Is *Helicobacter pylori* Good for You?  
To Treat or Not to Treat,  
That is the Question

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Disclosure

In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

Learning Objectives

- To demonstrate that *H. pylori* is responsible for a significant portion of gastroduodenal disease.
- To understand how the host immune response contributes to Helicobacter associated disease.
- To understand how the host immune response to Helicobacter infection might prevent asthma.
- To understand which patient populations should be treated.

*H. pylori* is an Important Human Pathogen

- *H. pylori* is a gram negative microaerophilic bacterium that selectively colonizes the stomach.
- It infects about 50% of the world's population.
- It is classically considered a non-invasive organism,
- There is a vigorous innate and adaptive immune response and inflammation that is Th1 predominant and includes (chronic) lymphocyte and (active) neutrophil components.
- Despite this response the bacterium generally persists for the life of the host.

World-Wide Prevalence of *H. pylori*
**Natural History of H. pylori infection**

- Initial infection (in childhood)
  - Chronic gastritis (universal)
  - Gastric atrophy (40%)
  - Gastric, duodenal ulcer (10%)
  - Gastric Adenocarcinoma (1%)
  - Lymphoproliferative disease (MALT) rare (<1%)

**Eradicating H. pylori Treats or Prevents:**

- Nonulcer Dyspepsia
- H. Pylori Infection (50% Worldwide Prevalence)
- Gastric Adenocarcinoma
- Gastric Ulcer
- Duodenal Ulcer
- Colon cancer

**Does H. pylori infection cause GI disorders in children?**

**Differences in H. pylori infection between children and adults**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphonuclear and mononuclear cell infiltration</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Gastric atrophy</td>
<td>Absent</td>
<td>Reduced</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>Absent</td>
<td>Reduced</td>
</tr>
<tr>
<td>Gastric epithelium</td>
<td>Intact</td>
<td>Reduced</td>
</tr>
<tr>
<td>Precancerous lesions</td>
<td>Absent</td>
<td>Reduced</td>
</tr>
<tr>
<td>Bacterial factor</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>Colonization level</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>Virulence factors</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>Bacteria genotype</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>Immune Response Treg</td>
<td>Increased</td>
<td>Reduced</td>
</tr>
<tr>
<td>Immune Response Th1</td>
<td>Increased</td>
<td>Reduced</td>
</tr>
<tr>
<td>Immune Response Th17</td>
<td>Increased</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

**How does H. pylori present in childhood?**

- H. pylori infection is generally asymptomatic in children!

**Should you test for H. pylori in children with abdominal pain?**
Association Between *H. pylori* and GI Symptoms in Children

Meta-analysis of cross-sectional studies concerning Unspecified Abdominal Pain (UAP) related to *H. pylori* infection.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies et al., 1992</td>
<td>0.48 (0.33, 0.72)</td>
</tr>
<tr>
<td>Shi et al., 2005</td>
<td>1.44 (1.01, 2.02)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.80 (0.44, 1.41)</td>
</tr>
</tbody>
</table>

Are there health benefits to children as a result of eradicating *H. pylori*?

With the exception of peptic ulcer disease, there is insufficient evidence to conclude that eliminating *H. pylori* results in health benefits to children.


Are there health benefits to children as a result of chronic *H. pylori* infection?

*H. Pylori* may play a protective role against bacterial diarrhea in children

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Shigella</th>
<th>Salmonella</th>
<th>HP Prevalence</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>204</td>
<td>0</td>
<td>0</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Bacterial diarrhea</td>
<td>112</td>
<td>65</td>
<td>52</td>
<td>4%</td>
<td>0.007</td>
</tr>
</tbody>
</table>

The prevalence of *H. pylori* infection in healthy children was higher than in patients with bacterial diarrhea, suggesting that *H. pylori* may protect children from that bacterial infection.


These findings are in line with other studies showing a protective role of *H. pylori* infection resulting in a reduced frequency of diarrheal illness.


• BMI following successful *H. pylori* eradication increased significantly in comparison to pre-treatment BMI
• Patients who failed *H. pylori* eradication had a non-significant decrease in BMI compared to baseline

Obesity and *H. pylori*

- *H. pylori* infection leads to chronic active gastritis in all infected individuals
- Interferes with the release of gastric hormones
- Hormones involved in regulation of appetite & food intake
- *H. pylori* infection leads to a decrease in circulating ghrelin and an increase in gastric leptin
  - (Ghrelin is an important factor in appetite and satiety regulation)
  - After *H. pylori* eradication, the number of ghrelin-positive cells in gastric mucosa return to normal
- Observations suggest weight gain occurs as a result of an increased appetite after *H. pylori* eradication


Can *H. Pylori* be treated with antibiotics?

The definitive cure of peptic disease and prevention of ulcer complications, as well as the cure of mucosa-associated lymphoid tissue (MALT) lymphoma, is dependent on the successful eradication of *H. pylori* infection.

Can *H. Pylori* be treated with antibiotics?

- Eradication rates range from 61% to 94%.
- Treatment success decreases to less than 90% when antibiotic resistance level exceeds 15%.
- Per the CDC, 29% of strains are resistant to one, and 5% are resistant to two or more antibiotics (*Emerg. Infect. Dis.*, 2004)
- Effective treatment regimens remain a challenge
Current antimicrobial therapies for the eradication of pediatric *H. pylori* infection are suboptimal and are becoming less effective. 

And

Eradicating *H. pylori* may promote asthma and allergies.

Asthma, Allergy and Atopic Diseases

- As the prevalence of *H. pylori* has decreased, the incidence of asthma and related disorders has dramatically increased, primarily in children.

- There is an inverse correlation between *H. pylori* infection (especially with CagA-expressing strains) and diagnosis of allergic asthma.

Inflammation of the gut is linked to elevated levels of IgE and other allergic responses, including asthma and atopic dermatitis.


There appears to be a connection between asthma and *H. pylori*. 

*What is the scientific basis for the inverse relationship between *H. pylori* infection and asthma?*

Why is *H. pylori* a Lifelong Infection?

The simple fact of the matter is that the body is designed to suppress the response to bacteria that colonize the gastrointestinal tract if they are not invasive or do not produce some potent inflammatory mediator. If this was not the case, we would all have IBD or worse.

*H. pylori*, unlike Salmonella or Shigella is particularly challenging because it remains noninvasive. It is a true mucosal colonizer.

*H. pylori* infection is always going to induce a potent regulatory T cell response. This response is very difficult to overcome.
**H. pylori–Exposed Tolerogenic DCs Drive Naive CD4+ T Cells to Become Tregs**


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**Hp-Infected Children Have Less Severe Gastric Inflammation Than The Infected Adults**

*Gastric Treg cell responses down-regulate the inflammation by Hp in children.*

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**Treg Polarization, Immune Tolerance, Persistent Infection**

*Harris, et al., Gastroenterology, 2008; 134: 491-499*

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**Cytokine Gastric Concentrations According to the Age in H. pylori-Positive Children and Adults**

*De Melo, et. al. JID 2013; 1-5*

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**Schematic Representation of the Current Model of H. pylori-Induced Immune Tolerance and Asthma Protection**

*Tolerogenic dendritic cells migrate to MLN and induce Treg cells, which inhibit allergen specific Th2 responses.*

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**Murine Asthma Model**

*Arnold et al. Frontiers in Cellular and Infection Microbiology; February 2012, 2:10; 1-11*

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*Measure airway resistance*
Experimentally Induced Asthma is Alleviated by *H. pylori* Infection

Airway Resistance in Response to the Highest Dose of Methacholine

Reduced Pulmonary Inflammation When Mice are Previously Infected with *H. pylori*

Tregs Accumulate in the Lungs of Infected Mice

Conclusion

Protection against allergen-induced airway disease was accomplished through *H. pylori* reprogramming DCs in an IL-18-dependent manner to a tolerogenic phenotype that induced Foxp3 expression in naïve, CD4⁺ T cells.

Conclusion

The decline in *H. pylori* prevalence in industrialized countries with an accompanying reduction in Treg protection offers a potential, albeit partial, explanation for the increasing prevalence of allergic diseases in developed countries.
Implications for Treating *H. pylori* in Children

- *H. pylori*-infected children and adults have different ratios of Treg and Th17 profiles infiltrating their gastric mucosa.
- *H. pylori*-infected children had more FOXP3+ Treg cells, more IL-10 (Treg-associated cytokine) and less IL-17 (Th17-associated cytokine) than infected adults.

Acknowldgements

Tom Blanchard
Hua Ding
Kathleen Anderson
John Nedrud
Raymond Redline
Marjan Mohammadi
Chris Garhart
Howard Carr
William T. Speck