Stressed Out: Evaluating the Need for Stress Ulcer Prophylaxis in the ICU

Josh Arnold, PharmD
PGY1 Pharmacy Resident

Pharmacy Grand Rounds
November 8, 2016
Objectives

• Identify the significance and potential mechanisms of stress ulcer development in critically ill patients

• Discuss evidence for the use of stress ulcer prophylaxis in specific patient populations

• Describe the implications and potential adverse effects associated with the use of stress ulcer prophylaxis
Significance and mechanisms

Populations

Implications and adverse effects
Epidemiology

• Incidence
  • Stress ulcers are present in the majority of critically ill patients
    • Within 24 hours of ICU admission, >75% of patients demonstrate evidence of mucosal damage
    • Approximately 5-25% will have bleeding
    • ~1-4% will have clinically significant bleeding

• Complications
  • Severe ulceration and bleeding can:
    • Lengthen ICU stay by up to 8 days
    • Increase mortality as much as 4-fold

Which of the following is a potential mechanism of stress ulcer development in the critically ill patient?

A. Increased gastrointestinal motility
B. Decreased splanchnic blood flow
C. Increased bicarbonate secretion
D. Decreased duration of mechanical ventilation
Critical Illness

- Increased Catecholamines
- Increased Vasoconstriction

Decreased Cardiac Output

Hypovolemia

Proinflammatory Cytokine Release

Splanchnic Hypoperfusion

- Reduced HCO$_3$ Secretion
- Reduced Mucosal Blood Flow
- Decreased GI Motility
- Acid Back-Diffusion

Mucosal Vulnerability

Additional factors

**Mechanical ventilation**
- Promotes RAAS activity and catecholamine release
- High PEEP decrease venous return and reduces preload

**Medications**
- Opiates and sedatives can decrease gut motility and impair venous return
- Systemic hemodynamic changes due to vasopressor therapy
- Glucocorticoids and NSAIDS

**Coagulopathy**
- Impaired ability to terminate active bleeding

Significance and mechanisms

Populations

Implications and adverse effects
In what populations do you recommend the use of stress ulcer prophylaxis?

A. Patients meeting guideline recommendations
B. Patients I believe are “high-risk”
C. All ICU patients
D. I ask a crystal ball
Cook et al. (1994)

- Prospective, multicenter, cohort study
- Primary endpoint: clinically important GI bleeding
- 2252 patients, 674 received SUP
  - 71.8% H$_2$RA; 0.3% omeprazole
- 33 patients met primary endpoint (1.5%)
- 1.6% patients diagnosed with sepsis
- 48.5% primary diagnosis of cardiovascular surgery
- Mortality 9.7%

<table>
<thead>
<tr>
<th>Independent Risk Factors</th>
<th>Odds Ratio</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation &gt;48 hrs</td>
<td>15.6</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>4.3</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

SUP: stress ulcer prophylaxis
GI: gastrointestinal

Original Guidelines - AJHP 1999

- Recommended SUP use in “high risk” patients
  - With coagulopathies
  - Requiring mechanical ventilation for >48 hours
  - With history of GI ulceration or bleed within 1 year
  - Special populations
  - Patients with ≥2 of the following

- Sepsis
- ICU stay >1 week
- Occult bleeding lasting ≥6 days
- High-dose steroids
Original Guidelines

- Number needed to treat
  - Low risk patients: >900
  - High risk patients: 30

- Limitations
  - Little data on use of PPI therapy
  - Low strength of evidence
  - Outdated

GCS: glasgow coma score
BSA: body surface area
PPI: proton-pump inhibitor

## What has changed? The 2000s

<table>
<thead>
<tr>
<th>Mechanical ventilation &gt;48 hrs</th>
<th>Coagulopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute renal insufficiency</td>
<td>Acute hepatic failure</td>
</tr>
<tr>
<td>Sepsis syndrome</td>
<td>High-dose corticosteroids</td>
</tr>
<tr>
<td>History of gastrointestinal bleeding</td>
<td>Thermal injury involving &gt;35% BSA</td>
</tr>
<tr>
<td>Severe head or spinal cord injury</td>
<td>Low intragastric pH</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Major surgery (&gt;4 hrs)</td>
<td>Acute lung injury</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>Number of comorbidities</td>
</tr>
</tbody>
</table>

BSA: body surface area

Do all our patients really need stress ulcer prophylaxis?
Krag et al. (2015)

- Prospective, observational, international, 7-day cohort study

- Primary outcome: clinically important gastrointestinal bleeding during ICU stay
  - Secondary outcomes: overt GI bleeding in ICU; 90 day mortality

- Total of 1,034 patients, with 27 patients developing clinically important GI bleed
Krag et al. (2015)

- 73% of patients received acid suppressant therapy during ICU stay
- 59% of patients with clinically important GI bleeding received SUP prior to bleed
- 90-day mortality
  - Overall: 26.2%
  - Without clinically important GI bleed: 25.4%
  - With clinically important GI bleed: 55.6%

### Independent Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th>Adj* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt GI bleeding</td>
<td>1.70 (0.70-4.10)</td>
<td>1.17 (0.43-3.21)</td>
</tr>
<tr>
<td>Clinically important GI bleeding</td>
<td>3.72 (1.72-8.04)</td>
<td>1.70 (0.68-4.28)</td>
</tr>
</tbody>
</table>

SUP: stress ulcer prophylaxis
GI: gastrointestinal
*adjusted for: age, gender, comorbidites, SOFA score, mechanical ventilation, coagulopathy, etc

When do patients bleed?

# What risks exist?

<table>
<thead>
<tr>
<th>Independent Baseline Risk Factors</th>
<th>Adj Odds Ratio (95% CI) for clinically important GI bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3 co-existing diseases</td>
<td>8.9 (2.7-28.8)</td>
</tr>
<tr>
<td>Co-existing liver disease</td>
<td>7.6 (3.3-17.6)</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>6.9 (2.7-17.5)</td>
</tr>
<tr>
<td>Co-existing coagulopathy</td>
<td>5.2 (2.3-11.8)</td>
</tr>
<tr>
<td>Acute coagulopathy</td>
<td>4.2 (1.7-10.2)</td>
</tr>
<tr>
<td>Use of SUP on ICU day 1</td>
<td>3.6 (1.3-10.2)</td>
</tr>
<tr>
<td>Higher organ failure score</td>
<td>1.4 (1.2-1.5)</td>
</tr>
<tr>
<td>Mechanical ventilation on ICU day 1</td>
<td>1.3 (0.6-3.1)</td>
</tr>
</tbody>
</table>

Coagulopathy: platelets <50,000 mm and/or INR >1.5 either during current hospitalization or on ICU admission

Summary

• Found the incidence of clinically important GI bleeding was low at 2.6%

• Surprising results:
  • Mechanical ventilation was not associated with increased risk of GI bleeding
  • The use of stress ulcer prophylaxis on ICU day 1 was associated with an increased risk of GI bleeding

• Influx of new data poses the question –

Is stress ulcer prophylaxis benefitting our patients?
Exclusion Criteria

Use of acid-suppressive therapy prior to admission; admission with GI bleeding, history of PUD, receiving >100mg daily of prednisolone, recent GI or cardiac surgery

Inclusion Criteria

Anticipate mechanical ventilation >24 hours and receive enteral nutrition within 48 hrs

Primary Objective

Evaluate if prophylactic PPI administration is overtly beneficial or harmful

Design

Single-center, prospective, randomized, double-blind, parallel-group study


PPI: proton pump inhibitor
PUD: peptic ulcer disease
# Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n=108)</th>
<th>Pantoprazole (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>52 (±17)</td>
<td>52 (±18)</td>
</tr>
<tr>
<td><strong>APACHE III score</strong></td>
<td>66 (±28)</td>
<td>66 (±26)</td>
</tr>
<tr>
<td><strong>End-stage renal failure</strong></td>
<td>0 (0%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td><strong>Non-operative</strong></td>
<td>68 (63%)</td>
<td>70 (66%)</td>
</tr>
<tr>
<td><strong>Post-operative</strong></td>
<td>31 (29%)</td>
<td>27 (25%)</td>
</tr>
<tr>
<td><strong>ICU diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trauma</strong></td>
<td>32 (30%)</td>
<td>31 (29%)</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td>26 (24%)</td>
<td>35 (33%)</td>
</tr>
<tr>
<td><strong>Respiratory/CV/Sepsis</strong></td>
<td>41 (38%)</td>
<td>31 (29%)</td>
</tr>
</tbody>
</table>

Unless specified, data are mean (SD)

## Outcomes

<table>
<thead>
<tr>
<th>Major Outcomes</th>
<th>Placebo (n=108)</th>
<th>Pantoprazole (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant GI bleeding</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Infective ventilator-associated complication</td>
<td>1 (0.9%)</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Positive <em>C. difficile</em> infection</td>
<td>0 (0%)</td>
<td>1 (0.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional Outcomes</th>
<th>Placebo (n=108)</th>
<th>Pantoprazole (n=106)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (days) in the ICU</td>
<td>7 (4-14)</td>
<td>6 (3-11)</td>
<td>p = 0.16</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>21 (4-25)</td>
<td>21 (0-25)</td>
<td>p = 0.69</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>25 (23.1%)</td>
<td>30 (28.3%)</td>
<td>p = 0.33</td>
</tr>
</tbody>
</table>

Strengths

• Prospective, randomized, double-blind trial
• Compared standard of care to placebo
• Only included mechanically ventilated patients
• Low risk of selection bias

Therefore, stress ulcer prophylaxis offers no benefit compared to placebo… right?
Limitations

• Insufficient sample size
• Low incidence of GI bleed
• Excluded 87% of patients recruited
• Unique characteristics of included patients
• Early implementation of other therapies
• Shorter duration of mechanical ventilation
Significance and mechanisms

Populations

Implications and adverse effects
Incorrect use of stress ulcer prophylaxis

- Rafinazari et al. (2016)

<table>
<thead>
<tr>
<th>Design</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, single center</td>
<td>160 (80%) received SUP</td>
<td>38.5% of patients did not receive appropriate SUP on ICU admission</td>
</tr>
<tr>
<td>200 randomly selected ICU patients over 9 months with stay &gt;72 hrs</td>
<td>44.4% did not have an indication*</td>
<td>81.2% were continued on inappropriate SUP upon transfer from ICU</td>
</tr>
<tr>
<td></td>
<td>6.3% did not receive SUP although indicated</td>
<td></td>
</tr>
</tbody>
</table>

*per ASHP guidelines
SUP: stress ulcer prophylaxis

Continued use after ICU stay

• Wohlt et al. (2007)

394 patients met eligibility criteria

357 patients prescribed SUP

80% continued SUP on transfer from ICU

60% of SUP continuation was inappropriate

24.4% discharged with inappropriate prescription

Unnecessary cost of $13,973

SUP: stress ulcer prophylaxis

Which of the following are potential adverse effects of acid-suppression therapy?

A. Drug interactions
B. Electrolyte abnormalities
C. *Clostridium difficile* infection
D. Nosocomial pneumonia
E. **All of the above**
## Clostridium difficile risk

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Population</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analyses(^{1-3})</td>
<td>~800,000</td>
<td>Community, general &amp; ICU</td>
<td>PPIs increase risk</td>
</tr>
<tr>
<td>MacLaren et al.</td>
<td>35,312</td>
<td>Intubated &gt;24 hours and SUP &gt;48 hours</td>
<td>OR (CI): 1.29 (1.04-1.64)</td>
</tr>
<tr>
<td>Faleck et al.</td>
<td>18,134</td>
<td>ICU ≥3 days</td>
<td>PPIs may have protective effect</td>
</tr>
</tbody>
</table>

Faleck DM et al. *Am J Gastroenterol* 30 Aug 2016; Advance online publication.
## Pneumonia risk

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Population</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alhazzani et al.</td>
<td>1,100</td>
<td>ICU</td>
<td>No difference in PPI vs. H₂RA</td>
</tr>
<tr>
<td>MacLaren et al.</td>
<td>35,312</td>
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<td>PPI increased risk vs. H₂RA</td>
</tr>
<tr>
<td>Alshamsi et al.</td>
<td>1,571</td>
<td>ICU</td>
<td>No difference in PPI vs. H₂RA</td>
</tr>
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</table>

Future Direction

• Further larger RCT are needed evaluating:
  • Specific risk factors for development of stress-related mucosal damage
  • Use of SUP compared to placebo in preventing clinically important GI bleed

• SUP-ICU trial

• ASHP is currently updating their guidelines, with plans for release in Spring 2017

RCT: randomized control trials
SUP: stress ulcer prophylaxis
GI: gastrointestinal

Recommendations

• Optimizing other therapies to prevent mucosal damage is highest priority

• Short-term use of SUP has a role in preventing clinically important gastrointestinal bleeding in high-risk populations

<table>
<thead>
<tr>
<th>Acute</th>
<th>Duration of ICU stay</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulopathy</td>
<td>Septic shock</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Thermal injury &gt;35% BSA</td>
<td>Continuation of therapy</td>
</tr>
<tr>
<td>Renal replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>therapy</td>
<td></td>
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</table>
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PPI vs H$_2$RA

The use of PPI for SUP is associated with significantly lower rate of clinically important GI bleeding compared to H$_2$RA.

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>$n$</th>
<th>Risk reduction (bleeding)</th>
<th>Risk reduction (mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alhazzani et al</td>
<td>1720</td>
<td>RR = 0.36 (95% CI, 0.19-0.67)</td>
<td>RR = 1.01 (95% CI, 0.83-1.24)</td>
</tr>
<tr>
<td>Pongprassobchai et al</td>
<td>569</td>
<td>OR = 0.42 (95% CI, 0.20-0.91)</td>
<td>n/a</td>
</tr>
<tr>
<td>Alshamsi et al</td>
<td>2117</td>
<td>RR = 0.39 (95% CI, 0.21-0.71)</td>
<td>RR = 1.05 (95% CI, 0.87-1.27)</td>
</tr>
</tbody>
</table>

PPI: proton pump inhibitor  
SUP: stress ulcer prophylaxis  
GI: gastrointestinal  
H$_2$RA: histamine 2 receptor antagonist  

PPI vs H₂RA

% of time gastric pH > 4

Day 1 | Day 2 | Day 3

Omeprazole
Ranitidine

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