Update on *Helicobacter pylori*

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Presence of an environmental agent

The variation in health status that arises from the different causal factors to which each birth cohort in the population is exposed as the environment and society changes.

Each consecutive birth cohort is exposed to a unique environment that coincides with its life span.

Sonnenberg A. Gastro, 2007

Outline

• Discovery, biology, and epidemiology
• Associated disease conditions
• Diagnostic testing and pitfalls
• Treatment and resistance

Discovery of *Helicobacter pylori*

• Gram negative bacterium on the luminal surface of the gastric epithelium
• Isolated by Warren and Marshall in 1983
  – Fulfilled the germ theory of disease
  – Induces acute and chronic inflammation
Epidemiology of HP

- Most common infection worldwide – 50% prevalence
- Majority of children infected by age 5 in developing world
- Western countries
  - 20% at age 20
  - 70% at age 70

Unique Microenvironment

- Survives in acidic environment
- High urease activity
- Converts urea present in gastric juice to alkaline ammonia and carbon dioxide

\[
\text{urea} + 2 \text{H}_2\text{O} \xrightarrow{\text{urease}} \text{NH}_4^+ + \text{CO}_2
\]

\(\text{ammonium carbonate}\)

\(\text{H. pylori}\) is LEAST associated with which of the following conditions?

A. Mucosa-associated-lymphoid tissue lymphoma
B. Idiopathic thrombocytopenic purpura
C. Dyspepsia
D. Non-ulcer dyspepsia
E. Iron deficiency

Cofactor in 3 Important GI diseases

Estimated lifetime incidence of disease

- Duodenal and gastric ulcers (up to 10%)
- Gastric cancer (1-3%)
- Gastric mucosa-associated lymphoid-tissue (MALT) lymphoma (<0.01%)
Case – Duodenal ulcer

- 45 year old man presents feeling light headed and says that he’s been having black stool for 2 days. He does not take NSAIDs.
- He is admitted and endoscopy confirms a duodenal ulcer

What is the probability that this is associated with HP?

Is the risk of recurrent ulcers reduced after HP treatment and by how much?

Prevalence of HP

- Asymptomatic: 20-45%
- Ulcer disease
  - Duodenal ulcer: 80-95%
  - Gastric ulcer: 65-95%
- Dyspepsia: 20-60%
- Gastric cancer: 70-90%


Association between HP and DU

- Longitudinal studies
  - Cohort of 5000 native Hawaiians with stored sera from late 1960s
  - 65 patients developed DU over 20 years
  - 92% were HP positive vs. 78% in controls producing an odds ratio of 4.0


Pathophysiology of PUD

- *Inflammation* most pronounced in the non-acid-secreting antral region of the stomach
  - Inflammation stimulates release of gastrin
  - Gastrin stimulates excess acid secretion
- *Acid load* damages duodenal mucosa, causing ulceration and gastric metaplasia
  - Metaplastic tissue can be further colonized by HP and contributes to the ulcer process
HP promotes excess acid secretion

Ulcer recurrence risk without eradication

Ulcer recurrence risk after eradication

Relapse rate at 1 year

Hopkins RJ et al. Gastroenterology 1996

McColl KE. J Infect 1997;34:7

Hopkins RJ et al. Gastroenterology 1996

Leodolter A. et al. Alim Pharm Ther, 2001
**HP and NSAID: Increased risk of ulcer disease?**

- However, other studies show little/no benefit
  - Placebo arm: PPI

**Summary: Ulcer disease**

- Recurrent ulcer rate is 60% if HP is untreated
  - < 5% recurrence if eradicated
- HP eradication reduces the risk of ulcers for patients starting long-term NSAID treatment
  - Empiric PPI use in HP (+) individuals on NSAID provides similar benefit

**Eradicate HP Before NSAID**

- Log-rank test, p<0.001

**Gastric Cancer**

Huang JQ et al. Lancet 2002
Gastric Cancer

• 58 year old Korean woman sees you in clinic for a check up.
• Her family history is notable for gastric cancer in her father.
• She asks you whether or not it is genetic and should she be tested for it.

Epidemiology of Gastric Cancer

• 2nd most common cause of cancer-related death in the world
  – Two morphologic types: intestinal and diffuse
• Decreasing in US since 1930

Biological Differences

Ulcer               Cancer

• Acid secretion normal or decreased
• 10 percent lifetime duodenal ulcer risk
• H. pylori eradication:
  - GERD should not develop
  - Reduced recurrence of DU

Highest risk in individuals with fundic and antral inflammation that leads to atrophy and subsequent intestinal metaplasia

Divergent effects: Acid & Disease

H. pylori + host

 UIApplication

** Acid

Normal or ↑ Acid

DU

No significant disease

Risk of Ca
**Prospective study HP and Cancer**

- 1526 patients with UGI disease
  - 1246 with HP and 280 without HP
  - Follow up for 7.8 years
- 36 (2.9%) with gastric cancers
  - All in HP (+) cohort
  - None in DU patients

**Hypothetical Benefits of Eradication**

- Stops acute gastritis
  - Reduces the progression to atrophic gastritis
- Reversal of atrophy or intestinal metaplasia
  - Maybe but little evidence

You explain to your patient that often, a bacteria is involved.

∴ Treatment of *H. pylori* reduces the risk of gastric cancer?

A. True
B. False
C. No or little evidence available

**HP eradication after early gastric cancer is effective for 2° prophylaxis**


**Gastric lymphoma**

- **Presentation**: epigastric pain, weight loss, anorexia, vomiting, bleeding
- **Lymphoma can arise from either lymph nodes or mucosal area**
  - Latter referred to as a mucosa-associated lymphoid tissue (MALT) tumor
  - Also extranodal marginal zone B-cell lymphoma
- **Epidemiologic studies demonstrate strong association with HP**
- **MALToma** – immune response to specific HP strains expressing CagA protein/antigens
- **Accounts for 3% of gastric neoplasms and 10% of lymphomas**

**2008 Asian-Pacific Gastric Cancer Consensus Conference**

- **Eradication of H. pylori reduces the risk of developing gastric cancer**
  - Limited to high risk individuals
    - Family history, serum pepsinogen levels, high risk populations
- **Potential risks of screening**
  - Antibiotic resistance
  - Clostridium difficile
  - Cost of screening will become prohibitive in certain populations

**Gastric mucosa-associated lymphoid tissue (MALT) lymphoma**

- Lower rate of gastric cancer (1.1 vs. 1.7%) among eradication group (RR 0.65, 95% CI 0.43-0.98)
- Eradication appears to reduce the risk of gastric cancer in high-risk populations

Regression of MALT lymphoma occurs after treatment of *H. pylori*

A. True  
B. False  
C. No or little evidence available

78%  
20%  
3%

Gastric MALToma

- Eradication causes regression of most localized gastric MALT lymphoma  
  - 90 patients with MALToma treated for HP  
    - 56 patients (62%) resolved  
    - minimal residual disease in 17 patients (18%)  
    - Partial remission in 11 patients (12%)  
    - no change in four patients (4%)  
    - progressive disease in two patients


Outcomes after HP Eradication

HP and MALToma

- First line therapy of MALToma with antibiotics is still considered experimental  
  - Limited to non-bulky flat mucosal lesions, localized disease, no lymph node spread  
  - < 10% are candidates for solely HP treatment  
  - *Documentation of cure of infection is essential*
Case - Dyspepsia

• 35-year-old woman with intermittent epigastric discomfort
• No alarm signs of weight loss or GI bleeding
• Denies NSAID use
• Exam notable for epigastric tenderness
• Serologic test for *Helicobacter pylori* is positive

Resolution of dyspepsia occurs after treatment of *H. pylori*

A. **True**
B. **False**
C. No or little evidence available

Dyspepsia

• Vague set of UGI symptoms characterized by epigastric pain or early satiety (dysmotility)
• Symptoms may not be attributable to stomach related pathology
• Benefit to treat HP if ...
  – It is for treatment of dyspepsia-associated ulcer disease

Support for Test and Treat for HP

• Randomized placebo controlled trial
  – 294 patients with *uninvestigated* dyspepsia with HP
  – 1-year rate of symptom resolution
    • 50% in those receiving HP therapy vs. 36% in placebo (p=0.02)
  – Benefit likely larger if restricted to those with PUD but identification of patients are difficult short of invasive testing
Non-Ulcer Dyspepsia & HP Treatment

- **HP(+) with negative endoscopy for ulcer**
  - No evidence that eradication of HP infection cures NUD
  - ~25% completely resolved after one year


Dyspepsia: Management Strategies

- Comparing test and treat strategy versus early endoscopy versus PPI therapy
  - Three strategies with similar degree of symptom improvement
  - Early endoscopy was more expensive
  - Test and treat unlikely to be cost effective when HP prevalence is less than 20%
    - Low HP prevalence, empiric PPI may be viable option


Dyspepsia Summary

- Uninvestigated dyspepsia
  - High HP prevalence: test and treat
  - Low HP prevalence: empiric PPI
- Majority of EGD for dyspepsia have no findings
  - Therefore, non-ulcer or functional dyspepsia
  - HP associated inflammation is of unclear significance
  - Randomized trials for NUD have shown no to little benefit

Back to our patient - Dyspepsia

- 35-year-old woman with intermittent epigastric discomfort
- No alarm signs of weight loss or GI bleeding
- Denies NSAID use
- Exam notable for epigastric tenderness
- Serologic test for *Helicobacter pylori* is positive
- She feels much better after treatment .... symptoms recur 6 weeks after treatment.

HP and GERD

Does treatment of HP cause GERD?

- Prevalence of HP in Western countries decreasing
  - Prevalence of GERD increasing
  - Incidence of esophageal adenocarcinoma
    - Negative association with HP
- Does HP have an effect on primary GERD disease determinants?
  - GEJ competence i.e. hiatal hernia
  - LES pressure or transient relaxation
  - Esophageal peristaltic activity

Raghunath A. BMJ 2003; de Martel C. J Infect Dis 2005

Does HP treatment induce GERD?

- Erosive GERD
  - Meta-analysis fails to support increased incidence or worsening of GERD after HP eradication.

Yaghoobi M. Am J Gastro 2010
Diagnostic testing for HP

Non-endoscopic Testing

- **Serologic test**
  - Sensitivity = 85%
  - Specificity = 80%
  - Unable to confirm eradication
- **Urea breath test**
  - Drink $^{13}$C-labeled urea $\rightarrow ^{13}$CO$_2$ by the urease
  - Sensitivity and specificity of 95%
- **Fecal antigen test**
  - Sensitivity and specificity of 95%
- **Stop** PPI for 2 weeks, H2RA for 24 hr, and antibiotics for 4 weeks $\Rightarrow$ otherwise reduced test sensitivity

Endoscopic Testing

- **Urease-based testing**
  - Solution of pH-sensitive dye + urea + biopsy
  - Presence of HP will increase the pH and change the color of the dye
  - **Stop** PPI x 2 weeks, H2RA x 1 day, and antibiotics
- **Histology**
  - Organism and associated gastritis visible
- **Culture**
  - Not routinely available but can offer antimicrobial sensitivity testing
HP Resistance Patterns

- 3400 HP isolates for resistance testing
  - Metronidazole: 22 – 39%, 36.9%
    - Highest among Asians
  - Clarithromycin: 11 – 12%, 10.1%
    - Highest in mid-Atlantic, northeast
  - Amoxicillin: rare, 1.4%
  - Tetracycline: rare
  - Higher in women and increasing age

Treatment Considerations

- Optimal regimen has not been defined
  - Besides effectiveness, consider cost, side effects, and ease of administration
- Review the following therapies
  - Triple
  - Quadruple
  - Sequential
- Resistance and salvage

Triple therapy

- PPI bid, amoxicillin 1 gm bid, clarithromycin 500 mg bid (10-14 days)
- Metronidazole 500 mg bid can be substituted for amoxicillin
  - Associated with increased treatment failure

Quadruple Therapy

- Comprised of PPI, tetracycline, metronidazole, and bismuth salt for 10-14 days
  - For use with a high prevalence of clarithromycin-resistant HP (i.e. > 20%)
  - Similar eradication rate ~75-80%
  - Alternative is sequential therapy

Treatment Summary

- Initial: Triple therapy
  - Metronidazole can replace amoxicillin
- Failure rate = 20%
- Retreatment: Quadruple therapy
  - PPI bid plus Bismuth + Metronidazole + Tetracycline qid
  - Consider sequential therapy
- Rescue: Levofloxacin 250, amoxicillin 1 gm, PPI twice daily
When should *H. pylori* eradication be confirmed?

A. Gastric or duodenal ulcer
B. Gastric MALT lymphoma
C. Early gastric cancer s/p endoscopic resection
D. Dyspepsia
E. **All of the above**
F. None of the above

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**American College of Gastroenterology**

- **Recommendations**
  - Testing for HP is indicated in patients
    - Active peptic ulcer disease
    - Past history of peptic ulcer
    - Gastric MALT lymphoma
  - Test-and-treat strategy is a proven management strategy for patients with uninvestigated dyspepsia who are under the age of 55 yr and have no “alarm features”

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**ACG Guidelines**

- Little evidence that *functional* dyspepsia will benefit from HP eradication
- No clear evidence that HP eradication worsens GERD
- HP and NSAIDs are independent factors for PUD.
- Association suggested between HP and iron deficiency (but no data for cause-effect)
- HP eradication reduces risk of gastric cancer

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**European guidelines ...**

- Recommend test/treate but with limited data
  - Eradicate HP in first-degree relatives of patients with gastric cancer
  - Patients with atrophic gastritis
  - Unexplained iron deficiency anemia
  - Chronic idiopathic thrombocytopenic purpura

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