Treatment and Screening of *H. pylori* Infection in Alaskan Populations

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**Learning Objectives – Pharmacist**

- Explain theories for the high prevalence of *H. pylori* infection in Alaskan populations.
- Discuss the risk factors for *H. pylori* infection, appropriate screening, and criteria for treatment.
- Outline the similarities and differences for *H. pylori* treatment using the current American College of Gastroenterology treatment guidelines and the Alaska Native Medical Center statewide guidelines.
- Differentiate post treatment testing methodologies and patient specific factors that predict *H. pylori* treatment success.

**Learning Objectives – Technician**

- Explain theories for the high prevalence of *H. pylori* infection in Alaskan populations.
- Discuss the common signs and symptoms associated with *H. pylori* infection.
- Recognize medication regimens for the treatment of *H. pylori* infection.

No conflicts of interest to disclose.

**Pre-learning Assessment**

Which of the following symptoms are considered alert symptoms?

a. early satiety  
b. post prandial belching  
c. unexplained weight loss  
d. dyspepsia

**Pre-learning Assessment**

Which of the following Alaskan patients would be candidates for endoscopy and possible *H. pylori* treatment?

a. A 27 y/o male who presents with several weeks of dyspepsia secondary to eating  
b. A 60 y/o male who has recent weight loss and complaints of dyspepsia  
c. A 38 y/o male reports with several weeks of epigastric pain secondary eating  
d. A 57 y/o female who has daily ibuprofen use for osteoarthritis and reports dyspepsia
Pre-learning Assessment

What specific factors influence the treatment of H. pylori treatment in Alaska versus the contiguous United States?

a. > 60% prevalence among patient populations
b. high rate of resistance
c. injudicious use of antimicrobials
d. crowded living considerations

Pre-learning Assessment

Which of the following are theories for the transmission of H. pylori?

a. fecal-oral
b. fomite associated
c. bodily fluids
d. oral-oral

H. pylori

- Genus Helicobacter
  - Gastric vs. Enterohepatic
- Helicobacter pylori
  - Microaerophilic
  - Gram negative
  - Morphology
    - Spiral shaped
    - Rod
  - Coccolith (viable?)
  - Highly motile

H. pylori

- Urease (+), Catalase (+), oxidase (+)
- Cryptic plasmids – not resistance associated
- Genetic heterogeneity
- Genetic rearrangement
- Rich G+C regions
- Lawn formation
- Poorly cultured

Koch’s Postulates – Theory Meets Practice

- Warren observed spiral bacteria in gastric biopsies
- Named them “Campylobacter like organisms”
- In 1985, Marshall ingested cultured bacteria and subsequently experienced gastritis
- Marshall and Warren awarded The Nobel Prize in Physiology and Medicine in 2005

Virulence Factors Mediate Pathogenesis

- Virulence factors
  - Adhesins
  - Exotoxins
  - Cytotoxins
**H. pylori intracellular modulation**

**Presentation**
- Dyspepsia
- Epigastric pain
  - Upper right or left quadrant
  - Worsens with eating
- Post-prandial belching
- Early satiety
- Nausea
- Reflux
  - Commonly associated with GERD

**Alarm Symptoms**

<table>
<thead>
<tr>
<th>Alarm Symptom</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>New onset dyspepsia</td>
<td>Epigastric pain of ≥ 60 y/o</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>Hematemesis, melaena, hematochezia, occult blood in stool</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Loss of appetite</td>
</tr>
<tr>
<td>Unexplained weight loss</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Difficulty swallowing</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>Pain on swallowing</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>GI cancer in 1st degree relative</td>
<td></td>
</tr>
</tbody>
</table>

**Implications of Non-treatment**
- International Agency for Research on Cancer listed as a class I carcinogenic substance
- Peptic ulcer disease
- Chronic gastritis
- Mucosa-associated lymphoid tissue (MALT) lymphoma
- Adenocarcinoma of the stomach

**Gastric Cancer Risk in Alaska Native Patients**

- 5th most diagnosed cancer in AN
- Mortality rate is three times what is seen in contiguous U.S.
- Presence of anti-H. pylori antibodies in patients with gastric cancer demonstrated a 2.63-fold increase in odds of cancer ($P=0.01$).
Transmission...a work in progress

- Epidemiological data suggest oral-oral transmission or fecal-oral transmission
- Recent studies suggest an environmental reservoir
- Possible a combination?
- Environmental risk factors?

Transmission Hypothesis

- The fecal oral hypothesis
  - Contaminated water sources
  - H. pylori PCR studies
- Oral–Oral hypothesis
  - Supported by higher rate in cohabitation
- H. pylori may be linked to hepatitis A infection (HAV)
  - Conflicting studies

Water as a reservoir?

- In Japan, Fujimura et al. compared three groups with different drinking water sources
  - River water vs. ground water
  - Lower prevalence in ground water
  - Insufficient N
- Mazari-Hiriart et al. utilized 16S rRNA and cagA sequencing to comment on H. pylori presence in drinking water
  - Detected DNA 16S rRNA 44% of sources and cagA gene 14% samples
  - Positive PCR correlate to viable infectious matter?
- Further Studies conducted by Bockleman et al. unable to find positive PCR samples in water samples from Spain, Italy and Belgium.

Intermediate Hosts and Biofilm Formation

- Cellini et al. discovered a strain of H. pylori in zooplankton
  - Reports of isolates producing biofilms
    - Metabolically inactive
    - Possibly persist in protozoa
  - intermediate host
- Reports of clinical strains producing ordered biofilms
  - Biofilms demonstrated through SEM in gastric mucosa samples

Environmental Risk Factors

- Higher prevalence among infected family members
- Acquisition rates are higher during childhood in developing countries than developed countries
- Impoverished areas with overcrowding
- Variable infection rates between developed vs. developing world and geographical regions

Krueger et al.

- National Health and Nutritional Examination Survey
  - 1999 – 2000
- Examined for Environmental H. pylori risk factors weighted to represent the U.S. population
- Multivariable linear regression estimated an adjusted odds ratio and 95% confidence interval
**Krueger et al. conclusions**

- Participants < 20 years of age
  - Having well water (aOR 1.7, 95% CI 1.1–2.6) and living in a more crowded home (aOR 2.3, 95% CI 1.5–3.7)
  - Participants ≥ 20 years of age
- Adults in soil-related occupations had significantly higher odds of seropositivity compared to those in non-soil-related occupations (aOR 1.9, 95% CI 1.2–2.9)
- Exposures to both well water and occupationally related soil increased the effect size of adults’ odds of seropositivity compared to non-exposed adults (aOR 2.7, 95% CI 1.3–5.6)

**High Risk Patients**

- Risk factors agreed upon in the literature:
  - Low socioeconomic status
  - Increasing number of siblings
  - Infected parent – especially mother
  - Men
  - Alaska Native/American Indian

**Application to Alaska Populations**

- Crowded living conditions
- More time spent indoors
- Limited access to clean water
- Overuse of antibiotics in remote areas
- Access to specialty services

**What else makes treatment of H. pylori unique in Alaska?**

**High prevalence in AI/AN**

- Seropositivity
  - 40% worldwide for industrialized countries
  - 80% - 90% in developing nations
- Alaska Natives
  - 75% overall
  - Ranges 64 – 83%, dependent on region
  - Puts treated individuals at high risk for reinfection... more later

**Rates of H. pylori infection in AN, 1980 - 1986**
Diagnosis – Endoscopy

- Invasive
- Gold standard
- Multiple methods
  - Biopsy
  - Urea testing (no PPI)
  - Culture (rare)
  - Histology

Noninvasive Diagnosis

- Urea breath testing
  - Consume carbon isotope
- Stool antigen testing
- Serology (IgA and IgG ELISA)
- PCR
- 13C-urea assay

American College of Gastroenterology (ACG) Clinical Guidelines

To treat or not to treat...

All patients with a positive test for an active infection should be offered treatment (strong recommendation)

Strong Recommendations

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active peptic ulcer disease (PUD)</td>
<td>High</td>
</tr>
<tr>
<td>Past history of PUD (except if previously eradicated)</td>
<td>High</td>
</tr>
<tr>
<td>Mucosa-associated lymphoid tissue (MALT) lymphoma</td>
<td>Low</td>
</tr>
<tr>
<td>History of early gastric cancer resection</td>
<td>Low</td>
</tr>
<tr>
<td>Patients gastric biopsies should be evaluated as &quot;H. pylori&quot;</td>
<td>High</td>
</tr>
<tr>
<td>Patients with typical symptoms of GERD and a history of PUD – no testing recommended</td>
<td>High</td>
</tr>
<tr>
<td>Patients initiating chronic treatment with NSAIDs</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
### Conditional Recommendations

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 y/o uninvestigated dyspepsia w/o alarm symptoms</td>
<td>High for efficacy; Low for threshold</td>
</tr>
<tr>
<td>Taking long term low dose ASA</td>
<td>Moderate</td>
</tr>
<tr>
<td>Patients already taking long term NSAIDs</td>
<td>Low</td>
</tr>
<tr>
<td>Unexplained iron deficiency anemia</td>
<td>High</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura (TTP)</td>
<td>Very low</td>
</tr>
</tbody>
</table>

**ACG Suggested Treatment Regimens**


### Management of *H. pylori* in high prevalence artic regions

**Figure 1**: Summary of a triads of *H. pylori* management regimens.


**Recommendations to follow**

- Expert commentary
- Literature review:
  - RCTs and longitudinal cohort studies
  - Cross-sectional studies
- Three face to face meetings
- Clinical practice experience

ACG Guidelines

- Developed for countries where *H. pylori* infection < 1/3 of population
- Test-and-treat strategy
  - Modest benefit
  - Mixed results from RCT
- Endemic area’s defined as >60% prevalence

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**Why is treatment not indicated?**

**High reinfection rates post confirmed eradication**

- Reinfection rates higher for urban and rural AI/AN (14.5% vs. 22.1%) as well as for urban Alaska non-native patients (12.0%)
  - Followed for 2 years post confirmed eradication
- Reinfection rate for U.S. is estimated to be < 5% at 2 years
- Rural AI/AN at highest risk for reinfection

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**Colonized household members predictive for reinfection**
Inconclusive benefit?

- Severe gastritis
  - w/o anemia
- Not NSAID or EtOH induced
- Lack of RCT
- Gastric cancer prevention
- Lack of quality RCT
- More long-term follow up needed

http://www.pathologyoutlines.com/topic/stomachacute gastritis.html

Lack of benefit?

- Many etiologies
  - GERD
  - IBD
- Gastric motility disorder
- Lack of symptomatic relief

http://www.pathologyoutlines.com/topic/stomachacute gastritis.html

Adult Empiric Therapy Recommendations in AN/AI

<table>
<thead>
<tr>
<th>Indication</th>
<th>Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Therapy</td>
<td>Metronidazole 500mg PO QID</td>
<td>14 days</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin 1000mg PO BID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Omeprazole 20mg PO BID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bismuth Subsalicylate 524mg PO QID</td>
<td></td>
</tr>
<tr>
<td>*PCN Allergy</td>
<td>Metronidazole 500mg PO QID</td>
<td>14 days</td>
</tr>
<tr>
<td></td>
<td>Doxycycline 100mg PO BID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Omeprazole 20mg PO BID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bismuth Subsalicylate 524mg PO QID</td>
<td></td>
</tr>
</tbody>
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*PCN Allergy: Patients with penicillin allergy


Resistance in H. pylori isolates from Alaska native persons

- Metronidazole
  - 42% (222/531) isolates had resistance
  - Women exhibited statistically significant more resistance than men (OR: 2.6; P < 0.0001)
  - No difference in urban vs. rural populations
  - Patients age 30 - 40 demonstrated the greatest resistance

- Amoxicillin
  - 2% (10/531) overall resistance
  - Varied year to year 0% - 4% (not significant)


Alaskan isolates resistance continued

- Clarithromycin
  - 30% (159/531) of isolates were resistant
  - Statistically higher resistance in woman (37%) than men (24%) (OR: 1.7; P = 0.001)
  - No statistical difference seen between age group, urban vs. rural, or referral institution

- Levofloxacin
  - 19% (30/155) of isolates are resistant
  - Urban areas isolates were approximately 5 times more likely to have resistance than rural areas
    - 38% vs. 13% (OR: 4.2; P = 0.005)
  - No differences in age group, gender, or referring institution

Alaskan isolates resistance continued

• Multidrug resistance
  • 15% (82/531) of isolates resistant to metronidazole and clarithromycin
  • Patients with metronidazole isolates were at higher risk for clarithromycin isolates than patients with metronidazole susceptible isolates (OR: 5.2; P = 0.002)
  • Females are more likely to be infected with metronidazole and clarithromycin resistant strains (OR: 2.4; P = 0.0004)


Resistance in H. pylori isolates from Alaska native persons

Past treatments with fluoroquinolones correlate with H. pylori levofloxacin resistance

H. Pylori resistance in North America


**H. pylori cagA and vacA genotypes in Alaska**

![Graph showing the distribution of cagA and vacA genotypes among Alaska natives.](image)

**Clinical presentation correlates to genotype**

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>cagA +</th>
<th>vacA +</th>
<th>cagA -</th>
<th>vacA -</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagitis</td>
<td>0.000</td>
<td>0.274</td>
<td>0.920</td>
<td>0.645</td>
<td>0.057</td>
</tr>
<tr>
<td>Gastritis</td>
<td>0.000</td>
<td>0.274</td>
<td>0.920</td>
<td>0.645</td>
<td>0.057</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>0.000</td>
<td>0.274</td>
<td>0.920</td>
<td>0.645</td>
<td>0.057</td>
</tr>
</tbody>
</table>

**Symptomatic Treatment**

- **Adults**
  - Omeprazole 20 mg PO BID
  - Ranitidine 150mg PO BID

- **Pediatrics**
  - Ranitidine 5-10 mg/kg/day divided into PO BID

**Special Populations**

- **Pregnancy**
  - Delay treatment postpartum
  - Tetracyclines: Avoid in pregnancy
  - Bismuth: Avoid in pregnancy

- **Breastfeeding**
  - Avoid
  - Metronidazole
  - Bismuth
  - Levofloxacin

**Recurrence/Treatment Failure**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole 500mg PO QID</td>
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<td></td>
</tr>
<tr>
<td>Bismuth-subalvolate 524mg PO QID</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin 1000mg PO BID</td>
<td>14 days</td>
</tr>
<tr>
<td>Levofloxacin 500mg PO Daily</td>
<td></td>
</tr>
<tr>
<td>Omeprazole 20mg PO BID</td>
<td></td>
</tr>
</tbody>
</table>
Treatment success predictors

- Adherence
- Resistance
- Cigarette smoking
- Diabetes

Treatment success confirmatory testing

- ACG recommends testing 4 weeks post treatment
- 1-2 weeks off PPI therapy
- No specific test preferred
- Urea breath test
- Fecal antigen test
- Endoscopic tests

Learning Assessment
Which of the following patient specific factors are predictive of successful *H. pylori* eradication?

- poor adherence to medication regimen
- low prevalence of *H. pylori* colonization
- diabetes
- cigarette smoker

Learning Assessment
Which of the following should be consideration when recommending an *H. pylori* eradication regimen?

- national antibiotic resistance
- patients poor adherence to medication regimens
- prevalence of *H. pylori* infection in your practice area
- patients past use of a PPI

Learning Assessment
Which of the following increase the risk of a patient becoming infected with *H. pylori*?

- poor social economic standing
- household crowding (>1.5 people/room)
- high prevalence of *H. pylori*
- age < 10y/o
- all of the above

Learning Assessment
Which of the following patients should be referred to a specialist for further evaluation?

- A 75 y/o male who presents with dyspepsia that he has been experience on and off for several years.
- A 27 y/o male who presents with 2 days of N/V.
- A 62 y/o male who reports dyspepsia that started several weeks prior. Patient states he has never experienced these symptoms before.
- A 52 y/o female who reports using high doses of ibuprofen for treatment of her osteoarthritis