**Helicobacter and Clostridioides difficile**

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- Research Grant - Pfizer (C. difficile pathogenesis)

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**HELICOBACTER PYLORI**

*The New England Journal of Medicine*

**Clinical Practice**

**Helicobacter pylori Infection**  
Sheila E. Crowe, M.D.

This journal feature highlights a case scenario highlighting a common clinical problem. Evidence supporting various strategies or interventions is presented, followed by a review of current guidelines, when they exist.

The article is well written with the author's clinical recommendations.

First isolated in 1983  
Nobel Prize (Marshall & Warren, 2005)  
NEJM 362: 1597, 2010

**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

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**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.

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**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

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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

Helicobacter 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

H. pylori is a World Health Organization-designated carcinogen & the strongest known risk factor for non-cardia gastric adenocarcinoma

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%

Questions:

Question #3

A 25-year-old African American woman complains of 6 weeks of symptoms: chest pain and 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. Hp stool antigen EIA for 2 weeks before Hp serology test

Diagnosis of H. pylori Infection

<table>
<thead>
<tr>
<th>Noninvasive (global)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breath Test (%)</td>
<td>&gt; 90 – 95%</td>
<td>&gt; 90 – 95%</td>
</tr>
<tr>
<td>Stool Antigen (monoclonal)</td>
<td>&gt; 90 – 95%</td>
<td>Live &amp; dead Hp</td>
</tr>
</tbody>
</table>

Serology: 80% 79% Detect exposure

<table>
<thead>
<tr>
<th>In vitro-based (sampling area)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid urease test</td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td>Histology</td>
<td>90 – 93%</td>
<td>95 – 98%</td>
</tr>
<tr>
<td>Culture</td>
<td>&gt; 90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

UUT considered best test. Antigen test is usually less expensive.

Use only monoclonal stool Ag tests.

Histology requires LAB and is not as visualizable.

NEJM 354: 1175, 2002
Gut 66:6, 2017
NEJM 362:1597, 2010
NEJM 380:1158-65, 2019
Gut 66:6, 2017
JAMA 282:2240, 1999
From T et al. Gut 2021;60:1831–1844

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Testing Limitations for Hp

- 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

Question #5

A 23 yo woman presents with persistent epigastric discomfort diagnosed as Hp+ gastritis by endoscopy. Fecal Hp antigen is also positive. Last year she was treated with azithromycin for a respiratory tract infection. 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

Who should be treated for H. pylori infection?

- "We recommend that all patients with active H pylori infection be treated"
- "Infection causes chronic progressive damage to the gastric mucosa that in 20%-25% of individuals will result in life-threatening clinical outcomes such as peptic ulcer or gastric cancer"

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

- PUD (active/prior hx)
- MALT lymphoma
- Atrophic gastritis
- After gastric CA resection
- ≥1 deg relative w/ gastric CA

*≥50% respond
**Goal: eradicate prior to atrophy or metaplasia. Treatment resolves atrophy but not metaplasia.

Consider

- Non-ulcer dyspepsia*
- Use of NSAIDs/ASA
- Long-term PPI use
- Fe deficiency anemia (unexplained)
- ITP (low evidence base)
- Live in high gastric Ca region
- Asymptomatic infection**
Principles of Helicobacter pylori Therapy

1. Ask about abx exposure for (clarithromycin/metronidazole/fluoroquinolones)
2. Discuss adherence
3. Use high dose PPI (BID dose, increase gastric pH 4-5)
   - H. pylori grows optimally at pH 6-8
   - Acidity hinders stability & activity of macrolides, amoxicillin
4. Longer (14 days) rather than shorter treatment courses
5. Combination drug therapy is essential
6. Consider abx resistance patterns & testing

Outcome is determined by H. pylori antibiotic sensitivity, drug dosing, treatment duration & treatment compliance, smoking habits, therapeutic responses etc.

*clarithromycin, metronidazole, levofloxacin

Eradication of Helicobacter pylori

- Triple therapy with a PPI, clarithromycin, & amoxicillin or metronidazole is not favored due to increased prevalence of macrolide resistance (but might still be an option on boards!)
- Clarithromycin resistance in the US now > 15%

- Use a bismuth-based quadruple therapy for 14 days as 1st-line therapy:
  - Bismuth subsalicylate or subcitrate
  - Tetracycline (not doxycycline)
  - Metronidazole
  - PPI

Question #6

After treatment of this patient for H. 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

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 TAKE AWAYS**

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

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

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

**Clostridioides Difficile**

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

**Common Clinical Manifestations**
- Watery & mucous diarrhea up to 10 - 15 times daily
- Lower abdominal pain & cramping
- Low grade fever (15%+)
- Leukocytosis (> 15,000 cells/μl = severe)
- 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**

### 2015

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>% of Cases</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. difficile</td>
<td>15</td>
<td>5</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</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Streptococcus</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 LTF
   - Increased exposure
3. Age > 65 years
   - Reduced gastric acidity
   - Impaired immunity
   - Altered microbiome

**Minor Risk Factors for Acquisition of CDI**

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

**REMEMBER:**
Even healthy people in the community without antibiotic exposure can get CDI
27 – Helicobacter and Clostridium Difficile
Speaker: David M. Aronoff, MD

CDI Severity

- Leukocytosis
- AKI
- Sepsis/shock
- Megacolon

Stool frequency is not part of severity assessment

C. difficle Diagnostic Testing

Whom to test?

- Appropriate epidemiology/fill 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. difficle Diagnostic Testing

Simplified approach:

Diarrhea* + Toxigenic C. difficle &/or toxin in stool → TREAT

*No laxatives or other obvious causes

C. difficle Diagnostic Testing

Glutamate dehydrogenase (GDH) antigen EIA:

Detects C. difficle bacteria by secreted antigen

Advantages
- High sensitivity
- Rapid
- Relatively inexpensive

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

Must be combined to test for toxin (NAAT or EIA)

C. difficle Diagnostic Testing

Toxin A/B detection by EIA:

Detects C. difficle 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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Patient with Sx of CDI

2-Stage Testing

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’

Question #7

67 year old woman develops diarrhea while hospitalized for community acquired pneumonia. She is afebrile, her WBC count is 12,000/μl, 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 qid x 10 days
- Vancomycin 125 mg PO qid x 10 days
- Bezlotoxumab + vancomycin x 10 days
- Fidaxomicin 200 mg PO BID + metronidazole 500 mg PO TID x 10 days

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 ≥1 in 5 patients

Recurrent CDI

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Supportive Critical Care</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First recurrence</td>
<td>VANCOMYCIN 125 mg po QID x 10 d</td>
<td>FIDAXOMICIN 200 mg po BID x 10 d</td>
</tr>
<tr>
<td>Second or subsequent recurrence</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
(unless mild disease, in young person, +/- cost constraints)
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
- ≥65 years old with >1 additional risk factor:
  - Experiencing 2nd episode of CDI within 6 mo
  - Immunocompromised, or severe CDI

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)

CDI TAKE AWAYS

Epidemiology
- Most CDI is health-care associated

Diagnosis
- Need to demonstrate toxin B in stool with NAATs, EIA
- Send only unformed stools when diarrhea meets CDC definition

Treatment: Primary or Recurrent CDI
- Vancomycin & fidaxomicin > Metronidazole
- Bezlotoxumab & fidaxomicin associated with lower risk for recurrent CDI
- Consider FMT for second or more recurrence

Prevention
- Hand wash as alcohol gels ineffective
- Bleach
- Antimicrobial Stewardship Programs

New Guidelines 2021

Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update
Guidelines on Management of Clostridioides difficile Infection in Adults

Stuart Johnson, Valery Lavigne, Andrew M. Skinner, Anne I. Gonzalez-Luna, Kevin W. Gamp, Marian P. Kelly, Mark W. Wilcox

Thank you

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