Stress Ulcer Prophylaxis: Guideline Update April 2014

Disclosure Statement
- No conflict of interest

Objectives
- Who should be receiving stress ulcer prophylaxis in your institution?
- Pathophysiology
- Risk Factors
- What medications are best to use to prevent stress ulcers?
- The great debate: PPI’s vs. H2RA’s vs. sucralfate
- What are the complications of providing stress ulcer prophylaxis?
- Strategies for gaining back the control
Why is this important?
- Unnecessary Costs
- Meds without an indication
- Inappropriate use
- Patients sent home on SUP agents
- Opportunistic Infections
  - C. difficile
  - Pneumonia
- Readmissions

Question 1
- Who’s been anxiously awaiting the release of the new Stress Ulcer Prophylaxis guidelines?
  A. Check ASHP website at least weekly
  B. What Guidelines
  C. I thought this was a Law Talk?
  D. None of the above

ASHP Guidelines

<table>
<thead>
<tr>
<th>Document</th>
<th>Published</th>
<th>Next Review Date</th>
<th>Estimated Publication Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic Prophylaxis in Surgery</td>
<td>2013</td>
<td>2016</td>
<td>--</td>
</tr>
<tr>
<td>Clinical Practice Guidelines for Intensive Care Unit Nursing</td>
<td>2002</td>
<td>In process</td>
<td>--</td>
</tr>
<tr>
<td>Clinical Practice Guidelines for Neuromuscular Blockade in the Critically Ill Patient</td>
<td>2013</td>
<td>2016</td>
<td>In process</td>
</tr>
<tr>
<td>Clinical Practice Guidelines for the Management of Pain, Agitation and Delirium in Multisystematically Ill Patients</td>
<td>2013</td>
<td>2016</td>
<td>In process</td>
</tr>
<tr>
<td>Gastrointestinal Stress Ulcer Prophylaxis</td>
<td>Now</td>
<td>In process</td>
<td>Q1 2014</td>
</tr>
</tbody>
</table>
The Guidelines
- Last updated 1999
- What's missing?
- Are they still relevant?

History
- 1800's: Erosions & Gastric Ulcers had been known to develop
- 1970's: Gastric Acid linked as possible cause of stress ulcer development
- 1980's: Incidence of stress ulcer-related bleeding was found to be decreased by increasing gastric pH

Background

- 1970
  - Skillman and Silen reported a clinical syndrome of fatal "stress ulceration" in patients with
    - respiratory failure
    - hypotension
    - sepsis in the ICU
- 1971
  - Lucas et al labeled this as "stress-related erosive syndrome"
- Today
  - Stress Related Mucosal Disease

Terminology

- Stress Ulcers
- Ulceration
- Stress erosions
- Stress gastritis
- Hemorrhagic gastritis
- Erosive gastritis
- Peptic Ulcers
- Gastric Ulcers
- Stress-Related Mucosal Disease
  - SRMD

Proposed mechanisms for development of stress ulceration. SRMD results from the complex interaction of multi-physiological systems. The specific physiologic link remains uncertain and hypothesis. Reprinted with permission from Bresalier.24

Figure Legend:
Proposed mechanism for development of stress ulceration. SRMD results from the complex interaction of multi-physiological systems. The specific physiological link remains uncertain and hypothesis. Reprinted with permission from Bresalier.24
GI Complications in Patients Receiving Mechanical Ventilation

Proposed mechanisms for the development of GI complications during MV include the following:

- **Impaired defense mechanisms:**
  - 
  - 
  - 

- **Stress Ulceration:**
  - Occurs in 50 to 70% of ICU patients within 12 to 24 hours
  - Pathogenesis of stress ulceration
    - GI Mucosal Ischemia
      - Acid Secretion
        - Impaired defense mechanisms:
          - H+ back-diffusion
          - Mucous/bicarbonate barrier
          - Prostaglandin production
          - Epithelial renewal
    - Stress Ulceration
      - Gastrointestinal bleed
        - Mortality rate is 50 to 70%

Classification of GI Bleeding

<table>
<thead>
<tr>
<th>Outcome Measure of GI Bleeding</th>
<th>Definition</th>
<th>Incidence in ICU patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic Evidence</td>
<td>Hemorrhagic evidence of gastroduodenal lesions</td>
<td>74 to 100%</td>
</tr>
<tr>
<td>occult</td>
<td>Gastric or duodenal ulcer</td>
<td>15 to 50%</td>
</tr>
<tr>
<td>overt</td>
<td>Hemorrhage or coffee grounds in nasogastric tube aspirate</td>
<td>5 to 20%</td>
</tr>
<tr>
<td>Clinically significant</td>
<td>Overt bleeding accompanied by hemodynamic compromise</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>

Pathogenesis of stress ulceration

- GI Mucosal Ischemia
- Acid Secretion
- Impaired defense mechanisms:
  - H+ back-diffusion
  - Mucous/bicarbonate barrier
  - Prostaglandin production
  - Epithelial renewal
- Stress Ulceration
- Gastrointestinal bleed
- Mortality rate is 50 to 70%
Appearance
- Appearance
- Diffuse sub-epithelial hemorrhage with or without erosions

Where is this occurring?
- Acid-producing areas of stomach
- Upper body
- Fundus

Outcomes
- Morbidity
  - Increases length of ICU stay from 4 to 8 days, or even 11 days longer stay
- Mortality
  - 50% - 75% of patients with clinically significant bleed
  - ~ 12% directly attributable to the bleed
- Cost of bleed
  - $7000 in 1999

Accessed from www.webmd.com
Question 2

Which of the following is a risk factor for stress-related ulcer bleeding in a 73 year old critically ill patient?

A. An INR of 5  
B. Acute renal failure  
C. ARDS with ventilator support for 72 hours  
D. All of the above

Risk factors for Stress Ulcer Bleeding in Critically Ill Patients

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Risk Factor</th>
<th>Multiple Regression Odds Ratio (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=2250</td>
<td>Respiratory failure</td>
<td>15.4*</td>
</tr>
<tr>
<td></td>
<td>Complications</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Central failure</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Identified as independent risk factor; P<0.001
Risk factors for SRMD
- Respiratory failure requiring mechanical ventilation ≥ 48 hrs
- Coagulopathy (INR > 1.5, PTT > 2x control or Thrombocytopenia)
- Acute renal insufficiency
- Sepsis, Shock requiring vasopressors
- Multi-organ Failure
- Extensive burn or thermal injury involving more than 35% of the BSA
- Severe head or spinal cord injury
- History of gastrointestinal bleeding
- Organ transplantation
- Ulcerogenic Drugs (NSAIDS, Aspirin, Corticosteroids)
- Fibrinolytics, Anticoagulants

Idaho Society of Health System Pharmacists 2014 Spring Conference

Degree of Acid Suppression Required Varies Depending on Indication

<table>
<thead>
<tr>
<th>Gastric pH</th>
<th>Physiologic Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 3.5</td>
<td>Decreased incidence of stress-induced bleeding</td>
</tr>
<tr>
<td>≥ 4.5</td>
<td>Pepsin inactivation</td>
</tr>
<tr>
<td>5</td>
<td>99.9% acid neutralization</td>
</tr>
<tr>
<td>&lt; 5 to 7</td>
<td>Alterations in coagulation and platelet aggregation</td>
</tr>
<tr>
<td>2.7</td>
<td>Potential decrease in incidence of rebleeding</td>
</tr>
<tr>
<td>2.8</td>
<td>Pepsin destruction</td>
</tr>
</tbody>
</table>

Question 3
- 57 year old male admitted to the ICU with sepsis 2 days ago
  - Placed on Mechanical Vent at that time due to respiratory failure
  - Also experiencing some acute renal failure, thrombocytopenia, and hypotension
- Which of the following can be used as first-line stress ulcer bleeding prevention?
  - A. Famotidine IV
  - B. Esomeprazole IV
  - C. Omeprazole NGT
  - D. Sucralfate NGT
Therapeutic Options

- Antacids
- Sucralfate
- Histamine 2 Receptor Antagonists (H2RA)
- Proton Pump Inhibitors (PPI)

Antacids
Dose: 30 – 60 mL q 1 – 2 Hrs with pH monitoring

- Rarely used today
- Disadvantages
  - Labor intensive – frequent dosing and frequent monitoring
  - Dosed to pH of 3.5 to 4
  - Required frequent monitoring
  - High volume may pre-dispose patients to aspiration pneumonia
  - GI disturbances
  - Electrolyte imbalances (magnesium and aluminum)
  - Metabolic acidosis
  - Numerous drug interactions (digoxin, quinolones, iron)
  - Not cost effective

Sucralfate
Dose: 1 to 2 grams Q 4 – 8 Hours

- Doesn’t change the pH of the stomach
- No pH monitoring required
- MOA:
  - In acidic environment forms a polymer that eventually binds with the protein in the exposed ulcer
- Disadvantages
  - Not available intravenously
  - Requires time spaced from enteral feeding tube occlusion
  - Aluminum toxicity
  - Hypophosphatemia
  - Constipation
  - Drug interactions via chelation
  - Quinolones, digoxin, warfarin, quinidine, lithium, amphotericin, tetracycline
Histamine-2 Receptor Antagonists (H2RA’s)
Cimetidine, Ranitidine, Famotidine, Nizatidine

Started in the mid 90’s with cimetidine infusion = well studied
- IV and PO formulation
- Cimetidine IV = only H2RA FDA approved for SUP
- Intermittent vs Continuous Infusions
- No advantage to pH monitoring vs no pH monitoring
- Tachyphylaxis with CI
- Renal dosing required
- Cost effective – generics available

IV PPI For Management of UGI Bleed: Tolerance
Omeprazole 80 mg + 8 mg/hr vs Ranitidine 50 mg + 0.25 mg/hr x 72 hrs
DB crossover with gastric pH

<table>
<thead>
<tr>
<th>Results (n=34 healthy volunteers)</th>
<th>Day One</th>
<th>Day Three</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median pH Omeprazole</td>
<td>6.1</td>
<td>6.3</td>
</tr>
<tr>
<td>Median pH Ranitidine</td>
<td>5.1</td>
<td>2.7</td>
</tr>
<tr>
<td>% pH &gt; 4 Omeprazole</td>
<td>95%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>% pH &gt; 4 Ranitidine</td>
<td>70%</td>
<td>26%</td>
</tr>
<tr>
<td>% pH &gt; 6 Omeprazole</td>
<td>59%</td>
<td>71%</td>
</tr>
<tr>
<td>% pH &gt; 6 Ranitidine</td>
<td>30%*</td>
<td>7%*</td>
</tr>
</tbody>
</table>

*p < 0.001, *p = 0.014

Histamine-2 Receptor Antagonists (H2RA’s)
Adverse Effects and DI’s
- CNS adverse effects
  - Confusion, hallucinations, agitation, dizziness, headaches
  - Cimetidine > ranitidine > nizatidine > famotidine
- Pneumonia – CAP
- Rapid IVF: hypotension and arrhythmias
- Pseudo-renal failure with cimetidine
- CYP-450 drug interactions: 3A4, 2D6, 2C19, 1A2
  - Phenytoin, warfarin, amiodarone, colchicine, BZDs, CCBs
  - Cimetidine >> ranitidine (low) > nizatidine: famotidine (none)
H2RA-Induced Thrombocytopenia

- Structure Related
- Onset is 4 – 7 days
- Can occur earlier with prior exposure
- Cross reactivity is 100%

Sucralfate vs. Ranitidine for Prevention of Upper GI Bleeding in Mechanically Ventilated Patients

Ranitidine 50 mg IV Q8H vs. Sucralfate 1 gm Q6H

P=0.19

N=1200


Question 4

- Which of the following is an adverse effect of PPIs?
  A. Interstitial nephritis
  B. Hypomagnesemia
  C. C. difficile diarrhea
  D. All of the Above
Proton Pump Inhibitors (PPIs)
Pantoprazole, Omeprazole, Lansoprazole, etc.
- Activated by protonation in parietal cells and then binds to H/K counter exchange ATPase to block acid production
- Most potent of gastric acid secretion agents
- Superior to H2RA’s in other settings
- Consistent pH control
- IV and PO forms
- Most trials studied enteral PPIs for SUP
- Lack of data for IV PPIs
- Becoming less expensive
- ADE’s
- Pneumonia
- C. diff
- Possible drug interactions
- P450’s and Clopidogrel
- Latest Sepsis Guidelines seem to favor PPIs

PPI Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route</th>
<th>Dose</th>
<th>Metabolized by Hepatic CYP450 enzymes</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole</td>
<td>PO, NG, IV</td>
<td>40 mg daily</td>
<td>2C19 &gt; 3A4</td>
<td>80% renal inactive metabolites, &lt; 1% parent drug in urine</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>PO, NG, IV</td>
<td>15 or 30 mg daily</td>
<td>15 mg = 81%, 30 mg = 91%</td>
<td>14 – 25% renal inactive metabolites, &lt; 1% parent drug in urine</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>PO, NG</td>
<td>20 to 40 mg daily</td>
<td>2C19 &gt; 3A4</td>
<td>77% renal inactive metabolites, “minimal” parent drug in urine</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>PO, NG, IV</td>
<td>40 mg daily</td>
<td>2C19 &gt; 3A4</td>
<td>71 – 82% renal inactive metabolites, no active drug in urine, 18 – 20% fecal</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>PO, NG</td>
<td>20 mg daily</td>
<td>2C19 &gt; 3A4</td>
<td>90% renal inactive metabolites, no active drug in urine, 10% fecal</td>
</tr>
</tbody>
</table>

PPI Adverse Effects
- Gastrointestinal
  - Diarrhea, nausea, vomiting, abdominal pain
  - Headaches (3 to 5%)
  - Acute Intestinal Nephritis
  - Rash, fever, arthralgias
  - Oliguric ARF, eosinophilia, eosinophiluria, pyuria, hematuria
  - Pneumonia – CAP, HAP, VAP
  - C. difficile Diarrhea
  - Hip Fractures
  - PPIs >> HrRAs
  - Hypomagnesemia with chronic use (3 months)
  - Seizures reported
  - PPIs may change interstitial absorption of Mg
  - Pantoprazole plus Magnesium supplements have been used
Clostridium difficile

- FDA Warning links PPIs to C. difficile-Associated Diarrhea
- Feb 8th, 2012
- FDA Safety Alert warned that PPI’s may be associated with an increased risk for Clostridium difficile associated diarrhea

PPIs and Risk of Community-Acquired CDAD
- 317 cases of community-acquired C. difficile-associated disease treated with oral vancomycin and 3167 controls

<table>
<thead>
<tr>
<th>Exposure within 90 days</th>
<th>Odds ratio for C. difficile-associated disease</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic</td>
<td>8.2</td>
<td>6.1 – 11.0</td>
</tr>
<tr>
<td>PPI</td>
<td>3.5</td>
<td>2.3 – 5.2</td>
</tr>
</tbody>
</table>

Questions
- Epidemiologic studies have limitations
- C. difficile-associated disease involves a complex interaction between host, pathogen, and environment

Use of Gastric Acid–Suppressive Agents and the Risk of Community-Acquired Clostridium difficile–Associated
Times to Health Care–Associated Clostridium difficile Infection and Colonization during Hospitalization.

- Health care–associated C. difficile infection
- Health care–associated C. difficile colonization

No. of Patients

Risk of Recurrent C. difficile
- 1166 patients
  - Metronidazole or Vancomycin treated C. difficile
  - 527 (45.2%) received PPI's
  - Similar antibiotic exposure in both groups
  - Results
    - 42% increased risk of recurrence

Proton Pump Inhibitors and Risk for Recurrent Clostridium difficile Infection

- Recurrence-free survival in those exposed vs unexposed to proton pump inhibitors (PPIs) during treatment for incident Clostridium difficile infection.
- Time to recurrence started from the incident case finding or the start of antibiotic treatment (≤3 days after dosing).

Figure Legend:
- Recurrence-free survival in those exposed vs unexposed to proton pump inhibitors (PPIs) during treatment for incident Clostridium difficile infection.

Use of Proton Pump Inhibitors and the Risk of Community-Acquired Pneumonia: A Population-Based Case-Control Study

Figure Legend: Association between current use of proton pump inhibitors (PPIs) and community-acquired pneumonia, according to the timing of first PPI prescription. OR indicates odds ratio.

<table>
<thead>
<tr>
<th></th>
<th>Current PPI Use OR (CI)</th>
<th>Current H2RA Use OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arch Intern Med 2007</td>
<td>1.5 [1.3 – 1.7]</td>
<td>1.10 [0.8 – 1.3]</td>
</tr>
<tr>
<td>Ann Intern Med 2008</td>
<td>1.02 [0.97 – 1.08]</td>
<td>0.99 [0.95 – 1.04]</td>
</tr>
</tbody>
</table>

Community-Acquired Pneumonia Comparing the Literature

<table>
<thead>
<tr>
<th></th>
<th>Recent PPI Initiation &amp; Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arch Intern Med 2008</td>
<td>2.45 [2.04 – 2.95]</td>
</tr>
<tr>
<td>Arch Intern Med 2007</td>
<td>2.30 [1.22 – 4.35]</td>
</tr>
<tr>
<td>JAMA 2004</td>
<td>2.34 [1.42 – 3.54]</td>
</tr>
<tr>
<td>Epidemiol 2009</td>
<td>1.21 [0.9 – 1.63]</td>
</tr>
<tr>
<td>Ann Int Med 2010</td>
<td>1.83 [1.24 – 2.70]</td>
</tr>
<tr>
<td>Overall CAP Risk*</td>
<td>1.92 [1.40 – 2.63]</td>
</tr>
</tbody>
</table>

* Dose response relationship also noted with high dose PPI use
Long-Term PI Use and Hip Fractures  
- Nested case-control study of patients aged > 50 years  
- 13,556 patients with hip fracture and 135,386 controls

<table>
<thead>
<tr>
<th>Exposure Group</th>
<th>Adjusted Odds Ratio for Hip Fracture</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 year of PPI therapy</td>
<td>1.44</td>
<td>1.30 – 1.59</td>
</tr>
<tr>
<td>Long-term high-dose PPI therapy</td>
<td>2.65</td>
<td>1.80 – 3.90</td>
</tr>
</tbody>
</table>

- Association stronger in men than women  
- Possible mechanisms  
  - Calcium malabsorption secondary to acid suppression  
  - Reduction in bone resorption through inhibition of osteoclastic vacuolar proton pumps  
- Did not include information on OTC calcium and vitamin D use

Stress  
- Impaired Proton Buffing  
- Impaired Proton Activation  
- Impaired Proton Removal  
- Impaired Blood Flow  
- Reperfusion Injury  
- Impaired Defense Mechanism  
- Acid Injury  
- Free Radical Formation & Inflammation  
- Acid Injury  
- Mucosal Ischemia  
- Impaired Blood Flow  
- Impaired Defense Mechanism  
- GI Bleed

PPI's & H2RA's
Does Enteral Nutrition Help?
- Benefits in critically ill
- Improves splanchnic blood flow
- Reduces macroscopic ulceration
- Does it reduce the risk of developing SRMD?
- Lack of significant evidence
- Bottom line
  - Don’t use enteral nutrition as sole SRMD prophylaxis measure

H2RA vs PPI
- Clinically Important GI Bleeding
- Meta-Analysis
**H2RA vs PPI**

- Clinically Important GI Bleeding
- Bias Risk

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Upper GI Bleeding Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conrad (2005)</td>
<td>350</td>
<td>Omeprazole IV, NGT Cimetidine IV</td>
</tr>
<tr>
<td>Kantorova (2004)</td>
<td>143</td>
<td>Omeprazole IV, Famotidine IV</td>
</tr>
<tr>
<td>Salvi (2008)</td>
<td>129</td>
<td>Ranitidine IV 55 mg/kg</td>
</tr>
<tr>
<td>Levy (1997)</td>
<td>30</td>
<td>Omeprazole PO/NGT Ranitidine IV</td>
</tr>
<tr>
<td>Somberg (2005)</td>
<td>200</td>
<td>Pantoprazole IV Cimetidine IV</td>
</tr>
</tbody>
</table>

**Is Stress Ulcer Prophylaxis Needed?**

(Prophylaxis is recommended for ICU patients with one or more risk factors)

- No Risk Factors Present:
  - Antisecretory IV H2RA (first line)
  - PPI if H2RA not tolerated

- Functional GI tract:
  - Consider oral therapy
  - IV therapy

**Additional Information:**
- Contraindications to stress ulcer prophylaxis include gastrointestinal bleeding, gastric outlet obstruction, and previous history of GI bleeding.
- For patients with a history of upper GI bleeding, consider proton pump inhibitors (PPIs) for prophylaxis.
- For patients with a history of lower GI bleeding, consider histamine-2 receptor antagonists (H2RAs).

**Summary:**
- The new stress ulcer prophylaxis guidelines are finally here, offering evidence-based recommendations for optimal patient care.
**When Do We Stop?**
- Patients should be reassessed daily
- Once the indication is removed the med should be discontinued

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**Transitions of Care**

<table>
<thead>
<tr>
<th>652 ICU Admissions</th>
<th>523 ICU Admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>246 patients initiated on Stress Ulcer Prophylaxis in ICU</td>
<td>307 patients received SUP in ICU</td>
</tr>
<tr>
<td>215/246 (84%) transferred from ICU on SUP</td>
<td>316/357 (89%) were transferred out of ICU on SUP</td>
</tr>
<tr>
<td>24% Discharged from hospital on SUP with no indication</td>
<td>24% Discharged from hospital on SUP without appropriate indication</td>
</tr>
</tbody>
</table>

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**What can we do?**
- Start with education
  - Hatch et al, 2010
  - Looked at educational intervention to reduce non-indicated prescribing of gastric acid suppressants for SUP
Pharmacist Intervention

1. Dosing card with indications
2. Pharmacist interaction during multidisciplinary rounds
3. Medication reconciliation by RPh at discharge

Results

- 356 patients included in study
- 158 (44%) were using acid-suppressing meds prior to admission, compared to 25.6% in Wohlt's study
- 308 received SUP while in ICU
- 11% had no identifiable indication
- 259 continued upon transfer out of the ICU
- 84 (24%) had no clear indication
- Improvement of 50.7% from previous study

Pharmacy Protocol

- Worked with the intensivists to create a Stress Ulcer Prophylaxis per Pharmacy Protocol
- When ‘SUP Per Pharmacy’ ordered, the pharmacist would identify risk factors
Applying this to your practice

H2RA's are the preferred agent for initial prevention of GI hemorrhage resulting from Stress Related Mucosal Disease in patients that are at risk.

PPI's should be reserved for patients unable to tolerate H2RA's.

Antacids are not recommended for prevention of SRMD.

Sucralfate may be used for SUP when H2RA's and PPI's cannot be used.

The need for SUP should be evaluated daily, and pharmacotherapy should be discontinued when the patient no longer has risk factors for SRMD.