

Stress Ulcer Prophylaxis—Is overuse harmful?

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Despite the publication of more than 100 studies on the frequency, risk factors, and treatment of stress ulcer bleeding, the area of stress ulcer prophylaxis (SUP) with acid suppressive therapy (AST), such as proton pump inhibitors (PPIs) or H₂ receptor antagonists (H₂RAs), continues to create controversy. While the evidence of AST for SUP has only been established in selected patients in the intensive care unit (ICU) setting, emerging data question the utility of AST in non-critically ill patients. In this article, we will address the risk factors associated with gastrointestinal bleeding resulting from stress ulceration, and the risks and benefits of SUP with AST.

The American Society of Health-System Pharmacists (ASHP) published guidelines in 1999 to direct health care professionals in the management of SUP. These guidelines recommend SUP in critical care patients requiring mechanical ventilation for more than 48 hours and those with coagulopathy, both of which are significant independent risk factors for GI bleed.¹ In a large prospective, multicenter, cohort study of ICU patients the risk of bleeding was increased 15-fold in those requiring mechanical ventilation and 4-fold in those non-oncology patients with coagulopathy (platelets < 50K, INR > 1.5, PTT > 2X normal).² Other studies further identified additional risk factors that increase the development of stress ulcers, including ICU patients with a head injury and a Glasgow Coma Score of <10, hypotension, burns involving >35% of BSA, hepatic and/or renal failure, organ transplant, multiple trauma with Injury Severity Score of ≥ 16, spinal cord injury, history of GI ulceration or bleed within 1 year prior to admission. These studies also identified, as additional risk factors, the presence of at least two of the following: sepsis, ICU stay > 1 week, occult or overt bleeding of ≥ 6 days, or > 250mg hydrocortisone or equivalent per day.^{1,2}

Through a collaborative effort between UWMC Gastroenterology and Pharmacy, guidelines for the appropriate use of SUP in critically ill patients were developed in 2002 and updated in 2006 for UWMC providers (Table 1, p2). These guidelines are intended to provide assistance to clinicians in determining the most appropriate agent for several common clinical situations.

While evidence supporting the effectiveness of SUP is well documented in selected critically ill patients, there is significant overuse of AST in non-critically ill hospitalized patients. This phenomenon may result from the extension of common practices in the ICU or the perception that PPIs and H₂RAs are safe. A retrospective chart review of 226 general medicine patients in a large community teaching hospital was conducted to determine the type of medication used, the timing of the prescription, and the indication for use.³ Nardino et al. found 54% of patients were receiving AST, most commonly H₂RAs and PPIs, and indications for 65% of those were deemed inappropriate by consensus review. Among the patients who received AST for SUP, 55% were discharged with the intent of continuing the therapy at home. These findings are consistent with previous reports that similarly demonstrate the overuse of AST in the hospital and community outpatient setting.⁴

Although PPIs and H₂RAs provide effective AST, there are potential drawbacks to the widespread and indiscriminate use of these agents. Gastric acidity constitutes a major defense mechanism against ingested pathogens, and rise in gastric pH is associated with increases in bacterial and virus colonization of the normally sterile upper gastrointestinal tract. For instance, elevated gastric pH is a known risk factor for infectious diarrheal illnesses such as travelers' diarrhea, salmonellosis, and cholera.⁵ Furthermore, recent reports indicate that both hospitalized and ambulatory patients are at increased risk for *Clostridium difficile* (*C. difficile*) diarrhea with AST use.^{6,7} *C. difficile* is one of the most common causes of nosocomial infectious diarrhea in industrialized countries, and the frequency and severity are

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increasing.^{8,9} According to the Centers for Disease Control and Prevention, the number of *C. difficile* infections doubled between 1993 and 2003. This organism is now responsible for tens of thousands of cases of diarrhea and at least 5,000 deaths annually in the United States. Additional risk factors for *C. difficile* include broad-spectrum antibiotic use, increasing age, and prolonged hospital stay.

An increase in gastric pH may also facilitate the survival and persistence of *C. difficile* and its toxins, (toxin A and toxin B).⁵ Thus, there is concern that AST, which elevates gastric pH, can increase the incidence and/or severity of *C. difficile* diarrhea. In particular, the correlation between *C. difficile* infection rates and PPI use is an area of active investigation.^{10,11,12} A cohort study by Dial et al. examined *C. difficile* diarrhea rates over a 9-month period in general medicine patients.¹³ The investigators matched type and number of antibiotics, the most important known risk factors for *C. difficile* diarrhea. A total of 1,187 patients were prescribed antibiotics while in the hospital; half received PPIs in addition to an antibiotic while the other half received antibiotics alone. *C. difficile* diarrhea developed in 81 (6.8%) of the patients. Of these, 55 (9.3%) of the 591 patients also received PPIs and 26 (4.4%) of the 596 patients did not receive these medications.

The odds ratio associated with the development of *C. difficile* and PPI use was 2.1 (95% CI: 1.2–3.5) after adjustment for type and number of antibiotics used. The results suggest that PPIs may be a previously unrecognized and potentially modifiable risk factor for occurrence of *C. difficile*. The use of these agents should be carefully evaluated in hospitalized patients receiving antibiotics, particularly those patients with *C. difficile* diarrhea.

Gastric acidity is important in the maintenance of normal gut flora, as discussed above. Alterations in gut flora due to an increase in the gastric pH may also allow colonization of the stomach with pathogenic bacteria, which may then spread to the lower respiratory tract. Gram-negative nosocomial pneumonia may result from retrograde colonization of the pharynx from the stomach.⁶ Driks et al. examined the effects of elevations in gastric pH on nosocomial pneumonia rates.¹⁴ They found that the rate of pneumonia was twice as high in intubated ICU patients in the group receiving H₂RAs as in those receiving sucralfate. In those patients receiving antacids or H₂RAs, gram-negative bacilli were isolated more frequently from the tracheal aspirates of patients with pneumonia. Moreover, mortality rates were 1.6 times higher in the antacid group than in the sucralfate

TABLE 1: UW GUIDELINES FOR APPROPRIATE USE OF SUP IN CRITICALLY ILL PATIENTS (from UWMC MUE 2006).

	MEDICATION CLASS	ROUTE OF ADMINISTRATION	MEDICATION	DOSE	COMMENTS
1st Line	H2 Antagonist	PO/PNG/PFT	Ranitidine	150 mg BID (if CrCl<50mL/min reduce to 150 mg daily)	<ul style="list-style-type: none"> Available in a liquid formulation. Case control trials have not conclusively demonstrated a correlation with H2 antagonist and thrombocytopenia
		IV		50 mg every 8 hours (if CrCl<50mL/min reduce to 50 mg daily)	
Move to 2nd line agents only if patients fails (bleeding) OR is intolerant OR has contraindication to 1st line therapy					
2nd line —treatment failure	Proton Pump Inhibitor	IV	Pantoprazole	40 mg IV every 12 hrs	<ul style="list-style-type: none"> Goal pH>4 Consider alternatives (PO or enteral) once active bleeding has resolved. For patients found to be at high risk via endoscopy – goal pH>6 with continuous infusion of PPI
2nd line —patient intolerant/ contraindication to 1st line therapy	Proton Pump Inhibitor	PO	Pantoprazole	40 mg daily	Tablet cannot be crushed
		NG/PFT	Lansoprazole solutab	30 mg daily	Tablet can be dispersed in water and then administered via tube

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group. The investigators concluded that gastric pH correlates with the incidence of nosocomial pneumonia in patients receiving ventilation by favoring gastric colonization with gram-negative bacilli.

AST have also been linked to increasing the risk for community-acquired pneumonia. Leheij et al. performed a large population-based cohort study evaluating the incidence of community-acquired pneumonia with the use of AST in an ambulatory setting.⁶ Overall, patients using acid-suppressive medications developed community-acquired pneumonia 4.5 times more frequently (CI 95%: 3.8-5.1) compared with those who did not use acid-suppressive drugs. The investigators found that the incidence of pneumonia with concurrent use of PPIs roughly translates to 1 case of pneumonia per 226 patients treated with PPIs and 1 case of pneumonia per 508 patients treated with H₂RAs. The authors concluded that in patients in an ambulatory practice setting who are at low risk for stress ulcerations, the use of acid-suppressive medications such as H₂RAs and PPIs increased the risk of pneumonia, likely as a result of a reduction of gastric acid secretion.⁶ The correlation between PPI use and pneumonia in the adult non-critically ill patient population is currently under intense investigation.

The risk of acquiring *C. difficile* diarrhea or pneumonia is of great concern in all hospitalized patients and these risks persist even after discharge. Many patients receive AST for SUP while in the hospital and after discharge despite lack of evidence supporting their use. A retrospective chart review was performed to assess the practice of SUP in hospitalized, non-ICU patients in a university hospital setting.¹⁵ Data collection focused on documentation in the medical record that AST was given for either “stress ulcer prophylaxis” or “GI prophylaxis”. The study revealed that of 1,769 consecutive patient admissions, 22% (389) of patients received AST for an indication of SUP. None of these patients, however, met criteria for appropriate SUP according to ASHP guidelines. More disturbingly, 54% (210) of these patients unnecessarily continued AST in the outpatient setting. In a similar study by Parente et al., investigators documented AST in all patients admitted to a general medical and surgical ward over a 1-month period.¹⁶ Of the patients receiving AST, 56% were discharged home on AST, despite the lack of a documented indication during hospitalization. These studies illustrate the importance of a comprehensive evaluation of the need for AST both during hospitalization of non-critically ill patients and after discharge.

The economic impact of inappropriate use of AST also warrants attention. As AST is overutilized in the non-ICU setting and patients are often discharged unnecessarily on these agents, significant expenditures can emerge. Heidelbaugh and Inadomi specifically considered resource utilization in 1,769 general internal medicine and family medicine patient hospital admissions.¹⁵ Inpatient costs for SUP in these non-critically ill patients totaled \$11,000 over the 4 months of the study. Assuming constant rates of SUP prescriptions, this represents an annual expenditure of \$44,000 [*sic*]. Outpatient costs based on discharge prescriptions were \$17,000. Assuming full patient compliance and unchanged prescription costs, this results in an annual expenditure of \$68,000 [*sic*]. Total AST costs for the study cohort was \$28,000 when both inpatient and outpatient medications were combined, which represents an annual expenditure of \$112,000 for AST prescribed for unnecessary SUP.¹⁵ Consequently, inappropriate use of AST for SUP in non-ICU hospitalized patients has substantial financial ramifications for both the patients and the hospital.

SUP with acid suppressive therapy is NOT necessary for most adult patients outside of the ICU and post-surgical settings.

SUP is not without risks (bacterial colonization with potential for nosocomial pneumonia and/or *C. difficile* infection) and thus, should be reserved for those patients at greatest risk for clinically significant bleeding.

SUP should be implemented in ICU patients with:

- Respiratory failure requiring > 48 hours of mechanical ventilation
- Coagulopathy in non-oncology patients (plts < 50K, INR > 1.5, PTT > 2X normal)^{1,2}

Prescribers will need to assess the risks vs. benefits of SUP for ICU patients with the following risk factors for stress-related mucosal damage:

- Hypotension
- Sepsis
- Hepatic and/or renal failure
- Head Injury w/ GCS of < 10
- Thermal Injury w/ > 35% of BSA
- Multiple trauma w/ Injury Severity Score of ≥ 16
- Spinal cord injury
- Organ transplant and/or > 250mg of hydrocortisone or equivalent per day^{1,2}

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Although specialists continue to voice opinions on AST, the debate over the appropriate use of these agents in the non-ICU population continues. No data exists, however, to support the use of AST for SUP in this population of patients. Overuse of resources is compounded by the frequent practice of continuing non-indicated AST after hospital discharge. This may increase the likelihood of *C. difficile* diarrhea and community acquired pneumonia, which may result in readmission to the hospital and a subsequent increase in health care costs. While the routine use of SUP has become standard practice in the ICU setting, the use of AST for the prevention of stress ulcers in general medicine patients is currently not recommended or supported in the published literature. Given the lack of indication, the increased risk of side effects, and the increase in associated costs, careful consideration of the use of SUP must be made. The future development of updated ASHP guidelines on SUP may address both the role of AST and resource utilization. In the meantime, practitioners should follow the UWMC institutional guidelines for the use of SUP for critically ill patients and continue to consult the published literature for appropriate use of AST in non-ICU patients.

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Inappropriate use of AST for SUP in non-ICU hospitalized patients has substantial financial ramifications for both the patients and the hospital.

Overuse of resources is compounded by the frequent practice of continuing non-indicated AST following hospital discharge.

Guidelines for appropriate use of SUP in critically ill patients at UWMC are detailed in Table 1.

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Correction to DTT February 2008: Nicotine Patch cash cost is \$440, not \$44.

P&T COMMITTEE BRIEF SUMMARY January 15, 2008

FORMULARY ADDITIONS	DOSAGE FORM(S), STRENGTH(S)	THERAPEUTIC CLASSIFICATION	USE	USUAL ADULT STARTING DOSE
Sunitinib (Sutent®)	12.5 mg, 25 mg, and 50 mg capsules	Antineoplastic agent	Treatment of advanced renal cell carcinoma and gastrointestinal stromal tumor (GIST)	50 mg orally once daily for 4 weeks, followed by 2 weeks off, then repeat
Temsirolimus (Torisel®)	25 mg per mL vial supplied with diluents	Antineoplastic agent	Treatment of advanced renal cell carcinoma	25 mg intravenously once weekly
Adalimumab (Humira®)	40 mg per 0.8 mL in prefilled syringe or pen 20 mg per 0.4 mL in prefilled syringe	Immunologic agent	Treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease	Administered by subcutaneous injection Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis • 40 mg every other week Crohn's Disease • 160 mg on day 1 • 80 mg on day 15 • 80 mg every other week starting on day 29 Plaque Psoriasis • 80 mg on day 1 • 40 mg every other week starting on day 8
Zoledronic acid (Reclast®)	5 mg per 100 mL vial	Bisphosphonate	Treatment of postmenopausal osteoporosis	5 mg intravenously once yearly

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Table, p2
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- P&T Committee Brief Summary,
January 2008, p5; February 2008, back cover

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P&T COMMITTEE BRIEF SUMMARY February 19, 2008

FORMULARY ADDITIONS	DOSAGE FORM(S), STRENGTH(S)	THERAPEUTIC CLASSIFICATION	USE	USUAL ADULT STARTING DOSE
Hyaluronic acid gel (Restylane® and Perlane®)	20 mg per mL prefilled syringe	Dermatological agent	Indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds	Typical usage for each treatment session is less than 2 to 3 mL per treatment site

Other Actions

MEDICATION	ACTION
Cinacalcet (Sensipar®)	MAINTAIN cinacalcet on formulary with use restricted to patients with secondary hyperparathyroidism due to chronic kidney disease intolerant and/or refractory to vitamin D sterol therapy and followed by Nephrology.
Levetiracetam (Keppra®)	MAINTAIN intravenous levetiracetam on formulary WITHOUT restriction for new starts to be initiated by the Epilepsy Service.