

Stress Ulcer Prophylaxis: When, What Drug and How Long?

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Stress ulcer prophylaxis is widely used in critically ill patients. With expansion of acid suppressant therapy options has come a tendency to overuse these agents for stress ulcer prophylaxis, in particular in subpopulations of patients with little or no supporting data for use. In a study by Nardino et al., the appropriate use of acid suppressive therapy was evaluated over a 3-month period in a 511-bed community teaching hospital.¹ The results indicated that 80 of 122 patients (65%) received acid suppressant therapy inappropriately. Of the 80 patients, 33 (41%) receiving acid suppressive therapy for stress ulcer prophylaxis were considered low-risk. In addition, when examining the unnecessary use of stress ulcer prophylaxis, researchers found 18 (55%) of 33 patients were discharged with a prescription for the medication. Based on the results of this study, there appears to be a high frequency of unnecessary use of acid suppressive therapies for stress ulcer prophylaxis in low-risk hospitalized patients. These findings are consistent with previously reported studies in the medical literature.²⁻³ This article will briefly review when stress ulcer prophylaxis is indicated and which drug regimens are rational.

Pathophysiology

In high-risk intensive care patients, stress-related gastroduodenal mucosal damage is still incompletely understood. Normal gastric homeostasis is a complex multifactorial process, involving adequate blood flow, production of gastric mucus and mucosal prostaglandins, acid-base balance, maintaining a pH gradient between the intracellular space and gastric lumen, and renewal of epithelial cells.⁴

In the critically ill patient, the initial decrease in gastric mucosal perfusion is believed to be secondary to a hypovolemic insult from acute blood loss, sepsis, or inadequate volume resuscitation.⁵ The resultant reduction in perfusion leads to a decreased ability to remove acid, with a back diffusion of acid resulting in added intramucosal hydrogen ions. In addition, a decrease in the delivery of bicarbonate occurs, all of which disrupt the gastric mucosal barrier, setting the stage for gastric mucosal damage, secondary to intraluminal acid. Due to the breakdown of the mucosal barrier and damage from gastric acid, these are key areas for targeting drug therapy. It is also important to note, that the direct correlation between intragastric pH and stress ulceration and bleeding has been difficult to prove, and the extent of stress ulceration to the absolute acid concentration or the ability to maintain pH >4 is not strongly linked.⁵

When is prophylaxis indicated?

Over the past two decades the reported incidence of stress ulceration in intensive care patients has decreased. Several reasons have been proposed for this decrease, including more rapid transport and earlier resuscitation by ambulance services, critical care specialists with advanced training, treatment for multi-organ dysfunction, maintenance of tissue oxygenation, correction of fluid and acid-base imbalances, and stress ulcer prophylaxis.⁶

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Stress Ulcer Prophylaxis: When, What, How Long? (cont.)

With the availability of several acid suppressant medications and various formulations, there is a potential for overuse of these agents for stress ulcer prophylaxis, in particular in subpopulations of patients with little or no supporting data for use.

In a study by Nardino, et al., 41% of patients receiving acid suppressive therapy for stress ulcer prophylaxis were considered low-risk. In addition, researchers found 55% of these patients were discharged with a prescription for the medication.

In a large, multi-center prospective cohort study, the only two independent risk factors identified were respiratory failure requiring mechanical ventilation >48 hours and coagulopathy.

Over the past two decades, the reported incidence of stress ulceration in intensive care patients has decreased.

It has been advocated that stress ulcer prophylaxis only be used in high-risk, critically ill patients.

With this in mind, it is now advocated that stress ulcer prophylaxis only be used in high-risk critically ill patients. Based on clinical trials and published guidelines, risk factors for critically ill patients at high-risk for stress ulceration are described below (see Table I).

In a prospective multi-center cohort study in 2252 critically ill patients, results showed clinically important bleeding in 33 (1.5%) patients and a mortality rate of 48.5% (compared to 9.1% for all other patients).⁷ The only two independent risk factors identified for clinically important bleeding were respiratory failure requiring mechanical ventilation for more than 48 hours (odds ratio 15.6) and coagulopathy (odds ratio 4.3). Of the 847 patients with one or both of these risk factors, 31 (3.7%) had clinically important bleeding and 2 (0.1%) of 1405 patients without one of these risk factors had clinically important bleeding.

Additional identified risk factors for intensive care patients are head injury with Glasgow Coma Score of ≤ 10 or inability to follow simple commands; thermal injury involving >35% of body surface area; partial hepatectomy; hepatic or renal transplantation; multiple trauma with Injury Severity Score ≥ 16 ; spinal cord injury; hepatic failure; history of gastric ulceration or bleeding during the year before admission; or the presence of at least two of the following risk factors: sepsis, intensive care unit (ICU) stay >1 week, occult or overt bleeding for ≥ 6 days, or corticosteroid therapy (>250mg of hydrocortisone or equivalent daily).⁸

Table I: Risk Factors for Stress Ulcer Prophylaxis in ICU Patients

<ul style="list-style-type: none"> • Mechanical ventilation >48 hours • Coagulopathy • Head injury with Glasgow Coma Score ≤ 10 • Thermal injury >35% body surface area • Partial hepatectomy • Hepatic or renal transplantation • Multiple trauma with Injury Severity Score ≥ 16 • Spinal cord injury 	<ul style="list-style-type: none"> • Hepatic failure • History of GI ulceration/bleeding within 1 year • Presence of ≥ 2 risk factors: <ul style="list-style-type: none"> Sepsis ICU stay >1 week Occult or overt bleeding ≥ 6 days Corticosteroid therapy >250mg hydrocortisone or equivalent daily
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In non-intensive care patients, little data is available to support the use of stress ulcer prophylaxis and recent American Society of Health-System Pharmacists (ASHP) therapeutic guidelines do not recommend its use in the non-intensive care setting.⁸ Only one randomized control trial has been published in non-intensive care patients that broadly defined bleeding in these patients and suggested that patients with two or more risk factors may be candidates for prophylaxis.⁹

Which prophylactic agents are rational for use?

The most commonly used agents for stress ulcer prophylaxis are histamine type 2 receptor antagonists (H_2 antagonists) and sucralfate. Proton pump inhibitors (PPIs) have also been used, but peer-reviewed evidence for the clinical superiority of this newer class of agents for this indication is lacking. In fact, only three small studies have been published on the use of PPIs as prophylaxis for stress ulcers; all three of these studies reported on the use of omeprazole.¹⁰⁻¹² However, due to the small number of study participants, the open-label study designs, the lack of control groups (2 studies), inconsistent predisposing risk factors, and other study limitations, to date there is insufficient data on which to base comparisons with the older, gold standard regimens.

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PPIs should continue to be third-line prophylactic agents, or for patients with contraindications or intolerance to H₂ antagonists or sucralfate.

Based on several meta-analyses, H₂ antagonists and sucralfate are considered to be equally efficacious in preventing clinically important bleeding.

Recommendations for discontinuation of prophylaxis is indicated after the resolution of risk factors.

Note: The editor gratefully acknowledges the assistance of John R. Horn, Pharm.D., and Michael D. Saunders, M.D., in reviewing this article.

References available on request.

Therefore, PPIs should continue to be third-line prophylactic agents, or for patients with contraindications or intolerance to H₂ antagonists or sucralfate.

Based on several meta-analyses, H₂ antagonists and sucralfate are considered to be equally efficacious in preventing clinically important bleeding.¹³⁻¹⁵ However, in a comparison trial of sucralfate and the H₂ antagonist ranitidine in 1200 mechanically ventilated patients, ranitidine was associated with a significantly lower rate of clinically important bleeding than was sucralfate.¹⁶ When examining rates of ventilator-associated pneumonia, duration of ICU stay, or mortality, there were no significant differences.

H₂ antagonists and PPIs exert their pharmacologic effects by inhibiting gastric acid secretion. In contrast, the primary effect of sucralfate is cytoprotection. Sucralfate's cytoprotective effects include a direct protective barrier, tissue growth and repair, inactivation of pepsin, increased mucus viscosity, and stimulation of prostaglandin and bicarbonate secretion.¹⁷ Since sucralfate works locally, it must be administered orally, or through a nasogastric, orogastric, or gastrostomy tube. Administration of sucralfate via a duodenal or jejunostomy tube will result in ineffectiveness, since these areas are beyond the site of action.⁸ Concerns associated with the oral administration of H₂ antagonists and PPIs in critically ill patients stem from the potential for malabsorption, since impaired gastrointestinal motility is common in these patients.^{18,19} Other concerns about H₂ antagonists are the problems of tachyphylaxis (observed to develop within 3-30 days),^{20,21} thrombocytopenia (incidence rare),²² and the risk of nosocomial pneumonia. Due to the acid inhibitory effects of H₂ antagonists and PPIs, gastric colonization is possible, leading to ventilator-associated pneumonia through retrograde colonization of the pharynx from the stomach.²³ Since, sucralfate does not alter gastric pH to a significant extent, it may be less likely than H₂ antagonists or PPIs to result in pneumonia; however, this data is conflicting.^{13-15,24,25}

The preferred H₂ antagonist on the UWMC/HMC Drug Formulary is ranitidine, due to the availability of both an oral and intravenous formulation. The dosing recommendation for ranitidine for stress ulcer prophylaxis is 150mg PO or via nasogastric tube twice daily, or 50mg IV Q 8 hours. In cases where creatinine clearance is <50 mL/minute, the recommended dose is 150mg PO or via nasogastric tube once daily, or 50mg IV once or twice daily. Sucralfate dosing is 1gm PO or via nasogastric tube Q 6 hours. No sucralfate dosage adjustment is necessary for renal dysfunction. If other medications are given, they should be administered 2 hours before sucralfate, to prevent altered absorption.

How long should prophylaxis continue?

Based on the ASHP therapeutic guidelines, discontinuation of stress ulcer prophylaxis is indicated after the resolution of risk factors.⁸ Additionally, it has been suggested that stress ulcer prophylaxis may be discontinued upon meeting enteral nutritional goals,^{26,27} but this data is limited and controversial.²⁸ In a national survey of ICU physicians, respondents reported discontinuation of stress ulcer prophylaxis when the patient was no longer "NPO" status, started on enteral feeding, or discharged from the ICU.²⁹

Conclusion

Based on the available evidence, the use of stress ulcer prophylaxis should be limited to ICU patients with the risk factors described in Table I. The most accepted stress ulcer prophylactic agents continue to be ranitidine and sucralfate. Until further evidence is available to support the use of PPIs, they should be reserved as third-line agents or for patients with contraindications or intolerance to H₂ antagonists or sucralfate.

Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost [‡]	Therapeutic Classification	Use	Usual Adult Starting Dose*
Diclofenac Sodium (Voltaren)	Tablet: 25mg-\$0.04, 50mg-\$0.06, 75mg-\$0.08	NSAID	Mild-moderate pain, osteoarthritis, rheumatoid arthritis	Varies with indication
Etodolac (Lodine)	Capsule: 200mg-\$0.11, 300mg-\$0.11 Tablet: 400mg-\$0.19, 500mg-\$0.21	NSAID	Mild-moderate pain, osteoarthritis, rheumatoid arthritis	Varies with indication

* Refer to product labeling for full prescribing information. ‡ Costs represent UWMC/HMC outpatient acquisition costs and do not include pharmacy dispensing fees.

Maximizing Value: What Every Practitioner Should Know About Drug Costs

Double-digit annual increases make pharmaceuticals the fastest growing component of health care costs. Efforts to contain these costs have become a major strain for our health systems. The University of Washington Pharmacy and Therapeutics (P & T) Committee has a long tradition of advising the Academic Medical Center on all aspects related to the rational and cost-effective prescribing of pharmaceuticals. To further educate practitioners about the factors behind the escalating drug costs and P & T Committee-based efforts to counter these trends, a Special Edition of this newsletter has been published and distributed to UW health care practitioners ("Maximizing Value: What Every Practitioner Should Know About Drug Costs." *Drug Therapy Topics* 2002; Volume 31 Special Edition). Additional copies are available from the Drug Information Center (598-6612; druginfo@u.washington.edu), or the document can be obtained electronically from the Internet (http://depts.washington.edu/druginfo/DTT/2002_Vol31_Files/V31SpecEd.pdf).

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