Helicobacter pylori: Update on disease, Diagnostics, and Discouraging Trends

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Relevant Disclosures

- Speaking fees – Meridian Biosciences
- Research funds – Meridian Biosciences
**Helicobacter pylori**

- Gram negative microaerophile
- Lophotrichous flagella
- Human 1° host
- Gastric pathogen

www.hpylori.com.au
**H. pylori Disease Associations**

- **Established:**
  - Peptic Ulcer Disease (PUD)
  - Dyspepsia
  - Non-ulcer dyspepsia (NUD)
  - Gastric adenocarcinoma
  - MALT lymphoma

- **Possible:**
  - Iron deficiency

- **Not associated:**
  - Gastroesophageal reflux disease (GERD)
  - Coronary artery disease (CAD)
Disease progression

Non-colonized mucosa → Superficial gastritis → Peptic ulcer disease → MALT Lymphoma

WHO classifies *H. pylori* as the only bacterial Class 1 Carcinogen

Virulence factors

- Urease and Flagella
- Multiple adhesins
- NAP (Neutrophil Activating Protein)
- VacA (Vacuolating Cytotoxin)
- CagA & Cag T4SS

Adapted from Amieva and El-Omar, Gastroenterology, 2008
VacA: Vacuolating Cytotoxin A

- Gene present in nearly all cultured strains\(^1\)
  - Protein expressed in almost all isolates
  - Active protein produced by 40% of isolates

- Implicated in peptic ulceration\(^2\)

- Forms channels that allow release of nutrients to extracellular space

- Pro-apoptotic & initiates proinflammatory response in conjunction with HP-NAP

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\(^1\) Atherton & Blaser, *Journal of Clinical Investigation*, 2009

CagA: Cytotoxicity Associated Gene

- Associated with severe disease state
  - “Oncoprotein”
- Alters cell cycle progression\(^1\)
  - Prolongs cell life
- Upregulates mitogenic genes implicated in carcinogenesis\(^2\)
- Interacts with proteins that lead to cytoskeletal rearrangement
  - Triggered by interaction with a cellular oncogene\(^3\)

\(^1\)Chang et al. Cell Microbiol, 2006  \(^2\)Franco et al. PNAS, 2005  \(^3\)Rieder et al. Current Opinion in Microbiology, 2005

Wild-type Infected

\[\Delta\text{cag} \text{ Infected}\]

Couturier et al. Infect & Immun, 2006
Summary of Virulence

- Motility
- Colonization
- Immune evasion
- Immune stimulation
- Cellular damage

Adapted from Amieva and El-Omar, Gastroenterology, 2008
Global epidemiology

Why are we concerned about *H. pylori*?
Epidemiological Trends

- Male skew in *H. pylori* infections (not true for children)
  - Males have higher PUD & gastric cancer rates
    (1.5 - 3.0 times more common)\(^1\)
- Infected mothers typically have infected children\(^2\)
- People of low socioeconomic standing are more likely to be infected\(^3\)
- In developed countries infection rates are higher in non-Caucasian individuals\(^3\)
- Occupational exposure to feces linked to increased infection rates\(^2\)

\(^1\)Replogle et al. *Am J Epidemiol*. 1995

\(^2\)Covacci et al. 1999 *Science*

\(^3\)Azevedo et al. 2009 *Helicobacter*
Worldwide epidemiology

- ~50% of the world infected
  - Developing world/impoverished areas primarily
  - Transmission mode still unclear (familial, fecal/oral?)

Couturier, Clin Microbiol News, 2012
• ~ 50% of the world infected
  – Developing world/impoverished areas primarily
  – Transmission mode still unclear (familial, fecal/oral?)

H. pylori in Northern-California

IgG based study of Northern California adults age 20-39

- Ethnic groups chosen based on different gastric cancer risks
- Confirmed sex skew in males for seropositivity
- Disparity between Caucasian-Americans and African & Hispanic Americans
- Increasing aged was a risk factor

<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Race/ethnicity†</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>African-American</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Japanese</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>20–24</td>
</tr>
<tr>
<td>25–29</td>
</tr>
<tr>
<td>30–34</td>
</tr>
<tr>
<td>35–39</td>
</tr>
</tbody>
</table>

**H. pylori** seroprevalence in US Army recruits

- Male & Female recruits age 17-26 (Ft. Jackson, SC)
  - No geographic or ethnic restrictions
- Age and race were strongest predictors of “infection”
- Median income is predictive for seropositivity (↓ = ↑)

H. pylori in low income African Americans from 13 southern states

• Patients self-identified as “white” or “African American”
  – Degree of African ancestry determined by genetic markers as “low, medium, and high”

• Seropositivity
  – 89% African Americans
  – 69% Caucasians

• African American race 2- to 6-fold increase odds of seropositivity for virulent (VacA+/CagA+) H. pylori

• ↑ odds of H. pylori-positivity with increased African ancestry
  – Medium and high ancestry carries 2.5- and 3.4-fold increase in H. pylori seropositivity

Arctic Epidemiology

Chesterfield Inlet/Repulse Bay

- Arctic towns share risk factors for *H. pylori* prevalence
  - Overcrowding
  - Inadequate drinking water
  - Poor sewage disposal

- 130 of 256 adults from communities tested

- 51 % *H. pylori* IgG seropositive
  - 62 % CagA seropositive

McKeown et al. 1999 Am J Gastro.
Aklavik, Northwest Territory

CANHelp project: Aklavik

• Population of 600
  – 60% Inuit, 25% Dene, 15% Alaskan

• Prevalence unknown

• 313 patients screened by UBT
  – 58% positive

• Three other communities now included in Yukon territory and Nunavut Territory

Cheung et al. Can J Gastroenterol, 2008
Cancer in Arctic First Nations

- Gastric cancer is 10th most common cancer in Canadian men\(^1,2\)
  - 5th most common cancer in NWT men\(^1\)
  - 2 X more gastric cancer in NWT (per capita)\(^1\)
  - 3rd leading cause of cancer-related death in NWT vs 9th for all of Canada\(^2\)

- Alaska natives have 3X more gastric cancer than Caucasian Americans\(^2\)

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**Top Three Cancer Diagnoses in Males by Ethnic Group**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Male</th>
<th>Male</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dene (n=109)</td>
<td>Inuit (n=32)</td>
<td>Other (n=193)</td>
</tr>
<tr>
<td>1</td>
<td>Colorectal (35%)</td>
<td>Trachea, Bronchus and Lung (25%)</td>
<td>Trachea, Bronchus and Lung (19%)</td>
</tr>
<tr>
<td>2</td>
<td>Trachea, Bronchus and Lung (19%)</td>
<td>Stomach (16%)</td>
<td>Colorectal (17%)</td>
</tr>
<tr>
<td>3</td>
<td>Prostate (7%)</td>
<td>x</td>
<td>Prostate (14%)</td>
</tr>
</tbody>
</table>

*Other* includes Non-Aboriginals and Métis. X = cells with less than five cases are suppressed. N values represent the number and % values represent the proportion of cases in each gender-specific ethnic group.

A prediction of antibiotic resistance

2003 study of Alaska Natives in Anchorage

- 30% of *H. pylori* isolates resistant to clarithromycin
  - 13% w/clari\(^S\) *H. pylori* failed clari-based treatment

- 66% resistant to metronidazole
  - 50% w/metro\(^S\) *H. pylori* failed therapy

- Resistance linked to previous macrolide or metronidazole use

- Reinfection rates
  - 7% at six months
  - 10% at one year
  - 15% at two years

Impact of Therapy

Hospitalization rates between 1998 and 2005 for PUD & related complications w/ special focus on *H. pylori* diagnosis in the USA

- 21% Decrease (Age adjusted)
- Decline in most ethnic groups
  - Lowest rates in whites & decrease in African Americans
  - No decline in Hispanics
  - Many native American tribes declined, others increased dramatically
- Hospitalization for PUD highest for ≥65 years old
  - Higher for men than women
- Age adjusted *H. pylori* hospitalization rates also declined overall

What effect will treatment have?

<table>
<thead>
<tr>
<th>Condition</th>
<th>H. pylori causation</th>
<th>Effect of H. pylori eradication</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUD</td>
<td>Yes</td>
<td>Reduces recurrence</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Yes in some</td>
<td>Symptom improvement in some</td>
</tr>
<tr>
<td>NUD</td>
<td>Possibly in few</td>
<td>Improvement in some</td>
</tr>
<tr>
<td>Gastric Cancer</td>
<td>Yes</td>
<td>Little effect if any</td>
</tr>
<tr>
<td>MALT lymphoma</td>
<td>Yes</td>
<td>Remission in $&gt;50%$</td>
</tr>
<tr>
<td>Iron Deficiency</td>
<td>Likely in some</td>
<td>Improvement in some</td>
</tr>
<tr>
<td>NSAID ulcers</td>
<td>Naïve users?</td>
<td>May reduce incidence</td>
</tr>
<tr>
<td>GERD</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>CAD</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>
To Treat or Not to Treat

...and how to treat
First we must decide whether to test
Current Dyspepsia Guidelines

• “Chronic or recurrent pain or discomfort centered in the upper abdomen”

• The AGA recommends that:
  “Patients 55 years of age or younger without alarm features should receive *H. pylori* test and treat followed by acid suppression if symptoms remain.”

• Despite this clear direction…
  this is not happening…

Talley et al. *Gastroenterology*, 2005
AGA Dyspepsia Guidelines

Dyspepsia without GERD or NSAIDs

Age > 55 or alarm symptoms* present

- EGD

Age < 55
No alarm symptoms

Test for H. pylori

- Negative
  - PPI trial 4-6 weeks
  - Fails
  - Reassurance, Reassess diagnosis
  - Fails
  - Consider EGD

- Positive
  - Treat for H. pylori
  - Fails
  - PPI trial 4 weeks

*Alarm features include:
- Age >55 w/ new onset dyspepsia
- Family h/o gastric cancer
- Unintended weight loss
- GI bleeding
- Persistent dysphagia
- Unexplained iron-deficiency anemia
- Persistent vomiting
- Palpable mass or lymphadenopathy
- Jaundice

EGD: esophagogastroduodenoscopy

Not only the AGA…

ACG Dyspepsia Guidelines

Dyspepsia (uninvestigated)

Age > 55 or alarm features*

- EGD

Age < 55
- No alarm features

*Alarm features include:
  - Age > 55 w/ new onset dyspepsia
  - Family h/o gastric cancer
  - Unintended weight loss
  - GI bleeding
  - Persistent dysphagia
  - Unexplained iron-deficiency anemia
  - Persistent vomiting
  - Palpable mass or lymphadenopathy
  - Jaundice

H. pylori prevalence <10%
- PPI trial
  - Fails
  - Test and treat for H. pylori
    - Fails
    - Consider EGD

H. pylori prevalence >10%
- Test and treat for H. pylori
  - Fails
- PPI trial
  - Fails
  - Consider EGD

EGD: esophagogastroduodenoscopy

Laboratory Testing Methods

Endoscopy-based (Invasive)
- Culture from biopsy & susceptibility
- Rapid urease from biopsy (CLO)
- Immunohistochemistry

Non-endoscopy (Non-invasive)
- Serology (IgA, IgM, IgG)
  - No longer recommended! Or performed by major laboratories
- Urea breath test
- Stool antigen test
Endoscopy-based: Culture

Advantages:
• Provides clinical isolate for susceptibility testing
• Direct evidence of infection

Disadvantages:
• Limited sensitivity
• Demands highly experienced microbiologists
• Invasive procedure
Endoscopy-based: Rapid Urease

Advantages:

• Direct evidence of infection with CLO
• Rapid turn around time
• Limited technical expertise required

Disadvantages:

• Non-specific
• Invasive procedure
Urea Breath Test

- Baseline Breath sample collected
- $^{13}$C-urea ingested by patient, wait 30 minutes
- Collect breath specimen; test for isotopic CO$_2$ in patient breath

Urea Breath Test

Advantages:

• Excellent performance pre- and post-treatment (diagnosis and confirming eradication)
• Direct measure of urease activity (indicative of *H. pylori*) infection
• High sensitivity
• FDA approved for pediatric use*

Disadvantages:

• Antibiotics & PPI must be stopped 2 weeks prior
• Complications in collection
• Not *truly* specific for *H. pylori*…but good PPV
• Limited availability & expensive
Stool Antigen Test

Immuonoassay detection of *H. pylori* antigen in the stool

**Advantages:**

- Excellent performance pre- and post-treatment (diagnosis and confirming eradication)
- High specificity and sensitivity (>90%)
- FDA approved for pediatric use
- Readily available

**Disadvantages:**

- Stigma in sample type
- PPIs & antibiotics must be stopped
- Variable performance across vendors (outside USA)

Vaira and Vakil, *Gut* 2001
Serology

Includes IgA, IgM, and IgG testing

**Advantages:**
- Non-invasive and inexpensive
- Not affected by antibiotic or PPI use
- Easily establish prevalence in research/epidemiological studies
- Familiarity with physicians

**Disadvantages:**
- Does NOT define an active infection
- Limited sensitivity; negative result does not rule out *H. pylori*
- CANNOT be used as test-of-cure
- Can lead to clinical confusion and **unnecessary therapy**
- May NOT reimburse in some states/insurance carriers
# Aggregate Test Performance of Non-Invasive Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool antigen test</td>
<td>90-95%</td>
<td>90-95%</td>
</tr>
<tr>
<td>Urea breath test</td>
<td>95-100%</td>
<td>90-95%</td>
</tr>
<tr>
<td>Serum IgG antibody</td>
<td>80-85%</td>
<td>75-80%</td>
</tr>
</tbody>
</table>

Vaira and Vakil, *Gut*, 2001
Serology - IgG

- Once considered a standard non-invasive Dx method
- Studies typically show higher positivity than UBT, SAT, or invasive methods…
  - Is this better sensitivity?
    - Depends on the “standard”

- Challenges
  - Also a marker of past infections/exposures
  - Lack of true prediction for active infections
  - Kit-to-kit variation across vendors
Serology - IgA

- Generally thought to represent a marker of mucosal infection, and should persist during active infection
  - Highly sensitive…but poor specificity versus invasive testing w/RUT and histology
  - Poor specificity and sensitivity versus SAT
  - No proven value in addition to IgG testing
  - Lack of prediction for active infections

Urita et al. Intern Med. 2004
Serology - IgM

• Once though to be consistently reactivated due to chronicity of infection...likely only during acute phase
  – Poor specificity versus SAT in adults and children
  – Poor specificity & sensitivity vs invasive testing
  – Lack of prediction for acute or active infections

**IgM testing plays no role in the diagnosis of *H. pylori*.
“We must do it right at UUHC”

<table>
<thead>
<tr>
<th>UU Hospital</th>
<th>UBT</th>
<th>SAT</th>
<th>IgG</th>
<th>IgG &amp; IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan – Dec 2011</td>
<td>104</td>
<td>319</td>
<td>290</td>
<td>384</td>
</tr>
</tbody>
</table>

- 2011 – 423 active tests / 674 serology
  - Or…the recommended test is correctly ordered only 39% of the time
Incorporate Ordering Rules in CPOE

• WARNING FLAG for IgG, IgA, IgM:

• “Do not use to diagnose *H. pylori*; order *H. pylori* urea breath test or fecal antigen by EIA”

• Active in March 2012
**Helicobacter pylori Testing**

**INDICATIONS FOR TESTING**
- Persistent dyspepsia, abdominal pain
  - Obvious cause
    - Nonsteroidal anti-inflammatory drug (NSAID) use
    - Known gastroesophageal reflux disease (GERD)
  - Remove cause if possible
  - Treat based on etiology
  - >55 years
  - OR
  - Alarm symptoms
    - Gastrointestinal bleeding
    - Unexplained iron deficiency anemia
    - Early satiety
    - Unexplained weight loss
    - Progressive dysphagia
    - Odynophagia
    - Recurrent vomiting
    - Family history of upper gastrointestinal cancer
    - Previous esophagogastric malignancy

**ORDER**
- Helicobacter pylori Breath Test
- Helicobacter pylori Antigen, Fecal by EIA

**Positive**
- Treat with triple therapy (amoxicillin or metronidazole, clarithromycin, and proton pump inhibitor) to eradicate *H. pylori*

**Negative**
- Empiric trial of proton pump inhibitor for 4-6 weeks

**Reevaluate after completion of therapy**
- Symptoms still present
  - Consider EGD
  - Consider repeat *H. pylori* testing during EGD
- No symptoms present
  - No further therapy required
**Helicobacter pylori Antibody, IgG**

**Ordering Recommendation**
Do not use to diagnose *H. pylori*; order *H. pylori* urea breath test (0020646) or fecal antigen by EIA (0065147). Use IgG only if breath and/or stool tests cannot be performed.

**Mnemonic**
G PYLORI

**Performed**
Sun-Sat

**Methodology**
Semi-Quantitative Enzyme Immunoassay

**Reported**
Within 24 hours
Test Utilization

Testing Proportions

Serology
Active Tests

Apr 2011 – Mar 2012
Apr 2012 – Mar 2013
Apr 2013 – Mar 2014
Apr 2014 – Mar 2015
Apr 2015 – Mar 2016

Active tests
Serology
Active Test Trend
Serology Test trend

Test Volumes
Evolving Issues with *H. pylori* testing

- Many major insurance carriers no longer reimbursing for certain *H. pylori* testing

- Serology becoming viewed as “medically unnecessary testing”

- SAT & UBT on a single patient is non-reimbursable
Serology non-reimbursement

- Several major insurance plans NOT reimbursing for serology
  - Aetna, Cigna, BC/BS, & Geisinger (Likely many others)

- States affected:
  - NY, CA, PA, FL, WV, KY, IN, MO, OH, WI, others?

- Specific CPT codes defined as: “medically unnecessary”
Final action on serology testing

- ARUP laboratory inactivated testing for all antibody subclasses for *H. pylori* in accordance to industry standards and professional guidelines
  - Commercial laboratories also following this pattern:
    - Quest Diagnostics (Oct 2015)
    - Mayo Medical Laboratories (March 2016)
    - LabCorp (pending?)
- More accurate diagnoses can be achieved using recommended, FDA cleared methods (UBT or SAT) (even on PPIs)
  - Reimbursement is excellent, despite higher cost than serology
- Despite concerns of rare instances where serology would be beneficial due to specimen collection challenges, physician ordering practices have shown that serology tests will continue to be misused unless completely inactivated
So we’ve correctly diagnosed

Now how do we treat???
## Helicobacter pylori treatment

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Regimen</th>
<th>Duration (Days)</th>
<th>Cure Rate</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple (clarithromycin)</td>
<td>PPI, clarithromycin, amoxicillin</td>
<td>10-14</td>
<td>70-85%</td>
<td>Primary therapy for patients with no macrolide exposure or penicillin allergies</td>
</tr>
<tr>
<td></td>
<td>PPI or H$_2$RA, clarithromycin, metronidazole</td>
<td>10-14</td>
<td>70-85%</td>
<td>Primary therapy for penicillin allergic patients with no macrolide exposure or patients unable to tolerate bismuth quadruple therapy</td>
</tr>
<tr>
<td>Quadruple</td>
<td>Bismuth subsalicylate, metronidazole, tetracycline, PPI</td>
<td>10-14</td>
<td>75-90%</td>
<td>Primary therapy for patients with macrolide exposure or patients with penicillin allergies</td>
</tr>
<tr>
<td>Sequential</td>
<td>PPI, amoxicillin</td>
<td>5</td>
<td>&gt;90%</td>
<td>Consider as alternative primary therapy to triple therapy (not validated in USA). May be effective in patients with macrolide resistant strains</td>
</tr>
<tr>
<td></td>
<td>PPI, clarithromycin, tinidazole</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
H. pylori re-treatment

• Salvage therapy indicated on treatment failures

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Regimen</th>
<th>Duration (Days)</th>
<th>Cure Rate</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadruple</td>
<td>Bismuth subsalicylate, metronidazole, tetracycline, PPI</td>
<td>7</td>
<td>68%</td>
<td>Salvage therapy after triple therapy failure</td>
</tr>
<tr>
<td>Triple (levofloxacin)</td>
<td>PPI, amoxicillin, levofloxacin</td>
<td>10</td>
<td>87%</td>
<td>Patients who failed triple and/or quadruple therapy. May not be effective in patients with prior quinolone exposure</td>
</tr>
</tbody>
</table>

Alternative salvage therapies include:

• Fluoroquinolones
• Rifabutin (TB drug) 40-90% effective
Helicobacter pylori treatment

- Recommended to not repeat the same therapy after initial failure
  - Avoid using therapy consisting of previously used antibiotics

- Re-infection:
  - 5% in developed countries\(^1\)
  - Re-infection may be a result of incomplete clearance i.e. relapse

\(^1\) Azevado et al. 2009 Helicobacter
Possible “reinfection” scenarios

$\ &= H_p\ (\text{clarithro}^R)\\
$\ &= H_p\ (\text{clarithro}^S)
Possible “reinfection” scenarios

\[ \$ = \text{Hp (clarithro}^R\text{)} \]

\[ \$ = \text{Hp (clarithro}^S\text{)} \]

Incomplete clearance

Cardiac sphincter

Pyloric sphincter

Fundus

Corpus

Antrum

Duodenal bulb
Possible “reinfection” scenarios

\[ \$ = \text{Hp (clarithro}^R\text{)} \]
\[ \$ = \text{Hp (clarithro}^S\text{)} \]

Incomplete clearance

Second Exposure
Possible “reinfection” scenarios

\[ \$ = \text{Hp (clarithro}^R\text{)} \]
\[ \$ = \text{Hp (clarithro}^S\text{)} \]

Incomplete clearance

Second Exposure

Resistance to treatment, reestablished infection
Summary

- *H. pylori* infections remain a global health issue
- Pathogenesis is complex and involves multiple unique virulence factors
- Genetic/ethnic/geographic/socioeconomic disparities exist
- Proper patient management: testing for active infection and appropriate antimicrobial therapy
- Antibiotic resistance and treatment failures are an ongoing challenge
Questions?
References (H. pylori)

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