

# Gastroenterology

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## *Helicobacter pylori* for the general physician

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In April 1982, Marshall and Warren in Perth, Australia, cultured a curved organism from the human stomach. This organism, *Helicobacter pylori*, was then demonstrated to be associated with gastritis, duodenal and gastric ulcers<sup>1</sup>. Few discoveries in recent years have so completely revolutionised our understanding of the aetiology and management of these common diseases.

### The bacterium

*H. pylori* is a curved microaerophilic Gram-negative rod with 4–6 flagellae at one end. It was initially thought to belong to the genus *Campylobacter*, and underwent a series of name changes before 16S ribosomal RNA analysis demonstrated that it was a new genus.

The stomach is a hostile environment for bacterial colonisation because of the presence of gastric acid, but *H. pylori* possesses a number of adaptive features that allow it to survive in this environment. On initial colonisation of the stomach, it induces a profound, though temporary, achlorhydria. *H. pylori*,

importantly, produces a urease which catalyses the breakdown of urea into ammonia and carbon dioxide. The ammonia dissolves in water to form the alkali ammonium hydroxide, which effectively neutralises the acid. It also possesses a proton pump which removes excess hydrogen ions from the bacterium. Finally, its flagellae allow the bacterium to be highly motile in the mucus gel layer.

*H. pylori* attaches itself to the gastric cells via bacterial adhesins, for example, Lewis B blood group antigen – which might explain why individuals who are secretors are less likely to have *H. pylori* clinging to their cells – and this influences the course of disease. *H. pylori* exists in many strains, some of which appear to be more associated with disease than others. The possession of a gene *cagA* is highly correlated with disease, as is the ability to produce a toxin called ‘vacuolating toxin’ (*vacA*).

### How is *Helicobacter pylori* spread?

The route of infection by *H. pylori* remains unclear, and may vary in different countries. The organism has been demonstrated in the water supply of developing countries, and is found more commonly in the lower socio-economic classes. It has also

been cultured from faeces, which may suggest an oral-faecal route of infection. The opposing view of an oral-oral route is probably less likely.

### *Helicobacter pylori* and gastritis

When *H. pylori* infects the stomach, it causes a gastritis. The initial infection is often asymptomatic but can cause nausea, vomiting and abdominal pain. The stomach is rendered temporarily achlorhydric, though it may remain so for some months before acid secretion recovers.

*H. pylori* has evolved mechanisms to thrive in the hostile gastric environment. It is not cleared by the host, and thus causes a chronic infection. Most individuals with *H. pylori*-associated chronic gastritis remain asymptomatic, but it predisposes to clinically significant conditions, including gastric and duodenal ulcers, gastric cancer and lymphoma. The factors that lead to disease have not been fully elucidated but involve bacterial factors, host factors and environmental influences. Bacterial factors that predispose to disease states include the virulence factors *cagA* and *vacA*. These bacterial proteins, together with urease and heat-shock protein, produce an inflammatory response in the gastric mucosa. Bacteria which lack these virulence factors produce a milder inflammatory response.

Other important factors that influence disease outcome after infection with *H. pylori* are the type and site of the gastritis, which may be partly due to host response to the infection.



*H. pylori* produces both a chronic superficial gastritis and an atrophic gastritis. The former is associated with prepyloric and duodenal ulcers, and the latter may lead to gastric cancer. A few patients develop lymphoid follicles which may predispose them to develop mucosa associated lymphoid tissue lymphomas (MALTomas). Most patients develop a mild pangastritis and are asymptomatic, others who develop a gastritis chiefly of the antrum of the stomach tend to develop duodenal ulcers, while some develop a gastritis of the body of the stomach, which leads to gastric ulcers, gastric atrophy and, in the unfortunate, gastric adenocarcinoma (Fig 1).

**Helicobacter pylori and duodenal ulcer disease**

The most dramatic change in gastroenterological practice in recent years has been the discovery that *H. pylori* is the major cause of duodenal ulcer disease, with over 90% of duodenal ulcer patients infected. Other contributing factors include smoking, family history and male sex. Perhaps the most persuasive evidence that *H. pylori* is the causative agent is that eradication of the offending microbe leads to the cure of the disease in most patients.

Figure 2 displays schematically our current understanding of the pathogenesis of duodenal ulcers. The infection in these patients mainly affects the antrum of the stomach. This part of the stomach controls acid secretion and contains the G and D cells. The G cells secrete gastrin in response to stimulation by food. Gastrin stimulates acid secretion from the parietal cells in the corpus of the stomach. The D cells act as a negative feedback loop, secreting somatostatin in response to the acid, which in turn inhibits gastrin secretion. Gastrin levels are elevated and somatostatin levels depressed in *H. pylori*-infected duodenal ulcer patients. Some agent produced by the bacteria is probably responsible for inhibiting somatostatin release. As a result, there is more gastrin, and consequently

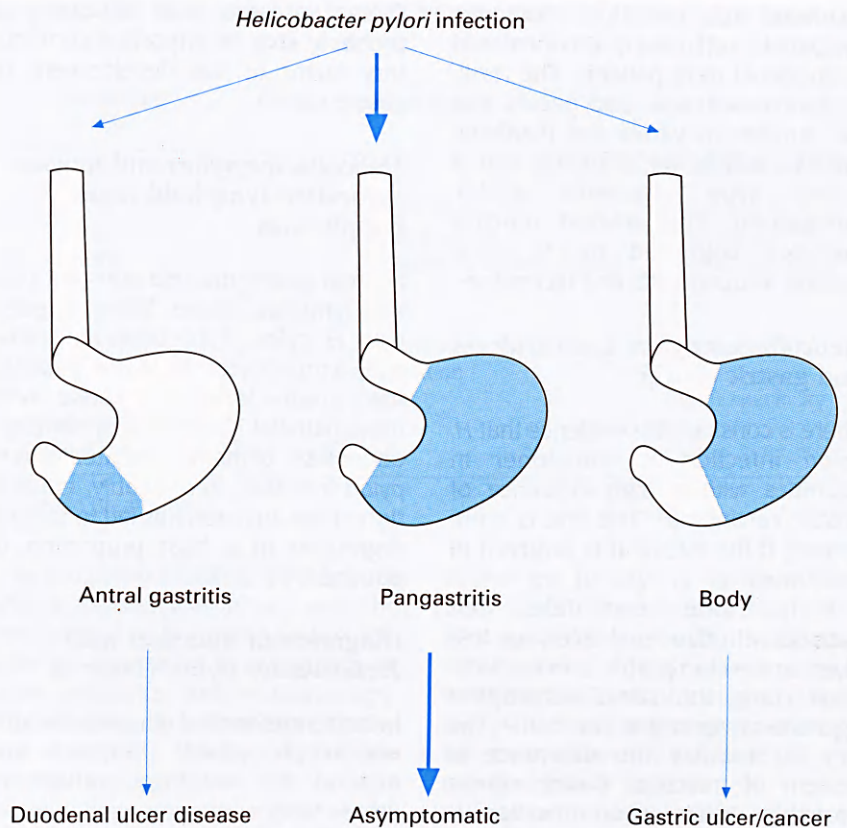
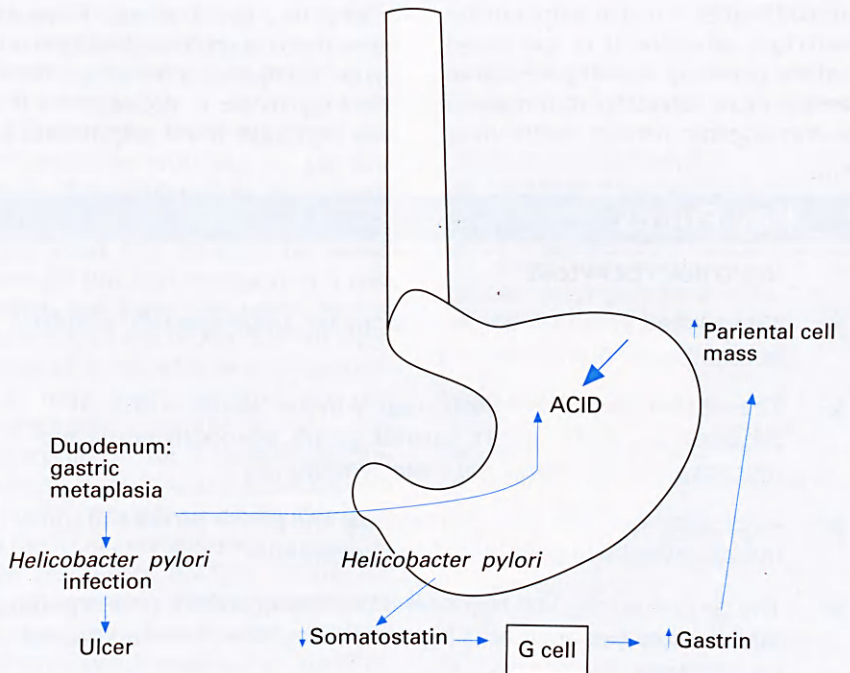


Figure 1. The main consequences of Helicobacter pylori infection.

Figure 2. Postulated mechanism for the pathogenesis of duodenal ulcers.





increased acid secretion. Moreover, the parietal cell mass is also increased in duodenal ulcer patients. The resultant increased acid load passes into the duodenum where the duodenal mucosa adapts by changing into a gastric type (duodenal gastric metaplasia). This altered mucosa becomes colonised by *H. pylori* leading to duodenitis and ulceration<sup>2</sup>.

## ***Helicobacter pylori*, gastric ulcers and gastric cancer**

There is considerable evidence that *H. pylori* infection is commoner in countries with a high incidence of gastric carcinoma<sup>3</sup>. The link is more striking if the infection is acquired in childhood.

It has long been noted that patients with duodenal ulcers are less likely to develop gastric cancers. How then could the same aetiological agent be responsible for both? The key is probably the difference in pattern of infection. Gastric cancer probably results when infection is chiefly in the body of the stomach where the parietal cells are located. This leads to atrophy and reduced acid secretion with corresponding hypergastrinaemia but without gastric autoantibodies – unlike autoimmune pernicious anaemia. It is speculated that the relatively neutral pH environment is more conducive to formation of carcinogenic nitroso compounds.

Dietary ascorbic acid deficiency is probably also an important contributory factor to the development of gastric cancer.

## ***Helicobacter pylori* and mucosa associated lymphoid tissue lymphomas**

Normal gastric mucosa does not contain lymphoid tissue. When infected with *H. pylori*, it becomes infiltrated with lymphocytes. In a few patients, low grade MALTomas arise with intraepithelial lymphocyte infiltration, about 93% of them associated with *H. pylori* infection. Remarkably, eradication of the infection has led to tumour regression in a high proportion of patients<sup>4</sup>.

## **Diagnosis of infection with *Helicobacter pylori* (Table 1)**

Invasive methods of diagnosis require endoscopic gastric biopsies and depend on histology, culture or urease tests.

### *Histology*

Histologists are now adept at identifying the bacteria in tissue sections, helped by special stains. However, other bacteria are sometimes seen in hypochlorhydric stomachs, hence histology alone is not specific. It is also expensive if the only reason for

doing it is to establish whether the patient is infected with *H. pylori*. In patients with gastric ulcers, biopsies are mandatory to exclude malignancy, and follow-up biopsies are required until healing is complete.

### *Culture*

Gastric biopsies can be cultured in special media under anaerobic conditions for three days. However, the detection rate varies greatly between laboratories. The best results require prompt culture, use of an appropriate transport medium and technical expertise. The test is expensive, but has the advantage of identifying antibiotic resistance.

### *Urease tests*

The simple urease test, which is cheap and reliable, depends on the production by *H. pylori* of a powerful urease. The biopsy is embedded in a gel containing urea and a pH indicator which changes colour when the alkaline ammonia is released. Results are seen within a few minutes, and the patients can be told of the diagnosis and treatment be given by the time they recover from the endoscopy.

### *Non-invasive tests*

The main non-invasive tests in routine use are serology and the urea breath test. Serology is cheap and readily available. The commonest version uses an enzyme-linked immunoassay which requires a serum sample. Kits which require only capillary blood from a finger-prick are available, and may be particularly useful in the primary care setting (or for self diagnosis). A serological response may persist after eradication, so it is not recommended as a method of checking whether the infection has been eradicated.

<sup>13</sup>C- or <sup>14</sup>C-urea breath tests also use the ability of the bacteria to break down urea. The urea is labelled either with a stable (<sup>13</sup>C) or a radioactive (<sup>14</sup>C) carbon which is released as carbon dioxide in the breath and

## Key Points

### **HELICOBACTER PYLORI**

- ▶ **A flagellated, curved, urease-producing organism specially adapted to colonise the human stomach**
- ▶ **The most important aetiological agent in the causation of most duodenal and gastric ulcers, gastritis, gastric adenocarcinoma and mucosa associated lymphoid tissue lymphomas**
- ▶ **Eradication can effect cure of duodenal and gastric ulcers and some mucosa associated lymphoid tissue lymphomas**
- ▶ **The current eradication regime is triple therapy with a proton pump inhibitor and two antibiotics (eg clarithromycin and metronidazole) for one week**



**Table 1.** The sensitivity, specificity, and main advantages and disadvantages of tests used for the diagnosis of *Helicobacter pylori* infection.

Test	Sensitivity (%)	Specificity (%)	Advantage	Disadvantage
<i>Invasive tests</i>				
CLO	95 at 24 hours	97	Simple, quick	Invasive
Histology	85	100	Highly specific	Expensive
Culture	≤95	100	Antibiotic sensitivity testing	Slow, expensive
<i>Non-invasive tests</i>				
<sup>13</sup> UBT	97	95	Non-invasive, check eradication	Expensive
Serology	70–90 Varies with kits	50–80 Variable, depending on kits/country	Cheap	Poor specificity

CLO = urease test on biopsy sample

UBT = urease breath test

analysed either by atomic absorption (<sup>13</sup>C) or by scintillation (<sup>14</sup>C). The <sup>13</sup>C urea breath test (<sup>13</sup>C-UBT) is the most widely used in the UK; its price has come down considerably, but it is still more expensive than serology because it requires additional nursing time to conduct the test. It is safe and sensitive, and its main advantage over serology is that it can be used to check for successful eradication.

### Who needs treatment?

Many national and international guidelines have been drawn up with a remarkable degree of agreement. European gastroenterologists produced an evidence-based consensus document at a meeting in Maastricht in 1996. Their current recommendations are given in Table 2.

### What treatment?

Earlier regimens for eradication were based on the use of *bismuth compounds* which are bactericidal to *H. pylori*. These agents were combined with antibiotics in various combinations: for example, 'classical triple therapy' was bismuth subcitrate (DeNol) 120 mg bd, metronidazole 400 mg tds and tetracycline 500 mg qds for two weeks. It was often poorly tolerated and complex to take; it is contraindicated in renal failure.

*Proton pump inhibitors* (PPI) have a modest bactericidal effect and, by increasing the pH in the stomach, allow for maximum bioavailability of some antibiotics. Hence 'duotherapy' with omeprazole and amoxicillin for two weeks was developed, but the combination is of low efficacy and has now been abandoned.

The most consistently effective regimens in terms of eradication rates and low adverse reactions are based on triple therapy with a PPI and two antibiotics for seven days<sup>5</sup>. The macrolide clarithromycin is particularly effective. Our current recommendation is a PPI (omeprazole 20 mg bd or lansoprazole 30 mg bd), clarithromycin 250 mg bd and metronidazole 400 mg bd for one week. This combination gives eradication rates of about 95%. Amoxicillin 1 g bd may be substituted for the clarithromycin at a cost saving, but there are rather poorer eradication rates (80%), and an alternative to metronidazole is tinidazole<sup>6</sup>.

It may seem sensible to use omeprazole, clarithromycin and amoxicillin for metronidazole-resistant *H. pylori*, and the need to test for metronidazole sensitivity depends on the local prevalence of metronidazole resistance. Routine testing for eradication by breath testing is unnecessary unless the patient remains symptomatic. For patients who fail with the first course, a further

course for 10 days is recommended after establishing whether the patient is complying with therapy. Alternatively, 'quadruple therapy', with the addition of omeprazole 20 mg bd to the classical triple therapy for seven days may be used, but it is cumbersome to take<sup>7</sup>.

Eradication of *H. pylori* results in healing of both gastric and duodenal ulcers. There is therefore no need for 'healing courses' of H<sub>2</sub>-receptor antagonists or PPIs for uncomplicated *H. pylori*-infected peptic ulcers. However,

**Table 2.** Recommendations for *Helicobacter pylori* eradication in patients.

#### *Eradication recommended:*

- gastric or duodenal ulcers, whether active or not
- mucosa associated lymphoid tissue lymphomas
- severe symptomatic gastritis
- after resection for early gastric cancer

#### *Eradication to be considered:*

(less scientific evidence in support):

- functional dyspepsia,
- non-steroidal anti-inflammatory drug therapy
- family history of gastric cancer
- long-term proton pump inhibitors for reflux disease

#### *No treatment (pending controlled trials):*

- asymptomatic disease



gastric ulcers require follow-up endoscopies to ensure cancers are not missed. Complicated ulcers (ie bleeding, perforated) or those associated with non-steroidal anti-inflammatory drugs should have a precautionary 'healing course' of four weeks with a PPI or an H<sub>2</sub> receptor antagonist.

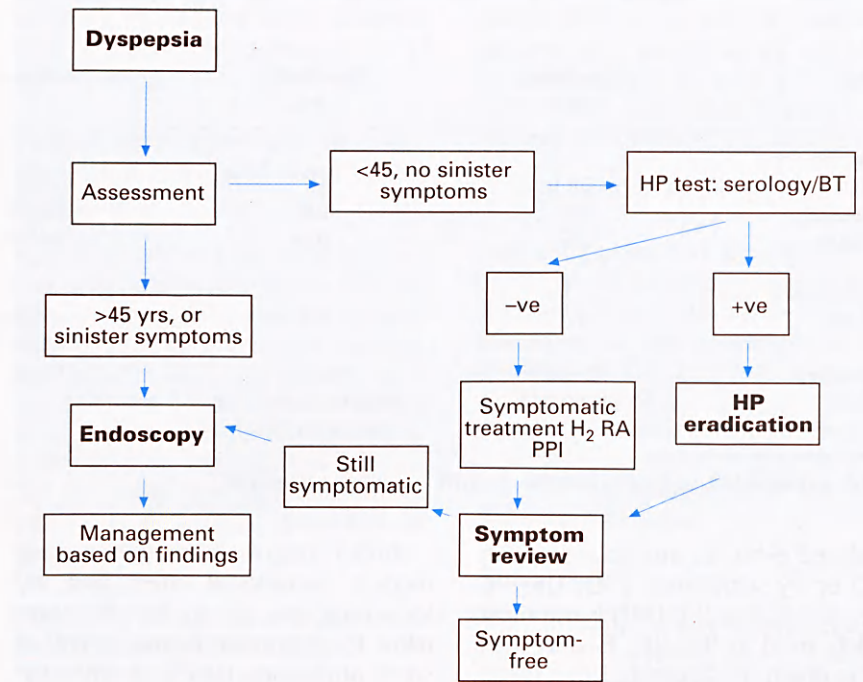
**Treatment strategies**

*Dyspepsia in the community*

Young dyspeptics (under 45 years) can have their *H. pylori* status ascertained by serology or breath test, without endoscopy, while those with positive tests can undergo treatment to eradicate *H. pylori* (a typical schedule is shown in Fig 3). The physician must, however, remain vigilant in looking for gastric carcinomas, and any sinister symptoms such as weight loss, dysphagia or vomiting should prompt endoscopy. He must also be alert for alternative diagnoses, particularly gastro-oesophageal reflux and biliary disease.

*Asymptomatic subjects*

Screening the whole population for *H. pylori* and treating all who are positive would be expected to prevent almost all duodenal ulcer disease and most stomach cancers. The pros and cons of treating asymptomatic subjects have been argued by Axon and Forman<sup>8</sup>. The side effects of therapy, including pseudomembranous colitis, are a weightier consideration when treating those without symptoms. The risk of producing antibiotic-resistant strains of *H. pylori* and other intestinal organisms is a major deterrent. There is even the possibility that some strains of *H. pylori*, which have co-evolved with *Homo sapiens*, confer some benefit. Several controlled trials are in progress or planned which should demonstrate the cost benefit of this eradication strategy, but they



**Figure 3.** Schedule of assessment and treatment of patients with dyspepsia unresponsive to simple measures and antacid (BT = breath test; HP = *Helicobacter pylori*; H<sub>2</sub>RA = H<sub>2</sub> receptor antagonist; PPI = proton pump inhibitor).

are unlikely to continue long enough to give decisive information on cancer. A long-term alternative, which has stimulated much interest in recent years, would be the development of a safe effective vaccine against *H. pylori*.

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**Editor's note:** For a more detailed discussion of the pathogenic role of *Helicobacter pylori*, see page 512