What SUP?.... With Stress Ulcer Prophylaxis

Alabama Society of Health System Pharmacists

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Disclosure

• The author of this presentation has no financial or personal interests to disclose
Objectives

Technicians
• Describe the pathophysiology of an acute stress ulcer
• Review the pharmacology of H2-antagonists, proton pump inhibitors, and sucralfate
• Discuss side-effects and concerns associated with agents for stress ulcer prophylaxis

Pharmacists
• Discuss clinical indications for stress ulcer prophylaxis and review recommended pharmacologic treatment options
• Examine the guidelines and medical evidence on stress ulcer prophylaxis
• Review when to initiate and when to discontinue stress ulcer prophylaxis
Questions to Consider

• What is the importance of Stress Ulcer Prophylaxis (SUP)?
• Are the published guidelines still relevant?
• Are PPI’s for SUP considered controversial?
• Are the risks of SUP greater than the benefits?
• In whom and when is SUP important?
• What do a couple of the more recent studies on SUP tell us?
• Is SUP being used properly in your facility?
What is a stress ulcer?

Image adapted from N Engl J Med 2018;378:2506-16
Critically ill patients have a compromised network of defenses

- Increase in catecholamines, vasoconstriction and systemic inflammation & decrease in cardiac output → → → Leads to splanchnic hypoperfusion
- As blood flow is diverted to major organs ischemia, it induces reperfusion and a low gastric intramuscular pH.
- Reduce bicarbonate secretion, decreased mucosal blood flow and GI motility, & increased acid secretion → → → breaks down the mucosa defense/ barrier in the gut
- Low pH and lack of mucosal barrier → → → stress ulcers formation
What are Stress Ulcers?

| Gastric Antral Erosions | Pyloric Ulcer with Adherent Clot |
Self-Assessment Question #1

True or False – Stress ulcers primarily form in critically ill patients as result of an over-production of acid in the stomach?

• False – while acid production certainly contributes, a reduction in the gastric lining protective measures has more to do with the development of stress ulcers
Definitions and Incidence

- **Mucosal or sub-mucosal ulceration** - Endoscopically documented gastroduodenal mucosal or submucosal erosions or ulcerations; 75-100% incidence among selected critically ill patients; generally asymptomatic

- **Occult Bleeding** - Gastric or fecal samples w/ guaiac-positive testing for blood; approx. 15-50% in critically ill patients

- **Overt Bleeding** – Hematemesis, frank blood or coffee-grounds in nasogastric aspirate, or melena – historically around 5% in critically ill patients; approximately 0.3% among general med-surg patients

- **Clinically Important Bleeding** – Approximately 3% in critically ill; defined as Overt bleeding in addition to one or more of the following:
  - Spontaneous ↓ in BP; orthostatic ↑ in Pulse, ↓ in Hgb of ≥ 2g/dL over 24hr; transfusion > 2 units PRBCs w/i 24hr after start of bleeding; or invasive interventions (i.e. therapeutic endoscopy or vasopressor initiation or increase)

Acute illness

- Shock
- Respiratory failure
- Head trauma
- Thermal injury

Chronic conditions:

- Coagulopathy
- Renal dysfunction liver disease
- Helicobacter pylori

Drugs:

- Anticoagulants
- Antiplatelet agents
- NSAIDs

Devices:

- Mechanical ventilation
- Renal-replacement therapy
- Extracorporeal life support

Risk for Upper Gastrointestinal Bleeding
Pharmacotherapy for Stress Ulcer Prophylaxis

- PROTON PUMP INHIBITORS
- HISTAMINE 2 RECEPTOR ANTAGONISTS
- CRYOPROTECTIVE AGENTS
Pharmacology

- H2-Antagonists
  - Ranitidine (Zantac)
  - Famotidine (Pepcid)
  - Cimetidine (Tagamet)

- Proton Pump Inhibitors
  - Pantoprazole (Protonix)
  - Omeprazole (Prilosec)
  - Esomeprazole (Nexium)

- Sucralfate
Histamine 2 Receptor Antagonist

**Mechanism of Action:**
Competitive inhibition of histamine at H₂ receptors of the gastric parietal cells, which inhibits gastric acid secretion

**Adverse Effects:**
Headache, dizziness, fatigue, tolerance, CNS confusion

**Medications:**
- Famotidine (most commonly used)
- Ranitidine
- Cimetidine
- Nizatidine
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Famotidine</td>
<td>Oral, Nasogastric tube, IV → 20 mg twice a day</td>
</tr>
<tr>
<td></td>
<td>Continuous infusion: 1.7mg/hr</td>
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<tr>
<td>Ranitidine</td>
<td>Oral or Nasogastric tube → 150 mg twice a day</td>
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<tr>
<td></td>
<td>IV → 50 mg every 6-8 hrs</td>
</tr>
<tr>
<td></td>
<td>Continuous infusion: 6.25mg/hr</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Oral, Nasogastric tube, IV → 300mg four times a day</td>
</tr>
<tr>
<td></td>
<td>Continuous infusion: 50mg/hr</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>Dosing for this indication has not been established</td>
</tr>
</tbody>
</table>
Proton Pump Inhibitors

**Mechanism of Action:**
- Suppresses gastric basal and stimulated acid secretion by inhibiting the parietal cell H+/K+ ATP pump

**Adverse Effects:**
headaches, nausea, vomiting, diarrhea, fractures, and possible association with nosocomial infections such as pneumonia & CDI infections

**Medications:**
- **Pantoprazole** ➔ Most commonly used
  - Omeprazole
  - Lansoprazole
  - Rabeprazole
  - Esomeprazole
  - Dexlansoprazole
Dosing: Proton Pump Inhibitors

Pantoprazole
- Oral or Nasogastric tube → 40 mg once daily
- IV → 40mg loading dose, followed by 20 mg once daily

Omeprazole
- Oral or Nasogastric tube → 40 mg once daily
- IV → 40mg loading dose, followed by 20 mg once daily

Lansoprazole
- Oral or Nasogastric tube → 30 mg once daily

Rabeprazole, Esomeprazole, Dexlansoprazole: Dosing for this indication has not been established
Cyprotective Agents: Sucralfate

Mucosal coating agent

Mechanism of Action: Forms a complex by binding with positively charged proteins in exudates, forming a viscous paste-like, adhesive substance. This selectively forms a protective coating that acts locally to protect the gastric lining against peptic acid, pepsin, and bile salts.

Adverse Effects: constipation

Dosing: Oral or Nasogastric tube: 1 gram four times daily
Pharmacology: Sucralfate

Adapted from: https://www.picmonic.com/learn/sucralfate-carafate_2084
Self-Assessment Question #2

Which of the following side effects is most commonly associated with sucralfate?

A. Diarrhea  
B. Insomnia  
C. Constipation  
D. Psychosis  
E. Headache

Answer: C - Constipation is the most commonly reported side effect associated with sucralfate with an incidence of around 2%
Guidelines on Stress Ulcer Prophylaxis

Guidelines published on SUP

• ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis (1998)
• DASAIM/DSIT: Guidelines for Stress Ulcer Prophylaxis in the ICU (2014)
• Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock (2016)
What was happening in 1998?

The year the ASHP Guidelines were published: 1998

January 26 – President Clinton becomes embroiled in the Lewinsky scandal

March 27 – The Food and Drug Administration approves Viagra for use as a treatment for erectile dysfunction, the first pill to be approved for this condition in the United States.

June 14 – The Chicago Bulls win their 6th NBA title in 8 years when they beat the Utah Jazz, 87–86 in Game 6. This is also Michael Jordan's last game as a Bull, clinching the game in the final seconds on a fadeaway jumper.

July 24 - Saving Private Ryan premieres in movie theaters.

September 4 – Google, Inc. is founded in Menlo Park, California, by Stanford University Ph.D. candidates Larry Page and Sergey Brin.[6]
ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis: November 14, 1998

Major Indications:
- Mechanical Ventilation >48hrs
- Coagulopathy
  - INR >1.5
  - Platelet count: < 50
  - PTT: > 2x baseline

Minor Indications: Any 2 of the following:
- Sepsis,
- ICU stay >7 days,
- occult bleeding lasting >6 days,
- High daily dose steroid that exceeds: Hydrocortisone 250mg, Methylprednisolone 50mg, Prednisone 50mg, Dexamethasone 10mg

May be Considered Indications:
- Glasgow Coma Score <10,
- Burns affecting >35% of total body surface
- Major trauma with an injury severity score of >16,
- Hepatic failure
- Spinal cord injury
- History of GI bleed or ulceration within last year
- Major surgery lasting > 4 hrs

Special Considerations:
- Partial hepatectomy,
- Poly-trauma w/ISS 16,
- Transplants,
- Hepatic failure
## Indication:

**Level 1 Recommendation:** SUP is recommended for all patients with:
- Mechanical ventilation
- Coagulopathy
- Traumatic brain injury
- Major brain injury

**Level 2 Recommendation:** SUP recommended for all ICU patients with:
- Multi-trauma
- Sepsis
- Acute renal failure

**Level 3 Recommendation:** SUP recommended for all ICU patients with:
- ISS > 15
- Requirement of high dose steroids

## Treatment:

**Level 1 Recommendation:** No difference between H2-antagonists, cytoprotective agents, and some PPIs

**Level 2 Recommendations**
- Aluminium-containing compounds should not be used in patients on dialysis

**Level 3 Recommendations:**
- Enteral feeding alone may be insufficient for SUP

## Duration:

**Level 2:** Continue until extubated or out of ICU

**Level 3:** Continue until tolerating enteral nutrition
Consensus Recommendations of Danish Experts based on published literature

**SUP vs. Placebo in the ICU?**
- SUP vs. Placebo/No Prophylaxis - No firm evidence for benefit or harm of SUP as compared to placebo or no prophylaxis

**PPI vs. H2RA?**
- Suggest using PPIs when SUP is indicated in adult critically ill patients in the ICU

**SUP and Enteral Nutrition?**
- Insufficient evidence to make any recommendation

**SUP in ICU Subpopulations: Trauma, Burn, Septic, and Cardiothoracic Patients?**
- Insufficient evidence to make any recommendation

**Summary:**
Recommend not using SUP routinely for critically ill patients in the ICU outside of the context of randomized clinical trials; however if SUP is considered clinically indicated...use a PPI.

- Sepsis/septic shock **PLUS** risk factors
- Strongest clinical predictors of GIB risk MV > 48 hrs and coagulopathy
- Preexisting liver disease, need for RRT, and higher organ failure scores were independent predictors of GIB risk
- Recommends against SUP in patients without risk factors
- Suggest EITHER PPI or H2RB for SUP
## Guidelines on Stress Ulcer Prophylaxis

**ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis 1998**

**EAST: Practice Management Guidelines for Stress Ulcer Prophylaxis: 2008**

**Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016**

### Indications for SUP

<table>
<thead>
<tr>
<th>Major Indications:</th>
<th>Level 1: Patients who are recommended for stress ulcer prophylaxis:</th>
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<tr>
<td>• Mechanical Ventilation &gt;48hrs</td>
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<th>Level 2: For all ICU patients with</th>
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<td>• Acute renal failure</td>
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<td>• High dose steroid that have a daily dose that exceeds</td>
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  o Hydrocortisone 250mg, |
  o Methylprednisolone 50mg |
  o Prednisone 50mg |
  o Dexamethasone 10mg |

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<tr>
<th>Special Indications:</th>
<th>Level 3:</th>
</tr>
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<tbody>
<tr>
<td>• Glasgow Coma Score &lt;10,</td>
<td>• ISS &gt; 15</td>
</tr>
<tr>
<td>• Burns affecting &gt;35% of total body surface</td>
<td>• Requirement of high dose steroids ( &gt;250mgs hydrocortisone or equic per day)</td>
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<tr>
<td>• Hepatic failure</td>
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<td>• spinal cord injury</td>
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<tr>
<td>• History of GI bleed or ulceration within last year</td>
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<tr>
<td>• Major surgery lasting &gt; 4 hrs</td>
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<th>May be Considered: Partial hepatectomy, Polytrauma w/ISS 16, Transplants, Hepatic failure</th>
<th>Duration:</th>
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<tbody>
<tr>
<td></td>
<td>Level II</td>
</tr>
<tr>
<td></td>
<td>Continue until extubated or out of ICU</td>
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<td></td>
<td>Level III</td>
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- **Sepsis/septic shock PLUS risk factors**
- **Strongest clinical predictors of GIB risk MV > 48 hrs and coagulopathy**
- **Preexisting liver disease, need for RRT, and higher organ failure scores were independent predictors of GIB risk**
- **Recommends against SUP in patients without risk factors**
- **Either PPI or H2RB appropriate for SUP**

**Danish Consensus Guidelines on SUP in the ICU (2014)**

- **No firm evidence for benefit or harm of SUP compared to placebo/no prophylaxis**
- **Suggest using a PPI when SUP is indicated in adult critically ill patients in the ICU**
- **Insufficient evidence that enteral nutrition helps**
- **SUP in ICU Sub-populations: Trauma, Septic, and Cardiothoracic Patients – insufficient evidence of benefit.**
Which is better?

• Meta analysis data have demonstrated proton pump inhibitors to be more effective in critically ill patients for reducing CIGIB compared to an H2RB.¹

• Other studies have suggest H2RB’s are associated with significantly lower CIGIB.²

• Additional large scale clinical trials are needed to determine the comparative efficacy of PPIs vs. H2RAs in stress ulcer prophylaxis.

• More data is needed comparing the treatment impact of both treatments on mortality and length of stay.

¹-Crit Care Med 2013; 41:693-705
²-CHEST 2018; 154:557-566
Is SUP Appropriate?

Main Reasons for Overuse of PPIs in SUP

- Use low-risk patients and in non-intensive care units
- Use in patients on steroid therapy alone
- Use in anticoagulant treatment without risk factors of GI injury
- Overtreatment of functional dyspepsia
- Wrong diagnosis of acid-related disorders

Accepted Uses of PPIs

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<thead>
<tr>
<th>Accepted Indications for PPI Use (FDA in USA and NICE in UK)</th>
</tr>
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<tbody>
<tr>
<td>✓ Healing and maintenance of of erosive esophagitis</td>
</tr>
<tr>
<td>✓ GERD (including NERD, esophageal strictures, and Barrett’s esophagus)</td>
</tr>
<tr>
<td>✓ Treatment of H. pylori infection in combination w/ ABX</td>
</tr>
<tr>
<td>✓ Short-term treatment of H. pylori-negative peptic ulcer and maintenance of healed ulcer</td>
</tr>
<tr>
<td>✓ NSAID-induced dyspepsia</td>
</tr>
<tr>
<td>✓ Healing of NSAID associated gastric ulcer</td>
</tr>
<tr>
<td>✓ Risk reduction of NSAID associated gastric ulcer</td>
</tr>
<tr>
<td>✓ Pathologic hypersecretory conditions (i.e. Zollinger-Ellison Syndrome = ZES)</td>
</tr>
<tr>
<td>✓ Critically ill patients on prolonged mechanical ventilation</td>
</tr>
<tr>
<td>✓ Short-term treatment with regular review of patients with functional dyspepsia</td>
</tr>
</tbody>
</table>
When to discontinue SUP

1. As the number of risk factors diminish as a patient progresses, the need for SUP does as well.

2. In most clinical trials, SUP was discontinued when evidence of clinical bleeding and extubation was gone.

3. Studies also discontinued SUP when the patients were discharged from the intensive care.

4. It is reasonable to presume that SUP can be stopped once the risk factors are resolved.

5. In ASHP guidelines SUP is not recommended in non-ICU patients, medical, surgical patients and patients with fewer than 2 risk factors.
Consequences of unnecessary acid suppression:

- **Infection** - Acid suppression may impair the destruction of ingested microorganisms, resulting in overgrowth of bacteria
  - Overuse of PPIs → increase risk of infections such as *Clostridium difficile* and community acquired pneumonia

- **Bone fractures** - PPIs lower gastric acidity, and can inhibit intestinal calcium absorption. Thus, PPIs may directly inhibit bone resorption by osteoclasts.

- **Drug Interactions** (i.e. **Reduction in clopidogrel efficacy**) - Competitive inhibition of CYP2C19, which is necessary to metabolize clopidogrel

- **Unnecessary cost - Overprescribing** cost patients and hospitals for unnecessary therapy

Arch Intern Med 2010;170:784-90
Aliment Pharmacol Ther. 2011;34;1269-81
Crit Care Med 2010;38:2222-8
Am J Gastroenterol; 2007:2047-56
Pantoprazole vs. Placebo in High Risk ICU Patients

- SUP-ICU Trial Group
- Multicenter, blinded, randomized parallel-group placebo-controlled.
- N=3298
- 1:1 assignment
  - 1645 Pantoprazole; 1653 Placebo
- Patients had at least one risk factor for CIGIB:
  - shock, anticoagulation, renal replacement therapy, mechanical ventilation (expected to last ≥24hrs), liver disease, or coagulopathy

NEJM 2018;379:2199-208
Pantoprazole vs. Placebo in High Risk ICU Patients

Primary Outcome
- Mortality at 90 days

Secondary
- Composite endpoint
  - Clinically important GI bleeding
  - New-onset pneumonia
  - C. difficile infection
  - Acute myocardial infarction

Results
- 510 of 1642 (31.1%) Pantoprazole patients had died at 90 days
- 499 of 1640 (30.4%) in the placebo group had died at 90 days.
- 2.5% of Pantoprazole patients had CIGIB
- 4.2% of placebo patients had CIGIB
- Other secondary outcomes were similar

NEJM 2018;379:2199-208
PEPTIC STUDY

Rationale:
• Data suggests PPIs reduce bleeding risk and are prescribed more frequently, but many clinicians prescribe H2RBs.
• Previous meta-analysis concluded that PPIs might be more effective than H2RBs in preventing GI bleeding, however data is limited and there are still questions regarding the robustness of the data.
• Uncertainty as to which class of agents to use is a decision that affects an estimated 2.5 million critically ill patients per year in developed high-income countries alone.
• The relative difference in SUP drugs on mortality rates are unknown.

JAMA 2020; 323: 616-626
PEPTIC Study: Pantoprazole vs. H2RBs in the ICU

Key Points:

Question: What is the comparative effect on in hospital mortality of using PPIs vs. H2RBs for SUP among adults requiring mechanical ventilation in ICU.

Trial Design: International open-label, Cluster Crossover, registry-embedded randomized clinical trial

Setting: 50 ICUs in 5 countries between Aug 2016 – Jan 2019

Patients: N=26,982 pts

JAMA 2020;323(7):616-626
PEPTIC Study: Pantoprazole vs. H2RBs in the ICU

Intervention:
- ICU pts requiring mechanical ventilation were randomized by site to a PPI strategy or an H2RB strategy for SUP

Primary Outcome
- All-cause Mortality at 90 days during index hospitalization

Secondary
- Clinically important UGI Bleeding
- C. difficile infection
- ICU and Hospital LOS

JAMA 2020;323(7):616-626
PEPTIC Study: Pantoprazole vs. H2RBs in the ICU

Results

Primary Outcome
- **Mortality**
  - 18.3% In-hospital Mortality rate for patients at sites randomized to PPIs
  - 17.5% in-hospital Mortality for patients at sites randomized to H2RB

Secondary Outcome
- **Clinically Significant Upper GI Bleeding**
  - 172 of 13,434 pts (1.3%) in the PPI group vs.
  - 239 of 13,392 pts (1.8%) in the H2RB group
- **Clostridioides difficile infection diagnosis**
  - 40 of 13,436 pts (0.30%) in the PPI group vs.
  - 57 of 13,392 pts (0.43%) in the H2RB group
- **Hospital LOS** – no significant between group differences

JAMA 2020;323(7):616-626
PEPTIC Study: Pantoprazole vs. H2RBs in the ICU

Limitations

- Predominately male patient population
- Open label, cluster
- 4.1% of patients in the PPI arm received at least 1 dose of a H2RB
- 20.1% of patients in the H2RB are received at least 1 PPI dose
- Potential for non-adherence bias as clinicians could over-ride the default SUP
- Patients given default SUP regardless of home medication regimen

JAMA 2020;323(7):616-626
Question: Can Clinical Pharmacists impact Inappropriate SUP Use in hospitalized patients?
Population: N=1134 unique patients consisting of 16,415 patient days were evaluated.
Design: Retrospective pre- & poststudy design before and after pharmacist led stress ulcer prophylaxis management program

In this facility prescriptive authority for SUP was granted to clinical pharmacists
Impact of a Clinical Pharmacist SUP Management program on Inappropriate Use in Hospitalized patients

Figure 2: Inappropriate stress ulcer prophylaxis continuation upon hospital discharge rates. ICU = intensive care unit.
Self-Assessment Question #3

True or False – Pharmacy teams can have a positive impact on reducing unnecessary and inappropriate use of acid suppressive therapy?

- True – Absolutely- Pharmacists and Technicians can play a integral role in reducing and de-escalating unnecessary and inappropriate stress ulcer prophylaxis therapy.
Summary

• Critically ill patients are at risk of stress-related GI mucosal damage, ulceration, and bleeding

• Stress Ulcer Prophylaxis is an important consideration for patients in the ICU who are at risk for clinically important gastrointestinal bleeding

• SUP does not come without risk and this treatment should be routinely re-evaluated

• Providers should de-escalate SUP when patient risk factors moderate

• Pharmacists and technicians can play a key roles in assisting with re-evaluation and de-escalation of unnecessary SUP therapy
OUTTA BULLET POINTS
ANY QUESTIONS?
References:

- The PEPTIC Investigators: Effect of stress ulcer prophylaxis with proton pump inhibitors vs. histamine-2 receptor blockers on in-hospital mortality among ICU patients receiving invasive mechanical ventilation (The PEPTIC Randomized Clinical Trial). JAMA 2020;323:616-626.
References:


