OBJECTIVES

- Review pharmacology of PPIs
- Discuss possible association between PPI use and development of the following:
  - Pneumonia (community-acquired and hospital-acquired)
  - Clostridium difficile infection
- Discuss overuse and inappropriate use of acid suppressive therapy

PPI PHARMACOLOGY

- Inhibit terminal acid secretion from parietal cells by blocking \( H^+ / K^+ \) - ATPase pump

PPI Indications

- Approved:
  - GERD
  - Helicobacter pylori
  - Esophagitis/Barrett’s esophagus
  - Gastric/Duodenal ulcer
  - Hypersecretory conditions
  - Prevention of NSAID induced ulcers

- NOT indicated for:
  - Mallory–Weiss tear
  - Esophageal varices
  - Diverticular bleeding
  - Arteriovenous malformation
  - Hemorrhoidal bleeding

PPIs

- Short-term use generally considered safe
- Widely available
  - Prilosec OTC™
  -Prevacid 24Hour™
- Prescribe first for simple GI symptoms (“diagnostic therapeutics”)
- 3rd highest selling class of drugs in U.S.

PNEUMONIA
PPIs and CAP #2

- Retrospective chart review
  - Cases: admissions with CAP (n=7642)
  - Controls: matched to age and gender (4:1 ratio) (n=34,176)
- Exposure to PPI
  - Current use: active Rx within 90 days of admission
  - Past use: Rx >90 days before admission
- Logistic regression
  - Controlled for covariates: corticosteroids, antipsychotics, COPD, DM, renal failure, cirrhosis, IHD, HF, stroke, psychiatric disorder


Results

<table>
<thead>
<tr>
<th>Table 1. Relative Risk of Community-Acquired Pneumonia by Exposure to Gastric Acid-Suppressive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposure to H2-Receptor Antagonists</strong></td>
</tr>
<tr>
<td><strong>Exposure to Proton Pump Inhibitors</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Peri-pyelitis</td>
</tr>
<tr>
<td>No. of cases of pneumonia</td>
</tr>
<tr>
<td>Unadjusted OR</td>
</tr>
<tr>
<td>(95% CI)</td>
</tr>
</tbody>
</table>
PPIs and HAP

- Retrospective Cohort Study
- All inpatient admission with LOS ≥3 days
  - Excluded ICU stay of any length
- Exposure to acid-suppressing medications
  - Active Rx for PPI or H2RA during admission
- Primary Outcome: Development of HAP
- Logistic Regression
  - Controlled for covariates: HF, IHD, COPD, cancer, DM, CKD, corticosteroids, sedating medications (benzodiazepines, opiates, antipsychotics)

Results

| Table: Role of Hospital-Acquired Pneumonia According to Acid Suppression Medication Status |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | No PPI          | PPI             | Adjusted OR (95% CI) | Adjusted OR (95% CI) |
| Hospital-acquired pneumonia    | 110 (8.8)       | 92 (7.2)        | 1.3 (1.0-1.6)       | 1.3 (1.0-1.6)       |
| Aspiration pneumonia           | 91 (2.3)        | 80 (2.1)        | 1.1 (0.6-2.0)       | 1.1 (0.6-2.0)       |
| Non-pneumonia pneumonia        | 130 (0.6)       | 90 (0.6)        | 2.6 (2.2-3.4)       | 2.6 (2.2-3.4)       |
| Rate of HAP according to PPI status |
| Total admissions                 | 2,572           | 1,972           | 56,500             | 56,500             |
| Hospital-acquired pneumonia     | 175 (6.8)       | 150 (7.2)       | 1.2 (1.0-1.4)       | 1.2 (1.0-1.4)       |
| Hospital-acquired pneumonia     | 176 (6.9)       | 150 (7.1)       | 1.2 (1.0-1.4)       | 1.2 (1.0-1.4)       |

Clostridium difficile

- Spore-forming gram (+) bacilli
- Most common cause of nosocomial infectious diarrhea
- Toxins A&B
  - Cause cell dysfunction and death
- Rates & severity increasing
- NAP-1 strain (2000)
  - 16x more Toxin A and 32x more Toxin B
- ↑ healthcare costs, LOS, morbidity
- Risk factors
  - Antimicrobial use

Clostridium difficile infection

- Infection increases healthcare costs, LOS, and morbidity
- Risk factors include antimicrobial use
- NAP-1 strain dominates in recent years
- Increased rates of multidrug-resistant strains
- Impact on healthcare systems

Herzig SJ et al. Acid-Suppressive Medication Use and the Risk for Hospital-Acquired Pneumonia. *JAMA* 2009;301(20):2120-2128
PPIs and C. Diff
- Retrospective Cohort Study
- Subjects ≥18yo and LOS ≥3 days
- Exposure to acid suppression
  - No acid suppression therapy
  - H2RA therapy
  - Daily PPI
  - Multiple PPI doses per day
- Primary outcome: C. difficile infection
- Logistic Regression
  - Controlled for covariates: IHD, HF, CVA/TIA, COPD, DM, CKD, Cancer
- Also classified Abx as ‘high’ or ‘low’ risk

Howell MD. Iatrogenic Gastric Acid Suppression and the Risk of Nosocomial Clostridium difficile Infection. Arch Intern Med 2010;170(9):784-790

PPIs and Recurrent C. Diff
- Retrospective Cohort Study (VA population)
- Cohort
  - Subjects with 1st positive C. diff toxin
- Exposure variable
  - PPI exposure during C. diff txt (n=527)
  - NO PPI exposure during C. diff txt (n=639)
- Outcome variable
  - Positive C. diff tox in 15–90 days after incident C. diff diagnosis date
- Controlled for covariates: HTN, DM, IHD, COPD, PUD, cancer, rheumatologic diseases, antibiotic use, corticosteroids

Linsky A. Proton Pump Inhibitors and Risk for Recurrent Clostridium difficile Infection. Arch Intern Med 2010;170(9):772-778
Results

Table 2. Association of CDI Treatment-Concurrent PPI Exposure With Recurrent CDI Within 90 Days

<table>
<thead>
<tr>
<th>Model</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.42 (1.11-1.82)</td>
<td>.006</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.42 (1.10-1.85)</td>
<td>.008</td>
</tr>
<tr>
<td>Age stratified, y*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65 (n=107)</td>
<td>1.19 (0.86-1.65)</td>
<td>.38</td>
</tr>
<tr>
<td>60-80 (n=560)</td>
<td>1.32 (0.94-1.87)</td>
<td>.11</td>
</tr>
<tr>
<td>&lt;60 (n=203)</td>
<td>1.06 (1.15-8.01)</td>
<td>.91</td>
</tr>
<tr>
<td>Non-CDI antibiotic exposure stratified*</td>
<td>1.77 (1.31-2.64)</td>
<td>.01</td>
</tr>
<tr>
<td>No additional antibiotic exposure</td>
<td>1.30 (0.94-1.79)</td>
<td>.12</td>
</tr>
</tbody>
</table>

Abbreviations: CDI, Clostridium difficile infection; CI, confidence interval; HR, hazard ratio; PPI, proton pump inhibitor.
* Adjusted for age, incident CDI treatment, additional antibiotic exposure, length of hospital stay, ischemic heart disease, endocarditis disease, rheumatologic disease, peptic ulcer disease, pulmonary disease, and systemic corticosteroid use.

Results

Table 3. Relationship between therapies and continuation of inappropriate acid suppression on discharge

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Discharged on acid suppression</th>
<th>Not Discharged on acid suppression</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose NSAI</td>
<td>28</td>
<td>46</td>
<td>0.42</td>
</tr>
<tr>
<td>High-dose NSAI</td>
<td>5</td>
<td>5</td>
<td>0.42</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>10</td>
<td>14</td>
<td>0.42</td>
</tr>
<tr>
<td>Steroids</td>
<td>5</td>
<td>20</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Conclusions

- PPIs (and potentially H2RAs) appear to increase risk of pneumonia and C. diff
  - Prospective Studies needed

- Misuse and overuse of acid suppressive therapy appears to be significant
  - "Stress Ulcer Prophylaxis" appears to be common indication
  - ASHP Criteria for SUP
    - Mechanical ventilation >48 hours
    - Coagulopathy (INR >1.5 or plts <50,000)

Recommendations

- Routinely review indications for acid suppressive therapy with patients
  - Ask about OTC use

- Drug holidays if appropriate?

- Evaluate need for Stress Ulcer Prophylaxis
  - Especially on general medical floor patients

- Evaluate need for continued acid suppressive therapy on discharge