RAPID RECOMMENDATIONS

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

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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.
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**Visual summary of recommendation**

**Population**

- Critically ill patients

**Including:**
- Patients admitted to intensive care units

**Does not apply to:**
- Patients receiving gastric acid suppression for another therapeutic indication
- Patients admitted to intensive care units

**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**

- Strong
- Weak

**Prophylaxis**

- Weak
- Strong

- 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

- **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

**SUGGESTED CUT POINT FOR OFFERING PROPHYLAXIS**

For patients near this threshold, individual values and preferences become more important.
### Proton pump inhibitors

- **Evidence profile**
  - **No prophylaxis**
  - **No important difference**
  - **Proton pump inhibitor**

#### Important bleeding (1-2% risk)
- **Events per 1000 people:**
  - 12
- **Evidence quality:**
  - Moderate

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.

#### Important bleeding (2-4% risk)
- **Events per 1000 people:**
  - 30
- **Evidence quality:**
  - Low

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

#### Important bleeding (4-8% risk)
- **Events per 1000 people:**
  - 60
- **Evidence quality:**
  - Moderate

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.

#### Important bleeding (8-10% risk)
- **Events per 1000 people:**
  - 90
- **Evidence quality:**
  - Moderate

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

#### Mortality
- **Events per 1000 people:**
  - 304
  - 317
- **Evidence quality:**
  - Moderate

Proton pump inhibitors probably do not have an important effect on mortality.
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### Pneumonia

Proton pump inhibitors *may* increase the risk of pneumonia.

**Evidence quality**
- **Mean days**: 7.7 (No important difference)
- **Evidence quality**: Moderate

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

### Clostridium difficile infection

Proton pump inhibitors *probably* do not have an important effect on Clostridium difficile infection.

**Evidence quality**
- **Mean days**: 7.4 (No important difference)
- **Evidence quality**: Moderate

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

### Evidence profile Histamine-2 receptor antagonist

**No prophylaxis** vs **Histamine-2 receptor antagonist**

**Important bleeding (1-2% risk)**
- No prophylaxis: 12 events per 1000 people
- Histamine-2 receptor antagonist: 6 events per 1000 people
- **Evidence quality**: Moderate
- **Risk of Bias**: No serious concerns
- **Imprecision**: No serious concerns
- **Indirectness**: No serious concerns
- **Inconsistency**: No serious concerns
- **Publication bias**: No serious concerns

**Important bleeding (2-4% risk)**
- No prophylaxis: 30 events per 1000 people
- Histamine-2 receptor antagonist: 14 events per 1000 people
- **Evidence quality**: Low
- **Risk of Bias**: No serious concerns
- **Imprecision**: Serious
- **Indirectness**: No serious concerns
- **Inconsistency**: No serious concerns
- **Publication bias**: No serious concerns

Histamine-2 receptor antagonists 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. 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.
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| Important bleeding (4-8% risk) | 60 | 31 fewer | 29 | **Moderate** | More |
|--------------------------------|----|----------|----|--------------|------|
| Histamine-2 receptor antagonists 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 | 46 fewer | 44 | **Moderate** | More |
|--------------------------------|----|----------|----|--------------|------|
| Histamine-2 receptor antagonists reduce the risk of gastrointestinal bleeding. For people with an 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 | 295 | **Moderate** | More |
|-----------|-----|-------------------------|-----|--------------|------|
| Histamine-2 receptor antagonists **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 |  |

| Pneumonia | 162 | 34 fewer | 196 | **Low** | More |
|-----------|-----|----------|-----|----------|------|
| Histamine-2 receptor antagonists **may** increase the 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 | 15 | No important difference | 15 | **Very low** | More |
|--------------------------------|----|-------------------------|----|--------------|------|
| Whether Histamine-2 receptor antagonists **increase** the risk of *Clostridium difficile* infection or not is **very uncertain**. | Very low GRADE score, because of: |
|  | Risk of Bias | Serious |  |
|  | Imprecision | Very serious |  |
|  | Indirectness | No serious concerns |  |
|  | Inconsistency | No serious concerns |  |
|  | Publication bias | No serious concerns |  |

| Mean days | Evidence quality |
|-----------|------------------|
| Length of stay in intensive care | 7.7 | **No important difference** | 7.3 | **Moderate** | More |
| Histamine-2 receptor antagonists **probably** do not have an important effect 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 |  |
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**Individual considerations**

**Key practical issues**

| No prophylaxis | Proton pump inhibitors | Histamine-2 receptor antagonists |
|----------------|-------------------------|---------------------------------|
| None           | Can be administered intravenously or enterally | Typically administered one or 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.

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**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.

**Strong recommendation**

All or nearly all informed people would likely want this intervention. Benefits outweigh harms for almost everyone

**Weak recommendation**

Most people would likely want this intervention. Benefits outweigh harms for the majority, but not for everyone.

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**Legend**

- **PPI**: Proton pump inhibitor
- **H2RA**: Histamine-2 receptor antagonist
- **SAF**: Sucralfate
- **S**: Strong recommendation
- **W**: Weak recommendation
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| Evidence profile | Proton pump inhibitor versus histamine-2 receptor antagonist |
|------------------|-------------------------------------------------------------|
| **Proton pump inhibitor** | **No important difference** | **Histamine-2 receptor antagonist** |
| **Events per 1000 people** | **No important difference** | **Evidence quality** |
| Important bleeding (1-2% risk) | 7 | 12 | **Low** |
| **Risk of Bias** | No serious concerns | **Uncertainty in baseline risk for some risk factors** |
| **Imprecision** | Serious | |
| **Indirectness** | No serious concerns | |
| **Inconsistency** | No serious concerns | |
| **Publication bias** | No serious concerns | |
| **Important bleeding (1-2% risk)** | **No important difference** | **Evidence quality** |
| 7 | 12 | **Low** |
| **Risk of Bias** | No serious concerns | **Uncertainty in baseline risk for some risk factors** |
| **Imprecision** | Serious | |
| **Indirectness** | No serious concerns | |
| **Inconsistency** | No serious concerns | |
| **Publication bias** | No serious concerns | |
| **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** |
| **Risk of Bias** | No serious concerns | **Uncertainty in baseline risk for some risk factors** |
| **Imprecision** | Serious | |
| **Indirectness** | No serious concerns | |
| **Inconsistency** | No serious concerns | |
| **Publication bias** | No serious concerns | |
| **Important bleeding (2-4% risk)** | 19 | 32 | **Low** |
| **Risk of Bias** | No serious concerns | **Uncertainty in baseline risk for some risk factors** |
| **Imprecision** | Serious | |
| **Indirectness** | No serious concerns | |
| **Inconsistency** | No serious concerns | |
| **Publication bias** | No serious concerns | |
| **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** |
| **Risk of Bias** | No serious concerns | **Uncertainty in baseline risk for some risk factors** |
| **Imprecision** | Serious | |
| **Indirectness** | No serious concerns | |
| **Inconsistency** | No serious concerns | |
| **Publication bias** | No serious concerns | |
| **Important bleeding (4-8% risk)** | 37 | 62 | **Moderate** |
| **Risk of Bias** | No serious concerns | **Uncertainty in baseline risk for some risk factors** |
| **Imprecision** | Serious | |
| **Indirectness** | No serious concerns | |
| **Inconsistency** | No serious concerns | |
| **Publication bias** | No serious concerns | |
| **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** |
| **Risk of Bias** | No serious concerns | **Uncertainty in baseline risk for some risk factors** |
| **Imprecision** | Serious | |
| **Indirectness** | No serious concerns | |
| **Inconsistency** | No serious concerns | |
| **Publication bias** | No serious concerns | |
| **Important bleeding (8-10% risk)** | 57 | 94 | **Moderate** |
| **Risk of Bias** | No serious concerns | **Uncertainty in baseline risk for some risk factors** |
| **Imprecision** | Serious | |
| **Indirectness** | No serious concerns | |
| **Inconsistency** | No serious concerns | |
| **Publication bias** | No serious concerns | |
| **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** |
| **Mortality** | 317 | 295 | **Very low** |
| **Risk of Bias** | No serious concerns | **Uncertainty in baseline risk for some risk factors** |
| **Imprecision** | Extremely serious | |
| **Indirectness** | No serious concerns | |
| **Inconsistency** | No serious concerns | |
| **Publication bias** | No serious concerns | |
| **Whether there is an important difference between proton pump inhibitors and histamine-2 receptor antagonists on the risk of death or not is very uncertain** |
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| Risk Factor                          | Evidence Quality | GRADE Score | Risk of Bias | Imprecision | Indirectness | Inconsistency | Publication bias | Recommendation |
|--------------------------------------|------------------|-------------|--------------|-------------|--------------|---------------|-----------------|----------------|
| Pneumonia                            | *No important difference* | Low         | Serious      | Serious     | No serious concerns | No serious concerns | No serious concerns | There may be no important difference between proton pump inhibitors and histamine-2 receptor antagonists on risk of pneumonia |
| Clostridium difficile infection       | *No important difference* | Low         | Serious      | Serious     | No serious concerns | No serious concerns | No serious concerns | There may be no important difference between proton pump inhibitors and histamine-2 receptor antagonists on risk of Clostridium difficile infection |
| Length of stay in intensive care     | Mean days        | High        | No serious concerns | No serious concerns | No serious concerns | No serious concerns | No serious concerns | There is no important difference between proton pump inhibitors and histamine-2 receptor antagonists on length of stay in intensive care |
| Proton pump inhibitor versus sucralfate | Evidence profile | Proton pump inhibitor | *No important difference* | Sucralfe     | 16 fewer   | 61  Very low | No serious concerns | Very low GRADE score, because of: Uncertainty in baseline risk for some risk factors |
| Important bleeding (1-2% risk)       | Events per 1000 people | Very low     | No serious concerns | Very serious | No serious concerns | No serious concerns | No serious concerns | 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 |
| Important bleeding (2-4% risk)       | 19  42 fewer   | Very low     | No serious concerns | Very serious | No serious concerns | No serious concerns | No serious concerns | 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 |
For people with 4 to 8% risk of clinically important gastrointestinal bleeding, proton pump inhibitors may reduce the risk compared with sucralfate.

For people with 8 to 10% risk of clinically important gastrointestinal bleeding, proton pump inhibitors may reduce the risk compared with sucralfate.

Whether there is an important difference between proton pump inhibitors and sucralfate on the risk of death or not is very uncertain.

Proton pump inhibitors may increase the risk of pneumonia compared with sucralfate.

There is probably no important difference between proton pump inhibitors and sucralfate on length of stay in intensive care.
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**Evidence profile**  
Histamine-2 receptor antagonist versus sucralfate

| Important bleeding (1-2% risk) | 6 | 13 | No important difference | 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 |

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.

| Important bleeding (2-4% risk) | 14 | 16 fewer | 30 | 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 |

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

| Important bleeding (4-8% risk) | 29 | 32 fewer | 61 | 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 |

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

| Important bleeding (8-10% risk) | 44 | 47 fewer | 91 | 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 |

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

| Mortality                       | 295 | 280 | No important difference | 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 |

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

**Evidence quality**

- Important bleeding (1-2% risk): No important difference, Low GRADE score
- Important bleeding (2-4% risk): 16 fewer, Low GRADE score
- Important bleeding (4-8% risk): 32 fewer, Moderate GRADE score
- Important bleeding (8-10% risk): 47 fewer, Moderate GRADE score
- Mortality: 295, No important difference, Moderate GRADE score
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Histamine-2 receptor antagonists may increase the risk of pneumonia compared with sucralfate.

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

Individual considerations

Key practical issues

Proton pump inhibitors
- Can be administered intravenously or enterally
- Typically administered once per day

Histamine-2 receptor antagonists
- Typically administered two or three times per day

Sucralfate
- Must be given enterally
- 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

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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 6 7 | 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 score |
| DASAIM and DSIT, 2014 8 9 | PPIs rather than H2RAs (weak recommendation) | Insufficient evidence to make any recommendation |
| Eastern Association for the Surgery of Trauma, 2008 10 | 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 |

PPIs are the most commonly used agents, followed by H2RAs; sucralfate and antacids are seldom used.4 5 Most guidelines recommend using either a PPI or H2RA, but there is some variation in the preferred agent.6

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.3 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

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/J6g2L)
- Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

1 DASAIM and DSIT, 2016
2 SCCM = Society of Critical Care Medicine; ESICM = European Society of Intensive Care Medicine; DASAIM = Danish Society of Anaesthesiology 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.
Rapid Recommendations

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 studies (4,928 patients)
- Europe: 20 studies (3,104 patients)
- Asia: 19 studies (2,099 patients)
- Oceania: 3 studies (330 patients)
- South America: 1 study (108 patients)
- North America, Asia, and Oceania: 1 study (108 patients)

Comparisons

- Proton Pump Inhibitors
- Histamine-2 Receptor Antagonists
- Sucralfate
- Placebo (no prophylaxis)

Outcomes

- Mortality: 51 studies (10,277 patients)
- Pneumonia: 40 studies (9,288 patients)
- Clostridium difficile infection: 5 studies (3,849 patients)
- Length of stay in intensive care: 17 studies (3,933 patients)
- Clinically important gastrointestinal bleeding: 43 studies (10,096 patients)
- Overt gastrointestinal bleeding: 65 studies (11,662 patients)
- Length of hospital stay: 7 studies (831 patients)
- Duration of mechanical ventilation: 23 studies (3,625 patients)

Patient Characteristics

- Mean age at baseline: Min 24.0, Max 72.0, Mean 51.3
- Sex: % women Min 4.0, Max 45.6, Mean 35.7
- APACHE II score at baseline: Min 12.3, Max 55.3

Funding
- 15 trials industry funded
- 16 trials were publicly/hospital/university funded

Pre-registration
- 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
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 *Clostridium 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. 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,
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 no longer present. Long term use of gastric acid suppressants confers additional risks, costs, and burdens.
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 *Clostridium 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 3 on bmj.com).

The panel followed the BMJ Rapid Recommendations procedures for creating a trustworthy recommendation, including using the GRADE approach to critically appraise the evidence and create recommendations (appendix 5 on bmj.com). 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. Following the GRADE approach, recommendations can be either strong or weak for or against a specific course of action. 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.

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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

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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