Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline

Ye, Zhikang; Reintam Blaser, Annika; Lytvyn, Lyubov; Wang, Ying; Guyatt, Gordon H; Mikita, J Stephen; Roberts, Jamie; Agoritsas, Thomas; Bertschy, Sonja; Boroli, Filippo; Camsooksai, Julie; Du, Bin; Heen, Anja Fog; Lu, Jianyou [**and 6 more**]

How to cite

YE, Zhikang et al. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. In: BMJ (Clinical Research Edition), 2020, vol. 368, p. l6722. doi: 10.1136/bmj.l6722

This publication URL: https://archive-ouverte.unige.ch/unige:141566

Publication DOI: 10.1136/bmj.l6722

thebmj

RAPID RECOMMENDATIONS

Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline

Zhikang Ye,[1 2] Annika Reintam Blaser,[3 4] Lyubov Lytvyn,[2] Ying Wang,[1] Gordon H Guyatt,[2 5] J Stephen Mikita,[6] Jamie Roberts,[7] Thomas Agoritsas,[2 8] Sonja Bertschy,[9] Filippo Boroli,[10] Julie Camsooksai,[11] Bin Du,[12] Anja Fog Heen,[13] Jianyou Lu,[14] José M Mella,[15] Per Olav Vandvik,[16] Robert Wise,[17 18] Yue Zheng,[19] Lihong Liu,[1] Reed A C Siemieniuk[2]

Full author details can be found at the end of the article

Correspondence to: L Liu
liulihong@bjcyh.com

Cite this as: *BMJ* 2020;368:l6722
doi: 10.1136/bmj.l6722

This *BMJ* Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (http://magicproject.org/) and *The BMJ*. A summary is offered here and the full version including decision aids is on the MAGICapp (https://app.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article.

ABSTRACT

Clinical question What is the role of gastrointestinal bleeding prophylaxis (stress ulcer prophylaxis) in critically ill patients? This guideline was prompted by the publication of a new large randomised controlled trial.

Current practice Gastric acid suppression with proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) is commonly done to prevent gastrointestinal bleeding in critically ill patients. Existing guidelines vary in their recommendations of which population to treat and which agent to use.

Recommendations This guideline panel makes a weak recommendation for using gastrointestinal bleeding prophylaxis in critically ill patients at high risk (>4%) of clinically important gastrointestinal bleeding, and a weak recommendation for not using prophylaxis in patients at lower risk of clinically important bleeding (≤4%). The panel identified risk categories based on evidence, with variable certainty regarding risk factors. The panel suggests using a PPI rather than a H2RA (weak recommendation) and recommends against using sucralfate (strong recommendation).

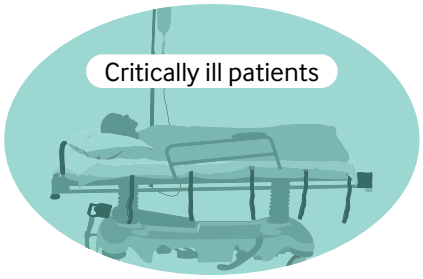
How this guideline was created A guideline panel including patients, clinicians, and methodologists produced these recommendations using standards for trustworthy guidelines and the GRADE approach. The recommendations are based on a linked systematic review and network meta-analysis. A weak recommendation means that both options are reasonable.

The evidence The linked systematic review and network meta-analysis estimated the benefit and harm of these medications in 12 660 critically ill patients in 72 trials. Both PPIs and H2RAs reduce the risk of clinically important bleeding. The effect is larger in patients at higher bleeding risk (those with a coagulopathy, chronic liver disease, or receiving mechanical ventilation but not enteral nutrition or two or more of mechanical ventilation with enteral nutrition, acute kidney injury, sepsis, and shock) (moderate certainty). PPIs and H2RAs might increase the risk of pneumonia (low certainty). They probably do not have an effect on mortality (moderate certainty), length of hospital stay, or any other important outcomes. PPIs probably reduce the risk of bleeding more than H2RAs (moderate certainty).

Understanding the recommendation In most critically ill patients, the reduction in clinically important gastrointestinal bleeding from gastric acid suppressants is closely balanced with the possibility of pneumonia. Clinicians should consider individual patient values, risk of bleeding, and other factors such as medication availability when deciding whether to use gastrointestinal bleeding prophylaxis. Visual overviews provide the relative and absolute benefits and harms of the options in multilayered evidence summaries and decision aids available on MAGICapp.

Visual summary of recommendation

Population



Including:

- ✔ Patients admitted to intensive care units

Does not apply to:

- ✖ Patients receiving gastric acid suppression for another therapeutic indication

On average, 4% of critically ill patients develop gastrointestinal bleeding. One cause is physiologic stress leading to stress ulcers in the oesophagus, stomach, or duodenum, but critical illness is also associated with other forms of upper gastrointestinal bleeding.

Recommendation 1

No prophylaxis		Prophylaxis	
Strong	Weak	**Weak**	Strong

or

"We suggest using acid suppression prophylaxis for people with higher risk of gastrointestinal bleeding (4% or higher)"

Calculating bleed risk

Highest risk	8-10%	Mechanical ventilation without enteral nutrition Chronic liver disease
High risk	4-8%	Concerning coagulopathy 2 or more factors from 2-4% category
		SUGGESTED CUT POINT FOR OFFERING PROPHYLAXIS For patients near this threshold, individual values and preferences become more important
Moderate risk	2-4%	Mechanical ventilation with enteral nutrition Acute kidney injury Sepsis Shock
Low risk	1-2%	Critically ill patients without any risk factor Acute hepatic failure Use of steroids or immunosuppression Use of anticoagulants Cancer Male gender

Evidence profile Proton pump inhibitors

No prophylaxis | No important difference | Proton pump inhibitor

	Events per 1000 people			Evidence quality	
Important bleeding (1-2% risk)	12	No important difference	7	★★★☆ Moderate	More

Proton pump inhibitors reduce the risk of gastrointestinal bleeding. For people with a 1-2% risk of clinically important bleeding however, the effect is **probably** small enough that most people would choose not to use them

Moderate GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	No serious concerns
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Uncertainty in baseline risk for some risk factors

Important bleeding (2-4% risk)	30	No important difference	19	★★☆☆ Low	More

Proton pump inhibitors reduce the risk of gastrointestinal bleeding. For people with a 2-4% risk of clinically important bleeding however, the effect **may** be small enough that most people would choose not to use them

Low GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Uncertainty in baseline risk for some risk factors

Important bleeding (4-8% risk)	60	23 fewer	37	★★★☆ Moderate	More

Proton pump inhibitors reduce the risk of gastrointestinal bleeding. For people with a 4-8% risk of clinically important bleeding, the effect is **probably** large enough that most people would choose to use them

Moderate GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Important bleeding (8-10% risk)	90	33 fewer	57	★★★☆ Moderate	More

Proton pump inhibitors reduce the risk of gastrointestinal bleeding. For people with a 8-10% risk of clinically important bleeding, the effect is **probably** large enough that most people would choose to use them

Moderate GRADE score, because of:

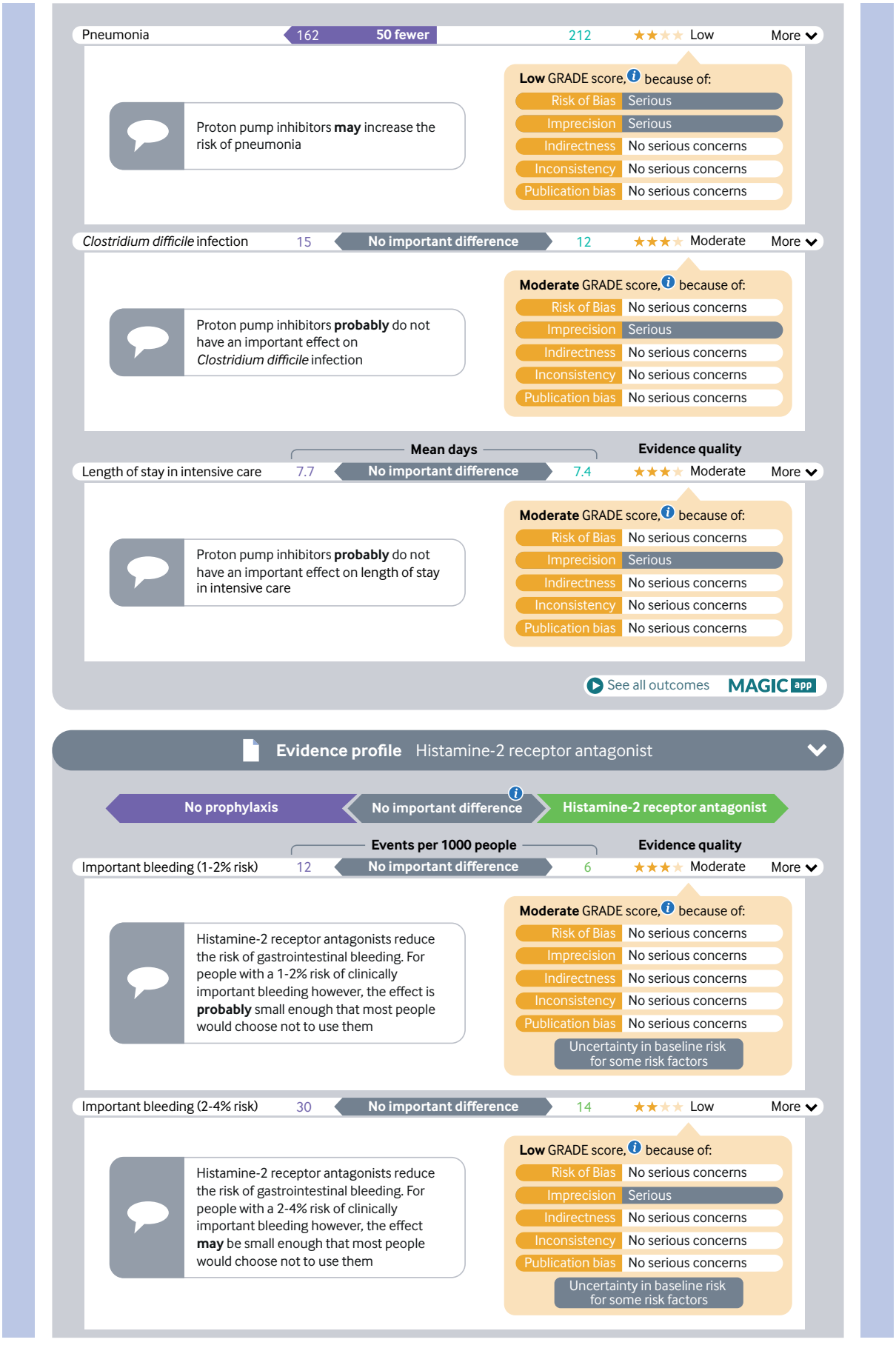
Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

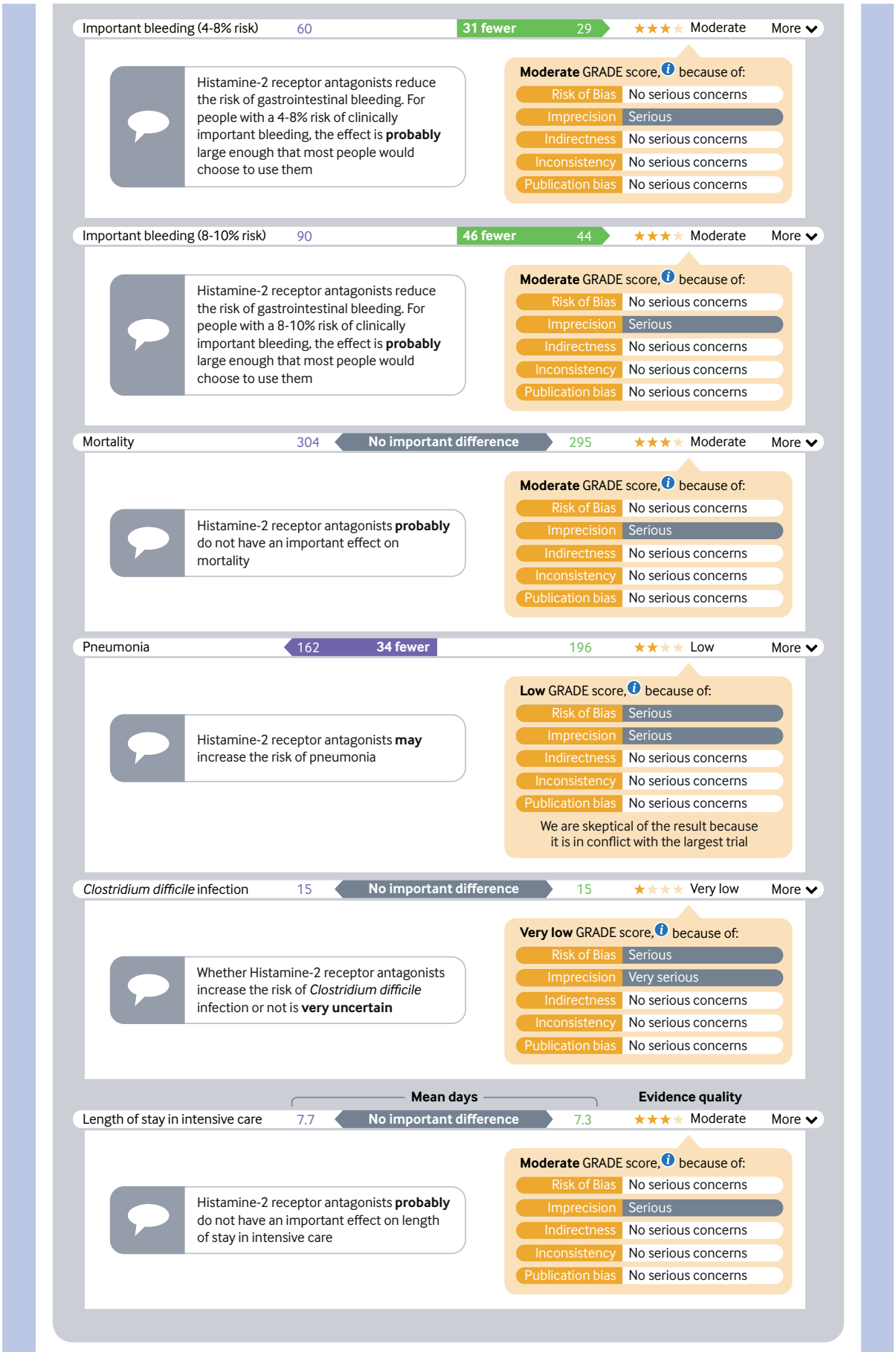
Mortality	304	No important difference	317	★★★☆ Moderate	More

Proton pump inhibitors **probably** do not have an important effect on mortality

Moderate GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns





Individual considerations

Key practical issues

No prophylaxis	Proton pump inhibitors	Histamine-2 receptor antagonists
None	Can be administered intravenously or enterally	
	Typically administered once per day	Typically administered two or three times per day

Duration of treatment

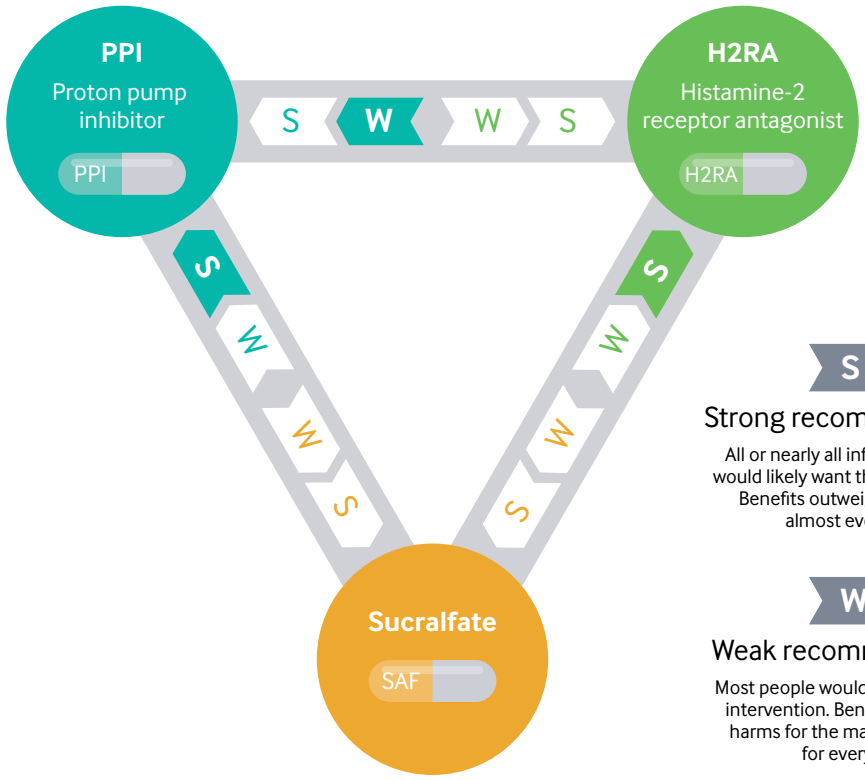
A system should be in place to prevent inadvertent continuation of gastric acid suppression

Values and preferences

It may be challenging to implement shared decision making because there are often many other more important decisions. However, shared decision making should be pursued whenever possible.

Recommendation 2

> In critically ill patients who are going to receive prophylaxis against gastrointestinal bleeding, we suggest a proton pump inhibitor. A histamine-2 receptor antagonist is also a reasonable choice. We recommend not using sucralfate



Evidence profile Proton pump inhibitor *versus* histamine-2 receptor antagonist

Proton pump inhibitor	No important difference	Histamine-2 receptor antagonist

	Events per 1000 people			Evidence quality	
Important bleeding (1-2% risk)	7	No important difference	12	★★☆☆ Low	More

For people with 1 to 2 % risk of clinically important gastrointestinal bleeding, there **may** be no important difference between proton pump inhibitors and histamine-2 receptor antagonists

Low GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Uncertainty in baseline risk for some risk factors

Important bleeding (2-4% risk)	19	13 fewer	32	★★☆☆ Low	More

For people with 2 to 4 % risk of clinically important gastrointestinal bleeding, proton pump inhibitors **may** reduce the risk more than histamine-2 receptor antagonists

Low GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Uncertainty in baseline risk for some risk factors

Important bleeding (4-8% risk)	37	25 fewer	62	★★★☆ Moderate	More

For people with 4 to 8 % risk of clinically important gastrointestinal bleeding, proton pump inhibitors **probably** reduce the risk more than histamine-2 receptor antagonists

Moderate GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Important bleeding (8-10% risk)	57	37 fewer	94	★★★☆ Moderate	More

For people with 8 to 10 % risk of clinically important gastrointestinal bleeding, proton pump inhibitors **probably** reduce the risk more than histamine-2 receptor antagonists

Moderate GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Mortality	317	No important difference	295	★☆☆☆ Very low	More

Whether there is an important difference between proton pump inhibitors and hastamine-2 receptor antagonists on the risk of death or not is **very uncertain**

Moderate GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Extremely serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Pneumonia	212	No important difference	196	★★☆☆ Low	More

There **may** be no important difference between proton pump inhibitors and histamine-2 receptor antagonists on risk of pneumonia

Low GRADE score, because of:

Risk of Bias	Serious
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Clostridium difficile infection	12	No important difference	15	★★☆☆ Low	More

There **may** be no important difference between proton pump inhibitors and histamine-2 receptor antagonists on risk of *Clostridium difficile* infection

Low GRADE score, because of:

Risk of Bias	Serious
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

	Mean days			Evidence quality	
Length of stay in intensive care	7.4	No important difference	7.3	★★★★ High	More

There **is** no important difference between proton pump inhibitors and histamine-2 receptor antagonists on length of stay in intensive care

Moderate GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	No serious concerns
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Evidence profile Proton pump inhibitor *versus* sucralfate

Proton pump inhibitor | No important difference | Sucralfate

	Events per 1000 people			Evidence quality	
Important bleeding (1-2% risk)	7	16 fewer	23	★☆☆☆ Very low	More

For people with 1 to 2% risk of clinically important gastrointestinal bleeding, whether there is an important difference between proton pump inhibitors and sucralfate on clinically important gastrointestinal bleeding or not is **very uncertain**

Very low GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Very serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Uncertainty in baseline risk for some risk factors

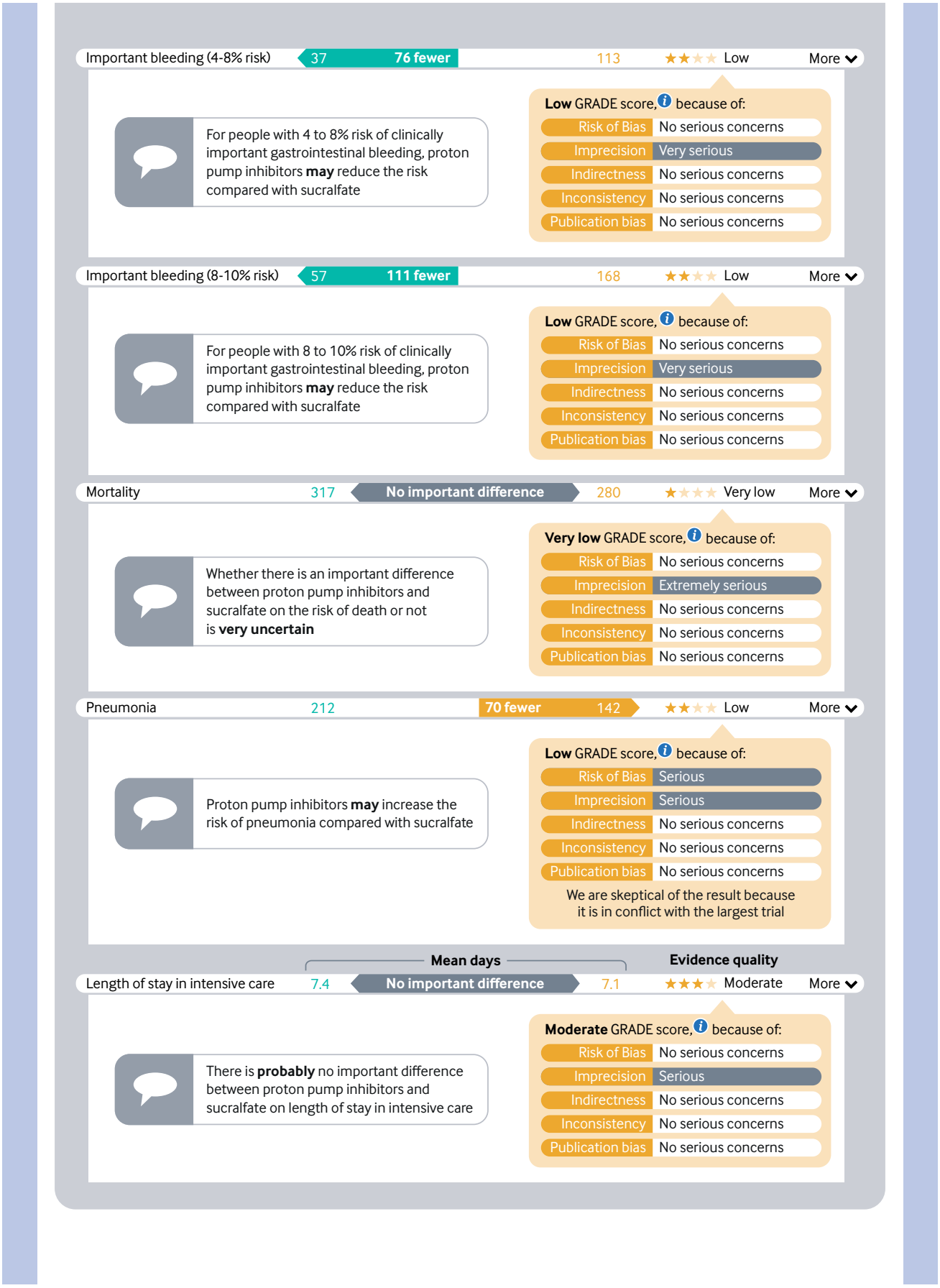
Important bleeding (2-4% risk)	19	42 fewer	61	★☆☆☆ Very low	More

For people with 2 to 4% risk of clinically important gastrointestinal bleeding, whether there is an important difference between proton pump inhibitors and sucralfate on clinically important gastrointestinal bleeding or not is **very uncertain**

Very low GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Very serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Uncertainty in baseline risk for some risk factors



Evidence profile Histamine-2 receptor antagonist *versus* sucralfate

Histamine-2 receptor antagonist	No important difference	Sucralfate	Events per 1000 people	Evidence quality	
Important bleeding (1-2% risk)	6	No important difference	13	★★☆☆ Low	More

For people with 1 to 2 % risk of clinically important gastrointestinal bleeding, there **may** be no important difference between histamine-2 receptor antagonists and sucralfate on clinically important gastrointestinal bleeding

Low GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Uncertainty in baseline risk for some risk factors

Important bleeding (2-4% risk)	14	16 fewer	30	★★☆☆ Low	More

For people with 2 to 4 % risk of clinically important gastrointestinal bleeding, histamine-2 receptor antagonists **may** reduce the risk compared with sucralfate

Low GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Uncertainty in baseline risk for some risk factors

Important bleeding (4-8% risk)	29	32 fewer	61	★★★☆ Moderate	More

For people with 4 to 8 % risk of clinically important gastrointestinal bleeding, histamine-2 receptor antagonists **probably** reduce the risk compared with sucralfate

Moderate GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Important bleeding (8-10% risk)	44	47 fewer	91	★★★☆ Moderate	More

For people with 8 to 10 % risk of clinically important gastrointestinal bleeding, histamine-2 receptor antagonists **probably** reduce the risk compared with sucralfate

Low GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Mortality	295	No important difference	280	★★★☆ Moderate	More

There is **probably** no important difference between histamine-2 receptor antagonists and sucralfate on the risk of death

Moderate GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Pneumonia	196	53 fewer	142	★★☆☆ Low	More

Histamine-2 receptor antagonists **may** increase the risk of pneumonia compared with sucralfate

Low GRADE score, because of:

Risk of Bias	Serious
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Length of stay in intensive care	Mean days: 7.3	No important difference	Mean days: 7.1	Evidence quality: ★★★☆ Moderate	More

There is **probably** no important difference between histamine-2 receptor antagonists and sucralfate on length of stay in intensive care

Moderate GRADE score, because of:

Risk of Bias	No serious concerns
Imprecision	Serious
Indirectness	No serious concerns
Inconsistency	No serious concerns
Publication bias	No serious concerns

Individual considerations

Key practical issues

Proton pump inhibitors	Histamine-2 receptor antagonists	Sucralfate
Can be administered intravenously or enterally		Must be given enterally
Typically administered once per day	Typically administered two or three times per day	Typically administered four times per day

Values and preferences

We think that all or almost all patients would prefer to use a gastric acid suppressant with proven effectiveness

Costs

Intravenous formulations are usually more expensive than enteral formulations. Costs vary between specific agents

Critically ill patients are at risk of gastrointestinal bleeding. The mechanisms vary and include physiologic stress that can lead to stress ulcers in the oesophagus, stomach, or duodenum. Clinicians can prescribe gastric acid suppressants for prophylaxis against clinically important gastrointestinal bleeding in critically ill patients. Clinically important bleeding is overt and has important consequences: about half of affected patients receive endoscopy or surgery, and approximately half of patients receive a transfusion of at least two units of packed red blood cells.[1]

This *BMJ* Rapid Recommendation was triggered by SUP-ICU, a randomised controlled trial published in October 2018.[1] It found no significant net benefit, and raised questions about the widespread use of gastrointestinal bleeding prophylaxis.

We aimed to translate this new evidence for clinicians and patients using the GRADE approach and standards for trustworthy guidelines.[2 3] The guideline committee asked two key questions:

1 In which patients, if any, should gastrointestinal bleeding prophylaxis be used?
2 If gastrointestinal bleeding prophylaxis is used, what agent is best?

The box shows all publications linked in this rapid recommendation package. The main infographic provides an overview of the absolute benefits and harms for four interventions: proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), sucralfate, and no prophylaxis.

Current practice

Existing recommendations vary in the indications for gastrointestinal bleeding prophylaxis (see table 1). There are no recommendations for critically ill patients as a broad target group, and guidelines that apply to specific subgroups of patients (such as those with trauma or sepsis) do not consider differences in importance of individual risk factors. They also do not present the benefits and harms in a way that is usable for individualised decision making. Inappropriate overuse of gastrointestinal bleeding prophylaxis is not only a serious problem in critical care but also general inpatient and outpatient settings.[4 5]

Table 1 | Current recommendations for stress ulcer prophylaxis

Guideline	Agents to be used	Indications for prophylaxis
SCCM and ESICM "Surviving sepsis," 2016[15]	PPIs or H2RAs (weak recommendation)	Patients with sepsis or septic shock with risk factors for gastrointestinal bleeding, which include mechanical ventilation for >48 hours, coagulopathy, pre-existing liver disease, need for RRT, and higher organ failure scores
DASAIM and DSIT, 2014[16]	PPIs rather than H2RAs (weak recommendation)	Insufficient evidence to make any recommendation
Eastern Association for the Surgery of Trauma, 2008[17]	PPIs or H2RAs or cytoprotective agents	Mechanical ventilation; coagulopathy; traumatic brain injury; major burn; ICU patients with multi-trauma, sepsis, or acute renal failure; ICU patients with ISS>15 or receiving high dose corticosteroids

SCCM=Society of Critical Care Medicine; ESICM=European Society of Intensive Care Medicine; DASAIM=Danish Society of Anesthesiology and Intensive Care Medicine; DSIT=Danish Society of Intensive Care Medicine; PPIs=proton pump inhibitors; H2RAs=histamine-2 receptor antagonists; RRT=renal replacement therapy ICU=intensive care unit; ISS=Injury Severity Score.

Linked resources in this *BMJ* Rapid Recommendations cluster

- Ye Z, Reintam Blaser A, Lytvyn L, et al. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. *BMJ* 2019;367:l6722
  - Summary of the results from the Rapid Recommendation process
- Wang Y, Ye Z, Ge L, et al. Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: systematic review and network meta-analysis. *BMJ* 2019;367:l6744
  - Review and network meta-analysis of all available randomized trials that assessed prevention of gastrointestinal bleeding in critically ill patients
- MAGICapp (https://app.magicapp.org/public/guideline/j96g2L)
  - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

PPIs are the most commonly used agents, followed by H2RAs; sucralfate and antacids are seldom used.[6 7] Most guidelines recommend using either a PPI or H2RA, but there is some variation in the preferred agent.[8]

The evidence

The SUP-ICU trial was incorporated into a linked systematic review and network meta-analysis comparing PPIs, H2RAs, and sucralfate versus one another or placebo (no prophylaxis). The review included 72 randomised controlled trials and 12 660 patients admitted to intensive care units comparing PPIs, H2RAs, sucralfate versus one another or no prophylaxis. Figure 2 provides an overview of the trials and participants.

How we stratified the risk of bleeding

Prophylaxis cannot reduce the risk of bleeding to zero, but the higher the risk of bleeding, the larger is the expected benefit of prophylaxis. Therefore, we first searched for evidence on risk factors for bleeding; we used evidence from a systematic review of risk factors.[9] Based on studies that we considered low risk of bias, we grouped patients into four categories: low risk, moderate risk, high risk, and highest risk (see table 2 and appendix 1 on bmj.com for details). We had varying degrees of certainty in different risk factors. In particular, the available evidence may underestimate the risk of bleeding for several possible risk factors in the low and moderate risk categories (that is, acute hepatic failure and use of anticoagulation might increase the risk of bleeding more than we estimated).

Gastrointestinal bleeding

Clinically important gastrointestinal bleeding is typically defined as evidence of upper gastrointestinal bleeding with any of the following: significant haemodynamic changes not explained by other causes, need for transfusion of more than two units of blood, significant decrease in haemoglobin level, evidence of bleeding on upper gastrointestinal endoscopy, or need for surgery to control bleeding. Both PPIs and H2RAs reduce the risk of clinically important bleeding compared with no

DATA SOURCES

Use this information to gauge how similar your patients' conditions are to those of people studied in the trials

TOTAL TRIALS 72

TOTAL PATIENTS 12 660

TRIAL CHARACTERISTICS

Geographic regions

North America: 28 trials, 4928 patients	Europe: 20 trials, 5104 patients	Asia: 19 trials, 2099 patients
Oceania: 3 trials, 330 patients	South America: 1 trial, 108 patients	North America, Asia and Oceania: 1 trial, 91 patients

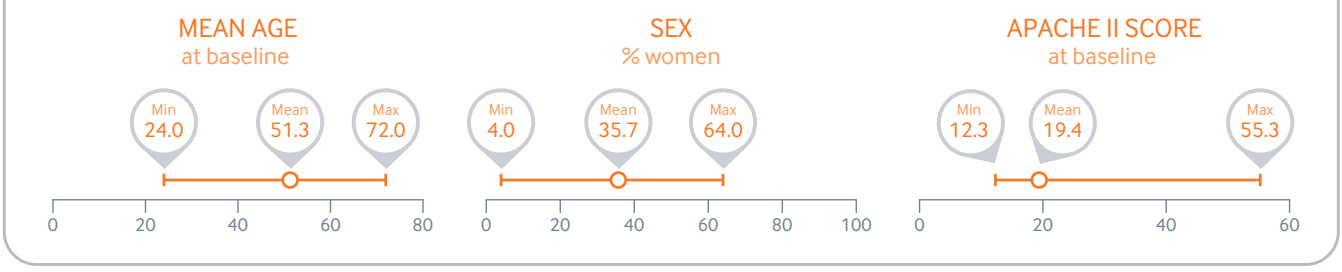
Comparisons

Proton Pump Inhibitors	Histamine-2 Receptor Antagonists	Sucralfate	Placebo (no prophylaxis)	Trials	Patients
vs				7	4222
	vs			24	1893
		vs		2	424
vs				15	1940
vs	vs			1	148
	vs	vs		14	2782
vs	vs	vs		2	206
	vs	vs	vs	4	500
vs	vs	vs		2	258
vs	vs	vs	vs	1	287

Outcomes

Mortality: 51 trials, 10 277 patients	Pneumonia: 40 trials, 9288 patients	*Clostridium difficile* infection: 5 trials, 3849 patients	Length of stay in intensive care: 17 trials, 3533 patients
Clinically important gastrointestinal bleeding: 43 trials, 10 096 patients	Overt gastrointestinal bleeding: 65 trials, 11 662 patients	Length of hospital stay: 7 trials, 831 patients	Duration of mechanical ventilation: 23 trials, 3625 patients

PATIENT CHARACTERISTICS



FUNDING: 15 trials industry funded; 16 trials were publicly/hospital/university funded

PREREGISTRATION: 10 trials were publicly preregistered

PATIENT PARTNERSHIP: No trials reported patient involvement

Fig 2| Characteristics of patients and trials included in systematic review of gastrointestinal bleeding prophylaxis in critically ill adults

Table 2 | Baseline risk of clinically important gastrointestinal bleeding for each risk factors

Risk factors	Risk of clinically important gastrointestinal bleeding (per 1000)		Risk of overt gastrointestinal bleeding (per 1000)	
	Baseline risk	Representative risk chosen for evidence profile	Baseline risk	Representative risk chosen for evidence profile
Low risk group*				
Critically ill without any risk factor Acute hepatic failure Use of corticosteroids or immunosuppression Use of anticoagulants† Cancer Male gender	10-20	12	20-60	26
Moderate risk group				
Mechanical ventilation with enteral nutrition Shock‡ Sepsis Acute kidney injury	21-40	30	61-90	75
High risk group				
Coagulopathy§ Two or more of factors in moderate risk group	41-80	60	91-160	125
Highest risk group				
Mechanical ventilation without enteral nutrition Chronic liver disease¶	81-100	90	161-220	190

*Including proposed risk factors without evidence that they substantially increase risk of gastrointestinal bleeding.
†Vitamin K antagonists, direct acting oral anticoagulants, therapeutic doses of unfractionated or low molecular weight heparin, intravenous direct thrombin (II) inhibitors, adenosine diphosphate receptor inhibitor and similar drugs.
‡Continuous infusion with vasopressors or inotropes, systolic blood pressure <90 mm Hg, mean arterial blood pressure <70 mm Hg, plasma lactate level ≥4 mmol/l.
§Platelets $<50\times10^9$/L, international normalised ratio >1.5, or prothrombin time >20 seconds.
¶Portal hypertension, cirrhosis proved by biopsy, computed tomography, ultrasound scan, or medical history of variceal bleeding or hepatic encephalopathy.

prophylaxis, but the magnitude of benefit depends on the baseline risk of bleeding without prophylaxis. In patients at highest risk (>8%), PPIs and H2RAs reduce clinically important bleeding by 3-5%. In critically ill patients at low risk (<2%), PPIs and H2RAs reduce clinically important bleeding by less than 1%.

Overt bleeding (that is visible as haematemesis, haematochezia, or melaena) does not always have important consequences: overt bleeding, which includes important and unimportant bleeding, is more common than clinically important bleeding. The absolute reduction of overt bleeding achieved with prophylaxis is approximately twice that of clinically important bleeding (see full evidence profile in MAGICapp).

In the linked meta-analysis, results from head-to-head clinical trials suggest that PPIs possibly reduce the risk of clinically important bleeding more than H2RAs, but the confidence interval includes no difference (odds ratio 0.58 (95% confidence interval 0.29 to 1.17)). PPIs do reduce the risk of overt bleeding more than H2RAs.

Sucralfate does not seem to reduce the risk of clinically important bleeding compared with placebo (odds ratio 0.76 (0.36 to 1.62)).

Pneumonia

Both PPIs and H2RAs might increase the absolute risk of pneumonia compared with no prophylaxis by approximately 4%, but certainty is low. The credible intervals include no difference, and the most recent and the largest blinded randomised controlled trial suggested that there may not be a difference in risk of pneumonia between the PPI and placebo groups.[1]

Other outcomes

Gastric acid suppression did not seem to affect any other important outcomes, including mortality, length of hospital stay, length of intensive care stay, duration of mechanical ventilation, or *C difficile* infection. Quality of evidence varied across these outcomes; for *C difficile* infection, quality was low.

Understanding the recommendations

Strong recommendations suggest that all or nearly all patients would choose the recommended option. Weak recommendations reflect the uncertainty in the typical patients' preferences, as well as the likely wide variability in preferences between patients.

Who does it apply to?

This guideline applies to critically ill patients. Patients who have a substantial short term risk of dying due to an acute illness are considered critically ill and are commonly treated in an intensive care unit. Accordingly, studies performed in patients admitted to intensive care were considered in the linked systematic review. However, admission practices of intensive care units are variable, and defining critical illness is difficult, so clinical judgment regarding whether this guideline applies to a specific patient may be warranted.

Our recommendations do not apply to patients who have other indications for gastric acid suppression (such as peptic ulcer disease, gastroesophageal reflux disease, Zollinger-Ellison syndrome, or eradication of *Helicobacter pylori*). Patients already taking gastric acid suppressants should probably continue to receive them during an acute illness because abrupt withdrawal may cause rebound acid hypersecretion.[10] However, prolonged use of acid suppressants without clear indication is not advocated.

Values and preferences

We did not find any published evidence addressing patient values and preferences (appendix 2 on bmj.com). Overall,

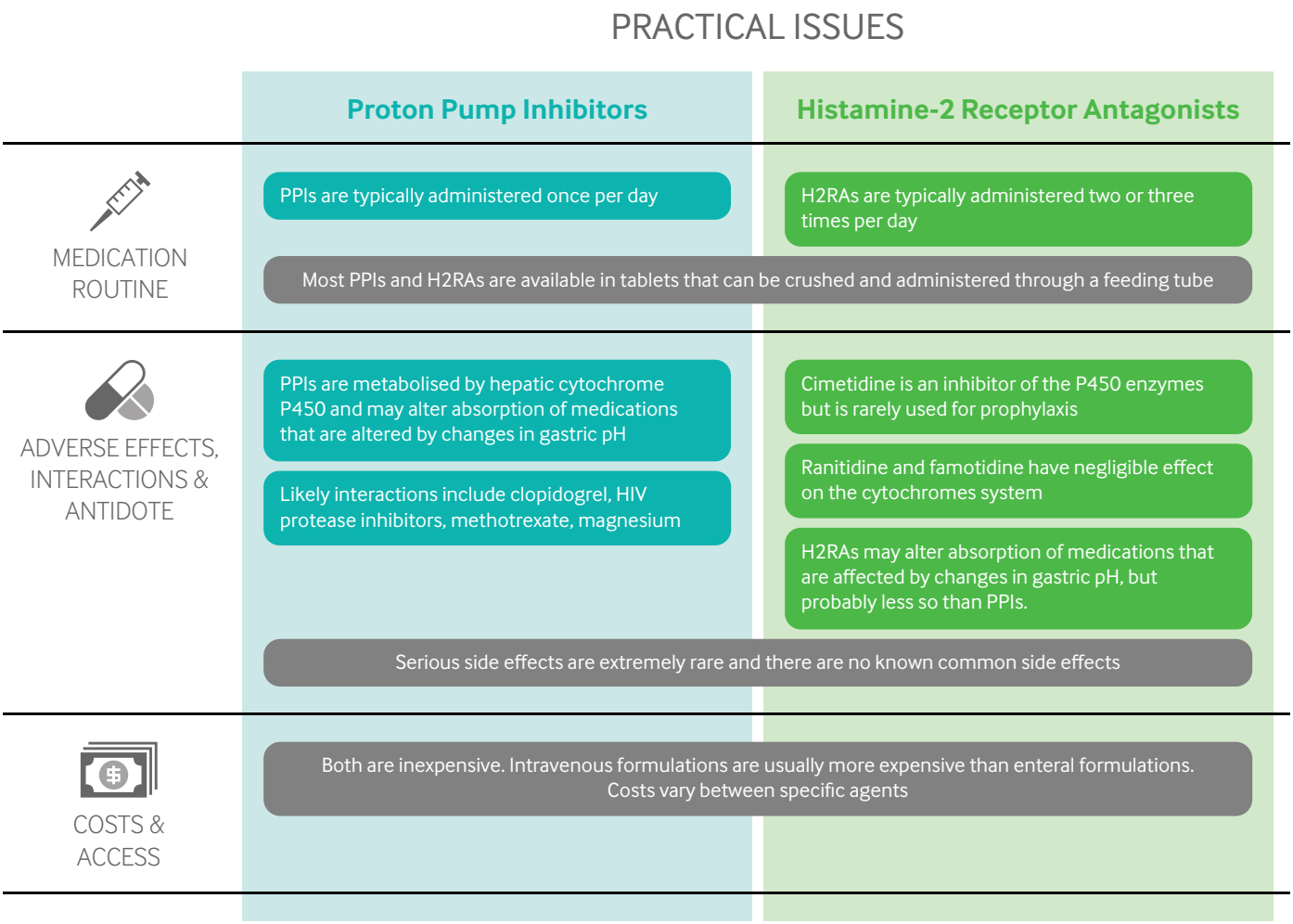


Fig 3| Practical issues about gastrointestinal bleeding prophylaxis for critically ill patients

most of our panellists thought that most patients would consider the benefits, harms, and burdens to be minimal. The panel agreed that there is probably great variability among patients in how much they value bleeding and a possible increased risk of pneumonia. Given the burdens and harms, including a possible increased risk of pneumonia, the panel believed that most patients would require a reduction in clinically important bleeding by at least about 20 per 1000 patients in order to choose acid suppression; the panel was, however, very uncertain about this threshold. The importance of overt bleeding not advancing to clinically important bleeding is questionable and may be altogether unimportant.

Shared decision making

Shared decision making should be pursued whenever possible. This will be challenging with critically ill patients because they are typically not able to have complex discussions about their care. Moreover, the effects of gastric acid suppression are modest, and there are many other more important decisions that often need to be made when caring for critically ill patients (such as probability of survival and/or regaining reasonable quality of life with or without different possible interventions).

Practical considerations

Figure 3 outlines the key practical issues regarding the use of acid suppressants for preventing gastrointestinal bleeding in critically ill patients. For both PPIs and H2RAs, the best specific agent is uncertain and was not addressed by our guideline panel. Pantoprazole, omeprazole, lansoprazole, esomeprazole, and rabeprazole were the most commonly used PPIs in the RCTs and are reasonable choices. Ranitidine and famotidine were the commonly used H2RAs in the RCTs and are reasonable choices.

Dosing and duration

Dose and duration varied between the included studies and were not specifically addressed in this guideline. Typically, PPIs were prescribed once per day and H2RAs two or three times per day. Both can be administered intravenously or enterally, and there is no evidence to suggest that the route of administration alters effectiveness. Unless there is another indication for gastric acid suppression, clinicians should take care to ensure that acid suppression medications are stopped when the patient is no longer critically ill or the risk factor triggering prophylaxis is no longer present. Long term use of gastric acid suppressants confers additional risks, costs, and burdens.[11 12]

Table 3 | New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article.				

Cost and resources

We did not explicitly consider cost effectiveness of gastric acid suppression. PPIs and H2RAs are generally inexpensive compared with the overall expense of intensive care and are widely available.

Future research

Future research should prioritise several areas:

- Randomised controlled trials to clarify
  - Whether gastric acid suppressants increase the risk of pneumonia
  - Whether gastric acid suppression is less effective in patients receiving enteral nutrition (subgroup analyses)
  - Possible impact on outcomes such as *C difficile* infection
  - Head to head comparison of PPIs and H2RAs.
- Observational studies of risk factors for gastrointestinal bleeding; development of a risk prediction model or score.
- Evidence about patient values and preferences on the importance of bleeding versus possible adverse effects.

HOW THIS RECOMMENDATION WAS CREATED

Our international panel included methodologists, intensivists, pharmacists, a gastroenterologist, a nurse, patient partners who have been hospitalised in intensive care, and a caregiver for a patient who had been hospitalised in intensive care and mechanically ventilated (see appendix 3 on bmj.com for details of panel members). The panel decided the scope of the recommendation and rated the outcome importance to patients.

The panel judged the following as patient-important outcomes for decision making: clinically important bleeding, pneumonia, *Clostridium difficile* infection, mortality, length of hospital stay, length of stay in intensive care, and duration of mechanical ventilation.

The panel met online to discuss the evidence and to formulate recommendations. No panel member had relevant financial conflicts of interest; intellectual and professional conflicts were minimised and transparently described (see appendix 4 on bmj.com).

The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation,[2] including using the GRADE approach to critically appraise the evidence and create recommendations (appendix 5 on bmj.com).[3] The panel considered the benefits, harms and burdens of gastrointestinal bleeding prophylaxis, the certainty (quality) of the evidence for each outcome, variations in patient values and preferences, acceptability, and feasibility.[13] Following the GRADE approach, recommendations can be either strong or weak for or against a specific course of action.[14] The recommendations take a patient-centred perspective. Healthcare systems can adapt these recommendations by including costs and other key issues of relevance, contextualised to national and local circumstances.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The Rapid Recommendation panel included three patients who have experienced intensive care and a family caregiver of a patient.

Updates to this article

Table 3 shows evidence that has emerged since the publication of this article. As new evidence is published, the BMJ Rapid Recommendations collaboration will assess the new evidence and if the new evidence might change the recommendation, we will update the meta-analysis and recommendations (see appendix 5 on bmj.com).

Contributors: All panel members participated in the teleconferences or email discussions and met all authorship criteria. We thank Dr Tessa Richards for providing input as a patient into discussions on selecting and rating patient-important outcomes and subgroups, and values and preferences related to outcomes, during one of the guideline panel meetings.

Funding: This guideline was funded by the Digestive Medical Coordinated Development Center of Beijing Hospitals Authority. The funding did not play any role in the guideline development.

Competing interests: All authors have completed the BMJ Rapid Recommendations interests disclosure form, and a detailed description of all disclosures is reported in appendix 4 on bmj.com. As with all *BMJ* Rapid Recommendations, the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions.

Transparency: ZY affirms that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

Provenance and peer review: Commissioned; externally peer reviewed

1 Krag M, Marker S, Perner A, et al. SUP-ICU trial group. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med* 2018;379:2199-208. 10.1056/NEJMoa1714919. pmid:30354950.
2 Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191. 10.1136/bmj.i5191. pmid:27680768.
3 Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. 10.1136/bmj.39489.470347.AD. pmid:18436948.
4 Farrell CP, Mercogliano G, Kuntz CL. Overuse of stress ulcer prophylaxis in the critical care setting and beyond. *J Crit Care* 2010;25:214-20. 10.1016/j.jcrc.2009.05.014. pmid:19683892.
5 Bez C, Perrottet N, Zingg T, Leung Ki EL, Demartines N, Pannatier A. Stress ulcer prophylaxis in non-critically ill patients: a prospective evaluation of current practice in a general surgery department. *J Eval Clin Pract* 2013;19:374-8. 10.1111/j.1365-2753.2012.01838.x. pmid:22420909.
6 Barletta JF, Kanji S, MacLaren R, Lat I, Erstad BL. American-Canadian consortium for Intensive care Drug utilization (ACID) Investigators. Pharmacoepidemiology of stress ulcer prophylaxis in the United States and Canada. *J Crit Care* 2014;29:955-60. 10.1016/j.jcrc.2014.06.025. pmid:25081626.
7 Krag M, Perner A, Wetterslev J, et al. SUP-ICU Collaborators. Stress ulcer prophylaxis in the intensive care unit: an international survey of 97 units in 11 countries. *Acta Anaesthesiol Scand* 2015;59:576-85. 10.1111/aas.12508. pmid:25880349.
8 Ye ZK, Liu Y, Cui XL, Liu LH. Critical appraisal of the quality of clinical practice guidelines for stress ulcer prophylaxis. *PLoS One* 2016;11:e0155020. 10.1371/journal.pone.0155020. pmid:27152836.
9 Granholm A, Zeng L, Dionne JC, et al. GUIDE Group. Predictors of gastrointestinal bleeding in adult ICU patients: a systematic review and meta-analysis. *Intensive Care Med* 2019;45:1347-59. 10.1007/s00134-019-05751-6. pmid:31489445.
10 Reimer C, Søndergaard B, Hilsted L, Bytzer P. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. *Gastroenterology* 2009;137:80-7, 87.e1. 10.1053/j.gastro.2009.03.058. pmid:19362552.
11 Tariq R, Singh S, Gupta A, Pardi DS, Khanna S. Association of gastric acid suppression with recurrent Clostridium difficile infection: a systematic review and meta-analysis. *JAMA Intern Med* 2017;177:784-91. 10.1001/jamainternmed.2017.0212. pmid:28346595.

12 Shin S. Evaluation of costs accrued through inadvertent continuation of hospital-initiated proton pump inhibitor therapy for stress ulcer prophylaxis beyond hospital discharge: a retrospective chart review. *Ther Clin Risk Manag* 2015;11:649-57. 10.2147/TCRM.S81759. pmid:26005351.
13 Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;66:726-35. 10.1016/j.jclinepi.2013.02.003. pmid:23570745.
14 Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. Going from evidence to recommendations. *BMJ* 2008;336:1049-51. 10.1136/bmj.39493.646875.AE. pmid:18467413.
15 Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017;43:304-77. 10.1007/s00134-017-4683-6. pmid:28101605.
16 Madsen KR, Lorentzen K, Clausen N, et al. Danish Society of Intensive Care Medicine Danish Society of Anesthesiology and Intensive Care Medicine. Guideline for stress ulcer prophylaxis in the intensive care unit. *Dan Med J* 2014;61:C4811.pmid:24814922.
17 Guillamondegui OD, Gunter OL Jr, Bonadies JA, et al. Practice management guidelines for sress ulcer prophylaxis. https://www.east.org/education/practice-management-guidelines/stress-ulcer-prophylaxis 2008.

[1]Department of Pharmacy, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China
[2]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
[3]Department of Intensive Care Medicine, Lucerne Cantonal Hospital, Lucerne, Switzerland
[4]Department of Anaesthesiology and Intensive Care, University of Tartu, Tartu, Estonia
[5]Department of Medicine, McMaster University, Hamilton, Canada
[6]Spinal Muscular Atrophy Foundation, United States
[7]Duke University, United States
[8]Division of General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland
[9]Hospital of Lucerne, Switzerland
[10]Adult intensive care unit, Department of Acute Medicine, University Hospitals of Geneva, Geneva, Switzerland
[11]Critical Care, Poole Hospital NHS FT, United Kingdom
[12]Medical intensive care unit, Peking Union Medical College Hospital, Beijing, China
[13]Department of Medicine, Innlandet Hospital Trust, Gjøvik, Norway
[14]Peking KF Tech.co, Beijing, China
[15]Gastroenterology and Endoscopy Unit, Hospital Alemán, Buenos Aires, Argentina
[16]Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway
[17]Discipline of Anaesthesia and Critical Care, School of Clinical Medicine, University of KwaZulu-Natal, Durban, South Africa
[18]Adult Intensive Care, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, United Kingdom
[19]Surgical Intensive Care Unit, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Appendices

Appendix 1: Estimation of baseline risk of clinically important gastrointestinal bleeding for patients with different risk factors

Appendix 2: A systematic review of literature of critically ill patients' values and preferences on gastrointestinal bleeding

Appendix 3: Details of members of the Rapid Recommendation panel

Appendix 4: Details of panel members' declarations of interests

Appendix 5: Methodology for development of BMJ Rapid Recommendations