PRACTICE MANAGEMENT GUIDELINES FOR STRESS ULCER PROPHYLAXIS

EAST Practice Management Guidelines Committee

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Statement of the Problem

Stress ulcer prophylaxis has historically been a disease process with a high degree of prevalence in the setting of burns and trauma. Multiple protocols exist for prophylaxis of stress ulcer, but there are no universally accepted regiments. This has led to nationwide disorganization in current practice a stress ulcer prophylaxis. There also remains no universal determination of need for stress ulcer prophylaxis in the trauma population.

The development of clinically significant gastrointestinal hemorrhage has been associated with significant increase of morbidity and mortality. Increase of mortality may be increased as high as 50%.

Process

A MEDLINE search was performed from the years 1990 to present with the following subject words: Gastrointestinal prophylaxis, gastrointestinal hemorrhage, intensive care unit, stress ulcer prophylaxis, trauma, and critical care. All articles pertaining to the critically ill patient were reviewed by 8 trauma intensivists for adequacy and pertinence to the subject.

Quality of the references
The initial literature review identified 119 articles. Of these, 73 were removed secondary to inadequate or inappropriate data. A table of evidence was constructed using the 46 references that were identified. See table 1. (1-46)

The article was entered into a review data sheet that summarized the main conclusions of the study and identified any deficiencies. Reviewers classified each references Class I, Class II or Class III data.

The references were classified using methodology established by the Agency for Health Care Policy and Research (AHCPR) of the U. S. Department of Health and Human Services. Additional criteria and specifications were used for Class I articles from a tool described by Oxman et al. (47)

Articles were categorized as Class I, Class II or Class III data according to the following definitions:

**Class I:** A prospective randomized clinical trial.

**Class II:** A prospective non-comparative clinical study or a retrospective analysis based on reliable data.

**Class III:** A retrospective case series or database review.

The 46 references that met criteria were classified as follows: 27 Class I, 9 Class II, and 10 Class III.
Recommendations from the practice management guideline committee were made on the basis of studies that were included in the evidentiary table. The quality assessment instrument applied to references was that developed by the Brain Trauma Foundation and subsequently adopted by the EAST Practice Management Guidelines Committee. (48) Recommendations were categorized based on the class of data from which they were derived.

**Recommendations**

*What are the risk factors for stress ulcer development and which patients require prophylaxis?*

1. **Level 1 recommendations**
   i. Prophylaxis is recommended for all patients with:
      1. Mechanical ventilation
      2. Coagulopathy
      3. Traumatic brain injury
      4. Major burn injury

2. **Level 2 recommendations**
   i. Prophylaxis is recommended for all ICU patients with:
      1. Multi-trauma
      2. Sepsis
3. Acute renal failure

3. Level 3 recommendations
   i. Prophylaxis is recommended for all ICU patients with:
      1. ISS>15
      2. Requirement of high-dose steroids (>250 mg hydrocortisone or equivalent per day)
   ii. In selected populations, no prophylaxis is necessary

*Is there a preferred agent for stress ulcer prophylaxis? If so, which?

1. Level 1 recommendations
   i. There is no difference between H₂ antagonists, cytoprotective agents, and some proton pump inhibitors
   ii. Antacids should not be used as stress ulcer prophylaxis.

2. Level 2 recommendations
   i. Aluminum containing compounds should not be used in patients on dialysis

3. Level 3 recommendations
   i. Enteral feeding alone may be insufficient stress ulcer prophylaxis
What is the duration of prophylaxis?

1. Level 1 recommendations
   i. There were no level 1 recommendations

2. Level 2 recommendations
   i. During mechanical ventilation or intensive care unit stay

3. Level 3 recommendations
   i. Until able to tolerate enteral nutrition

Scientific Foundation

Historical

Stress ulcer prophylaxis has been an important part of the care for critical illness for over 20 years. Maynard et al. demonstrated alterations in splanchnic blood flow during acute illness. (49) The physiology of critical illness is frequently complicated with multiple systemic inflammatory abnormalities as well as alterations in hemodynamic status. Systemic hypoperfusion with associated catecholamine search, decreased cardiac output, hypovolemia, vasoconstriction, and inflammatory cytokine release is associated with splanchnic hypoperfusion. In comparison to normal patients, critically ill patients may
have disturbances in their mucous and bicarbonate protective layer, owing to alterations in mucosal microcirculation. (26)

Overall, the rate of clinically important upper gastrointestinal hemorrhage is low, and is currently rarely seen as a complication of critical illness owing to several potential factors, including strict regimens of prophylaxis. Clinical importance has classically been described as obvious physiologic decline, the requirement of operative for endoscopic intervention, and transfusion requirement. Use of protective agents has historically led to at least a 50% decrease in clinically significant hemorrhage. (50)

Risk Factors

Multiple studies have identified a myriad of risk factors for the development of stress ulceration, although this has not been studied in recent years. Based on the current literature review, the most universally accepted risk factors for stress ulceration are prolonged mechanical ventilation and coagulopathy. (4, 22, 28, 30, 38) Other identified risk factors include multiple injuries, spinal cord injury, injury severity score greater than 15, acute renal failure, and requirement of high-dose steroids. (3, 6, 16, 26, 33, 34)

Timing and duration

If stress ulcer prophylaxis is to be initiated, it should be done so at the onset of risk factors. Based on the current literature review, it is unclear when prophylaxis should be discontinued. Although it has been recommended that prophylaxis be continued for at
least 7 days, this has failed to show a difference in outcomes of mortality or GI bleeding. Most studies recommend the continuation of stress ulcer prophylaxis throughout the duration of critical illness or intensive care unit stay. (29, 38, 41) This strategy would be individualized based on patient physiology. (27, 43)

Medication Choice

There are multiple pharmacologic options for the prophylaxis of stress ulceration.

Histamine-2 receptor antagonists

As a measure efficacy, gastric pH should be greater than 4. Tolerance to these medications has been seen, requiring increased dosing based upon gastric pH measurements. (51-53) Several studies have evaluated histamine receptor antagonists in comparison to cytoprotective agents, proton pump inhibitors, placebo, and various routes and dosages of administration with mixed results.

Proton pump inhibitors

All studies have shown them to be equivocal to histamine receptor antagonists. Tolerance has not been demonstrated to these medications, however. There currently are no large studies that prove superiority of proton pump inhibitors to histamine receptor antagonists for stress ulcer prophylaxis. (2, 54) Omeprazole suspension has been shown to be effective by any enteral route, and is superior to placebo in the prevention of stress ulceration. (34, 35)
Cytoprotective agents

Sucralfate has been the best studied and the most widely used agent in this category. Its use has not been associated with an increase in stress ulceration. Sucralfate has been shown to alter intraluminal pH levels which may affect the portion of further orally administered pharmacologic agents. (24, 46) Numerous studies have shown that the impact on gastric pH is less than that associated with histamine receptor antagonists or proton pump inhibitors which may impact gastric colonization. (4, 5, 8, 9, 14, 22, 27, 38, 43) One study showed increased potential of aluminum toxicity using sucralfate in patients with renal impairment. (55)

Antacids

Use of antacids has been associated with a potential increase in the risk of hemorrhage. These agents also have been implicated in an increase in mortality, and are currently not recommended for use. (43)

Enteral feeding

Currently, there is limited data supporting the use of enteral nutrition as the sole means of stress ulcer prophylaxis. There is controversy with regard to enteral nutrition administration in the setting of hemodynamic instability requiring pressor agents. Enteral feeding also has failed to show significant increases in gastric pH. There is controversy regarding protective effects of enteral nutrition and whether it is enough to warrant discontinuation of stress ulcer prophylaxis. (8, 19, 46)
No prophylaxis

There have been some retrospective studies that have evaluated the need for prophylaxis at all. These studies have been in a mixed ICU population primarily composed of medical patients, as opposed to trauma patients alone. (12, 17, 44, 45) Adequate prospective data is lacking to warrant recommending cessation of prophylaxis.

Summary

All critically ill patients with associated risk factors should receive chemical prophylaxis for stress ulceration. All agents (with the exception of antacids) appear equally adequate for prophylaxis against stress ulceration. The agent of choice should be based upon cost-effective arrangements between vendors and individual hospitals. The duration of treatment is ill-defined, but should be maintained while risk factors are present, the patient is admitted to the intensive care unit, or for a least one week after onset of critical illness. There is currently insufficient evidence to warrant cessation of prophylaxis in the setting of enteral nutrition if other risk factors exist, or to eliminate stress ulcer prophylaxis entirely.
References


48. Eastern Association for the Surgery of Trauma, EAST Ad Hoc Committee on Practice Management Guideline Development.


<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Reference Title</th>
<th>Reference</th>
<th>Study Design</th>
<th>Class of data for article</th>
<th>What are the risk factors for stress ulcer development in critically ill patients?</th>
<th>Class of data for question</th>
<th>Is there a preferred agent for stress ulcer prophylaxis? If so, what?</th>
<th>Class of data for question</th>
<th>What is the appropriate duration for stress ulcer prophylaxis in this population?</th>
<th>Class of data for question</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Baghaie AA</td>
<td>1995</td>
<td>Comparison of the effect of intermittent and continuous infusion of ranitidine on gastric pH in critically ill patients results of a prospective randomized crossover study</td>
<td>Crit Care Med 1995 23(3):607-1</td>
<td>Prospective, crossover study on 15 patients comparing gastric pH during continuous and bolus ranitidine administration</td>
<td>2 Did not address this question</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Continuous infusion is more effective than intermittent dosing in maintaining the appropriate gastric pH necessary for SUP</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Comparator group was continuous infusion.</td>
</tr>
<tr>
<td>Baghaie AA</td>
<td>1995</td>
<td>Nursing-sensitive effects on gastric pH in critically ill patients</td>
<td>Am J Gastroenterol 1997 92(1):79-83</td>
<td>Prospective, non-randomized, single-institutional trial on 383 patients in the ICU looking at effects of omeprazole and ranitidine on gastric pH</td>
<td>2 Did not address this question</td>
<td>Yes, omeprazole</td>
<td>2 Did not address this question</td>
<td>Ranitidine maintained an appropriate pH of &gt; 4.5 and was cost-effective in comparison to ranitidine alone</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Comparator group was ranitidine alone.</td>
<td></td>
</tr>
<tr>
<td>Ben Menachem</td>
<td>1984</td>
<td>Prophylaxis for stress ulcer hemorrhage in the ICU</td>
<td>Am J Med 1984 Oct 76(4):694-75</td>
<td>Prospective, randomized double-blind study of cimetidine versus placebo.</td>
<td>2 Did not address this question</td>
<td>No difference between cimetidine, sucralfate, and placebo</td>
<td>1 Did not address this question</td>
<td>Medical patients only. Patients with GI bleed 2 pts.</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Comparator group was cimetidine versus placebo.</td>
<td></td>
</tr>
<tr>
<td>Bonten MJ</td>
<td>1994</td>
<td>Continuous enteral feeding counteracts prevention measures for gastric colonization in ICU patients</td>
<td>Crit Care Med 1995 Apr 23(4):760-5</td>
<td>Single-center RCT comparing enteral feeding vs no feeding in 42 pts. stratified by gastric pH: Outcome measures: VAP, gastric pH, gastric colonization</td>
<td>1 Mechanical ventilation</td>
<td>No difference between enteral feeding and usual care</td>
<td>2 Did not address this question</td>
<td>Did not address this question</td>
<td>VAP rates, mortality rates, colonization rates were all similar</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Comparator group was no feeding.</td>
</tr>
<tr>
<td>Botet P</td>
<td>1995</td>
<td>The role of intragastric acidity and stress ulcer prophylaxis on colonization and infection in mechanically ventilated ICU patients. A stratified randomized double-blind study of cimetidine versus placebo.</td>
<td>Dig Dis Sci. 1995 Nov;30(4):645-50</td>
<td>Single-center, RCT 34 patients with traumatic brain injury. Nonrandomized trial comparing intragastric pH and colonization</td>
<td>1 Severe TBI, mechanical ventilation, renal insufficiency, hypotension, surgery, multi-trauma</td>
<td>2 Yes, ranitidine</td>
<td>1 3 days minimum</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Yes, omeprazole</td>
<td>Comparator group was placebo.</td>
<td></td>
</tr>
<tr>
<td>Conrad SA</td>
<td>2005</td>
<td>Randomized, double-blind comparison of intravascular versus intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients.</td>
<td>Crit Care Med 2005 Apr;33(4):760-5</td>
<td>RCT, multi-institutional. 339 pts. 2005 randomized to cimetidine, Outcome of GIB and change in gastric pH.</td>
<td>1 Did not address this question</td>
<td>Yes, omeprazole</td>
<td>1 Did not address this question</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Comparator group was intravascular cimetidine.</td>
<td></td>
</tr>
<tr>
<td>Cooke O</td>
<td>1996</td>
<td>A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation.</td>
<td>Engl J Med 1996 Mar 19;338(12):793-8</td>
<td>Multicenter, RCT, 1300 pts. Comparator group was sucralfate with Ranitidine. Outcome: GIB</td>
<td>1 Did not address this question</td>
<td>Yes, ranitidine</td>
<td>1 Did not address this question</td>
<td>Ranitidine superior for prevention of GIB in surgically and ICU patients.</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Comparator group was sucralfate.</td>
<td></td>
</tr>
<tr>
<td>Cooke O</td>
<td>1999</td>
<td>Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation.</td>
<td>Crit Care Med 1999 Dec;27(12):2171-7</td>
<td>Multicenter, RCT, 1077 pts. Comparison: ranitidine IV vs sucralfate</td>
<td>1 Thrombocytopenia, ARF, MOD, NPO</td>
<td>2 Ranitidine</td>
<td>2 Ranitidine</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Comparator group was ranitidine.</td>
<td></td>
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<tr>
<td>Cooke O</td>
<td>2001</td>
<td>The attributable mortality and length of ICU stay of clinically important upper gastrointestinal bleeding in critically ill patients.</td>
<td>Crit Care Med 2001 Dec;29(12):2461-9</td>
<td>Retrospective study of 83 ICU pts. Outcome of ICU LOS and GIB</td>
<td>3 Mechanical ventilation</td>
<td>2 Did not address this question</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Did not address this question</td>
<td>Comparator group was ranitidine.</td>
<td></td>
</tr>
</tbody>
</table>

**Evidence Table EAST Stress Ulcer Prophylaxis Practice Management Guideline 2007**
61. retrospective study, single center, 2323 pts. Comparison: GIB vs no GIB.
2. Respiratory failure, shock, sepsis, cardiac arrest, liver failure, ARF, coagulopathy, peptic ulcer, high-risk endoscopy, organ transplantation, anti-coagulation
3. Did not address this question
When risk factors are no longer present
2. Most important risk factors on mechanical ventilation greater than 48 hours and coagulopathy. Prophylaxis decreases bleeding risk by 30%.

74. Retrospective study of ICU patients, single institution. Outcomes: endoscopic GI stress ulceration.
3. Did not address this question
No prophylaxis is necessary
3. Did not address this question
MCU study proving that stress ulcer prophylaxis does not improve endoscopic GIB.

6. single-center, retrospective, non-randomized, 360 trauma patients. Comparison: Outcomes: Cost, GIB. (Pharmacy study).
3. TBI, SO, coagulopathy, mech vent, pO2<70, PUD, age >65, mech ventilation, NO2 preference
3. Yes, cimetidine
3. Did not address this question
Discontinue after pts tolerating a diet or enteral feeding. Gave cimetidine Saved $8000 in 150 patients, and had no GI bleeding complications

918. single-center RCT. Comparison: sucralfate versus placebo. Outcomes: stress ulceration, GIB, gastric pH.
1. ICU pts with mech vent and high risk for stress ulceration
2. Yes, sucralfate
1. Did not address this question
Small study showing no benefit endoscopic evidence of stress ulcer or hemorrhage.

1016. Single-center RCT, single institution, 26 pts. sucralfate vs placebo.
1. Did not address this question
Sucralfate
1. Did not address this question
Small study showing no benefit endoscopic evidence of stress ulcer or hemorrhage.

7. single-center RCT, comparing sucralfate vs placebo and ranitidine vs placebo. Outcomes: Stress ulceration, Gastric pH, GIB.
1. Did not address this question
No difference between sucralfate and ranitidine
1. Did not address this question
No difference in GIB or GI bleeding with or without prophylaxis. Recommended further study.

1. Spinal cord injury
2. No difference between cimetidine and sucralfate
2. Discontinued with discharge or death, minimum of 3 days.
2. No difference in VAP rates.

Felder C. 2003. Clinically significant gastrointestinal bleeding in critically ill patients with and without stress ulcer prophylaxis. intensive Care Med 2003 May;31(5):839-
3. Mechanical ventilation greater than 48 hours, coagulopathy and acute renal failure
3. No prophylaxis is necessary
3. Did not address this question
No difference in GIB or GI bleeding with or without prophylaxis. Recommended further study.

1. Did not address this question
No difference between ranitidine and placebo
3. Did not address this question
No difference between interval of bolus ranitidine.

6. retrospective study, single center. comparison: placebo and ranitidine treatment. Outcomes: Stress ulceration, GIB.
3. Did not address this question
Antacids +/- cimetidine
3. Continued until able to tolerate enteral nutrition.
3. Did not address this question
Stopped treatment with enteral feeding, no real data significance between ranitidine vs placebo, enteral feeding had increased mortality.

2. ICU and mechanically ventilated
2. No
2. Did not address this question
No difference between ranitidine and placebo with regard to VAP. Placebo (group had less incidence of GIB (prophylaxis to study this effect).

81. single-center RCT, 41 patients. Comparison: continuous vs bolus famotidine. Outcomes: Gastric pH,
1. Did not address this question
Famotidine bolus followed by infusion
1. Did not address this question
No statistical difference in GI bleeding and hospital mortality, pH increased in a bolus followed by infusion.

Kantorova I. 2004. Stress ulcer prophylaxis in critically ill patients: a randomized controlled trial. Hepatogastroenterol. 2004 May;51(70/71):753-
1. Coagulopathy
1. No
1. Did not address this question
No difference between any treatment arm and GIB, procoagulation increased gastric pH may increase procoagulation risk.

Killer ME. 1990. Preventing postoperative acute bleeding of the upper part of the gastrointestinal tract. Surgery Gynecol Obstet 1990 Nov;171(5):38-
42. Prospective randomized trails, 296 trauma patients. Comparison: bolus following, vs bolus followed by infusion, and placebo.
1. Critically ill patients in the ICU, age >50 yrs.
2. No
1. Did not address this question
No difference in the bleeding biomarkers in the ICU. No significant differences in the treatments. Age >50 yrs was a risk for bleeding. Small study.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Study Design</th>
<th>Setting</th>
<th>Intervention(s)</th>
<th>Comparator(s)</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Findings</th>
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<tr>
<td>Pemberton LB</td>
<td>1995</td>
<td>One-randomized trial</td>
<td>Single-center</td>
<td>Single-center prophylaxis</td>
<td>Ranitidine 30 mg four times daily</td>
<td>No, not equivalent to ranitidine</td>
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<td>Only lased at 24 hr. Treatment did not effect overall costs.</td>
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<td>Single-center prophylaxis</td>
<td>Ranitidine 30 mg four times daily</td>
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<td>Martin LP</td>
<td>1992</td>
<td>One-randomized trial</td>
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<td>Ranitidine 30 mg four times daily</td>
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