean Difference (IV, Random, 95% CI)	0.15 [-2.12, 2.43]
6 Duration of ICU stay	6	1791	Mean Difference (IV, Random, 95% CI)	0.01 [-1.92, 1.95]
6.1 Cimetidine vs sucralfate	1	213	Mean Difference (IV, Random, 95% CI)	0.0 [-3.05, 3.05]
6.2 Famotidine vs sucralfate	1	140	Mean Difference (IV, Random, 95% CI)	2.20 [-0.96, 5.36]
6.3 Ranitidine vs sucralfate	4	1438	Mean Difference (IV, Random, 95% CI)	-0.43 [-2.70, 1.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Number of participants requiring blood transfusion	9	1095	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.70, 2.23]
7.1 Cimetidine vs sucralfate	5	732	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.47, 2.16]
7.2 Ranitidine vs sucralfate	4	363	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [0.71, 4.39]
8 Units of blood transfused	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Cimetidine vs sucralfate	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Adverse events of interventions	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Thrombocytopaenia	2	240	Risk Ratio (M-H, Fixed, 95% CI)	4.72 [0.56, 39.47]
9.2 Nausea and vomiting	2	137	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.01, 0.54]
9.3 Hypermagnesaemia	1	40	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [0.31, 23.93]
9.4 Rash/Erythema	2	233	Risk Ratio (M-H, Fixed, 95% CI)	3.06 [0.32, 28.87]
9.5 Confusion	3	382	Risk Ratio (M-H, Fixed, 95% CI)	4.48 [0.77, 26.00]
9.6 Neutropaenia	1	114	Risk Ratio (M-H, Fixed, 95% CI)	5.18 [0.25, 105.47]
9.7 Dryness of mouth	1	67	Risk Ratio (M-H, Fixed, 95% CI)	5.15 [0.26, 103.33]
9.8 Leucopaenia	1	163	Risk Ratio (M-H, Fixed, 95% CI)	3.11 [0.13, 75.26]

Analysis 11.1. Comparison 11 H2 receptor antagonists versus sucralfate, Outcome 1 Clinically important upper GI bleeding.

Analysis 11.2. Comparison 11 H2 receptor antagonists versus sucralfate, Outcome 2 Nosocomial pneumonia.

Analysis 11.3. Comparison 11 H2 receptor antagonists versus sucralfate, Outcome 3 All-cause mortality in ICU.

Analysis 11.4. Comparison 11 H2 receptor antagonists versus sucralfate, Outcome 4 All-cause mortality in hospital.

Analysis 11.5. Comparison 11 H2 receptor antagonists versus sucralfate, Outcome 5 Duration of intubation.

Analysis 11.6. Comparison 11 H2 receptor antagonists versus sucralfate, Outcome 6 Duration of ICU stay.

**Analysis 11.7. Comparison 11 H2 receptor antagonists versus sucralfate,
Outcome 7 Number of participants requiring blood transfusion.**

Analysis 11.8. Comparison 11 H2 receptor antagonists versus sucralfate, Outcome 8 Units of blood transfused.

Analysis 11.9. Comparison 11 H2 receptor antagonists versus sucralfate, Outcome 9 Adverse events of interventions.

Comparison 12. H2 receptor antagonists versus anticholinergics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	3	556	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.58, 3.26]
1.1 Cimetidine vs pirenzepine	1	55	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.26, 7.99]
1.2 Ranitidine vs pirenzepine	2	501	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.50, 3.67]
2 Nosocomial pneumonia	3	544	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.50, 1.84]
2.1 Famotidine vs pirenzepine	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.42]
2.2 Ranitidine vs pirenzepine	2	501	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.53, 2.01]
3 All-cause mortality in ICU	2	501	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.21, 3.87]
3.1 Ranitidine vs pirenzepine	2	501	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.21, 3.87]
4 Number of participants requiring blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Ranitidine vs pirenzepine	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Adverse events of interventions	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Tachycardia	1	55	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.90]
5.2 High temperature	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.21, 1.32]

Analysis 12.1. Comparison 12 H2 receptor antagonists versus anticholinergics, Outcome 1 Clinically important upper GI bleeding.

Analysis 12.2. Comparison 12 H2 receptor antagonists versus anticholinergics, Outcome 2 Nosocomial pneumonia.

Study or subgroup	H2 receptor antagonists n/N	Anticholinergics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for subgroup differences: $\chi^2=0.51$, $df=1$ ($P=0.48$), $I^2=0\%$					
			Favours H2 RA		Favours anticholinergics

Analysis 12.3. Comparison 12 H2 receptor antagonists versus anticholinergics, Outcome 3 All-cause mortality in ICU.

Study or subgroup	H2 receptor antagonists n/N	Anticholinergics n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
12.3.1 Ranitidine vs pirenzepine					
Hanisch 1998	7/57	12/44		53.98%	0.45[0.19,1.05]
Tryba 1988	8/200	4/200		46.02%	2[0.61,6.54]
Subtotal (95% CI)	257	244		100%	0.89[0.21,3.87]
Total events: 15 (H2 receptor antagonists), 16 (Anticholinergics)					
Heterogeneity: $\tau^2=0.85$; $\chi^2=4.08$, $df=1$ ($P=0.04$); $I^2=75.5\%$					
Test for overall effect: $Z=0.15$ ($P=0.88$)					
Total (95% CI)	257	244		100%	0.89[0.21,3.87]
Total events: 15 (H2 receptor antagonists), 16 (Anticholinergics)					
Heterogeneity: $\tau^2=0.85$; $\chi^2=4.08$, $df=1$ ($P=0.04$); $I^2=75.5\%$					
Test for overall effect: $Z=0.15$ ($P=0.88$)					
			Favours H2 RA		Favours anticholinergics

Analysis 12.4. Comparison 12 H2 receptor antagonists versus anticholinergics, Outcome 4 Number of participants requiring blood transfusion.

Study or subgroup	H2 receptor antagonists n/N	Anticholinergics n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
12.4.1 Ranitidine vs pirenzepine				
Hanisch 1998	3/57	3/44		0.77[0.16,3.64]
			Favours H2 RA	Favours anticholinergics

Analysis 12.5. Comparison 12 H2 receptor antagonists versus anticholinergics, Outcome 5 Adverse events of interventions.

Study or subgroup	H2 receptor antagonists n/N	Anticholinergics n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.5.1 Tachycardia					
Barandun 1985	0/28	4/27		100%	0.11[0.01,1.9]
Subtotal (95% CI)	28	27		100%	0.11[0.01,1.9]
Total events: 0 (H2 receptor antagonists), 4 (Anticholinergics)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=1.52$ ($P=0.13$)					
			Favours H2 RA		Favours anticholinergics

Comparison 13. H2 receptor antagonists versus prostaglandin analogues

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Cimetidine vs misoprostol	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 All-cause mortality in ICU	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Cimetidine vs misoprostol	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 13.1. Comparison 13 H2 receptor antagonists versus prostaglandin analogues, Outcome 1 Clinically important upper GI bleeding.

Analysis 13.2. Comparison 13 H2 receptor antagonists versus prostaglandin analogues, Outcome 2 All-cause mortality in ICU.

Comparison 14. H2 receptor antagonists versus teprenone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Ranitidine vs teprenone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 All-cause mortality in ICU	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Ranitidine vs teprenone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Number of participants requiring blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Ranitidine vs teprenone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 14.1. Comparison 14 H2 receptor antagonists versus teprenone, Outcome 1 Clinically important upper GI bleeding.

Analysis 14.2. Comparison 14 H2 receptor antagonists versus teprenone, Outcome 2 All-cause mortality in ICU.

Analysis 14.3. Comparison 14 H2 receptor antagonists versus teprenone, Outcome 3 Number of participants requiring blood transfusion.

Comparison 15. H2 receptor antagonist + antacids versus sucralfate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	2	230	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.06, 0.95]
1.1 Cimetidine + antacids vs sucralfate	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.70]
1.2 Cimetidine or ranitidine + antacids vs sucralfate	1	130	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.41]
2 Nosocomial pneumonia	3	281	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.51, 2.32]
2.1 Cimetidine + antacids vs sucralfate	1	100	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.26, 1.07]
2.2 Ranitidine + antacids vs sucralfate	1	51	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.64, 2.53]
2.3 Cimetidine or ranitidine + antacids vs sucralfate	1	130	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.89, 4.58]
3 All-cause mortality in ICU	2	230	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.92, 2.05]
3.1 Cimetidine + antacids vs sucralfate	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.46, 2.19]
3.2 Cimetidine or ranitidine + antacids vs sucralfate	1	130	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.99, 2.50]
4 Duration of ICU stay	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Duration of intubation	2	230	Mean Difference (IV, Random, 95% CI)	-1.24 [-13.82, 11.33]
5.1 Cimetidine + antacids vs sucralfate	1	100	Mean Difference (IV, Random, 95% CI)	-8.8 [-20.11, 2.51]
5.2 Cimetidine or ranitidine + antacids vs sucralfate	1	130	Mean Difference (IV, Random, 95% CI)	4.20 [-0.54, 8.94]
6 Number of participants requiring blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 15.1. Comparison 15 H2 receptor antagonist + antacids versus sucralfate, Outcome 1 Clinically important upper GI bleeding.

Analysis 15.2. Comparison 15 H2 receptor antagonist + antacids versus sucralfate, Outcome 2 Nosocomial pneumonia.

Analysis 15.3. Comparison 15 H2 receptor antagonist + antacids versus sucralfate, Outcome 3 All-cause mortality in ICU.

Analysis 15.4. Comparison 15 H2 receptor antagonist + antacids versus sucralfate, Outcome 4 Duration of ICU stay.

Analysis 15.5. Comparison 15 H2 receptor antagonist + antacids versus sucralfate, Outcome 5 Duration of intubation.

Analysis 15.6. Comparison 15 H2 receptor antagonist + antacids versus sucralfate, Outcome 6 Number of participants requiring blood transfusion.

Comparison 16. Proton pump inhibitors versus teprenone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Proton pump inhibitors vs teprenone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 All-cause mortality in ICU	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Proton pump inhibitors vs teprenone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Number of participants requiring blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Proton pump inhibitors vs teprenone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 16.1. Comparison 16 Proton pump inhibitors versus teprenone, Outcome 1 Clinically important upper GI bleeding.

Study or subgroup	Proton pump inhibitors n/N	Teprenone n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
16.1.1 Proton pump inhibitors vs teprenone				
Hata 2005	0/70	4/70		0.11[0.01,2.03]

Analysis 16.2. Comparison 16 Proton pump inhibitors versus teprenone, Outcome 2 All-cause mortality in ICU.

Study or subgroup	Proton pump inhibitors n/N	Teprenone n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
16.2.1 Proton pump inhibitors vs teprenone				
Hata 2005	0/70	1/70		0.33[0.01,8.04]

Analysis 16.3. Comparison 16 Proton pump inhibitors versus teprenone, Outcome 3 Number of participants requiring blood transfusion.

Study or subgroup	Proton pump inhibitors n/N	Teprenone n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
16.3.1 Proton pump inhibitors vs teprenone				
Hata 2005	0/70	4/70		0.11[0.01,2.03]

Comparison 17. Proton pump inhibitor plus naloxone versus naloxone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 All-cause mortality in hospital	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Adverse events - gastrointestinal discomfort	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 17.1. Comparison 17 Proton pump inhibitor plus naloxone versus naloxone, Outcome 1 Clinically important upper GI bleeding.

Analysis 17.2. Comparison 17 Proton pump inhibitor plus naloxone versus naloxone, Outcome 2 All-cause mortality in hospital.

Analysis 17.3. Comparison 17 Proton pump inhibitor plus naloxone versus naloxone, Outcome 3 Adverse events - gastrointestinal discomfort.

Comparison 18. Proton pump inhibitors versus other medication (not defined)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Nosocomial pneumonia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 All-cause mortality in hospital	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 18.1. Comparison 18 Proton pump inhibitors versus other medication (not defined), Outcome 1 Clinically important upper GI bleeding.

Analysis 18.2. Comparison 18 Proton pump inhibitors versus other medication (not defined), Outcome 2 Nosocomial pneumonia.

Analysis 18.3. Comparison 18 Proton pump inhibitors versus other medication (not defined), Outcome 3 All-cause mortality in hospital.

Comparison 19. Antacids versus sucralfate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	16	1772	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.72, 1.39]
1.1 Antacids vs sucralfate	15	1705	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.69, 1.35]
1.2 Antacid + pirenzepine vs sucralfate + pirenzepine	1	67	Risk Ratio (M-H, Fixed, 95% CI)	5.15 [0.26, 103.33]
2 Nosocomial pneumonia	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Antacids vs sucralfate	7	996	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.30]
3 All-cause mortality in ICU	11	1249	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.93, 1.40]
3.1 Antacid vs sucralfate	10	1182	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.94, 1.41]
3.2 Antacid + pirenzepine vs sucralfate + pirenzepine	1	67	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.28, 3.78]
4 All-cause mortality in hospital	3	450	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.69, 1.39]
5 Duration of ICU stay	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Antacids vs sucralfate	2	227	Mean Difference (IV, Fixed, 95% CI)	-2.50 [-6.61, 1.61]
6 Duration of intubation	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Antacids vs sucralfate	4	281	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.41, 0.06]
7 Number of participants requiring blood transfusion	6	667	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.40, 1.34]
8 Adverse events of interventions	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Diarrhoea	6	599	Risk Ratio (M-H, Fixed, 95% CI)	12.40 [3.88, 39.64]
8.2 Hypermagnesaemia	4	317	Risk Ratio (M-H, Fixed, 95% CI)	4.72 [1.24, 17.95]
8.3 Nausea and vomiting	3	223	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.28, 1.41]
8.4 Thrombocytopenia	1	38	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 97.70]
8.5 Severe alkalosis	1	100	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.92]
8.6 Allergic reactions	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.06]

Analysis 19.1. Comparison 19 Antacids versus sucralfate, Outcome 1 Clinically important upper GI bleeding.

Analysis 19.2. Comparison 19 Antacids versus sucralfate, Outcome 2 Nosocomial pneumonia.

Analysis 19.3. Comparison 19 Antacids versus sucralfate, Outcome 3 All-cause mortality in ICU.

Analysis 19.4. Comparison 19 Antacids versus sucralfate, Outcome 4 All-cause mortality in hospital.

Analysis 19.5. Comparison 19 Antacids versus sucralfate, Outcome 5 Duration of ICU stay.

Analysis 19.6. Comparison 19 Antacids versus sucralfate, Outcome 6 Duration of intubation. **Analysis 19.7. Comparison 19 Antacids versus sucralfate, Outcome 7 Number of participants requiring blood transfusion.** **Analysis 19.8. Comparison 19 Antacids versus sucralfate, Outcome 8 Adverse events of interventions.**

Comparison 20. Antacids versus prostaglandin analogues

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	2	329	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.12, 0.91]
2 All-cause mortality in ICU	2	417	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.42, 1.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Adverse events of interventions	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Diarrhoea	1	368	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.64, 1.33]
3.2 Elevated serum bicarbonate	1	338	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [1.27, 3.87]
3.3 Phosphate levels < 2.5 mg/dL	1	276	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.01, 2.73]

Analysis 20.1. Comparison 20 Antacids versus prostaglandin analogues, Outcome 1 Clinically important upper GI bleeding.

Analysis 20.2. Comparison 20 Antacids versus prostaglandin analogues, Outcome 2 All-cause mortality in ICU.

Analysis 20.3. Comparison 20 Antacids versus prostaglandin analogues, Outcome 3 Adverse events of interventions.

Comparison 21. Antacids versus bioflavonoids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Number of participants requiring blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 21.1. Comparison 21 Antacids versus bioflavonoids, Outcome 1 Clinically important upper GI bleeding.

Study or subgroup	Antacids n/N	Bioflavonoids n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kitler 1990	6/113	7/85		0.64[0.22,1.85]

Favours antacids 0.2 0.5 1 2 5 Favours bioflavonoids

Analysis 21.2. Comparison 21 Antacids versus bioflavonoids, Outcome 2 Number of participants requiring blood transfusion.

Study or subgroup	Antacids n/N	Bioflavonoids n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kitler 1990	0/113	2/85		0.15[0.01,3.1]

Comparison 22. Sucralfate versus proton pump inhibitors

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Sucralfate vs omeprazole	3	287	Risk Ratio (M-H, Fixed, 95% CI)	2.58 [0.77, 8.63]
2 Nosocomial pneumonia	4	424	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.41, 1.09]
2.1 Sucralfate vs omeprazole	3	287	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.57, 1.36]
2.2 Sucralfate vs pantoprazole	1	137	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.20, 0.75]
3 All-cause mortality in ICU	4	424	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.68, 1.68]
3.1 Sucralfate vs omeprazole	3	287	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.75, 2.11]
3.2 Sucralfate vs pantoprazole	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.25, 1.68]
4 All-cause mortality in hospital	2	278	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.46, 1.37]
4.1 Sucralfate vs omeprazole	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.49, 1.91]
4.2 Sucralfate vs pantoprazole	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.21, 1.45]
5 Duration of ICU stay	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Sucralfate vs omeprazole	2	217	Mean Difference (IV, Fixed, 95% CI)	0.01 [-1.68, 1.70]
6 Duration of intubation	3	354	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-1.61, 1.28]
6.1 Sucralfate vs omeprazole	2	217	Mean Difference (IV, Fixed, 95% CI)	0.02 [-1.56, 1.60]
6.2 Sucralfate vs pantoprazole	1	137	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-4.69, 2.49]
7 Number of participants requiring blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Sucralfate vs omeprazole	1	70	Risk Ratio (M-H, Fixed, 95% CI)	5.91 [0.29, 118.78]
8 Adverse events of interventions	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Fever	1	137	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.70, 0.94]
8.2 Leucocytosis	1	137	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.55, 0.80]
8.3 Sudden purulent sputum	1	137	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.38, 1.86]
8.4 Sudden cough or aggravation of coughing	1	137	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.07, 0.79]
8.5 Dyspnoea	1	137	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.54, 0.87]
8.6 Rales or bronchial sounds	1	137	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.19, 0.51]
8.7 Aggravation of blood gas exchange	1	137	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.49, 1.18]
8.8 Change in sputum quality	1	137	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.13, 0.40]

Analysis 22.1. Comparison 22 Sucralfate versus proton pump inhibitors, Outcome 1 Clinically important upper GI bleeding.

Analysis 22.2. Comparison 22 Sucralfate versus proton pump inhibitors, Outcome 2 Nosocomial pneumonia.

Analysis 22.3. Comparison 22 Sucralfate versus proton pump inhibitors, Outcome 3 All-cause mortality in ICU.

Analysis 22.4. Comparison 22 Sucralfate versus proton pump inhibitors, Outcome 4 All-cause mortality in hospital.

Analysis 22.5. Comparison 22 Sucralfate versus proton pump inhibitors, Outcome 5 Duration of ICU stay.

Analysis 22.6. Comparison 22 Sucralfate versus proton pump inhibitors, Outcome 6 Duration of intubation.

Analysis 22.7. Comparison 22 Sucralfate versus proton pump inhibitors, Outcome 7 Number of participants requiring blood transfusion.

Analysis 22.8. Comparison 22 Sucralfate versus proton pump inhibitors, Outcome 8 Adverse events of interventions.

Comparison 23. Sucralfate versus bioflavonoids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Number of participants requiring blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 23.1. Comparison 23 Sucralfate versus bioflavonoids, Outcome 1 Clinically important upper GI bleeding.

Study or subgroup	Sucralfate n/N	Bioflavonoid n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kitler 1990	9/100	7/85		1.09[0.43,2.81]
Favours sucralfate				Favours bioflavonoids

Analysis 23.2. Comparison 23 Sucralfate versus bioflavonoids, Outcome 2 Number of participants requiring blood transfusion.

Study or subgroup	Sucralfate n/N	Bioflavonoid n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kitler 1990	1/100	2/85		0.43[0.04,4.61]
Favours sucralfate				Favours bioflavonoids

Comparison 24. Total parenteral nutrition (TPN) versus any other intervention + TPN

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 TPN vs ranitidine + TPN	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.05, 12.14]
1.2 TPN vs sucralfate + TPN	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.03, 3.26]
2 All-cause mortality in ICU	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 TPN vs ranitidine + TPN	1	54	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.41, 3.09]
2.2 TPN vs sucralfate + TPN	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.26, 1.52]
3 Duration of intubation	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 TPN vs ranitidine + TPN	1	54	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-9.53, 5.53]
3.2 TPN vs sucralfate + TPN	1	49	Mean Difference (IV, Fixed, 95% CI)	3.0 [-1.50, 7.50]

Analysis 24.1. Comparison 24 Total parenteral nutrition (TPN) versus any other intervention + TPN, Outcome 1 Clinically important upper GI bleeding.

Analysis 24.2. Comparison 24 Total parenteral nutrition (TPN) versus any other intervention + TPN, Outcome 2 All-cause mortality in ICU.

Analysis 24.3. Comparison 24 Total parenteral nutrition (TPN) versus any other intervention + TPN, Outcome 3 Duration of intubation.

Comparison 25. Bowel stimulation versus no prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 25.1. Comparison 25 Bowel stimulation versus no prophylaxis, Outcome 1 Clinically important upper GI bleeding.

Comparison 26. Nasojejunal nutrition versus nasogastric nutrition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically important upper GI bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Nosocomial pneumonia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 All-cause mortality in hospital	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Adverse events of interventions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 26.1. Comparison 26 Nasojejunal nutrition versus nasogastric nutrition, Outcome 1 Clinically important upper GI bleeding.

Analysis 26.2. Comparison 26 Nasojejunal nutrition versus nasogastric nutrition, Outcome 2 Nosocomial pneumonia.

Analysis 26.3. Comparison 26 Nasojejunal nutrition versus nasogastric nutrition, Outcome 3 All-cause mortality in hospital.

Analysis 26.4. Comparison 26 Nasojejunal nutrition versus nasogastric nutrition, Outcome 4 Adverse events of interventions.

Comparison 27. Enteral plus parenteral nutrition versus other nutrition regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nosocomial pneumonia	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.44, 1.40]
1.1 Enteral plus parenteral nutrition vs enteral nutrition	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.29, 1.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Enteral plus parenteral nutrition vs parenteral nutrition	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.47, 3.33]
2 All-cause mortality in hospital	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.20 [0.06, 0.60]
2.1 Enteral plus parenteral nutrition vs enteral nutrition	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.05, 1.30]
2.2 Enteral plus parenteral nutrition vs parenteral nutrition	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.03, 0.74]
3 Duration of ICU stay	1	120	Mean Difference (IV, Fixed, 95% CI)	-5.98 [-8.81, -3.16]
3.1 Enteral plus parenteral nutrition vs enteral nutrition	1	60	Mean Difference (IV, Fixed, 95% CI)	-3.81 [-7.59, -0.03]
3.2 Enteral plus parenteral nutrition vs parenteral nutrition	1	60	Mean Difference (IV, Fixed, 95% CI)	-8.72 [-12.97, -4.47]
4 Duration of intubation	1	120	Mean Difference (IV, Fixed, 95% CI)	-7.37 [-9.29, -5.45]
4.1 Enteral plus parenteral nutrition vs enteral nutrition	1	60	Mean Difference (IV, Fixed, 95% CI)	-4.17 [-6.96, -1.38]
4.2 Enteral plus parenteral nutrition vs parenteral nutrition	1	60	Mean Difference (IV, Fixed, 95% CI)	-10.24 [-12.88, -7.60]
5 Adverse events - stress ulcer	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.36, 1.33]
5.1 Enteral plus parenteral nutrition vs enteral nutrition	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.38, 3.45]
5.2 Enteral plus parenteral nutrition vs parenteral nutrition	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.23, 1.20]
6 Adverse events - diarrhoea	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.17, 1.02]
6.1 Enteral plus parenteral nutrition vs enteral nutrition	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.05, 0.59]
6.2 Enteral plus parenteral nutrition vs parenteral nutrition	1	60	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.35, 5.73]
7 Adverse events - pyaemia	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.37, 2.09]
7.1 Enteral plus parenteral nutrition vs enteral nutrition	1	60	Odds Ratio (M-H, Fixed, 95% CI)	4.11 [0.87, 19.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Enteral plus parenteral nutrition vs parenteral nutrition	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.11, 1.21]
8 Adverse events - intracranial infection	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.15, 1.25]
8.1 Enteral plus parenteral nutrition vs enteral nutrition	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.19, 3.63]
8.2 Enteral plus parenteral nutrition vs parenteral nutrition	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.05, 1.15]
9 Adverse events - hypoproteinaemia	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.04, 0.27]
9.1 Enteral plus parenteral nutrition vs enteral nutrition	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.20 [0.06, 0.72]
9.2 Enteral plus parenteral nutrition vs parenteral nutrition	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.04 [0.01, 0.19]

Analysis 27.1. Comparison 27 Enteral plus parenteral nutrition versus other nutrition regimens, Outcome 1 Nosocomial pneumonia.

Analysis 27.2. Comparison 27 Enteral plus parenteral nutrition versus other nutrition regimens, Outcome 2 All-cause mortality in hospital.

Analysis 27.3. Comparison 27 Enteral plus parenteral nutrition versus other nutrition regimens, Outcome 3 Duration of ICU stay.

Analysis 27.4. Comparison 27 Enteral plus parenteral nutrition versus other nutrition regimens, Outcome 4 Duration of intubation.

Analysis 27.5. Comparison 27 Enteral plus parenteral nutrition versus other nutrition regimens, Outcome 5 Adverse events - stress ulcer.

Analysis 27.6. Comparison 27 Enteral plus parenteral nutrition versus other nutrition regimens, Outcome 6 Adverse events - diarrhoea.

Analysis 27.7. Comparison 27 Enteral plus parenteral nutrition versus other nutrition regimens, Outcome 7 Adverse events - pyaemia.

Analysis 27.8. Comparison 27 Enteral plus parenteral nutrition versus other nutrition regimens, Outcome 8 Adverse events - intracranial infection.

Analysis 27.9. Comparison 27 Enteral plus parenteral nutrition versus other nutrition regimens, Outcome 9 Adverse events - hypoproteinaemia.

Study or subgroup	Enteral plus parenteral n n/N	Other nutri- tion regimen n/N	Odds Ratio					Weight	Odds Ratio	
			M-H, Fixed, 95% CI						M-H, Fixed, 95% CI	
Test for overall effect: Z=4.68(P<0.0001)										
Test for subgroup differences: Chi²=2.45, df=1 (P=0.12), I²=59.12%										
			0.010.1110100							
			Favours ent. + parent. n.					Favours other nutrition		

APPENDICES

Appendix 1. Glossary of medical terms

Antimicrobial – active against microbes.

Aspiration – action or process of drawing breath.

Bicarbonate ions - bicarbonate serves a crucial biochemical role in the physiological [pH buffering](#) system.

Bronchial - related to the bronchi or bronchioles.

Creatinine – compound that is produced by metabolism of creatine and is excreted in the urine.

Cytoprotective – providing protection to cells against harmful agents.

Enteral nutrition – nutrition passing through the intestine, either naturally via the mouth and oesophagus, or through an artificial opening.

Flora - population of microbes inhabiting the outside or inside surfaces of the body.

Gastric – concerning the stomach.

Gram stain – method used to distinguish different types of bacteria by staining them.

Haemoglobin - red protein responsible for transporting oxygen into the blood of vertebrates.

Hyperaemia - excess of blood in the vessels supplying an organ or another part of the body.

Hypermagnesaemia - high level of magnesium in the blood.

Hypomagnesaemia - low level of magnesium in the blood.

Hypoperfusion - decreased flow of blood through an organ.

Hypophosphataemia - abnormally low level of phosphate in the blood.

Infiltrate - substance denser than air such as pus, blood, or protein that lingers within the parenchyma of the lungs.

Interstitial nephritis – type of bacterial infection of the kidneys.

Ischaemia - inadequate blood supply to an organ or part of the body.

Lesion - region in an organ or tissue that has suffered damage through injury or disease.

Leucocytosis - increase in the number of white cells in the blood.

Leucopaenia - reduction in the number of white cells in the blood.

Luminal - concerning the interior of the gastrointestinal tract.

Microcirculation - circulation of the blood in the smallest blood vessels.

Morbidity - the condition of being diseased.

Mortality - the number of deaths in a given area or period, or from a particular cause.

Mucosal - concerning the mucosa.

Neutropaenia - presence of abnormally few neutrophils in the blood.

Nosocomial – originating in a hospital.

Occult bleeding – bleeding that is detectable only chemically or microscopically.

Cytochrome P-450 mediated drug interaction - a drug interaction mediated via the cytochrome P-450, a family of isozymes responsible for biotransformation of many drugs via oxidation.

Pathogenic – causing disease.

Pathophysiology - disordered physiological processes associated with disease or injury.

Pancreatitis - inflammation of the pancreas.

Peptic - related to digestion.

pH - figure expressing the acidity or alkalinity of a solution.

Pharmacological - concerned with uses, effects, and modes of action of drugs.

Pleural – concerning the serous membranes lining the thorax and enveloping the lungs.

Pneumonia - lung inflammation caused by bacterial or viral infection.

Postural – concerning the position in which someone holds his or her body when standing or sitting.

Prophylaxis - preventive treatment.

Prostaglandin - group of compounds with varying hormone-like effects.

Pulmonary – related to the lungs.

Purulent - consisting of, containing, or discharging pus.

Pyemia - blood poisoning caused by spread in the bloodstream of pus-forming bacteria.

Quinolones - antibiotic derived from quinoline.

Rales - abnormal rattling sounds heard when unhealthy lungs are examined with a stethoscope.

Renal – related to the kidneys.

Reperfusion - action of restoring the flow of blood to an organ or tissue.

Sepsis - presence in tissues of harmful bacteria and their toxins.

Splanchnic - related to the viscera or internal organs.

Tetracyclines - any of a large group of antibiotics with a molecular structure containing four rings.

Thrombocytopaenia - condition characterised by abnormally low levels of thrombocytes in the blood.

Tracheo-bronchial colonisation - colonisation of the lower airways by bacteria.

Ulceration – development of or affected by an ulcer.

Ventilator - appliance for artificial respiration.

Appendix 2. 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 waltan 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.
- 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 proulco 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 Oxiphenonium).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 aldrex 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 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.

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 bisubcit 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

Update search on 15 June 2016 and 22 August 2017:

1. exp Upper Gastrointestinal Tract/

2. (stomach or antrum or antral or pyloric or pylorus or gastri* or gastro* or duoden* or epigastri* or gastritis or duodenitis).tw,kw.

3. (esophag* or oesophag* or gastroduoden* or gastrointestinal).tw,kw.

4. exp Peptic Ulcer/

5. (peptic or ulcer* or upper GI or UGI or PUD).tw,kw.

6. or/1-5

7. (hemorrhag* or haemorrhag* or bleed* or rebleed* or re-bleed* or bled or rebled).tw,kw.

8. (mucosa* adj2 (injur* or damage* or lesion*)).tw,kw.

9. exp Hemorrhage/

10. or/7-9

11. 6 and 10

12. exp Gastrointestinal Hemorrhage/

13. exp melena/

14. (melena or melaena).tw,kw.

15. exp hematemesis/

16. (haematemesis or hematemesis).tw,kw.

- 17.((coffee adj ground) or "UGIB").tw,kw.
- 18.or/11-17
- 19.exp Intensive Care Units/
- 20.exp Critical Illness/
- 21.exp Critical care/
- 22.(intensive care or critical care or respiratory care or recovery room or close attention unit* or special care unit* or coronary care or burn unit* or ICU or RCU or CCU).tw,kw.
- 23.((critical or critically or severe or serious*) adj2 (ill or illness)).tw,kw.
- 24.((head or brain or severe or multiple) adj2 (injur* or trauma*)).tw,kw.
- 25.exp Respiration, Artificial/
- 26.(((mechanical* or artificial or controlled) adj2 (ventilat* or respiration)) or on ventilator or ventilated patients).tw,kw.
- 27.((prophylaxis or prophylactic or prevent*) and (((after or post) adj2 (surgery or operat*)) or postoperat* or sepsis or hepatic failure* or respiratory failure* or renal failure* or burns or transplantation or stroke or incubated or acute pancreatitis or intracerebral h*orrhag* or intracerebral bleed*)).ti,ab.
- 28.or/19-27
- 29.18 and 28
- 30.(stress adj2 (ulcer* or gastritis or bleed* or hemorrhage* or haemorrhage*)).tw,kw.
- 31.29 or 30
- 32.limit 31 to yr="2012 -Current"
- 33.remove duplicates from 32

Appendix 3. 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 epigastri\$ 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.
- 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 wazan 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 monolitus 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 Oxiphenonium).mp.
- 60.(Doxepin or adapin or apodoxepin or aponal or deptran or desidox or doneurin or doxepia or doxepinbiomo or espadox or mareen or pradoxin 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 aldrex 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 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.
- 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 bisubcit or de-nol or de-noltab or gastrodenol or sucrato or tripotassium dicitratobismuthate or ventrisol-polfa).mp.
- 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

Update search on 15 June 2016 and 22 August 2017:

1. exp Upper Gastrointestinal Tract/
2. (stomach or antrum or antral or pyloric or pylorus or gastri* or gastro* or duoden* or epigastri* or gastritis or duodenitis).tw,kw.
3. (esophag* or oesophag* or gastroduoden* or gastrointestinal).tw,kw.
4. exp Peptic Ulcer/
5. (peptic or ulcer* or upper GI or UGI or PUD).tw,kw.
6. or/1-5
7. (hemorrhag* or haemorrhag* or bleed* or rebleed* or re-bleed* or bled or rebled).tw,kw.
8. (mucosa* adj2 (injur* or damage* or lesion*)).tw,kw.
9. exp Hemorrhage/
- 10.or/7-9
- 11.6 and 10
- 12.exp Gastrointestinal Hemorrhage/
- 13.exp melena/
- 14.(melena or melaena).tw,kw.
- 15.exp hematemesis/
- 16.(haematemesis or hematemesis).tw,kw.
- 17.((coffee adj ground) or "UGIB").tw,kw.
- 18.or/11-17
- 19.exp Intensive Care Units/
- 20.exp Critical Illness/
- 21.exp Critical care/
- 22.(intensive care or critical care or respiratory care or recovery room or close attention unit* or special care unit* or coronary care or burn unit* or ICU or RCU or CCU).tw,kw.
- 23.((critical or critically or severe or serious*) adj2 (ill or illness)).tw,kw.
- 24.((head or brain or severe or multiple) adj2 (injur* or trauma*)).tw,kw.
- 25.exp Respiration, Artificial/
- 26.(((mechanical* or artificial or controlled) adj2 (ventilat* or respiration)) or on ventilator or ventilated patients).tw,kw.

- 27.((prophylaxis or prophylactic or prevent*) and (((after or post) adj2 (surgery or operat*)) or postoperat* or sepsis or hepatic failure* or respiratory failure* or renal failure* or burns or transplantation or stroke or incubated or acute pancreatitis or intracerebral h*morrhag* or intracerebral bleed*)).ti,ab.
- 28.or/19-27
- 29.18 and 28
- 30.(stress adj2 (ulcer* or gastritis or bleed* or hemorrhage* or haemorrhage*)).tw,kw.
- 31.29 or 30
- 32.randomized controlled trial.pt.
- 33.controlled clinical trial.pt.
- 34.random*.ab.
- 35.placebo.ab.
- 36.drug therapy.fs.
- 37.trial.ab.
- 38.groups.ab.
- 39.or/32-38
- 40.exp animals/ not humans.sh.
- 41.39 not 40
- 42.31 and 41
- 43.limit 42 to yr="2012 -Current"

Appendix 4. 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.Pro 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 epigastri\$ 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*morrhag\$ 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/
- 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 walfan 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 monolitus 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.
- 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 aldrex 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 bisubcit 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

Update search on 15 June 2016 and 22 August 2017:

1. exp upper gastrointestinal tract/
2. (stomach or antrum or antral or pyloric or pylorus or gastri* or gastro* or duoden* or epigastri* or gastritis or duodenitis).tw,kw.
3. (esophag* or oesophag* or gastroduoden* or gastrointestinal).tw,kw.
4. exp peptic ulcer/
5. (peptic or ulcer* or upper GI or UGI or PUD).tw,kw.
6. or/1-5
7. (hemorrhag* or haemorrhag* or bleed* or rebleed* or re-bleed* or bled or rebled).tw,kw.
8. (mucosa* adj2 (injur* or damage* or lesion*)).tw,kw.
9. exp bleeding/
- 10.or/7-9
- 11.6 and 10
- 12.exp gastrointestinal hemorrhage/
- 13.exp melena/
- 14.(melena or melaena).tw,kw.
- 15.exp hematemesis/

- 16.(haematemesis or hematemesis).tw,kw.
- 17.((coffee adj ground) or "UGIB").tw,kw.
- 18.or/11-17
- 19.exp intensive care unit/
- 20.exp critical illness/
- 21.exp intensive care/
- 22.(intensive care or critical care or respiratory care or recovery room or close attention unit* or special care unit* or coronary care or burn unit* or ICU or RCU or CCU).tw,kw.
- 23.((critical or critically or severe or serious*) adj2 (ill or illness)).tw,kw.
- 24.((head or brain or severe or multiple) adj2 (injur* or trauma*)).tw,kw.
- 25.exp artificial ventilation/
- 26.(((mechanical* or artificial or controlled) adj2 (ventilat* or respiration)) or on ventilator or ventilated patients).tw,kw.
- 27.((prophylaxis or prophylactic or prevent*) and (((after or post) adj2 (surgery or operat*)) or postoperat* or sepsis or hepatic failure* or respiratory failure* or renal failure* or burns or transplantation or stroke or incubated or acute pancreatitis or intracerebral h*orrhag* or intracerebral bleed*))ti,ab.
- 28.or/19-27
- 29.18 and 28
- 30.(stress adj2 (ulcer* or gastritis or bleed* or hemorrhage* or haemorrhage*)).tw,kw.
- 31.29 or 30
- 32.random::tw.
- 33.placebo::mp.
- 34.double-blind::tw.
- 35.32 or 33 or 34
- 36.31 and 35
- 37.limit 36 to yr="2012 -Current"

Appendix 5. 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]

Update search on 15 June 2016 and 22 August 2017:

((tw:(ulcer OR stomach OR antrum OR antral OR gastri* OR gastro* OR duoden* OR epigastri* OR gastritis OR duodenitis OR esophageal* OR oesophageal*)) AND (tw:(hemorrhag* OR haemorrhag* OR bleed* OR rebleed* OR re-bleed* OR bled OR rebled))) OR (tw:(stress ulcer*)) OR (mh: (c06.405.227))) AND (mh: (e02.760.190)) OR (tw: (intensive care OR critical care OR critically ill OR mechanical* ventilat*)) AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("clinical_trials"))

CONTRIBUTIONS OF AUTHORS

Ingrid Toews: searching for additional references, selecting studies, extracting data, assessing quality, locating and retrieving full-text articles, refining and updating the review, and writing and approving the final version of the review.

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

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

Luis Eduardo S Fontes: performing study selection, data extraction, and quality assessment; locating and retrieving full-text articles; refining and updating the review; and writing the Authors' Conclusions section.

Joerg Meerpohl: performing study selection, locating and retrieving full-text articles, and refining and approving the final version of the review.

DECLARATIONS OF INTEREST

All review authors declare no conflict academic or financial interests that will influence the conduct, interpretation, or reporting of this review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The number of participants requiring more than two units of blood was changed to not define the number of units transfused.

The outcome 'ventilator-associated pneumonia' was changed to 'nosocomial pneumonia including ventilator-associated pneumonia' because definitions varied across study reports.

'Potassium-competitive acid blockers' was added to list of eligible interventions.

INDEX TERMS

Medical Subject Headings (MeSH)

*Intensive Care Units; Anti-Ulcer Agents [therapeutic use]; Blood Transfusion [statistics & numerical data]; Cause of Death; Histamine H2 Antagonists [therapeutic use]; Length of Stay; Peptic Ulcer Hemorrhage [etiology] [*prevention & control] [psychology]; Pneumonia [epidemiology]; Proton Pump Inhibitors [therapeutic use]; Randomized Controlled Trials as Topic; Selection Bias; Stress, Psychological [*complications]; Sucralfate [therapeutic use]

MeSH check words

Humans