

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.

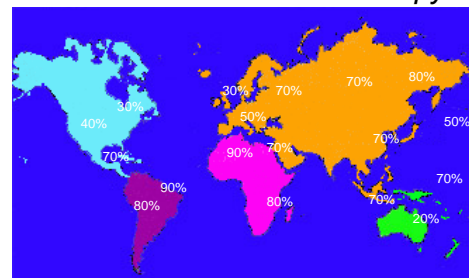
Learning Objectives

- 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

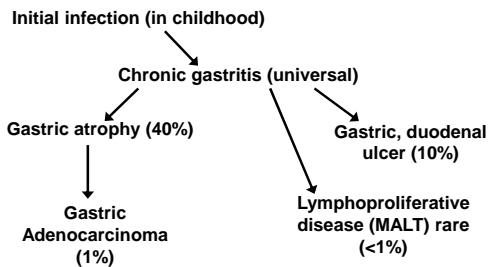
- *H. pylori* is a gram negative microaerophilic bacterium that selectively colonizes the stomach.
- It infects about 50% of the world's population.
- It is classically considered a non-invasive organism,
- There is a vigorous innate and adaptive immune response and inflammation that is Th1 predominant 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*

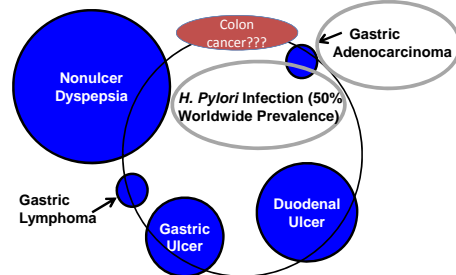


Marshall, 1995 JAMA 274:1064

Natural History of *H. pylori* infection



Eradicating *H. pylori* Treats or Prevents:



Adapted from Marshall, 1994

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

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

Inflammation	Children
Polymorphonuclear and mononuclear cell infiltration	Diminished
Gastroduodenal ulceration	
Gastric ulcer	Absent
Duodenal ulcer	Reduced
Epithelium	Intact
Precancerous lesions	Absent
Bacterial Factor	Children
Colonization level	Similar
Virulence factors	Similar
Bacteria genotype	Similar
Immune Response	Children
Treg responses	Increased but not maintained in adulthood
Th1 responses	Decreased
Th 17 responses	Decreased

Harris, et al. "Role of childhood infection in the sequelae of *H. pylori* disease." *Gut Microbes* 4:6, 426-438; November/December 2013.

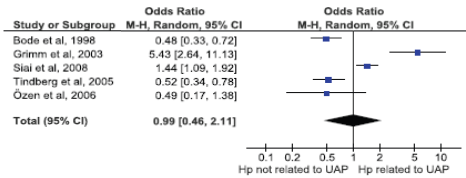
How does *H. pylori* present in childhood?

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

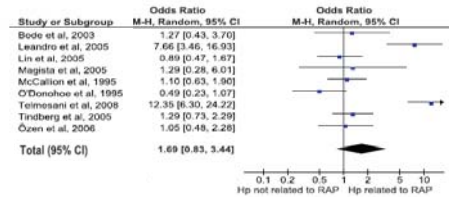
Meta-analysis of cross-sectional studies concerning Unspecified Abdominal Pain (UAP) related to *H. pylori* infection.



Spee et al, *Pediatrics* 2010;125:e651-e669

Association Between *H. pylori* and GI Symptoms in Children

Meta-analysis of cross-sectional studies concerning RAP related to *H. pylori* infection.



Spee et al, *Pediatrics* 2010;125:e651-e669

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.

Sierra, et al, *Gut Microbes* 2013; 4: 549

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

	N	Shigella	Salmonella	HP Prevalence	P Value
Control	204	0	0	13%	
Bacterial diarrhea	112	65	52	4%	0.007

Monajemzadeh, et al. The Relation Between Helicobacter pylori Infection and Acute Bacterial Diarrhea in Children. *International Journal of Pediatrics*; Feb 2014, 1-5

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.

Monajemzadeh, et al. The Relation Between Helicobacter pylori Infection and Acute Bacterial Diarrhea in Children. International Journal of Pediatrics, Feb 2014, 1-6

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

R. Ranjbar, M.Soltan Dalui, M.Talebi and M.R.Pourshafie; "Increased isolation and characterization of Shigella sonnei obtained from hospitalized children in Tehran, Iran," Journal of Health, Population and Nutrition, vol.26, no.4, pp.426-430,2008.

M.K.Bhan, R.Bahl, S.Sazawal et al., "Association between Helicobacter pylori infection and increased risk of typhoid fever" Journal of Infectious Diseases, vol. 186, no. 12, pp. 1857-1860, 2002.

Obesity and *H. pylori*

- 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

Helicobacter pylori and Obesity

- *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

*Wegi J, Maffeiheimer P. Influence of Helicobacter pylori on gastric regulation of food intake. Curr Opin Clin Nutr Metab Care 2009; 12:522-525.

*Takauchi A, Niyake K, Gudo K, et al. Effect of Helicobacter pylori infection on ghrelin expression in human gastric mucosa. Am J Gastroenterol 2004; 99:2121-2127.

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.

Niv, Y. and Hazazi, R. (2008). Helicobacter pylori Recurrence in Developed and Developing Countries: Meta-Analysis of 13C-Urea Breath Test Follow-up after Eradication. Helicobacter, 13: 56-61.

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

*Strachan DP. BMJ 1989; 299:1259-1260
*Reibman J, et al. PLoS One 2008; 3:e4060
*Chen Y, Blaser MJ. Arch Intern Med 2007; 167:821-827
*Blaser MJ, Chen Y, Reibman J. Gut 2008; 57:561-567

Inverse Association Between *Helicobacter pylori* Status and Dermatitis and Wheezing in Participants

Outcome	<i>H. pylori</i> status		OR (95% CI)*
	Negative (n = 4787)	Positive (n = 2625)	
Asthma history			
None	4108	2358	...
Ever	679	267	0.89 (0.68-1.16)
≥1 attack in past year	234	85	0.68 (0.44-1.05)
Dermatitis, eczema, or rash in past year			
No	3947	2356	...
Yes	514	234	0.73 (0.56-0.96)
Wheezing or whistling in chest in past year			
No	4126	2346	...
Yes	653	275	0.73 (0.57-0.94)
Wheezing disturbed sleep	339	144	0.68 (0.48-0.98)
Chest sounded wheezy during exercise	315	136	0.63 (0.44-0.90)
Took medication for wheezing	315	132	0.68 (0.48-0.94)
Visited physician's office or hospital for wheezing or whistling	298	118	0.66 (0.45-0.95)
Limited usual activities because of wheezing	257	105	0.57 (0.36-0.79)
Speech limited to 1-2 words between breaths because of wheezing	110	53	0.51 (0.29-0.90)
Missed work or school because of wheezing or whistling	139	50	0.56 (0.31-0.99)

Chen Y, Blaser MJ. JID 2008;198 (15 August) 553

Inverse Association Between *Helicobacter pylori* Status and Both Asthma and Allergic Rhinitis in Participants 3-13 Years of Age

Outcome	3-13 years		OR (95% CI)
	Negative (n = 1491)	Positive (n = 299)	
Allergic rhinitis in past year			
No	1325	281	...
Yes	156	18	0.31 (0.17-0.57)
Asthma history			
None	1249	261	...
Current	156	25	0.41 (0.24-0.69)
Ever, ≥first age*			
Overall	242	37	0.49 (0.30-0.80)
<5 years	211	45	0.58 (0.38-0.88)
2 to <5 years	103	16	0.32 (0.17-0.60)
≥5 years	194	51	0.78 (0.41-1.50)
Allergic rhinitis in past year and ever having asthma	45	6	0.35 (0.12-1.00)

Chen Y, Blaser MJ. JID 2008;198 (15 August) 553

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.

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H. pylori-Exposed Tolerogenic DCs Drive Naive CD4+ T Cells to Become Tregs

Lamina propria in stomach: *H. pylori* is phagocytosed by a Naive DC via TLR. This leads to a Tolerogenic DC with decreased cytokines and costimulatory molecules.

Mesenteric lymph node: The Tolerogenic DC interacts with a Naive CD4+ T cell, leading to its conversion into a FoxP3+ Treg. This process is associated with high IL-18 and TGF- β .

Matsushima K, Nagai, S. *Journal of Clinical Investigation*, 2012; 3: 122; 801-804.

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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.

A child: Histology image showing less severe inflammation.

B adult: Histology image showing more severe inflammation.

C: Bar graph showing Gastric Inflammation Score. Children have significantly lower scores than adults (****).

D: Bar graph showing Gastric Inflammation Score. In children, *H. pylori* infection is associated with significantly lower inflammation scores (****).

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

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Treg Polarization, Immune Tolerance, Persistent Infection

High IL-18 and weak TLR signaling lead to Treg polarization, immune tolerance, and persistent infection. Key molecules include CD80, CD86, CD28, and CD27.

Oertli M, Muller A. *Gut Microbes* 3:6, 566-571; 2012

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

IFN- γ (pg/mg of protein) vs Age range. Concentrations increase with age, with significant differences between 14-18 and 19-33 (****), and 19-33 and 34-48 (****).

De Melo, et al. *JD* 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.

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

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Murine Asthma Model

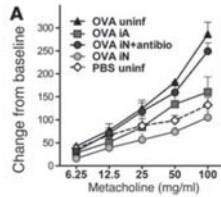
DAYS 1: Mouse, OVA/Alum injection.

28, 42: OVA/Alum injections.

59, 60, 61: Aerosol exposure to OVA 20 min/day.

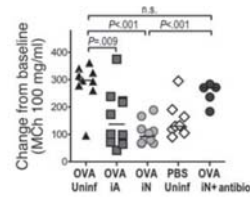
Measure airway resistance.

Experimentally Induced Asthma is Alleviated by *H. pylori* Infection



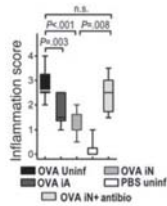
Arnold, E., et al.; J. Clin. Invest. 121: 8; 2011; 3089

Airway Resistance in Response to the Highest Dose of Methacholine



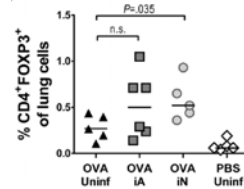
Arnold, E., et al.; J. Clin. Invest. 121: 8; 2011; 3089

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



Arnold, E., et al.; J. Clin. Invest. 121: 8; 2011; 3089

Tregs Accumulate in the Lungs of Infected Mice



Arnold, E., et al.; J. Clin. Invest. 121: 8; 2011; 3089

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.

Sheh, et al. "The role of the gastrointestinal microbiome in *Helicobacter pylori* pathogenesis." Gut Microbes 4:6, 505-531; November/December 2013.

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.

Sheh, et al. "The role of the gastrointestinal microbiome in *Helicobacter pylori* pathogenesis." Gut Microbes 4:6, 505-531; November/December 2013.

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.

de Melo et al. *Microbes Infect.* 14(4), 341–347 (2012).

Implications for Treating *H. pylori* in Children

It may be preferable to delay *H. pylori* treatment in children with a history of asthma/allergy until they are young adults given the vast majority of *H. pylori* associated pathologies typically develop in adulthood.

de Melo et al. *Microbes Infect.* 14(4), 341–347 (2012).

Acknowledgements

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