1. Patient presents with complaints of dyspepsia

2. EVALUATION
   Are other causes of symptoms ruled out?
   - Yes → ALTERNATIVE DIAGNOSIS
   - No → 3

3. ASSESSMENT
   Are alarm signs or symptoms present or patient is >40 yr?
   - Yes → SPECIALIST REFERRAL
     - Perform endoscopy
   - No → 4

4. CLINICAL CONSIDERATION
   Should patient be tested for the presence of H pylori?
   - No → See Dyspepsia Management Chart
   - Yes → 5

5. DIAGNOSIS
   Is test for H pylori positive?
   - No → ALTERNATIVE DIAGNOSIS
   - Yes → TREATMENT
     See page 4
Helicobacter pylori Infection (2 of 8)

1. DEFINITION

Dyspepsia
- Presence of ≥1 of the following: Bothersome postprandial fullness, early satiation, epigastric pain &/or epigastric burning &
- No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms (functional or non-ulcer dyspepsia)
- Symptoms were present w/in the last 3 mth w/ onset ≥6 mth prior to diagnosis (Rome III criteria)
- Though the relationship between functional dyspepsia & H pylori is unclear, improvement of functional dyspepsia symptoms was seen w/ elimination of H pylori infection

Helicobacter pylori
- A spiral-shaped Gram-negative bacterium involved in the development of gastritis, duodenal & gastric ulcers, & gastric cancer
  - Up to 90-95% of patients w/ NSAID-related duodenal ulcers & 80% of patients w/ non-NSAID-related gastric ulcers are infected
  - Infection is strongly associated w/ the development of gastric epithelial & lymphoid malignancies
- Acute infection is mostly asymptomatic & is acquired through human-to-human contact via gastro-oral & fecal-oral routes
- Adaptability in gastric conditions & production of urease allow it to colonize the stomach

2. EVALUATION

- Thorough history & physical exam should be done to rule out other causes for dyspeptic symptoms (eg cardiac, hepatobiliary, medication induced eg nonsteroidal anti-inflammatory drugs (NSAIDs), dietary indiscretion, lifestyle, etc)
  - See GERD Management Chart for details
- Eradication of H pylori in patients on long-term NSAID use does not enhance the healing of gastric or duodenal ulcers & these patients should be treated appropriately for NSAID-induced ulcer
  - See Peptic Ulcer Disease (PUD) Management Chart for details

3. ASSESSMENT

Patients w/ alarm symptoms require prompt endoscopic investigation
- Unexplained wt loss or anorexia
- Recurrent vomiting
- >50 yr old (cut-off age will depend on national cancer incidence rates)
- Evidence of GI bleeding or anemia or positive occult blood test
- Dysphagia or odynophagia
- Failure of multiple treatments
- Jaundice
- Presence of abdominal mass

4. CLINICAL CONSIDERATION

- Eradication of H pylori leads to ulcer healing & significantly diminished incidence of recurrence
  - Elimination of infection reduces gastric cancer incidence
  - Multidrug regimen, adequate duration of treatment, & adherence to therapy are needed for eradication
  - “Test & Treat” for H pylori
- It is strongly recommended that the following patients should be tested for H pylori & if they test positive for H pylori, treatment to eradicate the infection should be instituted:
  - Before starting NSAID treatment on patients w/ previous history of PUD or ulcer complication
  - NSAIDs increase the risk of developing complications in patients w/ concomitant H pylori infection
  - Patients w/ GERD requiring long-term proton pump inhibitor (PPI) therapy
  - Long-term PPI use of patients infected w/ H pylori may be associated w/ acceleration of atrophic gastritis
  - Complicated & uncomplicated peptic ulcers (active or healed)
  - Gastric mucosa-associated lymphoid tissue (MALT) lymphoma
  - Previous history of lymphoma while on NSAID therapy
  - Uninvestigated dyspepsia
  - After resection of early gastric cancer
  - Family history of gastric cancer
Helicobacter pylori Infection (3 of 8)

**DIAGNOSIS**

"Test & Treat" for Helicobacter pylori in Primary Care

- Routine testing is not recommended, performed only in patients who will require therapy if results are positive
- Two positive tests are required for Helicobacter pylori diagnosis
- Urea breath test (UBT) or stool antigen test are the preferred methods of diagnosis in the primary care setting
  - If UBT & stool antigen test are not available, serological test (mainly IgG) is a satisfactory alternative
  - A delayed test (either a UBT or histology) should be done within 4-8 weeks of an acute upper GI bleed following a negative endoscopy

<table>
<thead>
<tr>
<th>MODALITY</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea breath test (UBT)</td>
<td>Reliable, rapid, quantitative</td>
<td>Expensive instrumentation &amp; radioisotope</td>
</tr>
<tr>
<td></td>
<td>Highly specific &amp; sensitive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Most valuable for assessing response to therapy after 4-8 weeks</td>
<td></td>
</tr>
<tr>
<td>Stool antigen test</td>
<td>Enzyme-linked immunosorbent assay (ELISA) is the most accurate</td>
<td>Requires withholding of some medications prior to testing</td>
</tr>
<tr>
<td>Serology</td>
<td>Rapid, quantitative, inexpensive</td>
<td>Low sensitivity &amp; specificity</td>
</tr>
<tr>
<td></td>
<td>Not for eradication confirmation</td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopy w/ biopsy</td>
<td>Permits inspection of pathology</td>
<td>Invasive, expensive</td>
</tr>
<tr>
<td></td>
<td>Allows detection of ulcers/neoplasm</td>
<td>Unable to visualize ( H. pylori )</td>
</tr>
<tr>
<td>Culture</td>
<td>Permits determination of antimicrobial susceptibility</td>
<td>Low sensitivity</td>
</tr>
<tr>
<td></td>
<td>Requires several days for result</td>
<td>Requires several days for result</td>
</tr>
<tr>
<td>Histology</td>
<td>More sensitive than culture</td>
<td>Several days for result</td>
</tr>
<tr>
<td></td>
<td>Allows direct visualization of organism &amp; extent</td>
<td>Nature of tissue involvement</td>
</tr>
<tr>
<td></td>
<td>Observer variability</td>
<td>Observer variability</td>
</tr>
<tr>
<td>Urease detection</td>
<td>Rapid (most positive w/in 2 hr)</td>
<td>Increased sensitivity</td>
</tr>
<tr>
<td></td>
<td>Requires longer incubation</td>
<td>Requires withholding of some medications prior to testing</td>
</tr>
</tbody>
</table>

Other Patients

Adult patients <50 yr (≤40 yr in areas with high prevalence of gastric cancer) who present with persistent dyspepsia and/or predominant GERD symptoms, NSAID therapy and no alarm symptoms may be approached in 2 different ways:

- **Empiric therapy**
  - Treat empirically x 2-4 wk w/ appropriate antisecretory agent &/or prokinetic agent
  - If symptoms do not improve w/ appropriate trials of PPI, histamine-2 receptor antagonists (H₂RA) or prokinetic agents, consider endoscopy

- **May test for Helicobacter pylori prior to trial of medication**
  - These patients may be considered for "test & treat" but this is controversial in non-ulcer dyspepsia
  - It is unlikely that eradication of \( H. pylori \) will reduce symptoms but it may decrease future risk of PUD
  - Endoscopy may be performed 1st to identify PUD & treat \( H. pylori \) only in PUD patients
Helicobacter pylori Infection

**CONFIRMED H pylori INFECTION**

### Recommended Regimens

**Choice of antibiotic combination will depend on local H pylori resistance patterns**

One of the following drug regimens:
- Proton pump inhibitor (PPI) PO bid + Clarithromycin 500 mg PO bid + Amoxicillin 1000 mg PO bid x 14 days
- PPI PO bid + Clarithromycin 500 mg PO bid + Metronidazole 400-500 mg PO bid x 14 days
- Ranitidine bismuth citrate (RBC) 400 mg PO bid + Clarithromycin 500 mg PO bid + Amoxicillin 1000 mg PO bid
- RBC 400 mg PO bid + Clarithromycin 500 mg PO bid + Metronidazole 400-500 mg PO bid

### Alternative Regimens

- PPI PO bid + Amoxicillin 1000 mg PO bid + Metronidazole 400-500 mg PO bid x 7 days
- Colloidal bismuth subsalicylate/subcitrate 120 mg PO qid + Metronidazole 400-500 mg PO bid + Tetracycline 500 mg PO qid x 14 days

### FOLLOW-UP

Was treatment successful?

**Yes**

**Successful Treatment**
- Antisecretory therapy after H pylori eradication is not recommended in uncomplicated duodenal ulcer patients & in prevention of recurrent ulcer bleeding

**No**

### SPECIALIST REFERRAL

**A**

Alternative Regimen After Initial Treatment Failure

- PPI PO bid + Colloidal bismuth subsalicylate/subcitrate 120 mg PO qid + Metronidazole 400-500 mg PO bid + Tetracycline 500 mg PO qid

### FOLLOW-UP

Was treatment successful?

**Yes**

**No**

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Helicobacter pylori Infection (5 of 8)

Patient should be re-tested after a minimum of 4 wks after treatment
- It is advisable to confirm eradication of H pylori w/ a posttreatment UBT or a monoclonal stool test
- Antisecretory drugs esp PPIs should be discontinued at least 1 wk prior to posttest
- Patients w/ either gastric ulcers or complicated duodenal ulcers should have a repeat endoscopy & biopsy, UBT, or stool antigen test to rule out malignancy
- In patients w/ persistent H pylori infection, a culture & sensitivity may be done before retreatment
- Serology is not used in determining treatment response

Follow-up

Recommended Regimens

Regimen for H pylori should be easy to comply w/ & cost-effective
- Patients need to be advised that full compliance is important for treatment success

Recommended Regimen for Initial Therapy
- Triple therapy using PPI or RBC w/ Clarithromycin & Amoxicillin or Metronidazole is the recommended regimen
- Many studies have shown that regimens using RBC is as effective as using a PPI

PPI
- The PPIs appear to be equally effective when used in the standard dose
- Prolonging PPI therapy is recommended in gastric ulcer & complicated duodenal ulcer
- Action: The exact mechanism of action in H pylori eradication is unknown. H pylori prefers an acidic medium & it is postulated that the potent acid suppression w/ PPIs allows the antibiotics to act most effectively on the bacteria

Bismuth
- Actions: Cytoprotective effect on GI mucosa
  - Stimulation of prostaglandin production & modulation of immune response
  - Bismuth salt deposits adhere to H pylori cell wall, inducing vacuolization & distortion of bacterial cell & loss of adherence from gastric epithelium

RBC
- Actions: Acid suppression is not as potent as PPI, but has the advantage of added antimicrobial activity of Bismuth

Amoxicillin
- Action: Inhibits bacterial cell wall synthesis

Clarithromycin
- Action: Binds to ribosomes resulting in protein synthesis inhibition
  - Clarithromycin w/ Amoxicillin is considered the antibiotic combination of choice for initial therapy

Metronidazole
- Action: Causes cell death by inducing breakage of DNA double strands
  - It is thought that avoiding Metronidazole in initial therapy will give better results w/ the drug when it is used in quadruple therapy after initial treatment failure
  - Metronidazole should be substituted for Amoxicillin in Penicillin-allergic patients
  - If resistance to Metronidazole is a problem (which may be in developing countries), Furazolidone can be used as alternative

Tetracycline
- Action: Prevents protein synthesis

Adjuvant Therapy

Probiotics
- Live bacteria that help restore microbial balance in the intestine
- Reduces risk of adverse effects from H pylori treatment, though additional studies still need to be done

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**Helicobacter pylori Infection (6 of 8)**

### ALTERNATIVE REGIMEN FOR INITIAL TREATMENT FAILURE

- Treatment failure occurs when symptoms persist or recur w/in 14 days after completion of therapy
  - May be due to noncompliance, intake of NSAIDs, antimicrobial resistance, or cigarette smoking
- Quadruple therapy w/ PPI, Bismuth, Metronidazole & Tetracycline taken for 10-14 days is typically the preferred regimen after initial treatment failure & for high Clarithromycin resistance
- If Bismuth is not available, an alternative regimen consisting of triple therapy using PPI w/ a longer period of treatment has been used as a rescue therapy
  - Sequential therapy: PPI + Amoxicillin for 5 days followed by PPI + Clarithromycin + Metronidazole for another 5 days
- If the alternative regimen fails, patient should be referred to an expert & antibiotic susceptibility testing should be considered to guide retreatment

### Dosage Guidelines

#### ANTIULCERANTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bismuth Preparations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bismuth salicylate/subcitrate</td>
<td>120 mg PO 6 hrly</td>
<td>Adverse Reactions</td>
</tr>
<tr>
<td>Ranitidine bismuth citrate (RBC)</td>
<td>400 mg PO 12 hrly</td>
<td>- GI effects (N/V, darkening of stool or tongue); Bismuth toxicity can occur if used for long periods of time (GI disturbances, stomatitis, discoloration of mucous membranes, encephalopathy has occurred); Absorption of salicylate occurs w/ administration of Bismuth subsalicylate</td>
</tr>
<tr>
<td><strong>Proton Pump Inhibitors (PPIs)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Esomeprazole                     | 20 mg PO 12 hrly | Special Instructions 
- Avoid in patients w/ moderate-severe renal failure |
| Lansoprazole                     | 30 mg PO 12 hrly |                                             |
| Omeprazole                       | 20 mg PO 12 hrly |                                             |
| Pantoprazole                     | 40 mg PO 12 hrly |                                             |
| Rabeprazole                      | 20 mg PO 12 hrly |                                             |
| **Proton Pump Inhibitors (PPIs)**|            |                                                   |
| Esomeprazole                     | 20 mg PO 12 hrly | Special Instructions 
- Generally well tolerated; headache, diarrhea, rash |
| Lansoprazole                     | 30 mg PO 12 hrly | Special Instructions 
- Less common: Dizziness, fatigue, GI effects (constipation, flatulence, abdominal pain, N/V), arthralgia, urticaria; Rarely photosensitivity, severe hypersensitivity reactions, increased LFTs, hepatotoxicity |
| Omeprazole                       | 20 mg PO 12 hrly |                                             |
| Pantoprazole                     | 40 mg PO 12 hrly |                                             |
| Rabeprazole                      | 20 mg PO 12 hrly |                                             |

#### GIT REGULATORS, ANTIFLATULENTS & ANTI-INFLAMMATORIES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus</td>
<td>2 tabs daily</td>
<td>Special Instructions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Should be taken w/ food</td>
</tr>
</tbody>
</table>

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### MACROLIDE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>500 mg PO 12 hrly</td>
<td><strong>Adverse Reactions</strong>&lt;br&gt;• GI effects (N/V, abdominal discomfort, diarrhea &amp; other GI disturbances, antibiotic-associated diarrhea/colitis); Other effect (Candidal infections)&lt;br&gt;• Hypersensitivity reactions are uncommon (urticaria, pruritus, rash, rarely anaphylaxis); Rarely cardiotoxicity, hepatotoxicity; Dose-related tinnitus/hearing loss have occurred with some macrolides&lt;br&gt;<strong>Special Instructions</strong>&lt;br&gt;• May take with food to decrease gastric distress&lt;br&gt;• Use with caution in patients with hepatic dysfunction</td>
</tr>
</tbody>
</table>

### PENICILLIN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>1000 mg PO 12 hrly</td>
<td><strong>Adverse Reactions</strong>&lt;br&gt;• Hypersensitivity reactions (rash, urticaria, pruritus, severe reactions e.g. anaphylaxis can occur); GI effects (diarrhea, N/V, rarely antibiotic-associated diarrhea/colitis); Other effect (Candidal infections)&lt;br&gt;• Rarely hematologic effects; Renal &amp; hepatic effects have occurred; High doses may be associated with CNS effects (encephalopathy, convulsions)&lt;br&gt;<strong>Special Instructions</strong>&lt;br&gt;• Avoid in patients with Penicillin allergy&lt;br&gt;• Use with caution in patients with renal impairment</td>
</tr>
</tbody>
</table>

### TETRACYCLINE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>500 mg PO 6 hrly</td>
<td><strong>Adverse Reactions</strong>&lt;br&gt;• GI effects (N/V, diarrhea, antibiotic-associated diarrhea/colitis has occurred, dysphagia, esophageal ulceration has occurred when taken with an insufficient amount of liq); Dermatologic effects (photosensitivity); Other effects (Candidal infections, discoloration of teeth, interference with bone growth in young infants/pregnant women)&lt;br&gt;• Rarely renal dysfunction, hepatotoxicity, hematologic effects, increased intracranial pressure (ICP) with headache &amp; visual disturbances; Hypersensitivity reactions have occurred&lt;br&gt;<strong>Special Instructions</strong>&lt;br&gt;• Avoid long exposure to sunlight or tanning beds&lt;br&gt;• Take with plenty of fluid while sitting or standing &amp; well before retiring to bed&lt;br&gt;• Avoid in children ≤8 yr &amp; pregnant women&lt;br&gt;• Avoid in patients with systemic lupus erythematosus (SLE)&lt;br&gt;• Use with caution in renal or hepatic impairment</td>
</tr>
</tbody>
</table>

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### OTHER ANTIBIOTIC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroimidazole Derivative</td>
<td>400-500 mg PO 12 hrly</td>
<td><strong>Adverse Reactions</strong>&lt;br&gt;• GI effects (N/V, metallic taste, diarrhea, constipation)&lt;br&gt;• CNS effects have been reported (weakness, dizziness, headache, mood changes, peripheral neuropathy has occurred at high/prolonged doses); Hematologic &amp; hepatic effects have occurred; Rarely hypersensitivity reactions; May cause darkening of urine; Other effect (Candidal infection)&lt;br&gt;• High dose or prolonged use has caused peripheral neuropathy &amp; epileptiform seizures <strong>Special Instructions</strong>&lt;br&gt;• When given w/ alcohol, a Disulfiram-reaction can occur&lt;br&gt;• Use w/ caution in patients w/ severe hepatic impairment&lt;br&gt;• If given &gt;10 days, recommend monitoring CBCs &amp; clinical monitoring for CNS effects</td>
</tr>
</tbody>
</table>

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Helicobacter pylori Infection


