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Helicobacter pylori infection

When to search for it and how to diagnose it

The discovery of *Helicobacter pylori* in the mid-1980s sparked ongoing interest in its role in health and disease. *H. pylori* infection is associated with many other conditions and it is important to know when to diagnose and treat the infection.

LAY T. GAN
MB BS

ANNE DUGGAN
BMed, FRACP, MHP, PhD

Dr Gan is an Advanced Trainee in Gastroenterology and General Medicine at John Hunter Hospital. Professor Duggan is a Senior Staff Specialist in Gastroenterology at John Hunter Hospital, and Newcastle, Conjoint Associate Professor at the University of Newcastle, NSW.

The complete story about *Helicobacter pylori* is yet to evolve. Recent data indicate that the discovery of its association with peptic ulcer disease, gastric cancer and mucosa-associated lymphoid tissue (MALT) tumour may be just the first chapter in a complex story of its relation with humans. Since the turn of the century, *H. pylori* has dramatically reduced in incidence in most Western countries, and in some areas of the USA less than 10% of 10-year-old children have evidence of infection.

With the decline of *H. pylori* infection there has been an increase in rates of asthma, allergies, gastro-oesophageal reflux disease (GORD), adenocarcinoma of the oesophagus and obesity. The significance of this observation is not yet fully understood but is of sufficient interest for some researchers to suggest that *H. pylori* plays a pivotal role in determining susceptibility to these diseases. Some have also speculated that, in the future, children may be deliberately colonised with benign strains of *H. pylori* to protect them from these diseases and the diseases associated with more virulent strains of *H. pylori* .[1]

H. pylori is a bacterium that causes chronic gastritis in humans. The Australian researchers Barry J. Marshall and J. Robin Warren noted the presence of chronic gastritis and it was this that led to the recognition that in some individuals chronic

IN SUMMARY

- ***Helicobacter pylori* is usually acquired in early childhood through close contact with an infected person, and the infection persists for life unless treated.**
- ***H. pylori* infection accounts for up to 90% of duodenal ulcers and about 70% of gastric ulcers.**
- **Most individuals infected with *H. pylori* do not develop clinically significant disease during their lifetime.**
- **Proton pump inhibitor (PPI)-based triple therapy for seven days is highly effective and successfully eradicates *H. pylori* infection in more than 90% of cases.**
- **In most cases of ulcer disease, long-term PPI therapy is not warranted once *H. pylori* infection has been eradicated.**

infection with *H. pylori* causes peptic ulcer disease, distal gastric cancer and the rarer MALT lymphoma. Experience tells us that depending on the frequency of prescription of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin, *H. pylori* infection accounts for up to 90% of duodenal ulcers and about 70% of gastric ulcers. Fortunately, most individuals infected with *H. pylori* develop no clinically significant disease in their lifetime.

This article addresses the pathogenesis of *H. pylori* in causing disease, indications for diagnosis and treatment, tests available for *H. pylori* diagnosis and treatment options, and summarises the recommendations for the management of *H. pylori*-related disease.

Pathogenesis

H. pylori is usually acquired, possibly by the faecal–oral or oral–oral route, in early childhood through close contact with an infected person, and the infection persists for life unless treated. Once successfully treated, re-infection is rare. *H. pylori* is a Gram-negative spiral rod bacterium with flagella at one end, and is well adapted to evade the primary immune response mechanisms of the host. The organism produces urease, which breaks down endogenous urea to carbon dioxide and ammonia. This raises the gastric pH and allows *H. pylori* to survive in an otherwise acidic stomach.

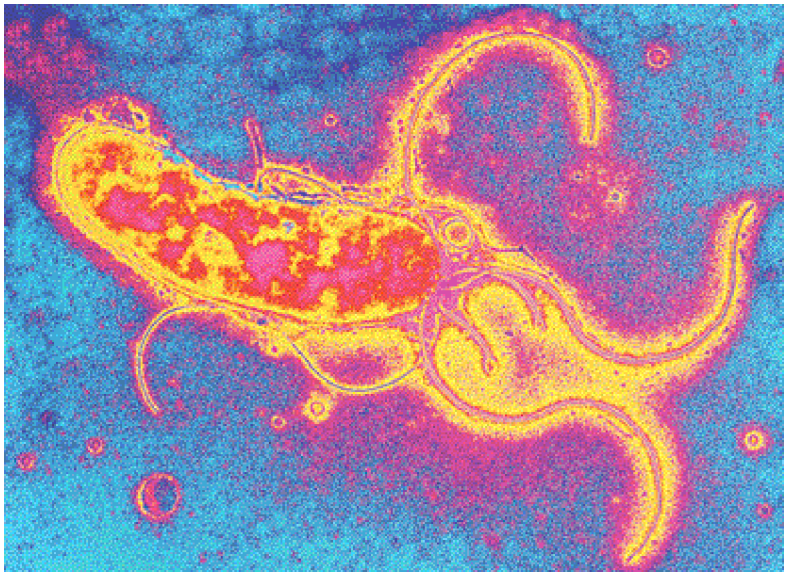
H. pylori infection induces a vigorous systemic and mucosal response. This rarely leads to its eradication but does contribute to tissue damage and chronic gastritis, the severity and sequelae of which is determined by the toxogenicity of the *H. pylori* strains acquired.

A brief overview of *H. pylori* infection and its clinical outcome is shown in the flowchart on page 42.

Indications for diagnosis and treatment of *Helicobacter pylori*

Duodenal ulcer disease

H. pylori is the cause of between 70 and 90% of duodenal ulcers, depending on the background prevalence of infection and NSAID use. Diagnosis is usually by gastroscopy, which also allows gastric biopsies to be obtained for rapid urease testing (CLO testing) for *H. pylori* infection.



PHOTOLIBRARY

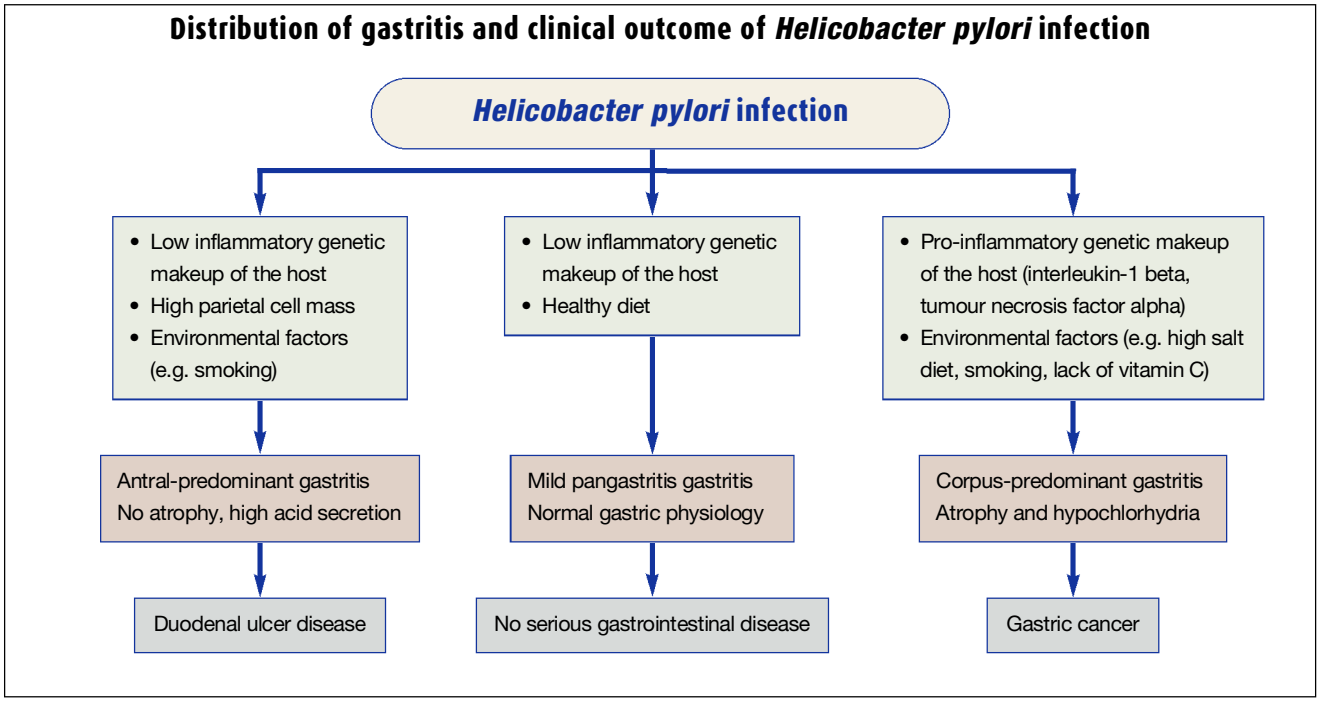
Figure. *Helicobacter pylori* (coloured transmission electron micrograph).

The eradication of *H. pylori* provides faster ulcer healing and reduced ulcer recurrence compared with acid-suppression therapy alone (Table 1). Uncomplicated duodenal ulcers heal quickly after triple therapy alone (Table 1). Current international recommendations are for a four-week course of acid-suppression therapy after a one-week course of *H. pylori* eradication therapy.

Symptoms that persist in patients after *H. pylori* eradication therapy are usually due to coexistent GORD. In these cases, symptom resolution with proton pump inhibitor (PPI) therapy after eradication therapy and rapid recurrence of symptoms after cessation of PPIs is diagnostic of GORD. In the absence of PPI therapy no symptoms at six months is a good indicator of successful treatment of ulcer diathesis.

Duodenal ulcers complicated by bleeding or perforation are uncommon but are associated with increased morbidity and mortality, particularly in the elderly and those with major comorbidities.

Confirmation of *H. pylori* eradication is not cost-effective in all patients because treatment is usually effective in more than 90% of cases. In patients who are at high risk of significant complications or death from peptic ulcer bleeding (e.g. those with multiple medical comorbidities) and those causing diagnostic uncertainty, confirmation of *H. pylori* eradication with a urea breath test is recommended.



Eradication of *H. pylori* infection markedly reduces but does not entirely eliminate the risk of ulcer recurrence. Lifelong maintenance therapy with a PPI is indicated in the following groups:

- high-risk patients, with coprescription of NSAIDs or aspirin
- patients in whom *H. pylori* eradication has failed despite reasonable attempts, for example, with second- and third-line therapy.

Failure of ulcer healing is usually due to noncompliance, antibiotic resistance or ongoing NSAID/aspirin use rather than the rarer causes of peptic ulcer disease, such as Zollinger Ellison syndrome.

Gastric ulcer disease

H. pylori infection is associated with about 70% of gastric ulcers. NSAID use in patients with or without *H. pylori* infection accounts for most other gastric ulcers, with gastric cancer being an increasingly rare cause. Nevertheless, diagnostic endoscopy and biopsy with repeat endoscopy at six weeks to confirm healing and exclude malignancy remains the gold standard.

Ulcer disease in association with NSAID or aspirin use

The relation between NSAID use and *H. pylori* infection remains controversial. Current management recommendations are based on a combination of evidence and consensus guidelines.[3,4] NSAID use and *H. pylori* infection are the major causes of ulcers, and ulcers are more frequent among patients who use NSAIDs and have *H. pylori* infection than among those who do not have *H. pylori* infection.

NSAID use and *H. pylori* infection are thought to cause ulcer disease via different mechanisms but work synergistically to cause ulcers and ulcer complications such as bleeding.[5] Patients who do not use NSAIDs appear to benefit from H. pylori eradication before starting NSAID use, with reduced occurrence of ulcers and ulcer bleeding. The evidence is not strong and current guidelines do not recommend screening all patients before starting NSAIDs.[6]

A reasonable approach is to eradicate *H. pylori* in patients with a higher risk of NSAID-associated ulcer complications because of older age and comorbidities (e.g. severe cardiorespiratory disease, severe chronic kidney disease). There is less evidence of benefit from *H. pylori* eradication in patients who use NSAIDs and have a history of ulcers. Nevertheless, current recommendations are that *H. pylori* infection if present be eradicated in high-risk patients and they be given cotherapy with a PPI.

In the presence of an ulcer, patients who use NSAIDs should have four to six weeks of PPI-based acid suppression before restarting NSAIDs if still indicated. Less toxic NSAIDs, such as ibuprofen (e.g. Nurofen) or diclofenac (e.g. Voltaren), should be considered; as should also low-dose aspirin (Astrix 100, Astrix Tablets, Cardiprin 100, Cartia), which has a cardioprotective effect and is safer than higher doses. Aspirin and standard or selective NSAIDs should not be administered at the same time.

Gastric cancer

In 1994, the evidence for a causal relation between *H. pylori* infection and gastric

cancer led the World Health Organization's Internal Agency for Research on Cancer to classify *H. pylori* as a group-one carcinogen.[7] Gastric cancer has a high incidence in areas where *H. pylori* infection is endemic because acute gastritis can lead to chronic then atrophic gastritis, intestinal metaplasia, dysplasia and gastric carcinoma.

It may appear logical to recommend secondary prevention of gastric cancer by eradicating *H. pylori* infection, especially in those with a family history of gastric cancer. However, there are no data on when eradication would be effective, although eradication before development of preneoplastic lesions (atrophic gastritis and intestinal metaplasia) would seem essential.[8] Current recommendations are to eradicate *H. pylori* infection if present in those with a personal or family history of gastric cancer.

In countries such as Australia, where the prevalence of *H. pylori* infection is low and gastric cancer is uncommon, enthusiasm for primary prevention has understandably waned.

Gastric MALT lymphoma

The relation between *H. pylori* infection and MALT lymphoma is interesting. Localised and low-grade lymphomas regress with *H. pylori* eradication in up to 90% of patients.[9] In contrast, advanced MALT lymphoma requires treatment with traditional chemotherapeutic agents.[10] Eradication of *H. pylori* infection seems a logical additional step.

Functional dyspepsia

Functional dyspepsia is dyspepsia in the absence of an identifiable cause and is extremely common. Less than half of patients who experience symptoms seek medical attention, but dyspepsia still accounts for 5% of all visits to the GP. There is no clear relation between *H. pylori* infection and functional dyspepsia. Guidelines from the American Gastroenterology Association recommend a 'test-and-treat' strategy (testing for *H. pylori* infection and treating infection if present with triple therapy) for patients with dyspepsia because it is less expensive than endoscopy and a proportion of patients treated would have peptic ulcer disease.[3,11]

However, with the falling prevalence of *H. pylori* infection this strategy unnecessarily exposes an increasing number of patients to testing. Where prevalence of *H. pylori* infection is low and there are no risk factors for ulcer disease, such as past or family history, smoking or current NSAID or aspirin use, current recommendations for the management of uninvestigated dyspepsia are for a trial of PPI therapy. This will both diagnose and treat GORD. Endoscopy still has a role when there are alarming symptoms, such as bleeding, anaemia, early satiety, unexplained weight lost, progressive dysphagia or odynophagia, recurrent vomiting, family history of gastrointestinal cancer or previous oesophagogastric malignancy (Table 2). Endoscopy is also still appropriate when risk factors for ulcer disease or symptoms do not respond to PPI therapy.

Table 1. *Helicobacter pylori* eradication treatment regimens[2]

	Drug	Dose	Duration
First-line therapy – no penicillin allergy*	PPI†	20 mg bd	7 days
	Amoxycillin	1 g bd	7 days
	Clarithromycin	500 mg bd	7 days
First-line therapy – penicillin hypersensitivity	PPI†	20 mg bd	7 days
	Metronidazole	400 mg bd	7 days
	Clarithromycin	500 mg bd	7 days
Second-line therapy if failure of eradication – first-line therapy	PPI†	bd	10 to 14 days
	Colloidal bismuth‡	120 mg qid	7 to 14 days
	Tetracycline‡	500 mg qid	7 to 14 days
	Metronidazole	400 mg tds	7 to 14 days
	OR		
	PPI†	bd	10 days
	Amoxycillin	1 g bd	10 days
	Rifabutin	150 mg bd	10 days

* Triple therapy is available as a combination treatment (Klacid HP 7, Nexium HP7). † PPIs available include esomeprazole (Nexium), lansoprazole (Zoton), omeprazole (Acimax, Losec, Meprazol, Omepral, Probitor), pantoprazole (Somac) and rabeprazole (Pariet). ‡ Available on Special Access Scheme.

Gastro-oesophageal reflux disease

Several epidemiological studies[3,12,13] have shown a lower prevalence of *H. pylori* infection in patients with GORD and some authors have speculated that the relation is mechanistic. Patients with antral-predominant (distal stomach) gastritis exhibit increased acid secretion, with an increased risk of duodenal ulcers. Conversely, patients who have corpus-predominant (body of stomach) gastritis

Table 2. When the use of the test-and-treat strategy would not be appropriate[4]

- Age ⩾50 years
- Anorexia or weight lost
- Dysphagia or odynophagia
- Vomiting
- Anaemia or positive faecal occult blood test
- Jaundice
- Failure of several treatments
- Strong history of familial cancer

Table 3. Diagnostic testing for *Helicobacter pylori* infection[3,15]

Diagnostic testing	Advantages	Disadvantages
Endoscopic		
Histology*	Excellent sensitivity Allows mucosal assessment	Expensive Invasive with a variable specificity
Rapid urease testing* (CLO testing)	Inexpensive and provides rapid results Excellent specificity	Sensitivity reduced after antibiotic use, upper gastrointestinal bleeding, recent PPI therapy and gastric atrophy
Culture*	Allows determination of antibiotic sensitivity	Expensive Difficult to perform Not widely available
Nonendoscopic		
Antibody testing (quantitative and qualitative)	Inexpensive Widely available Good NPV	PPV dependent on *H. pylori* prevalence Unable to differentiate between past and current infection
Urea breath test (^{13}C or ^{14}C)*†	Detects current *H. pylori* infection Excellent PPV and NPV Gold standard before and after *H. pylori* treatment	^{14}C is radioactive and contraindicated in pregnancy and ^{13}C is not radioactive Antibiotics and PPI therapy should be ceased two weeks before testing
Faecal antigen test*	Identifies active infection Excellent PPV and NPV	Need to collect stool specimen

*Sensitivity of these tests in identifying active *H. pylori* infection is reduced by recent use of a PPI, bismuth or antibiotics. Apart from for serobgical testing, PPIs and antibiotics should be stopped a minimum of two weeks before testing.
† Urea breath testing is currently reimbursable under the Medicare Benefit Scheme for either confirmation of *H. pylori* colonisation or monitoring of success of eradication.
ABBREVIATIONS: NPV = negative predictive value, PPI = proton pump inhibitors, PPV = positive predictive value.

have reduced acid secretion and are at a greater risk of developing gastric cancer. Theoretically, reversal of corpus-predominant *H. pylori* gastritis can lead to increased gastric acid secretion and reflux, but there is insufficient evidence that this is clinically relevant.[3,14] There is currently no clear evidence to implicate *H. pylori* eradication in the development of reflux symptoms and *H. pylori* eradication is not indicated in the treatment of GORD.

Other indications

Studies have suggested that *H. pylori* infection causes iron-deficiency anaemia and idiopathic thrombocytopenic purpura, and its eradication reverses anaemia and improves oral iron absorption. It has been claimed that *H. pylori* eradication induces a positive platelet response; however, in the case of both iron-deficiency anaemia and idiopathic thrombocytopenic purpura the data are inconclusive.[12]

Epidemiological data have revealed an increase in prevalence of asthma, hay fever and other atopic disorders in industrialised nations. Some cross-sectional studies have shown an inverse relation between asthma, atopic disorders and *H. pylori* seropositivity. Hypotheses to explain this observation include that *H. pylori* infection affects the balance between T helper 1 and T helper 2 cell immune responses. The results are inconclusive and the determination will be interesting.

Diagnosis of *Helicobacter pylori* infection

Population testing for *H. pylori* infection is not recommended. The 2007 American Gastroenterology Society Guidelines recommend testing in the following circumstances:[3]

- if the clinician plans to offer treatment for a positive result (this is at the clinician's discretion but should certainly be offered to high-risk patients with medical comorbidities)
- in patients with peptic ulcer disease (past or present), gastric adenocarcinoma or gastric MALT lymphoma
- for uninvestigated dyspepsia in patients under the age of 55 years with no 'alarm features', using the test-and-treat strategy rather than endoscopy, which has been shown to be less cost-effective[11] in areas where *H. pylori* is prevalent.

This strategy would only be applicable in developed countries like Australia in cohorts where *H. pylori* infection is common, such as in some immigrant populations from countries with a high

prevalence of *H. pylori* infection.

Table 3 summarises the diagnostic tests available and their advantages and disadvantages. Tests can be divided into endoscopy-based and nonendoscopy-based.

Treatment of *Helicobacter pylori* infection

PPI-based triple therapy (a PPI and two antibiotics; Table 1) for seven days is highly effective for the treatment of *H. pylori* infection, being successful in more than 90% of cases. Increasing resistance of *H. pylori* to clarithromycin and metronidazole poses a significant threat to effective *H. pylori* eradication.[16] In some countries, *H. pylori* resistance to metronidazole is reported to be as high as 40% in the USA and Europe, and clarithromycin resistance is reaching up to 15% in parts of Australia[17] and increasing in areas with a high use of macrolides. In the case of treatment failure, there are a number of options, including:

- repeat therapy with a first-line agent
- trial PPI-based quadruple therapy (Table 1)
- gastroscopy with gastric biopsy for culture to determine sensitivities
- consideration of long-term therapy with a PPI to reduce the risk of ulcer recurrence.

To prevent increasing antibiotic resistance it is essential that the initial indication for eradication is justified.

Recommended treatment regimens and their roles are provided below (Table 1).

Recommendations

The diagnosis and treatment of *H. pylori* infection is currently indicated for patients with:[3,12]

- peptic ulcer disease with or without a history of NSAID or aspirin use
- gastric MALT lymphoma, especially in the early stages of the disease
- early gastric cancer endoscopically resected
- a personal or family history of gastric cancer.

A more conservative approach to *H. pylori* infection in other clinical settings has been recommended because of the decline in the prevalence of *H. pylori* infection, the lack of evidence of harm for the majority of people infected with *H. pylori* the small risks associated with treatment (such as antibiotic-associated diarrhoea) and the controversial data suggesting an inverse relation between *H. pylori* infection and allergic diseases (such as asthma and atopy), GORD and oesophageal adenocarcinoma.

Urea breath testing is the most accurate noninvasive test for *H. pylori* diagnosis, with ^{13}C preferred over ^{14}C due to its non-radioactive properties. The concept underlying urea breath testing is basically the ingestion of labelled urea. This urea is metabolised by urease produced by *H. pylori*, resulting in labelled carbon dioxide. This is then exhaled through the lungs and the concentration of labelled carbon atoms can be determined in the exhaled air.[15]

PPI therapy and antibiotics should be stopped two weeks before all testing for *H. pylori* except serological testing. In children, whose co-operation may be unreliable, faecal antigen testing is acceptable.

Retesting after eradication of *H. pylori* infection is recommended in patients:

- with complicated ulcer disease (e.g. bleeding, gastric ulcers), the elderly or with significant comorbidities where ulcer recurrence would cause substantial morbidity
- with a past history of ulcer disease where it is unknown whether *H. pylori* testing and/or treatment occurred
- after endoscopic resection of early gastric cancer
- after treatment of *H. pylori* -associated early gastric MALT lymphoma
- after eradication of *H. pylori* infection where there is a recurrence of dyspeptic symptoms not thought to be due to GORD.

In all the above circumstances for retesting, serology testing should not be used for confirmation of eradication because serology can remain positive for up to 12 months after eradication.

For the compliant patient who fails first-line eradication therapy, we recommend the following options:

- repeat triple PPI-based or trial quadruple PPI-based therapy with extension of treatment from seven to 10 days
- other second-line treatment of PPI-based therapy (Table 1)
- referral to a gastroenterologist for endoscopy and biopsies for culture and sensitivity testing to guide treatment for subsequent antibiotic therapy.

In most cases of ulcer disease long-term PPI therapy is not warranted once eradication of *H. pylori* infection has occurred. It should be reserved for patients starting long-term aspirin or anti-inflammatory therapy. MT

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A list of references is available on request to the editorial office.

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LAY T GAN MB BS ANNE DUGGAN B MED, FRACP, MHP, PhD

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