STRESS ULCER PROPHYLAXIS

SUMMARY
The incidence of clinically important bleeding from 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 (H₂RAs), antacids, sucralfate, 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.

Acute Risk Factors for Stress Ulceration
- Mechanical ventilation (>48 hours)
- Coagulopathy
- Renal failure
- Hypoperfusion (sepsis, shock, or organ dysfunction)
- High-dose corticosteroids (>250 mg/day hydrocortisone or equivalent)
- Brain/spinal cord injury
- Significant burn injury (total body surface area >35%)

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 hemorrhage, peptic ulcer disease, or gastritis

RECOMMENDATIONS
- Level 1
  - A H₂RA (either enteral or intravenous) and enteral nutrition are indicated in patients with acute risk factors.
  - Discontinuation of therapy should be considered when full enteral feeding is tolerated and acute risk factors have resolved.
- Level 2
  - Sucralfate is an acceptable alternative to a H₂RA provided gastric access is available and no drug interactions are present.
  - A PPI is an acceptable alternative to either a H₂RA or sucralfate in situations where these agents cannot be used (i.e., patients demonstrating intolerance to a H₂RA or who have another indication for PPI therapy).
- Level 3
  - A H₂RA (either enteral or intravenous) is indicated in patients with potential risk factors for stress ulceration.

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.

Revised 1/15/04, 12/7/05
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 (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$_2$RAs, antacids, and sucralfate 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$_2$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. 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$^3$, INR >1.5, or aPTT > 2 times control) as independent risk factors for bleeding (3). 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 (4).

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 (3).

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 (5). 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 H2RAs 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 (6). 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 (7). 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 number of additional trials have been performed comparing the effects of H2RAs and PPI on gastric pH and/or prevention of upper gastrointestinal hemorrhage. However, the results are only published in abstract form at this time (8, 9, 10).

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 (11).

REFERENCES
Consider Stress Ulcer Prophylaxis

Are any acute risk factors present?

- NO: No Therapy Indicated
- YES: 
  
  Is patient on home proton pump inhibitor therapy?

- YES: Initiate enteral or parenteral proton pump inhibitor
- NO: Initiate enteral or parenteral H₂ blocker therapy or sucralfate

Notes:

Enteral therapy should be used whenever a functioning gastrointestinal tract is present and adequate absorption can be assumed.

Sucralfate is an acceptable substitute for H₂RA blocker therapy if:

1) no drug interactions are present (i.e., use of quinolones or levothyroxine) and
2) gastric access is available