HELICOBACTER PYLORI

Microbiology: Helicobacter pylori

Gastric Mucosa
- Spiral-shaped
- Flagellated
- Non-invasive

Agar
- Slow-growing (3-7 days)
- Gram negative rod
- Microaerophilic (5% O2)
- Catalase +
- Oxidase +
- Urease +
- Urea → CO2 + NH3 → ↑ pH

Survival
Colonization
Diagnostic testing

First isolated in 1983
Nakamura (Marshall & Warren, 2005)
NEJM 352: 1197, 2010

Question #1
A young woman undergoes upper endoscopy for unexplained nausea and vomiting. The stomach appears normal. Surveillance biopsies are taken and the gastric biopsy urease test is positive. The biopsies are most likely to show:

A. Hp organisms, but no gastric or esophageal inflammation.
B. Hp organisms plus gastric inflammation (gastritis).
C. Hp organisms plus esophagitis.
D. Neither Hp organisms, nor inflammation because the urease test is often false positive with a normal endoscopy.

Question #2
What is the most likely source for humans to acquire H. pylori infection?

A. Perinatally from mother
B. Ingestion of raw vegetables
C. Ingestion of undercooked meat
D. Ingested tap water from a municipal source
E. Contact with infected secretions from another human
56 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD

Helicobacter pylori: Key Points

- Humans are the only natural Hp host
- Infects > 50% of the world’s population
  - US ~20-40%
- A leading chronic infection in humans
  - Similar to dental caries
- Majority are asymptomatic but all have chronic active gastritis
- Severity of gastritis varies depending on the Hp strain & the host
  - At greater risk, African Americans, Hispanics, Native Americans

Transmission of H. pylori

- Exact route of transmission is not known
- Likely fecal-oral or oral-oral
- Intrafamilial spread – (person-to-person, esp. mother-to-child)
- Low socioeconomic status, poor sanitation, crowding associated with transmission

Disease Paths for Helicobacter pylori Infection

- Asymptomatic gastritis 85-90%
- Peptic ulcer (DU, GU) 1-10%
- Gastric cancer 0.1-3%
- MALT lymphoma <0.01%

H. pylori: Disease Associations

- #1 cause of chronic gastritis
- PUD: 90%, DU, 80% GU
- MALT lymphomas (72 – 98%)
- Gastric Cancer (60 – 90%)*
- Iron deficiency anemia, B12 deficiency, ITP
- Eradication Hp neither causes nor exacerbates GERD
- Hp poss. reduces risk for Barrett’s esophagus/esophageal CA

HP is classified by WHO as a Class 1 carcinogen.
MALT = mucosal-associated lymphoid tissue

Disease Paths for H. pylori Infection

Noninvasive (glob) Sensitivity Specificity

| Breath test (%) | > 90 – 95% | > 90 – 95% | Live Hp
|----------------|------------|------------|---------
| stool Antigen (monoclonal) | > 90 – 95% | > 90 – 95% | Live & dead Hp

Histology 85% 79% Detects exposure

Biopsy-based (sampling area) Sensitivity Specificity

| Rapid urease test | 90% | 95% | 2.5 bx Recommended
|-------------------|-----|-----|---------------------
| Histology         | 90 – 95% | 95 – 98% |
| Culture           | 75% | 100% | Difficult

*UTI considered best test. Antigen test is usually less expensive.
Use only monoclonal stool Ag tests.
Histology requires IFM organisms to visualize

Question #3

A 25-year-old African American woman complains of 6 weeks of symptoms: cans is left with dyspepsia unrelieved by current use of antacids & an OTC PPI.

The best approach to the diagnosis of H. pylori infection in this patient is:

A. Immediate Hp serology
B. Immediate Hp stool antigen EIA
C. Endoscopy with rapid urease test (RUT)
D. Immediate 13C Urea Breath Test
E. D/C PPI for 2 weeks then Hp stool antigen EIA

Diagnosis of H. pylori Infection

UTI considered best test. Antigen test is usually less expensive.
Use only monoclonal stool Ag tests.
Histology requires IFM organisms to visualize

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Testing Limitations for Hp

- Interfere with all Hp tests
- PPI
- Antibiotics
- Bismuth
- Bleeding

False negatives due to decreased Hp burden. Recommend delay diagnostic testing until:
- PPI stopped for 2-4 weeks (OTC antacids & H2RA do not affect UBT/SAT testing)
- Antibiotics, Bismuth stopped for 4 weeks
- Bleeding stopped for 4-8 weeks

Initial Diagnosis of H. pylori with Dyspepsia

- Stool antigen test (SAT)
- Urea Breath Test (UBT)
- "Test and Treat" in younger population (<60 yo)
- Endoscopy mandatory if ≥ 60 years old or "alarm symptoms or signs":
  - Unexplained iron-def anemia
  - GI bleeding
  - Unintentional weight Loss
  - Palpable mass
  - Severe abdominal pain
  - Persistent vomiting
  - Progressive dysphagia / odynophagia

Question #4

- Which of the following is the most appropriate next step for evaluating a 29 year old previously healthy but overweight male patient with typical retrosternal heartburn symptoms?
  - A. Stool antigen test for H. pylori
  - B. Urea breath test for H. pylori
  - C. No testing for H. pylori
  - D. Serological testing for H. pylori
  - E. Empiric therapy for H. pylori regardless of testing

Explanation for Q#4

- H. pylori is not implicated as an etiological factor in gastroesophageal reflux disease
- Treatment for (eradication of H. pylori) can increase the risk for Barrett's esophagus and esophageal adenocarcinoma
- Serology is not a recommended test for H. pylori anymore

Reference: Siddique O, et al. AJM 2018

Question #5

A 23 yo Eastern European woman presents with persistent epigastric discomfort diagnosed as Hp+ gastritis by endoscopy. Fecal Hp antigen is also positive. As a child, she was treated repeatedly with PCN/amoxicillin for recurrent tonsillitis.

What do you recommend for therapy?
- A. Clarithromycin + amoxicillin + PPI
- B. Metronidazole + erythromycin + PPI
- C. Bismuth subsalicylate + TCN + metronidazole + PPI
- D. Metronidazole + amoxicillin + PPI
- E. PPI therapy alone given her age

Question #6

After treatment of this patient for Hp gastritis, the H. pylori stool antigen test should be repeated:

- A. On the final day of H. pylori therapy
- B. Two weeks after completion of H. pylori therapy
- C. Eight weeks after completion of H. pylori therapy
- D. The test should not be repeated to assess cure

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Questions #5 & 6: Explanation

- Clarithromycin resistance in Hp is really common in Eastern Europe
- Repeated exposure to amoxicillin could increase risk for resistant Hp
- Note, tetracycline is better than doxycycline
- Test of cure should be done at least 4 weeks after therapy is completed


Who should be tested & treated for H. pylori infection?

Established Indications
- PUD (active/prior hx)
- MALT lymphoma
- Atrophic gastritis
- After gastric CA resection
- 1st degree relative w/ gastric CA

Consider
- Non-ulcer dyspepsia
- Use of NS AIDs/ASA
- Family history of gastric CA
- PPI refractory dyspepsia

*Some clinics recommend testing for all of the above


Principles of Hp Therapy

1. Ask about abx exposure hx (clarithromycin/metronidazole/fluoroquinolones)
2. Discuss adherence
3. Use high dose PPI (BID dose; increase gastric pH>4-5)
4. Longer (14 days) rather than shorter treatment courses
5. Combination drug therapy
6. Consider abx resistance patterns & testing

Outcome is determined by Hp antibiotic sensitivity, drug dosing, treatment duration & treatment compliance, & making mistakes therapeutic resistant.


Evidence-based Treatment Regimens for H. pylori Infection in North America

Table 5: Evidence-based Treatment Regimens for H. pylori Infection in North America, Listed in Recommended Order

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Components</th>
<th>Duration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin-based triple therapy</td>
<td>PPI, clarithromycin, and amoxicillin (2-4 weeks)</td>
<td>14</td>
<td>Recommended for patients with low resistance to clarithromycin</td>
</tr>
<tr>
<td>Sequential therapy</td>
<td>PPI and amoxicillin, then PPI (clarithromycin and amoxicillin, 2 wks)</td>
<td>14</td>
<td>Not appropriate in patients with high level of clarithromycin resistance or documented resistance to clarithromycin</td>
</tr>
<tr>
<td>Clarithromycin-based triple therapy</td>
<td>PPI, clarithromycin, and metronidazole (2-4 weeks)</td>
<td>14</td>
<td>Not appropriate in patients with high level of clarithromycin resistance or documented resistance to clarithromycin</td>
</tr>
<tr>
<td>Hybrid therapy</td>
<td>PPI and amoxicillin, then PPI (clarithromycin and amoxicillin) (2 wks)</td>
<td>14</td>
<td>Not appropriate in patients with high level of clarithromycin resistance or documented resistance to clarithromycin</td>
</tr>
<tr>
<td>Levofloxacin-based triple therapy</td>
<td>PPI, metronidazole (2 wks), and amoxicillin</td>
<td>14</td>
<td>Not appropriate in patients with high level of clarithromycin resistance or documented resistance to clarithromycin</td>
</tr>
<tr>
<td>Fluoroquinolone-based sequential therapy</td>
<td>PPI and amoxicillin, then PPI, levofloxacin, and amoxicillin (2 wks)</td>
<td>5-7</td>
<td>Recommended for patients with high level of clarithromycin resistance or documented resistance to clarithromycin</td>
</tr>
</tbody>
</table>

H. pylori & Antimicrobial Resistance

- Amoxicillin: Low (<5-10%)
- Tetracycline: Low (<5-10%)
- Clarithromycin: High (10-50%)
- Metronidazole: High (10-80%)*
- Levofloxacin: High (5-30%)

Ask about history: clarithromycin, quinolones & metronidazole

Rates of resistance show substantial geographic differences.

Prior, even distant, abx hx can inform likelihood of Hp abx resistance.

*Metronidazole resistance may be overcome by increased dosing (≥1500 mg/day).

Kasabian-Gi, Infect Drug Resist 13:1567-172, 2020

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Management Issue:
**Test of cure** for H. pylori Infection
- Stool antigen test: Perform ≥4 weeks post-rx*
- Urea Breath Test: Perform ≥4 weeks post-rx.
- Some recommend testing 6-8 wks post-rx.
- Endoscopy required if gastric ulcer, for example.

*FDA-approved

**KEY TAKEAWAYS**

**DIAGNOSIS:**
- In most: Stool Hp antigen test, UBT
- If ≥60 years old or alarm symptoms / signs then endoscopy is mandatory

**KEY TAKEAWAYS**

**TREATMENT:**
- Triple or Quadruple therapy
- Increasing emphasis on antibiotic resistance testing
  - Fecal or biopsy genotypic testing for clarithromycin
  - MIC testing for clarithromycin, nitroimidazole, FQ resistance

**KEY TAKEAWAYS**

**FOLLOW UP:**
- TOC mandatory (stool Hp antigen test, UBT)
- At least 4 weeks after completion of therapy

**C. DIFFICILE INFECTION (CDI)**

Most common health care-associated infection, USA
Leading cause of gastroenteritis death, USA


Antibiotic-associated Diarrhea (AAD)

- Common
  - In 5-25% of antibiotic treatment courses, especially with > 3 days of Abx, but one dose is sufficient
  - 10-40% of AAD is associated with C. difficile infection (CDI) but nearly all AA colitis is CDI
- Disruption of colon microbiome & bile acid physiology are key mechanisms

Pathogenesis of CDI

1. CDI spores survive in the environment for long periods of time. Following ingestion, they traverse the acidic environment of the stomach.
2. Spores germinate within the intestine.
3. Altered lower intestine flora due to antimicrobial use allows proliferation of C. difficile in colon.
4. Toxin A & B Production leads to colon damage +/- pseudomembrane.

Common Clinical Manifestations

- Watery & mucous diarrhea up to 10 - 15 times daily
- Lower abdominal pain & cramping
- Low grade fever (15%+)
- Leukocytosis (around 15,000 cells/µl)
- Nausea
- Anorexia
- Malaise

Complications of CDI

- Sepsis ± multiple organ dysfunction
- Megacolon: need for surgical intervention
  - Colectomy
  - Loop ileostomy
- Bowel Perforation
- Lack of treatment response
- Recurrent infection (20%+)
  - Relapse
  - Reinfection

Epidemiology of CDI

### Top Causative Pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>% of HAIC</th>
<th>HAIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. difficile</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>S. aureus</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>E. coli</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Enterococcus spp</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>K. pneumonia/oxytoc a</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>5</td>
<td>9</td>
</tr>
</tbody>
</table>

Major Risk Factors for Acquisition of CDI

1. Antibiotic use
   - Disruption of microbiome
2. Recent hospitalization or LTCF
   - Increased exposure
     - Co-morbidities reduce immunity or alter microbiome
3. Age > 65 years
   - Reduced gastric acidity
   - Impaired immunity
   - Altered microbiome

**REMEMBER:**

- Even healthy people in the community without antibiotic exposure can get CDI

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Minor Risk Factors for Acquisition of CDI

4. Gastric acid suppression (proton pump inhibitor)
   - Reduced biochemical defenses
   - Altered microbiome
5. Abdominal surgeries
   - Altered microbiome
6. Immunocompromised host
   - Impaired mucosal immunity
   - Altered microbiome

CDI Severity

- Leukocytosis
- AKI
- Sepsis/shock
- Megacolon

Stool frequency is not part of severity assessment

C. difficile Diagnostic Testing

Whom to test?

Appropriate epidemiology/ill with diarrhea/endoscopic findings
- No laxatives within last 48 hrs
- Test diarrheal stools (unless ileus). One stool.
- >3 liquid stools over 24h
- Only test specimens if patient >1 year old

C. difficile Diagnostic Testing

Simplified approach:

\[ \text{Diarrhea} + \text{Toxigenic } C. \text{ difficile } \&/\text{or toxin in stool} \rightarrow \text{TREAT} \]

*No laxatives or other obvious causes

C. difficile Diagnostic Testing

Nucleic acid amplification test (NAAT; PCR):

- Detects the gene for toxin B

  **Advantages**
  - High sensitivity
  - Rapid
  - Relatively inexpensive

  **Disadvantages**
  - Does not detect actual toxin
  - Cannot differentiate colonization from infection

Glutamate dehydrogenase (GDH) antigen EIA:

- Detects C. difficile bacteria by secreted antigen

  **Advantages**
  - High sensitivity
  - Rapid
  - Relatively inexpensive

  **Disadvantages**
  - Does not detect toxin
  - Detects NON-toxigenic strains
  - Cannot differentiate colonization from infection

Patient selection is critical

Must be combined to test for toxin (NAAT or EIA)
**C. difficile Diagnostics Testing**

Toxin A/B detection by EIA:

**Detects C. difficile toxin(s) directly**

**Advantages**
- Good specificity
- Rapid
- Relatively inexpensive

**Disadvantages**
- Poor sensitivity
- False positives possible

Usually used in a 2-step protocol with NAAT or GDH

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**CDI TAKE AWAYS**

Careful selection of patients for testing, especially with NAATs, is extremely important.

Only patients with diarrhea (≥3 stools in <24 hrs)

NO formed or soft stools (unless ileus)

NO 'Test of Cure'

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**Question #7**

- 67 year old woman develops diarrhea while hospitalized for community acquired pneumonia. She is afebrile, her WBC count is 12,000/uL, creatinine is 1.2 mg/dl (baseline 1.0 mg/dl) and she is experiencing 12 small loose stools daily with abdominal cramping. Stool PCR is positive for C. difficile toxin B. Which of the following therapies is recommended?
  - Metronidazole 500 mg po TID x 10 days
  - Vancomycin 500 mg PO qidx 10 days
  - Vancomycin 125 mg PO qidx 10 days
  - Bezlotoxumab + vancomycin x 10 days
  - Fidaxomicin 200 mg PO BID + metronidazole 500 mg PO TID x 10 days

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**Therapy of CDI**

- D/C antibiotics/change to 'lower risk abx'
- No antiperistaltics
- This is a time of transition for treatment guidelines
- Recurrent CDI occurs in 21 in 5 patients

---

**Therapy of CDI**

<table>
<thead>
<tr>
<th>Presumed infection</th>
<th>Treatment Guidelines</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting, severe electrolyte abnormality, low creatinine (less than 0.6 mg/dl)</td>
<td>VANCOMYCIN 125 mg po QID x 10 d</td>
<td>FIDAXOMICIN 200 mg po BID x 10 d</td>
</tr>
</tbody>
</table>

No more metronidazole

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Recurrent CDI

Bezlotoxumab, a monoclonal antibody directed against toxin B produced by C. difficile, has been approved as adjunctive therapy for patients who are receiving antibiotic treatment for CDI & who are at high risk for recurrence.

Prevention of C. difficile Disease (HCW & visitors)

- Contact precautions for patient care.
- Gloves, gowns while diarrhea persists.
- Single rooms
- Handwashing with SOAP & WATER
  - Alcohol gel rubs do not kill Cd spores
- Sporocidal solutions for hospital cleaning.
  - (eg. hypochlorite solutions)
- Antibiotic restriction policies
  - (Antimicrobial stewardship programs)
- Antimicrobial stewardship programs

CDI TAKE AWAYS

- Most CDI is health-care associated
- Need to demonstrate toxin B in stool with NAATs, EIA
- Send only unformed stools when diarrhea meets CDC definition
- Vancomycin & fidaxomicin > Metronidazole
- Bezlotoxumab & fidaxomicin associated with lower risk for recurrent CDI
- Consider FMT for second or more recurrence
- Handwash as alcohol gels ineffective
- Bleach
- Antimicrobial stewardship programs

Thank you
D.aronoff@vanderbilt.edu
@DMAronoff