Proton Pump Inhibitors vs. Histamine$_2$-Receptor Antagonists for Stress Ulcer Prophylaxis

Battle of the Acid Suppressants

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Learning Objectives:
1. Describe the pathophysiology associated with stress-related mucosal disease
2. Identify appropriate indications for stress ulcer prophylaxis
3. Identify when stress ulcer prophylaxis should be discontinued
4. Evaluate the safety and efficacy associated with histamine$_2$-receptor antagonists and proton pump inhibitors
Stress-Related Mucosal Disease

I. What is stress-related mucosal disease (SRMD)\(^2\)\(^3\)\(^4\)
   A. Acute superficial inflammatory lesions of the gastric mucosa
   B. Occurs during critical illness
   C. Continuum of manifestations

II. Definitions of gastrointestinal (GI) bleeding
   A. Occult bleeding\(^4\)
      i. Not visible to naked eye
      ii. Detected via guaiac test
   B. Overt bleeding\(^4\)
      i. Visible to naked eye
      ii. Examples include hematemesis, hematochezia, and coffee ground aspiration
   C. Clinically-significant bleeding\(^5\)
      i. Overt bleeding complicated by:
         1. Hemodynamic instability
         2. Decreased hemoglobin requiring blood transfusion
      ii. Should be used as outcome measure for all trials
      iii. Increased morbidity and mortality\(^6\)
         1. Increase intensive care unit (ICU) length of stay by 11 days
         2. Mortality increased seven-fold

III. What is the incidence of SRMD in the ICU\(^1\)
   A. 75-100% of patients have endoscopically detectable mucosal damage within 24 hours\(^6\)\(^7\)
   B. Up to 25% of patients develop overt gastric bleeding\(^6\)
   D. Clinically-significant GI bleeding ranges from 0.6-5%\(^6\)
IV. Pathophysiology of SRMD$^{1,3}$

![Pathophysiology of Stress Ulcers](image)

**Critical Illness**
- \( \downarrow \) Cardiac output
- \( \uparrow \) Catecholamines \( \rightarrow \) \( \uparrow \) Vasoconstriction
- Proinflammatory cytokine release

**Splanchnic hypoperfusion**
- \( \downarrow \) GI motility
- Mucosal ischemia
- Acid back diffusion
- Reduced HCO$_3$ secretion
- Impaired mucous production

**Acute stress ulcer**

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V. What are the risk factors associated with SRMD$^{1-4,7}$

A. Cook et al.$^5$ – prospective, multicenter cohort study
   i. 2,252 ICU patients evaluated for potential risk factors for stress ulceration
   ii. Two independent risk factors
      - Respiratory failure
      - Coagulopathy
   iii. Low incidence of clinically-significant bleeding
      - Patients with one or both independent risk factor(s) \( \rightarrow \) 3.7%
      - Patients with neither risk factor \( \rightarrow \) 0.1%

B. Hastings et al.$^8$ randomized 100 patients at risk for stress ulcers to prophylaxis vs. no prophylaxis
   i. Increased risk of bleeding with increasing number of risk factors
**Table 1. Risk Factors for SRMD**

<table>
<thead>
<tr>
<th>Mechanical ventilation &gt;48 hours*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulopathy*</td>
</tr>
<tr>
<td>INR &gt;1.5</td>
</tr>
<tr>
<td>PTT &gt;2 times control value</td>
</tr>
<tr>
<td>Platelet count &lt;50,000</td>
</tr>
</tbody>
</table>

Hypotension  
Severe sepsis  
Hepatic failure  
Spinal cord injury  
Hepatic or renal transplantation  
Thermal injury (>35% body surface area)  
Multiple trauma with Injury Severity Score ≥16  
General (medical, surgical, respiratory) ICU populations  
Head injury (GCS ≤10) or inability to obey simple commands  
History of gastric ulceration or bleeding during the year before admission  
Presence of at least 2 of the following:  
- Sepsis  
- ICU stay >1 week  
- Occult bleeding for ≥ 6 days  
- Corticosteroid therapy (>250 mg of hydrocortisone or equivalent daily)

*Independent risk factors; INR, International Normalized Ratio; PTT, Partial Thromboplastin Time; GCS, Glasgow Coma Scale

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### Stress Ulcer Prophylaxis

#### I. What are the indications for stress ulcer prophylaxis (SUP) in ICU patients?\(^1\)
A. Prophylaxis only recommended for subset of ICU patients (Table 1)  
B. Discontinue when risk factors have resolved

#### II. What is the role for SUP in the non-ICU setting?\(^1\)
A. Qadeer et al.\(^9\) (n=17,707 patients admitted to general medicine service)  
   i. Incidence of hospital-acquired GI bleeding → 0.4%  
   ii. No protective benefit seen with prophylactic use  
   iii. Rates of bleeding and all-cause mortality similar between two groups  
B. SUP not routinely indicated in this population

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**Figure 3. Stress Ulcer Prophylaxis Timeline**\(^{10,11}\)

- **1971** 1<sup>st</sup> reported case series of SRMD  
- **1977** 1970’s CSB ranged from 5.3% - 33%  
- **1983** FDA approved ranitidine  
- **1986** FDA approved famotidine  
- **1984-1994** CSB ranged from 0.1-39%  
- **1995** FDA approved lansoprazole  
- **1999** FDA approved omeprazole & pantoprazole  
- **2001** FDA approved esomeprazole  
- **2010’s** CSB reported incidence ≤ 5%

CSB: clinically significant bleeding;  
FDA: Food and Drug Administration
III. Why did the incidence of bleeding change over time?\textsuperscript{1,4}
   A. Enteral feeding
   B. Low tidal volume ventilation
   C. Prompt and adequate fluid resuscitation

IV. What are the options for SUP?\textsuperscript{1,4}
   A. Antacids
      i. Mechanism of action (MOA)
         1. Directly buffer or neutralize acid contents of stomach
      ii. Efficacy
         1. Hastings et al.\textsuperscript{8} randomized 100 patients at risk for stress ulcers
            a. Prophylaxis with antacids vs. no prophylaxis
            b. Decreased bleeding rate when antacid therapy titrated to pH >3.5 (p<0.005)
      iii. Limitations
         1. Administered every 1-2 hours for adequate acid neutralization
         2. High dose antacids increase risk of aspiration pneumonia and toxicity
            a. Highest risk in patients with renal dysfunction
   B. Sucralfate
      i. MOA
         1. Adheres to epithelial cells and forms protective barrier
         2. No acid-neutralizing activity
      ii. Efficacy
         1. Cook et al.\textsuperscript{12} randomized 1,200 ICU patients to intravenous (IV) ranitidine vs. sucralfate
            a. Clinically significant GI bleeding higher in the sucralfate group (3.8%) vs. ranitidine (1.7%) group (p=0.02)
            b. No significant difference in the incidence of pneumonia
      iii. Limitations
         1. Constipation
         2. Hypophosphatemia
         3. Nasogastric tube occlusion
         4. Aluminum toxicity (chronic renal insufficiency)
         5. Decreased absorption of concomitantly administered oral medications
   C. Histamine\textsubscript{2}-receptor antagonists (H\textsubscript{2}RAs)
      i. MOA (Figure 4)
         1. Inhibit histamine-stimulated acid secretion by blocking H\textsubscript{2}-receptor
         2. Highly selective with little or no effect on other histamine receptors
      ii. Efficacy
         1. H\textsubscript{2}RAs are significantly better than placebo, antacids and sucralfate\textsuperscript{9}
         2. Proton pump inhibitors vs. H\textsubscript{2}RAs → to be determined (TBD)
      iii. Adverse effects
         1. Tolerance
         2. Drug Interactions
            a. Cimetidine = primary offender
            b. Inhibition of cytochrome P450s
         3. Thrombocytopenia
         4. Renal dysfunction requires dose adjustment
iv. Agents
1. Ranitidine (Zantac®)
2. Famotidine (Pepcid®)
3. Cimetidine (Tagamet®)

D. Proton pump inhibitors (PPIs)
i. MOA (Figure 4)
   1. Inhibit gastric acid secretion by inhibition of H\(^+\)/K\(^+\) ATPase pump

ii. Efficacy
   1. PPIs vs. H\(_2\)RAs → TBD

iii. Adverse effects
   1. Drug interactions
   2. Hypomagnesemia
   3. Increased risk of infection
   4. Acute interstitial nephritis

iv. Warnings/Precautions
   1. Bone fracture
   2. Hypomagnesemia
   3. Vitamin B\(_{12}\) deficiency
   4. Clostridium difficile-associated diarrhea

v. Agents
1. Omeprazole (Prilosec®)
2. Pantoprazole (Protonix®)
3. Esomeprazole (Nexium®)
4. Lansoprazole (Prevacid®)
5. Rabeprazole (Aciphex®)

Figure 4. Mechanism of Action for H\(_2\)RAs & PPIs\(^{13}\)
Discontinuation of Stress Ulcer Prophylaxis

I. Is SUP used appropriately in the inpatient setting?¹
   A. Patients who are critically-ill with zero risk factors → 70% receive SUP
   B. Original risk factors resolve → SUP is continued after ICU downgrade
   C. SUP often used in medicine patients and continued on hospital discharge

II. What is the economic impact of the inappropriate use of SUP?¹
   A. Substantial economic impact on the overuse of SUP
      i. Heidelbaugh et al.¹⁴ (n=1,769 general medicine patients)
         1. Inappropriate SUP use increased annual inpatient and outpatient costs $111,791
      ii. Managed care organization¹⁵
         1. 20,000 patients prescribed PPI inappropriately at hospital discharge
         2. Inappropriate continuation for 30 days associated with cost of US $3 million over four years
      iii. Neither study accounted for costs incurred from complications of SUP

III. What strategies can reduce the overuse of SUP?¹
   A. Few studies have explored potential solutions
   B. Interventions that improve prescribing patterns
      i. Educational materials
      ii. Daily medication reconciliation
      iii. Pharmacist participation on rounds
   C. Additional strategies
      i. Reevaluate use of H₂RAs and PPIs on standardized order sets
      ii. Integrate decision-making prompts into the electronic medical record
   D. Quality improvement studies are needed
What is the efficacy associated with PPIs and H$_2$RAs?

I. Critique of meta-analyses
   A. Low quality studies
      i. Levy et al.\textsuperscript{19} compared omeprazole to ranitidine
         1. Included in all three meta-analyses
         2. Clinically-significant bleeding appropriately defined
         3. Differing number of risk factors between groups
            a. Ranitidine (2.7) vs. omeprazole (1.9) (p<0.05)

Table 2. Meta-Analyses Evaluating Safety and Efficacy of PPIs vs. H$_2$RAs for SUP\textsuperscript{16-18}

<table>
<thead>
<tr>
<th>Study Selection</th>
<th>Published Articles - 5</th>
<th>Published Articles – 8</th>
<th>Published Articles - 10</th>
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<tbody>
<tr>
<td>Powell 1993</td>
<td>Powel 1993</td>
<td>Powel 1993</td>
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<td>Kantorova 2004</td>
<td>Kantorova 2004</td>
<td>Kantorova 2004</td>
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<td>Conrad 2005</td>
<td>Conrad 2005</td>
<td>Conrad 2005</td>
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<td>Somberg 2008</td>
<td>Somberg 2008</td>
<td>Somberg 2008</td>
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<td></td>
<td>De Azevedo 2000</td>
<td>De Azevedo 2000</td>
<td></td>
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<tr>
<td></td>
<td>Morris 2001</td>
<td>Morris 2001</td>
<td></td>
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<tr>
<td></td>
<td>Fink 2003</td>
<td>Fink 2003</td>
<td></td>
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<tr>
<td></td>
<td>Pan 2004</td>
<td>Pan 2004</td>
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</table>

| N               | 936                     | 1,587                   | 1,720                   |

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Studies directly comparing any PPIs vs. any H$_2$RAs (any drug, dose, or route of administration)</th>
</tr>
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<tbody>
<tr>
<td>Exclusion</td>
<td>Studies using placebo, antacids or sucralfate rather than H$_2$RAs for comparator</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Incidence of stress-related upper GI bleeding</td>
</tr>
</tbody>
</table>
| Secondary Outcome | Nosocomial Pneumonia  
All-cause mortality  
ICU LOS            |
| Statistics      | Random effect model  
I$^2$ statistic to assess heterogeneity  
Pre-planned sensitivity & subgroup analysis  
Funnel plot to assess publication bias |
| Results         | No difference in 1$^o$ or 2$^o$ outcomes (Pooled risk difference 0.04; 95% CI, -0.09 to 0.01; p=0.08; i$^2$=66%) |
|                 | PPIs>H$_2$RAs for 1$^o$ outcome  
(OR 0.30; 95% CI, 0.17-0.54)  
No difference in 2$^o$ outcomes |
| NNT             | N/A                     | 39                      | 78                      |

No trials reported on C. difficile
4. High incidence of bleeding
   a. Ranitidine (31%) vs. omeprazole (6%) (p<0.05)
   b. Higher than reported rate (0-16%) from other studies
   c. Barkun et al. reported overall incidence of 1.3%

5. Study accounted for 20% of weight
ii. Brophy et al. compared lansoprazole to famotidine
   1. Only included in meta-analysis by Barkun et al.
   2. Clinically-significant bleeding appropriately defined
      a. Only overt bleeding reported
   3. Clinically-significant bleeding is secondary outcome
      a. Study not powered for outcome

B. Definitions of bleeding
   i. Variable from study to study
   ii. Few studies appropriately define clinically-significant bleeding
      iii. In Barkun et al. 7 studies have no definition

C. Data quality
   i. Positives
      1. Funnel plot performed
      2. All assessed heterogeneity
      3. Sensitivity and subgroup analysis preformed
      4. Trial quality assessed
         a. Higher quality studies showed smaller treatment effect
   ii. Negatives
      1. Heterogeneity seen in Lin et al.
         a. No heterogeneity seen in Barkun et al. and Alhazzani et al.
         b. Five studies and one abstract included in all three meta-analysis
      2. 40% of patients included → low risk of clinically significant bleeding
      3. Publication/language bias seen via funnel plots

II. Take home points
   A. Majority of studies included in meta-analyses did not appropriately define clinically-significant bleeding
   B. Significant heterogeneity among studies with regard to risk difference
   C. Superior efficacy of PPIs compared to H2RAs is difficult to support with current available evidence

What are the risks associated with PPIs and H2RAs?

I. PPIs are one of the most commonly prescribed classes of drugs worldwide
   A. Sales totaling US $26.9 billion dollars in 2005
   B. Experts generally view PPIs as safe
   C. Potential complications (↑ risk of infection) have caused concern

II. Community-acquired pneumonia (CAP)
   A. Proposed mechanisms
      i. Increase in gastric pH → bacterial overgrowth and colonization
         1. Subsequent translocation to lungs by aspiration
ii. $\text{H}^+/\text{K}^+$ ATPase also present in the respiratory tract
   1. PPIs may alter pH of seromucinous secretions $\rightarrow$ bacterial growth
iii. Acid-suppressive drugs may impair function of neutrophils and natural killer cells$^{23}$

Table 3. Studies Evaluating the Risk of CAP with PPIs & H$_2$RAs$^{24,25}$

<table>
<thead>
<tr>
<th>Objective</th>
<th>Laheij RJ et al. 2004</th>
<th>Gulmez SE et al. 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>To examine the association between the use of acid-suppressive drugs and the risk of PNA</td>
<td></td>
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<tr>
<td>Study Design</td>
<td>Nested case-control</td>
<td>Case-control</td>
</tr>
<tr>
<td>N</td>
<td>364,683</td>
<td>34,176</td>
</tr>
<tr>
<td>Patient Population</td>
<td>Primary care setting, data collected via IPCI</td>
<td>Inpatient setting, data collected via County of Funen</td>
</tr>
<tr>
<td>Inclusion</td>
<td>One year history of valid database history</td>
<td>Cases defined by first admission with CAP</td>
</tr>
<tr>
<td></td>
<td>No use of acid suppression before enrollment</td>
<td>Index date = first registered date of CAP diagnosis</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Diagnosis of PNA in preenrollment period (1 year)</td>
<td>Diagnosis of malignancy, recent d/c in last 7 days</td>
</tr>
<tr>
<td>Statistics</td>
<td>Nested case-control analysis performed to ↓ confounders</td>
<td>Controls randomly extracted from population</td>
</tr>
<tr>
<td></td>
<td>o 10 controls from cohort matched with each case of PNA</td>
<td>Matched by age &amp; sex to the cases with a 4:1 ratio</td>
</tr>
<tr>
<td></td>
<td>o Matched on sex, year of birth, &amp; index date (date of first PNA)</td>
<td>Logistic regression to estimate crude &amp; adjusted ORs</td>
</tr>
<tr>
<td></td>
<td>o RR of PNA estimated with OR &amp; adjusted for all covariates</td>
<td>Stratified analyses were conducted by:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Dose of PPI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Recency of PPI</td>
</tr>
</tbody>
</table>

Results

- 19,459* received 1st Rx for acid-suppression
  - H$_2$RAs: n=10,177
  - PPIs: n=2,337
- Pneumonia risk
  - PPIs & H$_2$RAs: adjusted OR, 1.27 (95% CI, 1.06-1.54)
  - PPIs alone: adjusted OR, 2.2 (95% CI, 1.4-3.5)
  - Significant dose response observed
  - H$_2$RAs alone: adjusted OR, 1.7 (95% CI, 0.8-2.9)
  - No dose response observed
- 7,642 cases met inclusion/exclusion criteria
  - H$_2$RAs: n=161
  - PPIs: n=817
- Pneumonia risk
  - PPIs alone: adjusted OR, 1.5 (95% CI, 1.3-1.7)
  - Highest risk in first 7 days (OR, 5.0; 95% CI, 2.1-11.7)
  - H$_2$RAs alone: adjusted OR, 1.1 (95% CI, 0.8-1.3)
  - No definite association found

<table>
<thead>
<tr>
<th>NNH</th>
<th>PPIs = 226</th>
<th>H$_2$RAs = 508</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPIs = 6</td>
<td>H$_2$RAs = N/A</td>
</tr>
</tbody>
</table>

Critique

- Large case-control study
  - Appropriate for study on adverse effect
- Nested analysis conducted to ↓ confounders
- Higher risk when evaluating only laboratory-confirmed PNA
- ↑ risk most pronounced with PPI use
  - Dose-response relationship
- NNH calculated for H$_2$RAs with no statistical significance
- Large case-control study
  - Appropriate for study on adverse effect
  - ↑ risk of CAP with PPI use
  - Highest risk seen in first seven days
  - No association observed in H$_2$RA users

PNA, pneumonia; IPCI, Integrated Primary Care Information; RR, relative risk; OR, odds ratio; Rx, prescription; CI, confidence interval; d/c, discharge; N/A, not applicable; *Some patients used both H$_2$RAs plus PPIs
B. Take home points
   i. Increased risk of CAP observed with PPI use and no risk observed in H$_2$RA users
   ii. Most pronounced risk seen in current users of PPIs and higher doses
   iii. Case-control study and meta-analysis report consistent results$^{26,27}$

III. Nosocomial pneumonia (PNA)
   A. Proposed mechanisms
      i. Same proposed mechanisms as CAP

| Table 4. Studies Evaluating the Risk of Nosocomial Pneumonia with PPIs & H$_2$RAs$^{22,28}$ |
|-------------------------------------------------|---------------------------------|----------------|----------------|---------------------------------|
| **Objective**                                  | Miano TA et al. 2009            | Eom CS et al. 2011 | To determine whether SUP with PPI ↑ PNA risk compared with H$_2$RA | To examine the association between acid-suppressive medication and PNA |
| **Study Design**                               | Retrospective cohort analysis   | Meta-analysis   | 31 studies | 5 case-control
|                                                 |                                 | o 3 cohort studies | o 23 randomized controlled trials |
| **N**                                         | 834                             | Observational studies: n=1,965,358 | RCTs: n=4,168 |
| **Patient Population**                        | Critically ill patients         | Mixed | Eight observational studies |
|                                                 | Cardiothoracic surgery patients | o Five evaluating risk of CAP |
|                                                 | All patients receiving acid-suppressive therapy | o Three evaluating risk of HAP |
|                                                 |                                 | o Evaluating risk of PNA with PPIs |
|                                                 |                                 | o ICU setting |
|                                                 |                                 | o Evaluating risk of HAP with H$_2$RAs |
| **Inclusion**                                 | Age > 18 years |
|                                                 | Admitted to cardiothoracic surgery service |
|                                                 | Received either pantoprazole or ranitidine without crossover |
|                                                 | Case-control study, cohort study or RCT; investigating the association between acid- suppressive drugs and risk of PNA |
| **Exclusion**                                 | Documented aspiration during hospital admission |
|                                                 | Diagnosis of PNA within preceding 3 months |
|                                                 | History of immunosuppression |
|                                                 | Diagnosis of HIV infection |
|                                                 | Recent SOT |
|                                                 | Study did not include data about risk of PNA |
|                                                 | Results for PPIs and H$_2$RAs not reported separately |
| **Statistics**                                | Propensity score analysis to balance the distribution of covariates |
|                                                 | Multivariate logistic regression model to control for selection bias |
|                                                 | Observational studies |
|                                                 | o Pooled OR & 95% CI from the adjusted ORs & 95% CIs reported in studies |
|                                                 | RCTs |
|                                                 | o Summary relative risk from the relative risks of individual trials |
|                                                 | Higgins I$^2$ used to assess heterogeneity |
|                                                 | Random-effects model for overall effect |
B. Take home points
   i. PPI use associated with increased risk of nosocomial PNA in ICU setting
   ii. Results echo CAP studies with highest risk in recent users and higher doses
   iii. Results of high-quality RCTs did not find an increased risk of PNA with H2RAs

IV. Clostridium difficile infection (CDI)21
   A. Proposed mechanism
   i. ↑ gastric pH > 4 allows ≥50% of ingested bacteria to escape acid barrier
   ii. Disruption in natural gut bacteria
      1. Lack of destruction of ingested microorganism
      2. ↑ ascending bacterial colonization from the intestine
<table>
<thead>
<tr>
<th>Objective</th>
<th>To determine if PPIs &amp; H₂RAs are risk factors for CDAD in hospitalized ICU patients</th>
<th>To evaluate risk of CDI with PPI use use or abx or + abx</th>
<th>To evaluate risk of CDI with H₂RAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Cohort study</td>
<td>C. difficile (+) MICU patients</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>N</td>
<td>827</td>
<td>313,000</td>
<td></td>
</tr>
<tr>
<td>Inclusion</td>
<td>MICU admission ≥ 24 hours</td>
<td>CDAD (+)</td>
<td>Diarrhea ≥ 24 hours</td>
</tr>
<tr>
<td>Exclusion</td>
<td>CDAD diagnosed before study period</td>
<td></td>
<td></td>
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<tr>
<td>Statistics</td>
<td>Kaplan-Meier curves constructed</td>
<td>Multivariate logistic regression model</td>
<td>Random effect model</td>
</tr>
<tr>
<td>Results</td>
<td>335 (40.5%) patients received PPI</td>
<td>470 (56.8%) patients received H₂RA</td>
<td>182 (22%) patients received no acid suppression</td>
</tr>
<tr>
<td></td>
<td>2.06 (95% CI, 1.06-4.00)</td>
<td>1.85 (95% CI, 1.07-3.17)</td>
<td>Independent risk factors</td>
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<tr>
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<td>1.06-4.00)</td>
<td>0.05</td>
<td>Age ≥ 65 years HR, 2.33 (95% CI, 1.23-4.40)</td>
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<td>Female sex HR, 1.68 (95% CI, 1.14-2.48)</td>
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<td></td>
<td>No significant difference in PPIs &amp; H₂RAs</td>
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<td>PPIs HR, 0.90 (95% CI, 0.59-1.38)</td>
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<td>H₂RAs HR, 0.78 (95% CI, 0.50-1.23)</td>
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<tr>
<td>NNH</td>
<td>N/A</td>
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<td>NNT</td>
<td>N/A</td>
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<tr>
<td>Critique</td>
<td>Risk of CDAD assessed in the ICU setting</td>
<td>No significant difference between no prophylaxis &amp; PPI/H₂RA use</td>
<td>Identified risk factors for developing CDAD</td>
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<tr>
<td></td>
<td>Limited data in this setting where SUP is mostly indicated</td>
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CDAD, Clostridium difficile-associated disease; MICU, medical ICU; CDI, Clostridium difficile infection; PPI, proton pump inhibitor; abx, antibiotic; H₂RAs, histamine₂-receptor antagonists; OR, odds ratio; RR, risk ratio; CI, confidence interval; *In comparison to PPIs

Table 5. Studies Evaluating the Risk of Clostridium difficile Infection with PPIs & H₂RAs

Beaulieu M et al. 2007
Kwok CS et al. 2012
B. Take home points
   i. Conflicting results
   ii. Significant unexplained heterogeneity also observed in Janarthanan et al. 31
      1. Janarthanan et al. 31 conducted a meta-analysis (n=288,620) to summarize the association between CDAD and PPIs
      2. Included similar studies as Kwok et al. 30 and heterogeneity unexplained by subgroup analysis
      3. Results showed a 65% increase in incidence of CDAD among PPI users
   iii. PPI use may be associated with an increase risk of CDI and recurrent CDI
      1. Quality of evidence is low → interpret cautiously

V. Summary of risks
   A. Studies have demonstrated association but not causality
   B. All associated risks were greater with PPIs as compared to H2RAs
   C. PPIs have also been linked to potential long-term side effects or complications21
      i. Fracture risk
      ii. Iron deficiency
      iii. Hypomagnesaemia
      iv. Vitamin B12 deficiency
   D. Many evaluations did not find a risk with H2RAs

<table>
<thead>
<tr>
<th>Table 6. Potential Adverse Effects with PPIs 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effect</td>
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<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>CAP</td>
</tr>
<tr>
<td>Nosocomial PNA</td>
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<tr>
<td>C. difficile Infection</td>
</tr>
</tbody>
</table>

CAP, community-acquired pneumonia; PNA, pneumonia; CDI, Clostridium difficile infection; OR, odds ratio

Summary and Recommendations

I. Summary
   A. SUP is important in preventing clinically significant bleeding
   B. Acid suppressive therapy is not indicated in everyone
   C. Discontinuation of SUP is warranted when original risk factors resolve
   D. Limitations of current available evidence make it difficult to claim PPIs as the superior agent
   E. Increases in gastric pH are associated with an increase risk of infection
      i. CAP 32
         1. Management of an uncomplicated case of PNA costs approximately US $7,000 dollars
         2. 40% attributable mortality in patients requiring admission to an ICU
ii. Nosocomial pneumonia\textsuperscript{33}
   1. Hospital-acquired pneumonia (HAP) has an associated cost of more than US $40,000 dollars
   2. Overall mortality attributed to HAP may be as high as 50%

iii. \textit{Clostridium difficile} infection\textsuperscript{34}
   1. 6% attributable mortality in critically ill patients

| Table 7. Comparison of Number Needed to Harm with PPIs and Attributable Mortality in ICU Patients |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| CAP | Nosocomial PNA | \textit{Clostridium difficile} Infection |
| NNH N=6 | Attributable Mortality | NNH N=13 | Attributable Mortality | NNH N=22 | Attributable Mortality |
| ![X Marks] | ![X Marks] | ![X Marks] | ![X Marks] | ![X Marks] | ![X Marks] |

II. Recommendations
   A. With advancements in medicine SUP may no longer be required
   B. Healthcare professionals should weigh the risks and benefits when choosing an agent for SUP
   C. If SUP is indicated, histamine\textsubscript{2}-receptor antagonists are the preferred agent of choice
References


# Appendix

## Appendix A. Summary of Individual Studies Included in Meta-Analyse

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Intervention</th>
<th>Definition of Bleeding</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powell et al. 1993</td>
<td>41</td>
<td>Omeprazole 80 mg IV bolus, then 40 mg IV bolus TID (n=10); omeprazole 80 mg IV bolus then 40 mg IV infusion TID (n=10); ranitidine 50 mg IV TID (n=11); placebo (n=10)</td>
<td>Bloody nasogastric tube aspirate</td>
<td>Clinically important bleeding; mortality</td>
</tr>
<tr>
<td>Levy et al. 1997</td>
<td>67</td>
<td>Omeprazole 40 mg NG daily (n=32); ranitidine 50 mg IV bolus, then 150 mg IV daily (n=35)</td>
<td>Gross bleeding as manifest by hematemesis, aspiration of coffee ground material from the NG tube, or melena, or a ↓ Hgb of &gt; 2 g/dL complicated by either the need for transfusion or hemodynamic instability</td>
<td>Clinically important bleeding; nosocomial PNA; mortality; ICU LOS</td>
</tr>
<tr>
<td>Kantorova et al. 2004</td>
<td>287</td>
<td>Omeprazole 40 mg IV daily (n=72); famotidine 40 mg IV BID (n=71); sucralfate 1 g NG QID (n=69); placebo (n=75)</td>
<td>Overt bleeding with one of the following: a) Drop in SBP &gt;20 mm Hg or rise in HR &gt;20 beats/min within 24 hrs of the onset of bleeding not explained by other causes; or b) Drop in Hgb by 2 g/dL or more not explained by other causes</td>
<td>Clinically important bleeding; nosocomial PNA; mortality; ICU LOS; adverse events</td>
</tr>
<tr>
<td>Conrad et al. 2005</td>
<td>359</td>
<td>Omeprazole suspension 40 mg NG BID loading, then 40 mg NG daily (n=178); cimetidine 300 mg IV bolus, then infusion at 50 mg/hr (n=181)</td>
<td>a) Bright right blood not clearing after tube adjustment and lavage with saline for 5-10 mins; b) 8 hrs of persistent gastro-occult positive coffee ground material with aspirates every 2 hrs not clearing with lavage; or c) Persistent gastro-occult positive coffee ground material over 2-4 hrs on d 3-14 in three consecutive aspirates not clearing with lavage</td>
<td>Clinically important bleeding; overt bleeding; PNA; mortality</td>
</tr>
<tr>
<td>Somberg et al. 2008</td>
<td>202</td>
<td>Pantoprazole 40 mg IV daily (n=32); pantoprazole 40 mg IV BID (n=38); pantoprazole 80 mg IV daily (n=23); pantoprazole 80 mg IV BID (n=39); pantoprazole 80 mg IV TID (n=35); cimetidine 300 mg IV bolus, then 50 mg/hr infusion (n=35)</td>
<td>a) Hematemesis or bright red blood in gastric aspirate that did not clear after adjustment of NG or OG tube and a 5- to 10-min lavage with iced water or saline; b) Persistent coffee ground material for 8 consecutive hrs that did not clear with a 100 mL lavage, or was accompanied by a 5% ↓ in Hct; c) A ↓ in Hct requiring one or more transfusions that occurred in the absence of any obvious source and required further diagnostic studies; or d) Melena or frank bloody stools from an upper GI source</td>
<td>Clinically important bleeding; PNA; mortality; adverse events</td>
</tr>
<tr>
<td>Hata et al. 2005</td>
<td>210</td>
<td>Rabeprazole PO 10 mg daily (n=70); ranitidine PO 30 mg daily (n=70); teprenone 150 mg NG daily (n=70)</td>
<td>Upper GI bleeding (hematemesis, coffee ground emesis, or melena) confirmed with gastroduodenoscopy</td>
<td>Overt bleeding; adverse events</td>
</tr>
<tr>
<td>Solouki et al. 2009</td>
<td>129</td>
<td>Omeprazole 20 mg NG BID (n=61); ranitidine 50 mg IV BID (n=68)</td>
<td>Overt bleeding associated with one of the following: a) A 20 mm Hg ↓ in SBP or DBP during the first 24 hrs after bleeding; b) A 20 beat/min ↑ HR or 10 mm Hg in SBP in a standing position; c) A 2 g/dL ↓ of Hgb or 6% decrease in Hct during the first 24 hrs after bleeding; d) Lack of ↑ in Hgb after infusing two units of packed cells</td>
<td>Clinically important bleeding; nosocomial PNA; mortality; ICU LOS</td>
</tr>
<tr>
<td>Azevedo et al. 2000</td>
<td>108</td>
<td>Omeprazole 40 mg IV BID (n=38); ranitidine 150 mg/day infusion (n=38); sucralfate 1 g NG QID (n=32)</td>
<td>Upper GI bleeding including hematemesis, bright red blood, coffee ground emesis or melena</td>
<td>Overt bleeding; nosocomial PNA; mortality; ICU LOS</td>
</tr>
<tr>
<td>Study</td>
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<tr>
<td>Pan et al. 2004</td>
<td>30</td>
<td>Rabeprazole PO 20 mg once daily (n=20); famotidine IV 40 mg BID (n=10)</td>
<td>Melena or hematemesis</td>
<td>Overt bleeding</td>
</tr>
<tr>
<td>Risaliti et al. 1993</td>
<td>28</td>
<td>Omeprazole 40 mg daily IV, then 20 mg PO daily (n=14); ranitidine 150 mg IV daily, then 300 mg PO daily (n=14)</td>
<td>No clear definition</td>
<td>Clinically important bleeding; overt bleeding; adverse events</td>
</tr>
<tr>
<td>Phillips et al. 1998</td>
<td>58</td>
<td>Omeprazole 40 mg NG loading, then 20 mg NG daily (n=33); ranitidine 50 mg IV loading, then 150-200 mg/day infusion (n=25)</td>
<td>No clear definition</td>
<td>Clinically important bleeding; PNA; adverse events</td>
</tr>
<tr>
<td>Fink et al. 2003</td>
<td>189</td>
<td>Randomization as follows: IV pantoprazole 40 mg daily, 40 mg BID, 80 mg daily, or 80 mg BID (n=158); IV cimetidine 300 mg bolus, then 50 mg/hr infusion (n=31)</td>
<td>No clear definition</td>
<td>UGI bleeding; mortality</td>
</tr>
<tr>
<td>Morris et al. 2001</td>
<td>202</td>
<td>Randomization as follows: IV pantoprazole 40 mg daily, 40 mg BID, 80 mg daily, 80 mg BID, or 80 mg TID (n=169); IV cimetidine 300 mg IV loading, then 50 mg/hr (n=33)</td>
<td>No clear definition</td>
<td>UGI bleeding; nosocomial PNA</td>
</tr>
<tr>
<td>Kotlyanskaya et al. 2007</td>
<td>66</td>
<td>Lansoprazole (suspension) NG (n=22); lansoprazole (tablet) NG (n=23); ranitidine (n=21) (dose and frequency not reported)</td>
<td>Overt bleeding associated with change in hemodynamics or drop in the Hgb</td>
<td>Clinically important bleeding; overt bleeding; nosocomial PNA; drug adverse events</td>
</tr>
<tr>
<td>Brophy et al. 2010</td>
<td>51</td>
<td>Lansoprazole (suspension) 30 mg NG daily (n=23); famotidine 20 mg IV BID (n=23)</td>
<td>Endoscopic evidence of stress-related mucosal bleeding, bright red blood per NG tube that did not clear after lavage, or overt bleeding (hematemesis, bloody gastric aspirate, melana, or hematochezia) plus either a ↓ in BP of 20 mm Hg, or a ↓ of 2 g/dL in Hgb and two units of blood transfused within 24 hrs</td>
<td>Time pH ≥ 4; percentage of time gastric residuals &lt; 28 mL; clinically significant bleeding</td>
</tr>
</tbody>
</table>

IV, intravenous; BID, twice daily; TID, three times daily; QID, four times daily; NG, nasogastric; OG, orogastric; Hgb, hemoglobin; Hct, hematocrit; PNA, pneumonia; LOS, length of stay; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; GI, gastrointestinal; hrs, hours; d, day