Gastroduodenal Ulcers: Still a Clinically Relevant Problem

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Objectives

1. To review the pathophysiology of PUD
   - Imbalance of aggressive and defensive factors
2. To discuss each major cause of PUD
   - Hypersecretion
   - H. pylori infection
   - NSAIDs
3. To review the complications of PUD
   - Bleeding

Peptic Ulcer Trends in the USA

Uncomplicated ulcers are declining:
- Frequent use of PPIs and H2RAs
- Disappearance/Rx of H. pylori infection
- Judicious use of NSAIDs and ASA, introduction of Coxibs
- Better management of ICU patients (less stress related mucosal disease (SRMD))

Bleeding ulcer prevalence is unchanged resulting in an increasing proportion overall

Peptic Ulcer Disease Pathogenesis

- ASA & NSAIDs
- H. pylori gastritis
- Hypersecretory states

Alterations in mucosal defense mechanisms
- Acid and pepsin

Mucosal barrier
- Bicarbonate
- Blood flow
- Cell regeneration
- Prostaglandins

Ulceration
i. Gastric Acid Hypersecretion

Zollinger Ellison Syndrome *

- Non-beta islet cell tumor (secretes gastrin)
- Gastric acid hypersecretion
- Fulminant peptic ulcer disease

* Zollinger and Ellison, 1955

ZES: Pathophysiology

ZES: Inappropriate Hypergastrinemia is the Hallmark

- Gastric acid hypersecretion (Gastric analysis)
  - isolated measurement of limited value
- Elevated gastrin level
  - isolated level of limited value
- Inappropriate hypergastrinemia is the hallmark
  - Elevated acid output AND serum gastrin

Consider ZES (<1/1000 DU’s)

- Severe peptic disease:
  - Multiple, recurrent, non-healing ulcers
- Acid hypersecretion:
  - Diarrhea
- Before anti-ulcer surgery:
  - Before it’s too late
- MEN-1 syndrome:
  - Pituitary, parathyroids, pancreas (3p’s)
- Non-NSAID, non-H. pylori ulcers

ii. NSAID Gastropathy
**NSAID Gastropathy**

- Upper GI symptoms (up to 50%)
  - Heartburn, nausea, vomiting, pain
  - Frequent reason for stopping / changing NSAID
- Mucosal lesions [NSAID gastropathy] (up to 30%)
- Ulcer complications (up to 4% per year)
  - Bleeding, perforation, gastric outlet obstruction

**Enteric-coated or Buffered Aspirin Does Not Lower GI Risk**

Risk of Upper GI Bleeding With Different Formulations of Low-dose Aspirin (≤ 325 mg)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Risk of Upper GI bleeding (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain Aspirin</td>
<td>2.6 (1.5-4.5)</td>
</tr>
<tr>
<td>Coated Aspirin</td>
<td>3.2 (1.9-6.0)</td>
</tr>
<tr>
<td>Buffered Aspirin</td>
<td>3.6 (1.3-9.8)</td>
</tr>
</tbody>
</table>

*This case-control study included 550 patients with upper GI bleeding admitted to hospital with melena or confirmed hematemesis and 1202 controls*


**NSAID Ulcers: 1st Symptom Can be a Serious GI Complication**

Most patients are asymptomatic prior to having an NSAID-related ulcer bleed, perforation, or obstruction (i.e., Endoscopy symptoms, prophylax risk)


**Lansoprazole and Misoprostol Provide Gastric Protection From NSAID Use**

<table>
<thead>
<tr>
<th>Lansoprazole &amp; Misoprostol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer free at 12 weeks</td>
<td>51</td>
</tr>
<tr>
<td>Experienced adverse effects</td>
<td>10</td>
</tr>
</tbody>
</table>

537 Long-term NSAID users with a history of gastric ulcer
All *H. pylori* negative


**Gastroprotection: Proton Pump Inhibitors**

% of patients with recurrent upper GI bleeding at 6 months

H. pylori eradication + NSAID (n=75)

76% RRR in upper GI bleeding; NNT = 7

**COX-2 Inhibitors: Less Risk for Upper GI Bleeding Compared With Other NSAIDs**

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>1.3</td>
</tr>
<tr>
<td>COX-2 Inhibitors</td>
<td>5.0</td>
</tr>
<tr>
<td>ASA 100 mg/day</td>
<td>2.4</td>
</tr>
<tr>
<td>NSAID + low-dose ASA</td>
<td>10.2</td>
</tr>
<tr>
<td>COX-2 + low-dose ASA</td>
<td>9.5</td>
</tr>
</tbody>
</table>


**Cumulative Incidence of Recurrent Ulcer Bleeding with Clopidogrel and with Aspirin plus Esomeprazole**

**Risk factors for NSAID-associated ulcer complications**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past complicated ulcer</td>
<td>13.5</td>
</tr>
<tr>
<td>Multiple NSAIDs (including aspirin)</td>
<td>9</td>
</tr>
<tr>
<td>High-dose NSAIDs</td>
<td>7</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>6.4</td>
</tr>
<tr>
<td>Past uncomplicated ulcer</td>
<td>6.1</td>
</tr>
<tr>
<td>Age &gt;70 years</td>
<td>2.2</td>
</tr>
<tr>
<td>Steroids</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Majority of patients who develop a serious GI adverse event on NSAIDs are asymptomatic prior to event. Risk is greatest in first three months of use.


**ACG Guidelines for the Prevention NSAID-related Ulcer Complications**

<table>
<thead>
<tr>
<th>GI Risk</th>
<th>Low (No risk factors)</th>
<th>Moderate (1-2 risk factors)</th>
<th>High (complication and/or &gt;2 risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Risk Low</td>
<td>NSAID alone</td>
<td>NSAID+PPI/ranitidine</td>
<td>Alternative therapy and/or Avoid NSAIDs/COX-2 inhibitors</td>
</tr>
<tr>
<td>CV risk High</td>
<td>Naproxen + PPI/ranitidine</td>
<td>Naproxen + PPI/ranitidine</td>
<td>Alternative therapy and/or Avoid NSAIDs/COX-2 inhibitors</td>
</tr>
<tr>
<td>CV risk Low</td>
<td>Acetylsalicylic acid</td>
<td>Acetylsalicylic acid</td>
<td>Alternative therapy and/or Avoid NSAIDs/COX-2 inhibitors</td>
</tr>
</tbody>
</table>

Note: Patients with a history of ulcers should also be tested for H. pylori and treated if positive.


**iii. Helicobacter pylori**

Peptic ulcer disease is an infection!

**The Spectrum of H. pylori Infection**

- Chronic gastritis (Koch’s postulate fulfilled)
- Duodenal ulcer (up to 90%)
- Gastric ulcer (about 70%)
- Gastric cancer
  - Chronic gastritis → atrophy → intestinal metaplasia → dysplasia → cancer
- Maltoma (lymphocytic gastritis)
- Non-Ulcer Dyspepsia (?) Associated
**H. pylori Affects Acid Secretion Three Ways**

- **A**: Antral predominant infection (GU)
- **B**: Hypochlorhydria or achlorhydria
- **C**: Gastric cancer, lymphoma

### Complications
- Chronic Superficial Gastritis

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**H. Pylori and Duodenal Ulcer: The Gastrin Hypothesis**

- Antral H. pylori infection inhibits somatostatin production leading to unopposed gastrin release
- Basal and meal-stimulated hypergastrinemia lead to inappropriate gastric acid hypersecretion
- Duodenal gastric metaplasia (possibly due to hypersecretion or a primary phenomenon) permits colonization in the duodenal bulb
- Local defences are undermined PLUS acid hypersecretion results in duodenal ulceration

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**Ulcer recurrence after treatment of H. pylori infection: Cochrane Collaboration meta-analysis**

- Recurrence rate at 1 year (%)
  - *p<0.05
  - ***p<0.001

<table>
<thead>
<tr>
<th></th>
<th>DU</th>
<th>GU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection treated</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Infection not treated</td>
<td>64</td>
<td>40</td>
</tr>
</tbody>
</table>

Meta-analysis of 52 trials: 2434 patients in DU trials, 774 patients in GU trials

Adapted from: Ford et al, Am J Gastroenterol 2004; 99: 1813
Two Key Questions:
PCN allergy; Prior macrolide exposure

Antibiotic Resistance rates in the USA 2009-2011

H. pylori gastritis and NSAID/ASA use often co-exist

iv. Complications of Peptic Ulcers
- Bleeding
- Perforation
- Obstruction

General Approach to the patient with Acute Upper GI Bleeding
- Guiding Principles
  - Restoration or maintenance of hemodynamic stability
  - Blood products if needed
  - Nasogastric lavage
  - Endoscopy with hemostasis if indicated
  - Antisecretory medications
  - Surgery if necessary
GI Bleed: Prognostic Factors

- Initial assessment of an acute upper GI bleed can predict risk of mortality and complications:
  - Age >60 years
  - Transfusion requirement of >6 units of blood
  - Shock
  - Presence of comorbidity (hepatic, renal, pulmonary disease, cancer, CHF)
  - Ongoing bleeding
  - Low systolic blood pressure
  - Elevated prothrombin time
  - Erratic mental status
  - Major stigmata of recent hemorrhage

Management of Acute GI Bleeding

- Initial Management
  - IV Access
  - Hemodynamic Assessment
  - CBC, PT/PTT, LFTs, electrolytes/creatinine
  - Resuscitation Measures
  - NPO

- Access Initial Risk
  - Age >60 years
  - Comorbidity
  - Low systolic blood pressure
  - Shock
  - Ongoing bleeding
  - Prolonged PT
  - Erratic mental status

- ICU/Surgical consult
- Med./Surg. Ward
- Endoscopy ± Hemostasis
- Med./Surg. Ward

- Assess Initial Risk
  - Age >60 years
  - Comorbidity
  - Low systolic blood pressure
  - Shock
  - Ongoing bleeding
  - Prolonged PT
  - Erratic mental status

- Endoscopy ± Hemostasis
- Med./Surg. Ward

GI Bleed: Risk of Rebleeding

- Clean Base
- Flat Spot
- Adherent Clot
- NBVV
- Active Bleed

Prevalence (%)
- 42
- 20
- 17
- 17
- 18

Rebleeding risk (%)
- 5
- 10
- 22†
- 43†
- 55†

Mortality (%)
- 2
- 3
- 7
- 7
- 11

Endoscopic Hemostasis in Nonvariceal UGI Bleeding

- Thermal, laser and injection therapy all decrease re-bleeding (OR 0.38), surgery (OR 0.36) and mortality (OR 0.55) in patients with active bleeding or visible vessels but not in those with flat spots or adherent clot
- Epinephrine + thermal methods or hemoclip
  - superior to epinephrine alone
  - not superior to thermal or hemoclip alone
- 2nd look endoscopy for rebleeding reduces the need for surgery without increasing complications

Adapted from Greenspoon et al., CGH 10:2012:234
Adapted from Greenspoon et al., CGH 10:2012:234
Randomized Placebo-Controlled Comparison of IV PPI in Bleeding Peptic Ulcer

- All patients had actively bleeding vessel or a non-bleeding visible vessel (NBVV) and received endoscopic therapy


IV PPI Therapy Alone is Insufficient

Adapted from: Sung et al, Am Intern Med. 2000; 138: 217

Cochrane review on PPIs before EGD in UGI bleeding: Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Odds Ratio M.H. Fixed, 95% CI</th>
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<tbody>
<tr>
<td>Daneshmand 1992</td>
<td>1.34 [0.82, 2.18]</td>
<td></td>
</tr>
<tr>
<td>Halkay 2001</td>
<td>0.90 [0.76, 2.07]</td>
<td></td>
</tr>
<tr>
<td>Halkay 1998</td>
<td>3.90 [0.90, 15.68]</td>
<td></td>
</tr>
<tr>
<td>Lau 2007</td>
<td>1.14 [0.41, 3.23]</td>
<td></td>
</tr>
<tr>
<td>Valter 1996</td>
<td>0.60 [0.14, 2.68]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1.12 [0.75, 1.68]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: CHI² = 2.3, df = 3 (P = 0.62)</td>
<td>P = 0.77</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: CHI² = 5.97 (P = 0.57)</td>
<td></td>
<td></td>
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Sreedharan et al, Gastroenterology 2009; 136 (Suppl. 1): 229
Used with Permission AGAI

Cochrane review on PPIs before EGD in UGI bleeding: EHT required at index endoscopy

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<tr>
<td>Daneshmand 1992</td>
<td>0.89 [0.44, 1.81]</td>
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<tr>
<td>Halkay 2001</td>
<td>1.01 [0.40, 2.44]</td>
<td></td>
</tr>
<tr>
<td>Lau 2007</td>
<td>0.60 [0.41, 8.89]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.68 [0.50, 8.03]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: CHI² = 1.77, df = 2 (P = 0.41)</td>
<td>P = 0.80</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: CHI² = 0.02 (P = 0.98)</td>
<td></td>
<td></td>
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Management of Patients with Ulcer Bleeding: ACG Practice Guidelines*

*Lists 30 recommendations for pre and post endoscopic management of patients with ulcer bleeding including follow up to prevent recurrent bleeding

<table>
<thead>
<tr>
<th>H. pylori Therapy</th>
<th>Document Cure Stop PPI/H2RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID Stop NSAID</td>
<td>If NSAID required, use coxib+PPI</td>
</tr>
</tbody>
</table>
| Low-dose aspirin  | 1. Primary CV Prevention Do not resume aspirin in most patients  
                    2. Secondary CV Prevention Resume aspirin soon after hemostasis (e.g. 1-7 days) in most patients and start PPI |
| Idiopathic        | Maintenance PPI |

Adapted from: Laine L and Jensen D. Am J Gastroenterol 2012, 107:345-60

Conclusions

- PUD results from an imbalance between aggressive and defensive factors
- The major causes of PUD are gastric acid hypersecretion, H. pylori infection and NSAID gastropathy
- Complications include bleeding, perforation and gastric outlet obstruction.
- Peptic ulcer bleeding requires risk stratification for ideal management