

Clinical Update on *Helicobacter pylori*[†]

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Introduction

Helicobacter pylori is one of the commonest infections in human, affecting 30% to 50% of people worldwide.¹ It is associated with the development of peptic ulcer, chronic gastritis and gastric cancer and may play a role in a small subset of patients with non-ulcer dyspepsia. *H. pylori* infection is of clinical importance because eradication of *H. pylori* infection in patients with peptic ulcer disease has been shown to prevent ulcer recurrence. The effectiveness of *H. pylori* eradication in prevention of cancer, however, remains unproven.

Microbiology

H. pylori appears as a Gram-negative bacterium. It is 2 to 4 µm long and 0.5 to 0.8 µm wide and has one to five sheathed flagella that are up to 25 µm long and originate from one of the poles. It has a translucent cytoplasmic region and a polar membrane. It is usually seen in gastric biopsies in the spiral form. *H. pylori* can lose its spiral morphology and turn into coccoid forms, as the culture ages.² Coccoid forms of *H. pylori* are usually non-culturable but viable, although dead, degenerative forms and viable but culturable forms probably exist. The coccoid forms of *H. pylori* may be important in transmission of the infection as they seem to survive in stool samples and in river water. It has also been postulated that coccoid forms may be responsible for some of treatment failures, as they could be resistant to the antibiotics used.

Epidemiology

The prevalence of *H. pylori* is higher in developing countries than in developed countries and rises with age up to 60 years.³ No significant difference in prevalence has been found between the two gender. Oral-oral transmissions from parents to children and between persons in crowded institutions seem to occur. In a recent report from Japan, *H. pylori* specific DNA obtained from water, soil, rivers, ponds around the residence of subjects who had participated in an epidemiological survey were found to be highly homologous with the *H. pylori* sequence in the Gen Bank

database suggesting that the subjects could have been infected by water containing *H. pylori*.⁴ A faecal-oral transmission through drinking water has been proposed. Food-borne infection is possible, as *H. pylori* has been shown under experimental conditions to survive in ready to eat food (milk and tofu) at 4°C.⁵

Diagnosis of *Helicobacter pylori*

The diagnosis of *H. pylori* infection can be made using several invasive or non-invasive techniques.

Invasive tests	Non-invasive tests
Endoscopy-based tests	C-urea breath test
Rapid urease test	Serology (IgG, IgA)
Direct microscopy	Stool antigen test (HpSA)
Histology	
Culture	
Polymerase chain reaction (PCR)	

Serology

Serological tests for diagnosis of *H. pylori* infection rely on detection of IgG antibodies to *H. pylori*. In children, false negative can occur from a few weeks to a few months after an infection before an immune response occurs. Serology is an unreliable method in determination of eradication because IgG levels remain detectable after treatment.

Urea Breath Test (UBT)

The UBT is a reliable test for *H. pylori* before and after treatment.

This is the test of choice for determining cure of infection when clinically indicated and when repeat endoscopy is unnecessary, as the sensitivity and specificity is ≥95%. When using a UBT to determine cure of *H. pylori* infection, it should be done at least 4 weeks after stopping treatment. Both C¹³ and C¹⁴ breath tests are available in Singapore.

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† Some questions on the topic are given at the end of this article. For answers, logon to Annals website at: <http://www.annalsmed.org>

Stool Antigen Test (HpSA)

A new test, which detects the presence of *H. pylori* antigen in the stool, has been introduced. Its sensitivity and specificity are comparable to C-UBT at 93.8% and 90%⁶ and is extremely useful in children. Like the C-UBT, it is very useful in monitoring the response to eradication therapy.

Invasive Tests

The invasive tests (which depend on obtaining gastric biopsies, rapid urease test, histology and culture) are routine and are useful in pre-treatment diagnosis as well as in monitoring effectiveness of eradication therapy.

H. pylori and Gastroduodenal Disease

1. Gastric Cancer

H. pylori is associated with the development of peptic ulcers (duodenal and gastric ulcers). Eradication of *H. pylori* prevents ulcer recurrence in 95% of patients. In addition, a strong association between *H. pylori* infection and gastric cancer has been reported based on epidemiological studies. A meta-analysis of cohort or case control studies showed that the odds ratio (OR) for gastric cancer in *H. pylori* infected patients is 1.92, and is equally associated with the intestinal or diffuse type of gastric cancer.⁷ *H. pylori* infection is associated with (distal) non-cardiac cancer and NOT with cardiac (proximal) cancer. *H. pylori* infection is also associated with MALT (mucosa-associated lymphoid tissue) lymphoma. Eradication of *H. pylori* is useful in the treatment of MALT lymphoma with a remission rate of about 75% at 2 years. There is as yet no definite evidence to show that eradication of *H. pylori* is useful in the treatment or prevention of gastric adenocarcinoma. *H. pylori* eradication is recommended after resection of early gastric cancer.

2. Non-ulcer Dyspepsia

Dyspepsia, defined as pain or discomfort centred in the upper abdomen, is extremely common. Under the Rome II definition, predominant symptoms of heartburn and reflux are excluded from dyspepsia. Non-ulcer dyspepsia is diagnosed when no structural or biochemical explanation is identified after appropriate investigation. Epidemiological data showed that prevalence of *H. pylori* infection in patients with non-ulcer dyspepsia is higher (but not reaching statistical significance) than in the community. In the last few years, several well-designed trials on the effect of eradication of *H. pylori* in patients with dyspeptic symptoms have been carried out.

Based on meta-analysis of 12 trials, Moayyedi⁸ showed that there was a small benefit of *H. pylori* eradication treatment at 12 months (relative risk reduction was 9%). It

was estimated that 15 patients needed to be treated to cure 1 extra case of non-ulcer dyspepsia. However, Laine et al⁹ showed that when only studies that used standard definition of dyspepsia (excluding reflux symptoms) were included in the analysis the OR was 1.04 and concluded there was little evidence to support the use of *H. pylori* eradication therapy in patients with non-ulcer dyspepsia. Outside Asia, a 'test and treat' strategy of dyspepsia i.e. treating patients with dyspepsia (with no alarm symptoms) with *H. pylori* eradication without further investigation has been recommended, although the evidence for such recommendation was lacking. Recent data from the Leeds HELP Study Group¹⁰ showed that 15% of dyspeptic patients who were infected with *H. pylori* could be cured by eradication therapy. Overall, it was estimated that 20 *H. pylori* positive dyspeptics needed to take eradication therapy for 1 dyspeptic patient to be successfully treated in the community. The study also revealed that *H. pylori* treatment had no significant effect on quality of life and the clinical effects of a 'test and treat' effect are small and the cause of dyspepsia uncertain.

In Singapore, the working party on *H. pylori* of the Gastroenterological Society of Singapore recommends empirical treatment (with antisecretory agents or prokinetics) followed by endoscopy for new onset uninvestigated dyspepsia, rather than a 'test and treat' strategy.¹¹

Peptic Ulcer Disease

Eradicating *H. pylori* infection in patients with peptic ulcer disease with complications such as bleeding leads to cure of the peptic ulcer and prevents relapse. This is true for both duodenal and gastric ulcers. In a person who had peptic ulcer disease and ingested non-steroidal anti-inflammatory drugs (NSAIDs), *H. pylori* infection and NSAIDs gastropathy should be treated independently i.e. eradicate *H. pylori*; prescribe co-medication using proton pump inhibitors (PPIs) or PGE₂ with NSAIDs; or use COX II inhibitors.

Reflux Oesophagitis

The relationship between gastro-oesophageal reflux disease (GERD) and *H. pylori* is unclear, although there is epidemiological data to suggest that *H. pylori* infection may have a protective role against reflux. Proton-pump inhibitors produce higher intragastric pH in *H. pylori* positive patients than *H. pylori* negative patients. A slightly higher number of *H. pylori* positive GERD patients respond to PPI therapy than *H. pylori* negative GERD.¹² This could be overcome by higher dose of PPI or nocturnal dose of H₂ blocker. There is concern that prolonged PPI given for treatment of reflux oesophagitis in the presence of *H. pylori* could result in greater risk of atrophic gastritis. To date, a

follow-up study of up to 11 years has failed to show a significant increase in atrophic gastritis in PPI users.¹³

Treatment

Currently, the treatment of *H. pylori* infection involves PPI (omeprazole, lansoprazole, rabeprazole, lansoprazole) combined with two antibiotics chosen from amoxycillin, metronidazole, clarithromycin given for 1 week. Metronidazole resistance affects triple therapy using the amoxycillin, metronidazole and PPI combination. An eradication rate of 94% has been reported in Southeast Asia with omeprazole 20 mg BD, amoxycillin 1 gm BD or metronidazole 400 mg BD and clarithromycin 500 mg BD.¹⁴ However, with PPI-metronidazole-clarithromycin there is the potential for resistance to both metronidazole and clarithromycin and PPI-amoxycillin-clarithromycin is the first-line treatment in countries where metronidazole resistance is high (>30%). When treatment failure with either of these regimens is encountered, quadruple therapy using PPI, tetracycline, metronidazole and bismuth for a week could result in eradication rate of 70%.

Newer salvage therapeutic regimens involving a new combination of PPI, rifabutin and clarithromycin have been reported in preliminary trials to produce an eradication rate of 84%.

Molecular Biology

The clinical outcome of *H. pylori* induced may be due to differences in virulence among specific strains, host factors or a virulent strain in a susceptible host. Virulence factors have been the subject of extensive study. Several genes have been identified that may play a role in the pathogenicity of *H. pylori*. VacA gene encodes a vacuolating toxin that becomes activated at low pH and leads to gastric epithelial erosions after active bacterial secretion. The gene is present in all *H. pylori* strains. The signal region is located at the 5' end of the gene, occurs as S₁ or S₂ allele. Vac A S₁ strains produce moderate to large amount of toxins whereas S₂ strains produce very little toxin. The cytotoxin associated antigen (CagA) is a surface¹⁵ protein encoded by CagA gene, which is one of the 40 genes contained in the PAI (pathogenicity island). Neither CagA or the PAI actually produces toxin. For some reason, however, VacA (the vacuolating toxin) is not secreted unless the PAI is present. Recently, the Cag pathogenicity island has been shown to encode a type IV bacteria secretion machinery and CagA has been found to be secreted into gastric epithelial cells, becomes phosphorylated and, becomes involved in bacteria-induced signal transduction. Cag PAI products induce interleukin-8 secretion from gastric epithelial cells and

cause inflammation. Host factors have been relatively less studied currently, but HLA, Lewis antigens and interleukin-1 have been proposed to have important roles. Currently, it is uncertain whether bacterial factors or host factors are more important in determining the clinical outcome of *H. pylori* infection.

REFERENCES

1. Lee A. Infections causes of gastroduodenal inflammation in humans. *Eur J Gastroenterol Hepatol* 1992; 4 Suppl 2:1-7.
2. Andersen LP, Dorland A, Karacan H, Colding H, Nilsson HO, Wadstrom T, et al. Possible clinical importance of the transformation of *Helicobacter pylori* into coccoid forms. *Scand J Gastroenterol* 2000; 35:897-903.
3. Graham D Y. *Helicobacter pylori*: its epidemiology and its role in duodenal ulcer disease. *J Gastroenterol Hepatol* 1991; 6:105-13.
4. Sasaki K, Tajiri Y, Sata M, Fuyii Y, Matsubara F, Zhao M, et al. *Helicobacter pylori* in the natural environment. *Scand J Infect Dis* 1999; 31:275-9.
5. Poms R E, Tatini S R. Survival of *Helicobacter pylori* in ready to eat foods at 4 degrees C. *Int J Food Microbiol* 2001; 63:281-6.
6. Manes G, Balzano A, Iaquinto G, Ricci C, Piccirillo M M, Giardullo N, et al. Accuracy of the stool antigen test in the diagnosis of *Helicobacter pylori* infection before treatment and in patients on omeprazole therapy. *Aliment Pharmacol Ther* 2001; 15:73-9.
7. Huang J Q, Sridhar S, Chen Y, Hunt R. Meta-analysis of the relationship between *Helicobacter pylori* seropositivity and gastric cancer. *Gastroenterology* 1998; 114:1169-79.
8. Moayyedi P, Soo S, Deeks J, Forman D, Mason J, Innes M, et al. Dyspepsia Review Group. Systematic review and economic evaluation of *Helicobacter pylori* eradication treatment for non-ulcer dyspepsia. *BMJ* 2000; 321:659-64.
9. Laine L, Schoenfeld P, Fennerty M B. Therapy for *Helicobacter pylori* in patients with non-ulcer dyspepsia. A meta-analysis of randomised, controlled trials. *Ann Intern Med* 2001; 134:361-9.
10. Moayyedi P, Feltbower R, Brown J, Mason S, Mason J, Nathan J, et al. Leeds HELP Study Group. Effect of population screening and treatment for *Helicobacter pylori* on dyspepsia and quality of life in the community: a randomised controlled trial. *Lancet* 2000; 355:1665-9.
11. Management of *Helicobacter pylori* infection. MOH Clinical Practice Guidelines 2/98. Singapore: Ministry of Health, 1998.
12. Holtmann G, Cain C, Malfertheiner P. Gastric *Helicobacter pylori* infection accelerates healing of reflux oesophagitis during treatment with the proton pump inhibitor pantoprazole. *Gastroenterology* 1999; 117:11-6.
13. Klinenberg-Knol, Nelis F, Dent J, Snel P, Mitchell B, Prichard P, et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease efficacy, safety and influence on gastric mucosa. *Gastroenterology* 2000; 118:661-9.
14. Fock K M, Chelvam P, Lim S G, and The South-East Asia Multicentre Study Group. Triple therapy in the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease: results of a multicentre study in South East Asia. *Aliment Pharmacol Ther* 2000; 14:225-31.
15. Axon A T. Are all helicobacters equal? Mechanism of gastroduodenal pathology and their clinical implication. *Gut* 1999; 45 Suppl 1:11-4.