

DISCLAIMER: These guidelines were prepared jointly by the Surgical Critical Care and Medical Critical Care Services at Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

## STRESS ULCER PROPHYLAXIS

### SUMMARY

The incidence of clinically important gastrointestinal bleeding due to stress ulceration has declined with advances in the resuscitation and management of critically ill patients. Maintaining adequate systemic perfusion and initiating early enteral nutrition play an important role in preventing stress ulceration. The efficacy of histamine-2 receptor antagonists (H<sub>2</sub>RAs), antacids, and proton-pump inhibitors (PPI) in preventing stress ulceration remains controversial. Prophylaxis using these medications is associated with potential adverse effects and drug interactions as well as additional cost. Given the controversial efficacy of these agents, their use should be limited to patients with acute risk factors and/or populations that have not been well-studied. In addition, these guidelines are not intended for patients that have an indication for treatment with acid suppressive therapy, such as duodenal ulcer disease, gastroesophageal disease, etc.

### RECOMMENDATIONS

- **Level 1**
  - **A H<sub>2</sub>RA (either enteral or intravenous) is indicated in patients with acute risk factors.**
  - **Therapy should be discontinued in patients that no longer have acute risk factors.**
- **Level 2**
  - **A PPI is an acceptable alternative to a H<sub>2</sub>RA in situations where these agents cannot be used (i.e., patients demonstrating intolerance to a H<sub>2</sub>RA or who have another indication for PPI therapy).**
  - **Discontinuation of therapy should be considered in all patients when full enteral feeding is tolerated except for mechanically ventilated patients.**
- **Level 3**
  - **A H<sub>2</sub>RA can be considered in patients that are NPO and have at least two potential risk factors for stress ulceration.**

#### Acute Risk Factors for Stress Ulceration

- **Mechanical ventilation (>48 hours)**
- **Coagulopathy**
- **Hypoperfusion (sepsis, shock, or organ dysfunction, i.e. acute renal failure)**
- **High-dose corticosteroids (>250 mg/day hydrocortisone or equivalent)**
- **Significant burn injury (total body surface area >35%)**
- **Severe brain/spinal cord injury (Glasgow Coma Scale ≤ 8)**

#### Potential Risk Factors for Stress Ulceration

- **Concomitant use of a non-steroidal anti-inflammatory drug (NSAID)**
- **Concomitant or recent corticosteroid use**
- **History of upper gastrointestinal (GI) hemorrhage, peptic ulcer disease, or gastritis**
- **Mild to moderate brain/spinal cord injury**

### EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

### LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

## **INTRODUCTION**

Stress ulceration is a form of hemorrhagic gastritis that may occur following trauma or critical illness (1). Although not completely understood, the pathophysiology is likely multifactorial. Inadequate systemic perfusion, mucosal blood flow, and cellular oxygenation play an important role in the development of stress ulceration (1). Decreased gastric pH, increased mucosal permeability, and alterations in normal protective mechanisms may also be contributing factors (1, 2). Since 1978, there has been a decrease in the incidence of clinically important bleeding due to stress ulceration (1). This can likely be attributed to improved resuscitation, earlier initiation of enteral feeding, and possibly the use of pharmacologic prophylaxis.

Medications used for stress ulcer prophylaxis act by inhibiting gastric acid secretion, neutralizing gastric acid, or protecting the gastric mucosa. The efficacy of H<sub>2</sub>RAs and antacids has been extensively studied. Both placebo-controlled trials and meta-analyses, however, have yielded conflicting results (1). Similarly, PPIs for stress ulcer prophylaxis have been evaluated in a limited number of published trials. Although these agents effectively maintain gastric pH  $\geq$  4, this endpoint has not been proven to improve clinical outcome. Additionally, superiority over H<sub>2</sub>RAs has not been demonstrated in a well-designed trial. Many investigators now question the value of pharmacologic prophylaxis, especially in the setting of improved resuscitation techniques and early enteral feeding. A randomized, controlled trial that compared a PPI, H<sub>2</sub>RA, and sucralfate with placebo in 287 high risk trauma/surgery patients demonstrated no difference in clinically significant upper GI bleeding with percentages of 1%, 3%, 4%, and 1%, respectively (3). Prophylactic medications are associated with potential adverse effects and drug interactions as well as additional cost.

## **LITERATURE REVIEW**

### **Risk Factors for Stress Ulceration**

In a multicenter study of 2252 patients, Cook et al. identified respiratory failure (mechanical ventilation for at least 24 hours) and coagulopathy (platelet count  $<$ 50,000 mm<sup>3</sup>, INR  $>$ 1.5, or aPTT  $>$  2 times control) as independent risk factors for bleeding (4). Of the 33 patients (1.5%) with clinically important bleeding, 23 (70%) were receiving stress ulcer prophylaxis. However, the use of prophylaxis was not controlled and various regimens were administered. Enteral nutrition was not addressed. Only a small number of trauma patients were represented (28 head injuries and 18 multiple traumas). (Class II)

A subsequent multivariate analysis by Cook et al. identified maximum serum creatinine as a risk factor (RR 1.16 [95% CI 1.02-1.32]) for clinically important upper gastrointestinal bleeding (2). All patients received either ranitidine or sucralfate. The use of enteral feeding was not randomized. Enteral nutrition (RR 0.3 [95%CI 0.13-0.67]) and ranitidine (RR 0.39 [95%CI 0.17-0.83]) were both protective against stress ulceration. The overall incidence of clinically important gastrointestinal bleeding was 2.8%. None of the 147 trauma patients had clinically important bleeding. (Class I)

Although other risk factors have been identified, they have not been well studied. These include sepsis, length of intensive care unit (ICU) stay greater than one week, presence of occult bleeding for at least six days, and high dose corticosteroids ( $>$ 250 mg/day hydrocortisone or equivalent) (1). There is evidence that the incidence of stress ulceration is higher when more than one risk factor is present (5).

Patients suffering burn or neurologic injury have frequently been excluded from studies due to their presumably high risk for the development of stress ulcers. Additional populations frequently excluded from clinical trials include patients with a history of upper gastrointestinal hemorrhage, peptic ulcer disease, or non-steroidal anti-inflammatory drug (NSAID) use. Whether these conditions translate into an increased risk of acute, stress-induced bleeding is therefore unknown (4).

### **Stress Ulceration and Enteral Feeding**

A meta-analysis published in 2010 included 17 randomized, controlled trials that enrolled a total of 1836 patients (6). This meta-analysis distinguished between studies that used early, adequate enteral nutrition from those that did not to assess the efficacy of stress ulcer prophylaxis. Results of the analysis

demonstrated a reduced risk of GI bleeding with use of a H<sub>2</sub>RA only in the sub-group of patients that did not receive enteral nutrition. Stress ulcer prophylaxis did not decrease the risk for GI bleeding in the patients that were fed enterally. Although prophylaxis with H<sub>2</sub>RAs had no effect on pneumonia and hospital mortality overall, there was an increase in the incidence of hospital-acquired pneumonia and hospital mortality in the subgroup of patients that received stress ulcer prophylaxis plus enteral feeds. (Class II)

### **Proton Pump Inhibitors (PPIs)**

Phillips et al. performed a prospective, open-label trial evaluating the efficacy of omeprazole suspension for stress ulcer prophylaxis in 75 critically ill patients (7). Patients were considered for the study if they were admitted to the surgical or burn ICU with an intact stomach, a nasogastric tube, and an anticipated ICU length of stay > 48 hours. They also had to have a gastric pH < 4, be on mechanical ventilation, and have an additional risk factor for stress ulceration. Patients were excluded if they were receiving enteral feedings through the nasogastric tube. Omeprazole suspension was administered as 40 mg, followed by a second 40 mg dose 6 to 8 hours later, then 20 mg daily until there was no longer a need for stress ulcer prophylaxis. Ten patients received H<sub>2</sub>RAs prior to omeprazole suspension. Of the 65 patients who received omeprazole suspension as their initial prophylaxis, none developed overt or clinically significant upper gastrointestinal bleeding. Omeprazole significantly increased the mean gastric pH within 4 hours of the start of therapy (3.5 to 7.1). (Class II)

In a similar study, the efficacy of omeprazole suspension was evaluated in 66 patients with severe trauma (8). In addition to mechanical ventilation, patients were required to have at least one other risk factor for stress ulceration. Patients were excluded if they were receiving gastric feedings. Omeprazole was administered as described in the previous study. None of the patients developed overt or clinically significant upper gastrointestinal bleeding. Gastric pH monitoring revealed a statistically significant increase following initiation of omeprazole therapy (3 patients required an increased dose to achieve adequate pH control). (Class II)

Levy et al. compared the efficacy of omeprazole versus ranitidine for prophylaxis against clinically important gastrointestinal hemorrhage in 67 patients admitted to an ICU who had at least one risk factor for stress ulceration (9). Patients were randomized to receive ranitidine (50 mg bolus followed by 150 mg daily by continuous infusion or intermittent administration) or omeprazole (40 mg daily orally or via nasogastric tube). Clinically important bleeding occurred in significantly more ranitidine patients compared to omeprazole patients (31% versus 6%; p=0.013). It should be noted that the ranitidine patients had significantly more risk factors for stress ulceration than the omeprazole patients did. The use of enteral nutrition was not addressed. (Class I)

A meta-analysis pooled a total of 936 patients from seven randomized, controlled trials to compare the efficacy and safety of H<sub>2</sub>RAs to PPIs for stress ulcer prophylaxis (10). There was not a statistically significant difference found in the incidence of upper gastrointestinal bleeding between PPIs and H<sub>2</sub>RAs. In addition, no significant difference was found in the safety outcomes of pneumonia and ICU mortality. (Class II)

A number of additional trials have been performed comparing the effects of H<sub>2</sub>RAs and PPI on gastric pH and/or prevention of upper gastrointestinal hemorrhage. However, the results are only published in abstract form at this time (11,12,13).

Allen and colleagues published a thorough review of stress ulcer prophylaxis in the post-operative period in which the most recent studies addressing this topic are discussed (14).

## REFERENCES

1. American Society of Health-System Pharmacists. ASHP therapeutic guidelines on stress ulcer prophylaxis. *Am J Health-Sys Pharm* 1999; 56:347-79.
2. Cook D, Heyland D, Griffith L, et al. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. *Crit Care Med* 1999; 27:2821-7.
3. Kantorova I, Svoboda P, Scheer P, et al. Stress ulcer prophylaxis in critically ill patients: a randomized controlled trial. *Hepato-Gastroenterology* 2004; 51:757-761.
4. Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med* 1994; 330:377-81.
5. Metz CA, Livingston DH, Smith S, et al. Impact of multiple risk factors and ranitidine prophylaxis on the development of stress-related upper gastrointestinal bleeding: A prospective, multicenter, double-blind, randomized trial. *Crit Care Med* 1993; 21:1844-9.
6. Marik P, Vasu T, Hirani A, et al. Stress ulcer prophylaxis in the new millennium: A systematic review and meta-analysis. *Crit Care Med* 2010; 38:1-7.
7. Phillips JO, Metzler MH, Palmieri TL, et al. A prospective study of simplified omeprazole suspension for the prophylaxis of stress-related mucosal damage. *Crit Care Med* 1996; 24:1793-1800.
8. Lasky MR, Metzler MH, Phillips JO. A prospective study of omeprazole suspension to prevent clinically significant gastrointestinal bleeding from stress ulcers in mechanically ventilated trauma patients. *J Trauma* 1998; 44:527-33.
9. Levy MJ, Seelig CB, Robinson NJ, et al. Comparison of omeprazole and ranitidine for stress ulcer prophylaxis. *Dig Dis Sci* 1997; 42:1255-9.
10. Lin PC, Chang CH, Hsu PI, et al. The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer prophylaxis among critical care patients: A meta-analysis. *Crit Care Med* 2010; 38:1197-1205.
11. Phillips JO, Metzler MH, Huckfeldt RE, et al. A multicenter, prospective, randomized clinical trial of continuous infusion I.V. ranitidine vs. omeprazole suspension in the prophylaxis of stress ulcers. *Crit Care Med* 1998; 26:101A.
12. Azevedo JR, Soares MG, Silva G, et al. Prevention of stress ulcer bleeding in high risk patients. Comparison of three drugs. *Crit Care Med* 1999; 27:A145.
13. Roberts KW, Pitcher D, Cryer B. Effect of lansoprazole suspension versus continuous intravenous ranitidine infusion on gastric pH of mechanically ventilated intensive care unit patients. *Pharmacother* 2000; 20:342.
14. Allen ME, Kopp BJ, Erstad BL. Stress ulcer prophylaxis in the postoperative period. *Am J Health-Syst Pharm* 2004; 61:588-96.

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