

Chapter 34. Prevention of Clinically Significant Gastrointestinal Bleeding in Intensive Care Unit Patients

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Background

Stress-related gastric ulceration was first described in the early 1970s,¹ and has since received extensive study. Appreciation of the physiologic changes that promote stress-related gastritis²⁻⁴ and general improvements in the care of critically ill patients have likely played a role in reducing the frequency of this complication.³ Nonetheless, the use of specific pharmacologic agents for the prevention of stress-related gastrointestinal (GI) bleeding is increasingly promoted as standard therapy in the ICU setting.⁵⁻⁸ Despite the common use of these agents, controversy about the evidence supporting this practice remains.^{5,9} Because specific pharmacologic prophylaxis for stress ulceration may increase the risk of other complications (eg, nosocomial pneumonia¹⁰) and is associated with significant costs,¹¹ recent efforts have focused on delineating an appropriate definition of clinically important GI bleeding and identifying patients who derive a clear benefit from pharmacologic prevention of this complication.

Practice Description

This chapter reviews evidence supporting the use of pharmacologic therapies for stress ulcer and GI bleeding prophylaxis in the ICU setting. We considered the use of histamine-2 receptor blocking agents (H₂-receptor antagonists) and sucralfate, a mucosal protecting agent. Although the efficacy of aluminum- and magnesium-based antacids has been demonstrated, their use is limited by dosing frequency and side effects.¹² Proton-pump inhibitors (PPIs) and enteral nutrition have also shown benefit in small studies, but there are yet no large randomized evaluations.^{6,12,13}

Prevalence and Severity of the Target Safety Problem

The risk of stress ulceration and subsequent GI bleeding depends on a patient's underlying illness, its severity, and related comorbidities. Using liberal criteria for assessment of bleeding, early reports estimated the incidence of GI bleeding due to stress ulceration in ICU patients to be as high as 5-25%.^{14,15} However, more recent prospective studies, using stricter definitions of clinically significant GI bleeding and following large cohorts of patients, have revealed more modest estimates of 0.1% in low-risk ICU patients and 2.8% in ventilated patients.^{2,13,16}

Opportunities for Impact

A recent, prospectively collected database of over 7000 patients admitted to surgical and medical intensive care units at a tertiary care center (1988-95) revealed that 59.9% of patients received pharmacologic prophylaxis with ranitidine or sucralfate for stress ulceration.¹⁶ Another study assessed the annual change in stress ulcer prophylaxis in nearly 3000 patients admitted to a medical intensive care unit at a tertiary care hospital from 1993 to 1996. It found a significant decrease in rates of prophylaxis, with a 71% rate in 1993 progressively decreasing to a 21% rate in 1996, likely reflecting emerging evidence regarding high and low-risk populations in the

literature during that time.¹⁷ Identifying appropriate patients for stress ulcer prophylaxis and avoiding its use in other cases both offer potential opportunities for improving patient safety in the ICU.

Study Designs

Although multiple meta-analyses have reviewed the prophylaxis of GI bleeding in critically ill patients, many were performed more than a decade ago.¹⁸⁻²⁰ Since then, results of additional randomized trials have been published. More recent, well-designed search strategies, strict quality-scoring of literature, and rigorous adherence to criteria defining clinically significant GI bleeding have improved the breadth and quality of literature captured, likely making older systematic reviews less relevant. Because of these changes in quality measures as well as overlap of information and trials from older reviews contained within more recent ones, only those meta-analyses published within the last 5 years (and large randomized controlled trials not included in these reviews) are included here.

A 1996 meta-analysis found 269 studies through a broad search of multiple databases and extensive efforts to find unpublished trials.⁵ Sixty-three of these met inclusion criteria. The analysis evaluated multiple types of prophylaxis for GI bleeding, including antacids, H₂-antagonists, and sucralfate. The study authors compared each type of prophylaxis to placebo and to each other when literature was available. The same study group then followed-up unanswered questions from their meta-analysis with a large randomized controlled trial (RCT) of 1200 patients, comparing ranitidine to sucralfate without a placebo group.²¹

A more recent meta-analysis abstracted evidence from the literature to compare ranitidine (instead of all H₂-antagonists) versus placebo, and sucralfate versus placebo for GI bleed prophylaxis in the ICU.⁹ The search methods were less rigorous and the target population narrower than the 1996 meta-analysis, but the authors claimed to assess a more clinically relevant population and outcome.

Results from 2 prospective cohort studies that evaluated risk factors for occurrence of clinically important GI bleeding also provide key recommendations regarding clinical practice.^{2,13}

Study Outcomes

Both meta-analyses and the large RCT reported outcomes of clinically important GI bleeding and nosocomial pneumonia (Level 1). The 1996 meta-analysis and randomized trial also evaluated overt GI bleeding and mortality. Cohort studies (Level 2) present results of multivariate regression analyses, identifying the salient risk factors for clinically important GI bleeding in the ICU patient.

Evidence for Effectiveness of the Practice

Table 34.1 summarizes the outcomes for the 2 meta-analyses and large RCT. The disparity in results of the meta-analyses is partly due to differing article selection criteria. While the 1996 analysis evaluated all H₂-antagonists, the 2000 study excluded trials evaluating cimetidine because of its virtual replacement (attributable to its undesirable side effect profile) by ranitidine in current clinical practice.^{5,9} Excluding studies with cimetidine substantially reduced the number of studies available for review. Additionally, the 1996 study evaluated comparisons of therapies to each other as well as to placebo, while the 2000 study only considered trials of effectiveness with a placebo control as relevant.

The 2000 meta-analysis found no statistically significant reduction in clinically important GI bleeding when comparing H₂-antagonist agents with placebo, or sucralfate to placebo.⁹ However, the 1996 study revealed a significant difference between ranitidine and placebo for clinically important GI bleeding.⁵ It was unable to demonstrate such a difference between ranitidine and sucralfate. The results of these 2 reviews reveal discrepant findings, in large part due to exclusion of cimetidine in the 2000 study. However, that study also included at least one moderate-sized trial that used remarkably strict criteria for defining clinically important GI bleeding. This factor likely contributed an element of bias towards the null result in that meta-analysis.

Furthermore, the large RCT (1998) comparing ranitidine to sucralfate, without a placebo comparison group, revealed a statistically significant difference in the rate of clinically important upper GI bleeding, favoring H₂-antagonists.²¹ In this RCT the number needed to treat (NNT) with ranitidine compared to placebo to prevent one clinically important GI bleed compared to placebo was 47. However, no reduction in mortality or length of ICU stay was found. Interpretation of the results of the RCT are complicated by: 1) wide confidence intervals surrounding the relative risk estimate; 2) very small numbers of patients with clinically important GI bleeding (ranitidine group: 10/596; sucralfate group: 23/604), only 42% of whom had endoscopic confirmation of the source of bleed; 3) a large number of patients (70%) receiving concomitant enteral nutrition, believed to reduce the risk of GI bleeding (see Chapter 33); and 4) unreported incidence of coagulopathy or duration of prophylaxis prior to GI bleeding.²²

The 2 large cohort studies found respiratory failure (odds ratio 15.6, p<0.001), coagulopathy (odds ratio 4.3, p<0.001), and renal insufficiency (relative risk 1.16, p=0.023) to be independent risk factors for predicting clinically important GI bleeding in ICU patients.^{2,13} Enteral nutrition had a protective effect on GI bleed outcome (relative risk 0.30, p=0.004). Even though previous studies found a high incidence of overt GI bleeding among head trauma patients, this was not supported by the most recent cohort study cited above, which evaluated ventilated head trauma patients.^{13,23}

Potential for Harm

Table 34.2 summarizes the harm evaluated in the 2 recent meta-analyses and large RCT. All 3 studies showed either a trend toward reduction or statistically significant reduction of nosocomial pneumonia in sucralfate groups compared with ranitidine groups.^{5,9,21} The number needed to harm (NNH) to cause one nosocomial pneumonia with ranitidine compared with sucralfate was calculated as 21 to 34 (see also Subchapter 17.4). However, this effect was not statistically significant in the RCT. No study demonstrated a harmful effect for ranitidine compared to placebo.

Costs and Implementation

One cost-effectiveness analysis extracted relevant literature from MEDLINE between 1985 and 1995, representing 15 controlled clinical trials (Level 1).¹⁹ Assumptions made in the analysis included equal efficacy for the H₂-antagonist cimetidine and sucralfate, a baseline risk of bleeding of 6%, and a 50% risk-reduction due to prophylaxis. The average cost per bleeding episode averted was \$1144 for sucralfate, but 6.5 times greater for cimetidine. However, low-risk patients amassed a cost per bleeding episode averted of \$103,725 compared to a cost of \$279 for very high-risk patients. Cost per bleeding episode averted increased significantly if the risk of nosocomial pneumonia was included in the analysis.

The large RCT reported no difference in the duration of ICU stay for the group treated with ranitidine compared with the group treated with sucralfate (9 days for each group).²¹ However, no placebo group was used.

Comment

Overall, the evidence available in the literature does not conclusively demonstrate that the benefits of GI prophylaxis outweigh its risks for every patient admitted to the intensive care unit. As refinements have been made in defining *clinically* important and significant episodes of GI bleeding, the population that may reap benefit from prophylaxis has narrowed substantially. In turn, a reduction in the use of prophylactic agents has followed. Most recent estimates reveal a negligible incidence of clinically important stress-related GI bleeding in low-risk ICU patients (approximately 0.1%) and a small incidence (less than 3%) in higher-risk patients. Improvements in overall ICU care and use of enteral nutrition may be contributing to this decrease in incidence.

Although a statistical benefit of H₂-antagonists compared with placebo or with sucralfate has been shown in some studies, the overall *clinical* benefit of these agents has been disputed. Some research shows a greater absolute number of nosocomial pneumonia cases related to therapy with H₂-antagonists than the benefit from reduction in GI bleeding, causing the NNH to be potentially smaller than the NNT (see Subchapter 17.4). Furthermore, the overall cost-to-benefit ratio of prophylaxis increases dramatically in lower-risk patients, as shown in the analysis noted above that accounted for increases in nosocomial pneumonia.²¹ Thus, the clear benefit of administering H₂-antagonists to prevent GI bleeding among many patients in an ICU remains to be shown. This is partly due to variations in the definition of clinically significant bleeding and pneumonia. Additional large trials are necessary to identify the patients who truly derive net benefit from this practice, as published evidence does not yet support this practice for many patients currently receiving the therapy.

At the present time, clinicians may consider use of prophylactic agents, an H₂-antagonist or sucralfate, to prevent clinically important GI bleeding in very high-risk patients admitted to the ICU. Such patients may include those with respiratory failure, coagulopathy, renal failure, and/or burns (the latter group has been excluded from most studies because its risk is believed to be so great). However, the risk of pneumonia may influence clinicians to use prophylactic agents only in patients with multiple risk factors for GI bleeding, and simply provide enteral nutrition to others at less risk. The use of PPIs requires further study before any recommendation can be made regarding them. Further research should focus on identifying subgroups of patients who do derive net benefit from ranitidine or other acid-reducing agents.

Table 34.1. Studies evaluating effectiveness of pharmacologic prophylaxis of ICU patients to prevent clinically significant GI bleeding*

EFFECTIVENESS			
Study	Study Design, Outcomes	Comparison Groups	Effect Size (95% CI)
Cook, 1996 ⁵	Level 1A, Level 1	H ₂ -antagonist vs. placebo	OR 0.44 (0.22-0.88)
		Sucralfate vs. placebo	OR 1.49 (0.42-5.27)
		H ₂ -antagonist vs. sucralfate	OR 1.28 (0.27-6.11)
Messori, 2000 ⁹	Level 1A, Level 1	Ranitidine vs. placebo	OR 0.72 (0.30-1.70)
Cook, 1998 ²¹	Level 1, Level 1	Ranitidine vs. sucralfate	RR 0.44 (0.21-0.92) NNT 47

* CI indicates confidence interval; NNT, number needed to treat (for benefit); OR, odds ratio; and RR, relative risk.

Table 34.2. Studies evaluating harm (nosocomial pneumonia) due to pharmacologic prophylaxis of ICU patients to prevent GI bleeding*

HARM			
Study	Study Design, Outcomes Measured	Comparison Groups	Effect Size (95% CI)
Cook, 1996 ⁵	Level 1A, Level 1	Sucralfate vs. H ₂ -antagonist	OR 0.78 (0.60-1.01)
Messori, 2000 ⁹	Level 1A, Level 1	Ranitidine vs. sucralfate	OR 1.35 (1.07-1.70) NNH 21
Cook, 1998 ²¹	Level 1, Level 1	Ranitidine vs. sucralfate	RR 1.18 (0.92-1.51) NNH 34

* CI indicates confidence interval; NNH, number needed to harm; OR, odds ratio; and RR, relative risk.

References

1. Lucas C, Sugawa C, Riddle J, Rector F, Rosenberg B, Walt A. Natural History and surgical dilemma of "stress" gastric bleeding. *Arch Surgery*. 1971;102:266-273.
2. Cook D, Fuller H, Guyatt G, Marshall J, Leasa D, Hall R, et al. Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med*. 1994;330:377-381.
3. Haglund U. Stress ulcers. *Scand J Gastroenterol*. 1990;175:27-33.
4. Shoemaker W, Bland R, PL A. Therapy of critically ill postoperative patients based on outcome prediction and prospective clinical trials. *Surg Clin North Am*. 1985;65:811-833.
5. Cook D, Reeve B, Guyatt G, Heyland D, Griffith L, Buckingham L, et al. Stress ulcer prophylaxis in critically ill patients: resolving discordant meta-analyses. *JAMA*. 1996;275:308-314.

6. Beejay U, Wolfe M. Acute gastrointestinal bleeding in the intensive care unit: the gastroenterologist's perspective. *Gastroenterol Clin North Am.* 2000;29:309-336.
7. Friedman S, Manaker S, Weinhouse G. Stress ulcer prophylaxis in the intensive care unit. In: Rose BD, ed. *UpToDate.* Wellesley, MA: UpToDate, Inc.; 2001.
8. ASHP Commission on Therapeutics. Therapeutic guidelines on stress ulcer prophylaxis. *Am J Health Syst Pharm.* 1999;56:347-379.
9. Messori A, Trippoli S, Vaiani M, Gorini M, Corrado A. Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials. *BMJ.* 2000; 21:1-7.
10. Ben-Menachem T, McCarthy B, Fogel R, Schiffman R, Patel R, Zarowitz B, et al. Prophylaxis for stress-related gastrointestinal hemorrhage: a cost effectiveness analysis. *Crit Care Med.* 1996;24:338-345.
11. Cook D. Stress ulcer prophylaxis gastrointestinal bleeding and nosocomial pneumonia. Best evidence synthesis. *Scand J Gastroenterol.* 1995;210:48-52.
12. Hastings P, Skillman J, Bushnell L, Silen W. Antacid titration in the prevention of acute gastrointestinal bleeding: a controlled, randomized trial in 100 critically ill patients. *N Engl J Med.* 1978;298:1041-1045.
13. Raff T, Germann G, Hartmann B. The value of early enteral nutrition in the prophylaxis of stress ulceration in the severely burned patient. *Burns.* 1997;23:313-318.
14. Ben-menachem T, Fogel R, Patel R, Touchette M, Zarowitz B, Hadzijahic N, et al. Prophylaxis for stress-related gastric hemorrhage in the medical intensive care unit: a randomized, controlled, single-blind study. *Ann Intern Med.* 1994; 21:568-575.
15. Shuman R, Schuster D, Zuckerman G. Prophylactic therapy for stress ulcer bleeding: a reappraisal. *Ann Int Med.* 1987;106:562-567.
16. Pimentel M, Roberts D, Bernstein C, Hoppensack M, Duerksen D. Clinically significant gastrointestinal bleeding in critically ill patients in an era of prophylaxis. *Am J Gastroenterol.* 2000;95:2801-2806.
17. Devlin J, Ben-Menachem T, Ulep S, Peters M, Fogel R, Zarowitz B. Stress ulcer prophylaxis in medical ICU Patients: annual utilization in relation to the incidence of endoscopically proven stress ulceration. *Ann Pharmacother.* 1998;32:869-874.
18. Tryba M. Prophylaxis of stress ulcer bleeding: a meta-analysis. *J Clin Gastroenterol.* 1991;3(Suppl. 2):S44-S55.
19. Lacroix J, Infante-Rivard C, Jenicek M, Gauthier M. Prophylaxis of upper gastrointestinal bleeding in intensive care units: a meta analysis. *Crit Care Med* 1989;17:862-869.
20. Cook D, Witt L, Cook R, Guyatt G. Stress ulcer prophylaxis in the critically ill: a meta analysis. *Am J Med.* 1991;91:519-527.
21. Cook D, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med.* 1998;338:791-797.
22. Hinds C, Fletcher S. Ranitidine reduced clinically important gastrointestinal bleeding in patients who required mechanical ventilation. *Gut.* 1999;44:10-11.
23. Burgess P, Larson G, Davidson P, Brown J, Metz C. Effect of ranitidine on intragastric pH and stress-related upper gastrointestinal bleeding in patients with severe head injury. *Dig Dis Sci.* 1995;40:645-650.
24. Cook D, Heyland D, Griffith L, Cook R, Marshall J, Pagliarello J. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. *Crit Care Med.* 1999;27:2812-2817.