Helicobacter pylori and NSAID Induced Peptic Ulcer Disease

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8/4/2011
Peptic Ulcer Disease

**Typical Symptoms**
- Epigastric pain
- Nausea
- Fullness
- Bloating
- Early Satiety
- Nocturnal Pain

**Alarm Symptoms**
- Anemia
- Hematemesis
- Melena
- Anorexia or weight loss
- Severe upper abdominal pain
Peptic Ulcer Disease
Conditions Associated with peptic ulcer disease

Gastric Ulcers
- H. pylori infection
- NSAID use
- Unknown
- ZES, other

Duodenal Ulcers
- H. pylori infection
- NSAID use
- Unknown
- ZES, other
NORMAL

Damaging Forces:
- Gastric acidity
- Peptic enzymes

INJURY

H. pylori infection
- NSAID
- Aspirin
- Cigarettes
- Alcohol
- Gastric hyperacidity
- Duodenal-gastric reflux

PEPTIC ULCERATION

INCREASED DAMAGE OR IMPAIRED DEFENSES

- Ischemia
- Shock
- Delayed gastric emptying
- Host factors

Defensive Forces:
- Surface mucus secretion
- Bicarbonate secretion into mucus
- Mucosal blood flow
- Apical surface membrane transport
- Epithelial regenerative capacity
- Elaboration of prostaglandins

Mucus

Mucosa

Muscularis mucosae

Submucosa

Necrotic debris (N)

Nonspecific acute inflammation (I)

Granulation tissue (G)

Fibrosis (S)
Ulcer Diet

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Most Important Australian Contributions
Barry Marshall

- Received Nobel Prize in Physiology in 2005 for study on relationship between H. pylori and gastritis and peptic ulcer disease

- Drank petri dish full of H. pylori bacterium and on day 5 developed abd pain and vomiting. On day 14 underwent an upper endoscopy which showed gastritis

- For his pompous, arrogant approach to clinical research he was awarded a faculty position at an institution well known for similar medicine residents...
Helicobacter pylori Epidemiology

- One of the most common chronic bacterial infections in humans (>50% of world’s population is infected)
- Gastric cancer is 2nd leading cause of cancer death worldwide
- Risk of infection related to housing density, crowded conditions, number of siblings, sharing a bed, lack of hot or running water
- Human is major reservoir but domestic cats can also harbor these organisms
Flagella
bacterial mobility & chemotaxis to colonize under mucosa

Urease
neutralize gastric acid
gastric mucosal injury (by ammonia)

Lipopolysaccharides
adhere to host cells
inflammation

Outer proteins
adhere to host cells

Exotoxin(s)
- vacuolating toxin (vacA)
gastric mucosal injury

Type IV secretion system
pilli-like structure for injection of effectors

Secretory enzymes
- mucinase, protease, lipase
gastric mucosal injury

Effectors (cagA e.t.c)
actin remodelling,
IL-8 induction, host cell growth and apoptosis inhibition
Diagram 1: Gastric fluid and Mucus layer interaction. 
Diagram 2: Urease enzyme action in neutralizing gastric acid. 
Diagram 3: Mucosal damage by bacterial mucinase. 
Diagram 4: Inflammation by gastric acid, proteases, and effector molecules. Mucosal cell death by cytotoxins and ammonia.
Interaction of Infection and Nonsteroidal Anti-Inflammatory Drugs in Gastric and Duodenal Ulcers
cag

- Results in more corpus inflammation
- Decrease in gastric acidity
- Increase in proinflammatory cytokines (IL-8, IL-1, TGF-β, TNF-α)
- Increased gastrin
- Increased risk of gastric cancer
- Decreased risk of GERD, Barrett’s, and esophageal adenocarcinoma)
Pathogenesis of Infection

Helicobacter
pages 14-20, 5 NOV 2010 DOI: 10.1111/j.1523-5378.2010.00781.x
Consequences of Infection

<table>
<thead>
<tr>
<th>Gastric</th>
<th>Extragastric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nothing</td>
<td>Iron deficiency anemia</td>
</tr>
<tr>
<td>Chronic active gastritis</td>
<td>ITP</td>
</tr>
<tr>
<td>Peptic Ulcer Disease</td>
<td>Thyroid disease</td>
</tr>
<tr>
<td>Gastric adenocarcinoma</td>
<td>HTN</td>
</tr>
<tr>
<td>Lymphoma of the gastric mucosa-associated lymphoid tissue</td>
<td>SIDS</td>
</tr>
<tr>
<td></td>
<td>Rosacea</td>
</tr>
<tr>
<td></td>
<td>Chronic urticaria</td>
</tr>
</tbody>
</table>
"I've had no appetite ever since I developed a bleeding ulcer!"
MALT-lymphoma

- For localized gastric MALT lymphoma, H. pylori treatment = tumor regression in 60-90% of patients
- H. pylori eradication in patients with low-grade MALT lymphoma = recurrence rates of 3-13% over 5 years

- More recent study showed
  - High grade MALT lymphoma
  - H. pylori eradication = complete remission in 64%
    - Of these, relapse rate = 0% at 5 yrs
Figure 2 Hypothetical model of gastric MALT lymphoma pathogenesis

Sagaert, X. et al. (2010) Gastric MALT lymphoma: a model of chronic inflammation-induced tumor development

Figure 4 The canonical NFκB signaling pathway

 Sagaert, X. et al. (2010) Gastric MALT lymphoma: a model of chronic inflammation-induced tumor development
### Who to test?

<table>
<thead>
<tr>
<th>Established</th>
<th>Controversial</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PUD</td>
<td>• High risk for Gastric Cancer (family hx)</td>
</tr>
<tr>
<td>• Gastric low-grade MALT lymphoma</td>
<td>• Unexplained iron deficiency anemia</td>
</tr>
<tr>
<td>• Uninvestigated dyspepsia</td>
<td>• Nonulcer dyspepsia</td>
</tr>
<tr>
<td>• After endoscopic resection of early cancer</td>
<td>• Chronic NSAID/ASA therapy</td>
</tr>
<tr>
<td>• Evaluate success of eradication therapy</td>
<td>• Chronic antisecretory therapy</td>
</tr>
<tr>
<td></td>
<td>• Relatives of patients who have H. pylori infection</td>
</tr>
</tbody>
</table>
CHEATER
AND NINE

TRUTH HURTS

Because Kent State doesn’t really prepare you for the SEC
<table>
<thead>
<tr>
<th>Non-endoscopic</th>
<th>Advantage</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serology</td>
<td>Widely available, inexpensive, good NPV</td>
<td>Not useful after tx</td>
</tr>
<tr>
<td>Urease Breath test</td>
<td>Identifies active infection, accurate, useful before and after treatment</td>
<td>Reimbursement, availability, affected by PPI and antibiotic use</td>
</tr>
<tr>
<td>Stool Antigen</td>
<td>Identifies active infection, accurate, useful before and after treatment</td>
<td>Affected by PPI and antibiotics use</td>
</tr>
<tr>
<td><strong>Endoscopic</strong></td>
<td><strong>Advantages</strong></td>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>Histology</td>
<td>Accurate, provides additional information on gastric mucosa</td>
<td>Expensive, observer variability, PPI and Abx</td>
</tr>
<tr>
<td>Rapid urease</td>
<td>Rapid results, no path cost,</td>
<td>PPI and Abx, requires endoscopy</td>
</tr>
<tr>
<td>Culture</td>
<td>100% specificity, allows antibiotic sensitivity</td>
<td>Expensive, difficult, tedious</td>
</tr>
<tr>
<td>PCR</td>
<td>Accurate, allows detection of antibiotic resistance</td>
<td>Expensive, not widely available</td>
</tr>
</tbody>
</table>
Urea breath test

![Diagram showing the process of the Urea breath test]

**13CO2 (μmol)**

*Time (hour)*

- **Positive Urea test**
- **Negative urea test**
Rapid Urease Test

- Biopsy urease testing
- Less expensive than histology
- Affected by antibiotics and PPI
Fecal Antigen Testing

Principle of the fecal antigen test. Polyclonal antibody to *H pylori* is adsorbed to microwells (1). Diluted patient samples are added to the wells, and any *H pylori* in the fecal sample is bound to the adsorbed antibody (2). A second *H pylori* antibody conjugated to peroxidase is added and binds to *H pylori* (3). After unbound material is washed off, a substrate is added that reacts with bound peroxidase enzyme to produce a yellow colour (4), the intensity of which can be measured to estimate *H pylori* levels.
# First line Treatment Regimen for H. pylori infection

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Duration</th>
<th>Eradication rates</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI, Clarithromycin 500mg BID, Amoxicillin 1000mg BID</td>
<td>10-14 days</td>
<td>70-85%</td>
<td></td>
</tr>
<tr>
<td>PPI, Clarithromycin 500mg BID, Metronidazole 500mg BID</td>
<td>10-14 days</td>
<td>70-85%</td>
<td>PCN allergic</td>
</tr>
<tr>
<td>PPI, Amoxicillin 1000mg BID then PPI, Clarithromycin 500mg BID</td>
<td>5 days</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>PPI, Clarithromycin 500mg BID, tinidazole 500 mg BID</td>
<td>5 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bismuth subsalicylate 525mg QID, Metronidazole 500mg QID, Tetracycline 500mg QID, PPI</td>
<td>10-14 days</td>
<td>75-90%</td>
<td>Inexpensive but complicated, PCN allergic or clarithromycin resistance</td>
</tr>
</tbody>
</table>
## Rescue Treatment for persistent H. pylori infection

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>Eradication rate</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth subsalicylate 525mg QID, Metronidazole 500mg QID, Tetracycline 500mg QID, PPI</td>
<td>14 days</td>
<td>70%</td>
<td>Inexpensive but complicated, PCN allergic or clarithromycin resistance</td>
</tr>
<tr>
<td>Amoxicillin 1000mg BID, Levofloxacin 250mg BID, PPI</td>
<td>10-14 days</td>
<td>57-91%</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin 1000mg BID, rifabutin 150 mg BID, PPI</td>
<td>14 days</td>
<td>60-80%</td>
<td>Expensive, adverse hematologic events</td>
</tr>
</tbody>
</table>
The Effect of Probiotics and Mucoprotective Agents on PPI-Based Triple Therapy for Eradication of Helicobacter

The Effect of Probiotics and Mucoprotective Agents on PPI-Based Triple Therapy for Eradication of Helicobacter

Helicobacter
When to Confirm Eradication

- Any patient with H. pylori associated ulcer
- Individuals with persistent dyspeptia despite test and treat strategy
- Patients with H. pylori associated MALT lymphoma
- Individuals who have undergone resection of early gastric cancer
NSAIDS

Patient’s perspective

Physician’s perspective

WOW! WHAT A DRUG.. AND NO SIDE EFFECTS SO FAR..
Mechanisms of NSAID-Related Ulcer Formation

NSAID → Epithelial injury → Prostaglandin-mediated effects
  ↓ Mucin
  ↓ Surface active phospholipids
  ↓ HCO₃ secretion
  ↓ Mucosal proliferation
  ↓ Direct effects
    ↓ Microvascular injury
        ↓ Increased adhesion molecule expression
            ↓ Neutrophil adherence
                ↓ Stasis
                    ↓ Microvascular ischemia
                        ↓ Free radical formation

Ulcer

**Fig. 3.** Mechanism of acute and chronic damage induced by NSAIDs such as aspirin (ASA) and *H. pylori* colonizing gastric mucosa. ASA attracts polymorphonuclear (PMN) cells and triggers production of reactive oxygen species (ROS) while inhibiting of the COX enzyme-derived prostaglandins (PGE2 and PGI2). *H. pylori* acts as a “Troyan horse” adhering to the surface epithelial cell compartment and injecting cytotoxins and ammonia responsible for the acquisition of the bacteria in acidic environment of the stomach and triggers the activation of neutrophils and inflammatory response mediated by proinflammatory cytokines (IL-8, TNF-alpha and IL-1β).

Fig. 4. Simplified demonstration of contribution of COX-1 and COX-2 enzyme activities and their products such as PGs and tromboxane A2 (TXA2) to the maintenance of gastric mucosal integrity including protection (COX-1) and adverse processes (inflammation mediated by COX-2) of different organs including stomach. Physiological stimuli such as vasodilators or mild irritants were reported to influence the COX-1 activity and exert gastroprotective influence whereas various cytokines and proteases are known to stimulate COX-2 mediated proinflammatory action. Both, the COX-1 and COX-2 activities are suppressed by ASA and other NSAIDs.

Fig. 5. Complex interactions between three independent risk factors of peptic ulcer disease such as stress, NSAIDs and *H. pylori* in the mechanism of gastric mucosal protection and ulcerogenesis. NSAIDs including ASA upregulate COX-2 expression, possibly compensating the suppression of COX-1 and COX-2 activity induced by this drug. *H. pylori* inhibits gene expression of constitutive nitric oxide (cNOS) while enhancing the expression of inducible NOS (iNOS) that may lead to overproduction of NO and excessive generation of toxic radical peroxynitrate involved in the gastric cell inflammatory response and cellular damage. Growth factors such as EGF, TGFalpha and VEGF contribute to gastroprotection by stimulation of COX and NOS enzymes expression and activities and by facilitating fast restitution process and mucosal repair of the gastric mucosa exposed to stress, or damaged by NSAIDs and *H. pylori*

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Use</th>
</tr>
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<tbody>
<tr>
<td>H2-receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine, roxatidine)</td>
<td>Acid inhibition</td>
</tr>
<tr>
<td>PPI (omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole)</td>
<td>Most potent acid inhibition</td>
</tr>
<tr>
<td>Prostaglandin analogues* (misoprostol)</td>
<td>Increase mucosal resistance; weak acid inhibition</td>
</tr>
<tr>
<td>H pylori eradication regimens (PPI plus two antibiotics)</td>
<td>Cure of H pylori infection</td>
</tr>
<tr>
<td>Bismuth salts (subcitrate, subsalicylate)</td>
<td>Weak antibacterial effect; increase of mucosal prostaglandin synthesis</td>
</tr>
<tr>
<td></td>
<td>In quadruple therapy for H pylori eradication</td>
</tr>
<tr>
<td>No gastrointestinal risk factors</td>
<td>One or two gastrointestinal risk factors</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------------------------------</td>
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<tr>
<td>Low cardiovascular risk (low-dose aspirin not needed)</td>
<td>NSAID</td>
</tr>
<tr>
<td>High cardiovascular risk (low-dose aspirin needed)</td>
<td>Naproxen plus PPI or misoprostol</td>
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</table>

The Lancet Volume 374, Issue 9699, 24 October 2009, Pages 1449-1461
PPIs More Effective Than H2RAs

N = 130 patients with aspirin-related peptic ulcers/erosions randomly assigned to H2RA† vs PPI‡ and aspirin (80 mg)

- GI Bleeding: H2RA 5/65 (7.7%) vs PPI 0/65 (0%)
  \[P = .029\]

- Recurrent Dyspepsia: H2RA 8/65 (12.3%) vs PPI 0/65 (0%)
  \[P = .003\]

\[H2RA = H2 receptor antagonist\]

†Famotidine 40 mg twice daily
‡Pantoprazole 20 mg

Figure 1

Omeprazole Compared with Misoprostol for Ulcers Associated with Nonsteroidal Antiinflammatory Drugs.
Hawkey, Christopher; Karrasch, Jeffrey; Szczepanski, Leszek; Walker, Donald; Barkun, Alan; Swannell, Anthony; Yeomans, Neville

Figure 1. Cumulative Rates of Healing of Gastric Ulcers, Duodenal Ulcers, and Erosions at Four and Eight Weeks during Treatment with 20 mg of Omeprazole Daily, 40 mg of Omeprazole Daily, or 200 microg of Misoprostol Four Times Daily.
Figure 2

Omeprazole Compared with Misoprostol for Ulcers Associated with Nonsteroidal Antiinflammatory Drugs.
Hawkey, Christopher; Karrasch, Jeffrey; Szczepanski, Leszek; Walker, Donald; Barkun, Alan; Swannell, Anthony; Yeomans, Neville

Figure 2. Kaplan-Meier Estimates of the Rates of Remission among Patients Treated with 20 mg of Omeprazole Daily, 200 microg of Misoprostol Twice Daily, or Placebo for up to 26 Weeks. P<0.001 for the comparison of omeprazole with placebo by the log-rank test, and P = 0.001 for the comparison of omeprazole with misoprostol by the log-rank test.