DOUGLASS HANLY MOIR PATHOLOGY
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Helicobacter pylori & Gastric Cancer

Helicobacter pylori is currently the only bacterium which has been categorised as a carcinogen by the WHO International Agency for Research on Cancer. The link between viral infection and cancer development is well-established and is the basis for several population-based screening and prevention programs. While the available evidence does not support widespread testing for and eradication of *H. pylori* in asymptomatic individuals, its global prevalence and known disease-associations make it a human pathogen of evolving importance.

Epidemiology and disease association

Since its recognition as a potential human pathogen in 1982, *Helicobacter pylori* has been implicated as a cause of chronic gastritis and peptic ulcers. It has been estimated to affect up to two thirds of the world's population, occurring at any age and across all socioeconomic groups, although the risk of acquisition is related to socioeconomic status and living conditions early in life.

H. pylori is transmitted via contaminated food and water and by direct mouth-to-mouth contact. Once acquired, infection persists, but in most people does not cause illness. However the high prevalence of infection and the well-established link between infection and gastric cancer gives *H. pylori* a significance which warrants wider recognition.

The organism

H. pylori is a spiral-shaped, Gram-negative bacterium which, while slow-growing, can be isolated readily in culture. Its most notable metabolic characteristic, and the basis for two widely used tests for the presence of *H. pylori* in the stomach, is the abundant production of the enzyme urease. There are more than 30 other species in the genus Helicobacter; non-pylori Helicobacter species have been detected in humans and have been occasionally associated with gastritis and peptic ulcer disease.

H. pylori and gastric cancer

Gastric cancer is the fourth most common cancer, worldwide, and the second most common cause of cancer-related deaths. It is less common in Western societies than it is in Asia and South America and infection with *H. pylori* is the primary identified cause. However, the association between *H. pylori* and cancer is complex; there is an increased risk of non-cardia gastric adenocarcinoma but also the possibility of reduced risk of carcinoma involving the cardia and the oesophagus.

- **Gastric adenocarcinoma:** Individuals infected with *H. pylori* have a risk of gastric adenocarcinoma (non-cardia) approximately eight times that of uninfected individuals.
- **MALT lymphoma:** This is a type of non-Hodgkin B-cell lymphoma affecting the lining of the stomach. Gastric mucosa usually lacks lymphoid tissue but its development is sometimes stimulated by *H. pylori* colonisation. This tissue can give rise to mucosa-associated lymphoid tissue (MALT) lymphoma and nearly all patients with this diagnosis are infected with *H. pylori*.

What is the mechanism behind the oncogenic potential of *H.pylori*?

There is a complex interplay between *H. pylori* and other components of the gastric microbiota, as well as host genetic polymorphisms and dietary factors, which determine the path to gastric cancer. An association has been made between cagA-mediated cytotoxin production, inactivation of tumour suppressor proteins and oncogenesis. Only cagA-positive strains of *H. pylori* have been associated with gastric cancer.

More recent evidence has established a link between chronic *H. pylori* infection, unremitting stem cell proliferation and carcinogenesis.

Does eradication of *H. pylori* reduce gastric cancer rates?

The role of *H. pylori* in the causation of gastric cancer raises the possibility of cancer prevention through screening and eradication. Long-term follow-up of patients who have received eradication treatment for *H. pylori* has been associated with a significantly higher rate of regression of precancerous lesions and a reduction in the incidence of gastric cancer.

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Diagnosis of *H. pylori* infection

1. Endoscopy and biopsy

The diagnosis of *H. pylori* can usually be established by endoscopy by one of three methods: direct urease testing, histology and bacterial culture.

- **Biopsy urease testing:** Antral biopsies can be tested for urease activity during the procedure, with a diagnostic sensitivity and specificity of approximately 95%.
- **Histology:** Histology of gastric biopsies not only detects *H. pylori* infection but also allows the diagnosis of associated gastritis, intestinal metaplasia and MALT lymphoma. While sampling variability may lead to occasional false-negatives (hence the recommendation for multiple biopsies), the diagnostic accuracy of histology is >95%.
- **Bacterial culture and sensitivity testing:** Rarely used for diagnosis but may guide antibiotic selection in cases of failed therapy.

2. Non-invasive methods (not requiring endoscopy)

These include urea breath testing (UBT), stool antigen testing and serology.

- **Urea breath testing:** A labelled carbon isotope is given by mouth; *H. pylori* liberates tagged CO_2 which can be detected in breath samples.

  There are two types of UBT, one using a ^{14}C isotope and the other ^{13}C, each with similar diagnostic accuracy. Limited availability of ^{13}C UBT has meant that the ^{14}C UBT is most widely used. The dose of radiation in the ^{14}C test is minimal (approximately 3 microSv) and equivalent to half a day's exposure to environmental radioactivity, such as sunlight. At such levels there is no theoretical reason for the test's unsuitability.

  The sensitivity and specificity of UBT are approximately 90–95% and 95–100%, respectively. False-negative results may occur in patients who are taking proton pump inhibitors (PPIs), bismuth or antibiotics. To reduce false-negative results, the patient should be off antibiotics for at least four weeks and off PPIs for at least one week. PPIs can be switched to H2 receptor antagonists until about six hours prior to the test.
- **Stool antigen assay:** *H. pylori* antigen is present in the stool of individuals with gastric colonisation and its detection is a sensitive and specific method for diagnosis. This approach is of particular use in patients who are unable (due to age or disability) to cooperate in performing a UBT. It is also the best alternative in patients who cannot fast for the required six hours before a breath test. The same requirement for antibiotic and PPI withdrawal prior to testing applies to antigen detection as it does to UBT.
- **Serology:** Detection of IgG antibodies to *H. pylori* has high sensitivity for past or current infection but cannot reliably distinguish between them. It is not recommended, either for routine diagnosis of infection or follow-up of therapy.

Confirmation of eradication

Confirmation of eradication should be considered for all patients receiving treatment for *H. pylori* because of the availability of accurate, non-invasive tests (UBT and stool antigen) and because of increasing antibiotic resistance.

Urea breath testing performed at least four weeks after treatment has been promoted as the test of choice to confirm eradication of infection. Stool antigen testing is an alternative where UBT is not available or not appropriate. Antibiotics and bismuth should be discontinued for at least four weeks and PPIs at least one week prior to testing.

Medicare rebate

The UBT is covered by Medicare for the confirmation of *H. pylori* colonisation and monitoring of the successful eradication of *H. pylori* .

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