An Update on *Helicobacter pylori* and Its Treatment

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Objectives

- Review the epidemiology of *Helicobacter pylori* (*H. pylori*)
- Explain the significance of *H. pylori* in the etiology and pathophysiology of peptic ulcer disease
- Discuss diagnostic tests for *H. pylori*
- Compare and contrast therapeutic strategies employed in *H. pylori* treatment
**Epidemiology**

- One of the most common worldwide human infections
- Higher prevalence in developing countries
- Acquisition occurs during early childhood
- Current rates are decreasing


**Risk Factors for Infection in Childhood**

- Infected family member
- Having ≥ 2 siblings
- Crowded living conditions
- Lower socioeconomic status
- Attendance at a daycare facility

**Mode of Transmission**

- Fecal – oral
- Oral – oral
- Gastric – oral


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**H. pylori and Peptic Ulcer Disease (PUD)**

- Once thought microorganisms could not survive in acidic environment of stomach
- Association between *H. pylori* & PUD
  - Most patients with PUD who are NOT taking NSAIDs have *H. pylori*
  - Eradication of *H. pylori* ↓ ulcer recurrence
- Few patients with *H. pylori* develop PUD

**H. pylori Self-Preservation**

**Morphology**
- Gram-negative
- Spiral-shaped
- Acid labile

**Virulence Factors**
- Flagella
- Adherence pedestals
- Urease
  \[ \text{Urea} \rightarrow \text{NH}_3 + \text{CO}_2 + \text{NaOH} \]

**Pathophysiology**

- **H. pylori**
  - Stomach lining
  - pH & adhesion
  - Ulceration
  - Damage
  - Cytokines

Dipiro. 6th ed
Pathophysiology

- Normal Gastric Mucosa
- Acquisition of H. pylori
- Acute Gastritis
  - Asymptomatic or Symptomatic Acquisition
  - Chronic Gastritis
    - Duodenitis
      - Duodenal Ulcer
    - Gastric Ulcer
      - Atrophic Gastritis
        - Intestinal Metaplasia
          - Gastric Cancer

Dipiro, 6th ed

Types of Peptic Ulcers

- Duodenal Ulcer
- Gastric Ulcer
**H. pylori Diagnosis**

- Multiple tests can be used for *H. pylori* diagnosis
- Testing should only be performed if the clinician plans to treat
- Choice of diagnostic test depends on:
  - Use of upper endoscopy
  - Strengths/weaknesses of each test
  - Cost of each test


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**H. pylori**

**Endoscopic Tests**

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>Considered &quot;gold standard&quot; where biopsy is examined by a pathologist</td>
<td>Good sensitivity and specificity (S &amp; S)</td>
<td>Expensive Trained personnel</td>
</tr>
<tr>
<td>Rapid urease test</td>
<td>Identifies active <em>H. pylori</em> infection via the organism's urease activity</td>
<td>Inexpensive Good S &amp; S in selected pts Antibiotic sensitivities</td>
<td>↓Sensitivity post tx.</td>
</tr>
<tr>
<td>Culture</td>
<td>Sample is cultured to determine presence of <em>H. pylori</em></td>
<td>Great specificity</td>
<td>Expensive Difficult to perform ↓ availability</td>
</tr>
</tbody>
</table>
**H. pylori**

**Non-Endoscopic Tests**

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<th>Test</th>
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<tbody>
<tr>
<td>Antibody detection</td>
<td>Detects antibodies to <em>H. pylori</em></td>
<td>Inexpensive</td>
<td>Not recommended after tx.</td>
</tr>
<tr>
<td>Urea breath test (UBT)</td>
<td>Urease breaks down ingested labeled C-urea; pt exhales CO₂</td>
<td>Identifies active infxn. Useful before and after tx.</td>
<td>Inconsistent reimbursement and availability</td>
</tr>
<tr>
<td>Fecal antigen test</td>
<td>Detects <em>H. pylori</em> antigen using polyclonal or monoclonal antibody in stool</td>
<td>Identifies active infxn. Useful before and after tx.</td>
<td>↑Unpleasantness Polyclonal test less validated than UBT</td>
</tr>
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**To Treat Or Not To Treat?**

**Treat**
- Active PUD
- Confirmed history of PUD
- Gastric history of mucosa associated lymphoid tissue lymphoma (MALT)
- After endoscopic resection of gastric cancer

**Do Not Treat**
- Non-ulcer dyspepsia
- Gastroesophageal reflux disease
- Persons using NSAIDs

Eradication

- Absence of the microorganism at least 4 weeks after cessation of therapy
- Results in:
  - Ulcer healing
  - \( \downarrow \) risk of recurrence to < 10% in 1 year
  - \( \downarrow \) risk of ulcer complications
- Urea breath test or fecal antigen test


Factors to Consider....

- Efficacy
- Tolerability
- Drug interaction potential
- Likelihood of compliance
- Antibiotic resistance
- Cost

Drug Strategies

- Antisecretory agents
  - Proton pump inhibitors (PPI), H₂ blockers (H₂B)
  - Enhance symptom relief
  - Promote ulcer healing
- Antibiotics
  - Penicillin, macrolides, tetracycline, metronidazole
  - Bacteriostatic or bacteriocidal to H. pylori
- Bismuth: exact mechanism unknown


Drug Strategies - Traditional

Three-Drug Strategies
- 2 antibiotics + PPI
- Good efficacy
- More expensive
- ↓ adverse effects
- Good compliance

Four-Drug Strategies
- 2 antibiotics + PPI + bismuth
- Good efficacy
- Least expensive regimen
- ↑ adverse effects
- ↓ compliance

**Drug Strategies - Sequential Therapy**

- Not widely used currently
- Has shown considerable efficacy
- Two five-day courses of therapy administered in succession
  - PPI + amoxicillin followed by
  - PPI + clarithromycin + metronidazole


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**Three-Drug Regimens**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin + Amoxicillin + PPI</td>
<td>500mg bid 1gm bid bid</td>
<td>10 – 14d</td>
<td>Excellent</td>
</tr>
<tr>
<td>Clarithromycin + Metronidazole + PPI</td>
<td>500mg bid 500mg bid bid</td>
<td>10 – 14d</td>
<td>Excellent</td>
</tr>
<tr>
<td>Amoxicillin + Metronidazole + PPI</td>
<td>1gm bid 500mg bid bid</td>
<td>10 – 14d</td>
<td>Good</td>
</tr>
</tbody>
</table>
### Four-Drug Regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth Metronidazole</td>
<td>525mg qid, 250mg qid, 500mg qid</td>
<td>14d</td>
<td>Excellent</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>As directed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI or H₂B</td>
<td>14d</td>
<td></td>
<td></td>
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<td>14d</td>
<td></td>
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</table>

### Antisecretory Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Healing</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>300 qid, 400 bid, 20 bid</td>
<td>400 – 800 qhs, 20 – 40 qhs</td>
</tr>
<tr>
<td>Famotidine</td>
<td>200 bid, 150 bid, 300 qhs</td>
<td>150 – 300 qhs</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>150 bid, 300 qhs, 150 bid</td>
<td>150 – 300 qhs</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>20 bid, 30 bid, 40 bid</td>
<td>20 – 40 qd, 15 – 30 qd</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 bid</td>
<td>20 – 40 qd</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30 bid</td>
<td>20 – 40 qd</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40 bid</td>
<td>20 – 40 qd</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>20 bid</td>
<td>20 – 40 qd</td>
</tr>
</tbody>
</table>
Drug Substitution

Do NOT substitute…
- Ampicillin for amoxicillin
- Doxycycline for tetracycline
- Azithromycin for clarithromycin

Administration

- Antibiotics: with meals
  - Tetracycline: avoid administration with dairy products
  - Metronidazole: avoid ethanol use
- Bismuth: with meals
- PPIs: 30 minutes prior to meals
- H₂B: no administration issues
### Adverse Effects – Antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Diarrhea, abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting, candidiasis</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Disulfarim-like reaction</td>
</tr>
<tr>
<td></td>
<td>Metallic taste</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Abnormal taste</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Photosensitivity, rash</td>
</tr>
<tr>
<td></td>
<td>Teeth discoloration</td>
</tr>
<tr>
<td></td>
<td><strong>Contraindicated &lt; 8 years old</strong></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Hypersensitivity reaction</td>
</tr>
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### Adverse Effects – Antisecretory Agents

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<tr>
<th>Drug</th>
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</tr>
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<tr>
<td>PPIs</td>
<td>Diarrhea, constipation, nausea</td>
</tr>
<tr>
<td></td>
<td>Vomiting, headache</td>
</tr>
<tr>
<td>H₂B</td>
<td>Diarrhea, constipation, dizziness</td>
</tr>
<tr>
<td>Bismuth salts</td>
<td>Black discoloration stool/tongue</td>
</tr>
<tr>
<td></td>
<td>Constipation, diarrhea, nausea</td>
</tr>
<tr>
<td></td>
<td><strong>Salicylate → contraindicated in children with virus</strong></td>
</tr>
</tbody>
</table>
Compliance

- Important factor for successful therapy
- Goal compliance = 80 – 90% of doses
- Decreases with:
  - Multiple medications
  - ↑ frequency of administration
  - ↑ length of treatment
  - Intolerable adverse effects

Antimicrobial Resistance

- Emergence has lead to concern
- Occurs in 20% of cases
- Important determinant of successful eradication

Minimal Resistance
- Amoxicillin
- Tetracycline
- Bismuth salts

Increased Resistance
- Metronidazole
- Clarithromycin

*Gut* 2004;53:1374-84.
Antimicrobial Resistance

Metronidazole
- Most common
- Varies depending on antibiotic exposure
- 4 drug combo still efficacious

Clarithromycin
- Less common
- Greater effect on clinical outcome
- ↑ macrolide consumption is a risk factor


Salvage Therapy

- Avoid antibiotics that have been used previously
- Bismuth-based quadruple therapy
- Levofloxacin triple therapy
  - Levofloxacin 500 mg qd - bid
  - Amoxicillin 1 gm bid
  - PPI

Gastroent Clin N Am 2006;35:229-34.
Patient Case

HP is a 25 y/o female who presents to the clinic with complaints of abdominal discomfort and a “burning” feeling. This had occurred for the past two months and she finally “could not take it anymore”. Endoscopy confirmed a duodenal ulcer.

Patient Case

What endoscopic test could be used to detect \textit{H. pylori}?  
1. Antibody detection  
2. Urea breath test  
3. Histology  
4. Fecal antigen test
Patient Case

A biopsy was performed that revealed *H. pylori*. Is an *H. pylori* eradication therapy regimen appropriate for HP?

1. Yes
2. No

Patient Case

You discover HP has a PCN allergy. What drug therapy would you recommend if you desired increased patient compliance?

1. Clarithromycin, metronidazole, PPI
2. Clarithromycin, amoxicillin, PPI
3. BSS, tetracycline, clarithromycin, PPI
4. BSS, tetracycline, metronidazole, PPI
Patient Case

Which regimen would likely be the least expensive for the patient?
1. Clarithromycin, metronidazole, H₂B
2. Clarithromycin, amoxicillin, PPI
3. BSS, tetracycline, clarithromycin, H₂B
4. Levofloxacin, amoxicillin, PPI

Summary

- *H. pylori* is a common microorganism that has an association with PUD
- It has multiple virulence factors that promote its survival in the stomach’s acidic environment
- It should be treated in all patients with active ulcer disease
<table>
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<tr>
<th>Summary</th>
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<tr>
<td>- Goal of therapy is permanent eradication</td>
</tr>
<tr>
<td>- Treatment regimens include antibiotics and antisecretory agents</td>
</tr>
<tr>
<td>- Adverse effects, compliance and cost should be considered when initiating therapy</td>
</tr>
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