

Helicobacter pylori—what do we know?

Helicobacter pylori is a Gram-negative bacterium that was discovered more than 15 years ago. We now know that this organism causes gastritis and peptic ulceration, and is an important factor in the causation of gastric cancer. When investigating any infection, one would be interested to know the nature of the infection; when and how to treat the infection; and how to prevent the infection. The nature of *H pylori* infection is peculiar. When *H pylori* infects a human, the infection is usually asymptomatic or may be mistaken for a case of 'stomach flu'; infection continues and is associated with the progression of gastritis. In susceptible hosts, mucosal damage and factors such as excessive gastrin and acid production result in peptic ulceration. The added effect of environmental factors means that the gastritis may progress to intestinal metaplasia, gastric atrophy, dysplasia, and possibly cancer of the stomach. Although some of the links remain to be proven, they act as useful working concepts in clinical management.

The seminar papers in this issue of the *Hong Kong Medical Journal* cover when and how to treat *H pylori* infection and whom to treat.¹⁻⁶ The seminar papers of Wu and Sung¹ and Ching and Wong² critically review whom should be treated for infections, and the key issues are well summarised in their tables. The guidelines have been drawn from three consensus meetings, two of which were from the West^{7,8}; the third was from the Asia-Pacific region.⁹ It is important to interpret recommendations at three levels before they can be applied to clinical practice. Firstly, when a recommendation is a complete consensus, as in the case of complicated or uncomplicated peptic ulceration; ulceration associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs); *H pylori*-positive ulceration; and mucosa-associated lymphoid tissue lymphoma and early gastric cancer, clinicians find no difficulty in making the decision to treat an infected individual by giving *H pylori* eradication therapy. Secondly, when the indications are advisable, such as prophylaxis for NSAID-users or when histological examination of the stomach shows precancerous changes, the data are conflicting but more inclined towards the eradication of *H pylori*. As Wu and Sung state, some of the scientific evidence is weak and some consensus statements have been derived from the voting by participants of consensus panels.¹ In these situ-

ations, it is important for clinicians to assess each patient—for example, to treat life-threatening complications, such as bleeding, and any other concurrent medical illnesses. Thirdly, when there is no real consensus, such as for the treatment of dyspepsia, it is reasonable to give *H pylori* eradication therapy after the conventional therapies for dyspepsia have failed. Two recent randomised placebo-controlled trials of *H pylori* eradication therapy to treat dyspepsia yielded conflicting results.^{10,11} And in the favourable study, symptomatic relief was achieved in only 27% of patients.¹¹ This form of therapy per se is thus unsatisfactory and its failure indicates that *H pylori* is unlikely to play a major pathogenetic role in dyspepsia.

The difficult question is whether eradication therapy should be given to people who are *H pylori*-positive, asymptomatic, and who have a healthy past history. The seminar paper of Ching and Wong² suggests that until results from intervention studies of the effect of eradication therapy on gastric cancer are known, it is inappropriate to give the therapy to all infected patients to try to reduce the risk of gastric cancer developing. This approach applies even when the histological examination shows premalignant gastric lesions such as intestinal metaplasia or gastric atrophy. What is scientifically correct may not be feasible clinically, and applying this treatment strategy to the local population may not be cost-effective. However, when individual patients ask for *H pylori* screening and the result is positive, they are counselled and offered eradication therapy. They are told that the Chinese population has a higher prevalence of gastric cancer, that *H pylori* is recognised by the World Health Organization as a major factor in carcinogenesis, that the side effects of eradication therapy are few and tolerable in most reported series, and that pseudomembranous colitis—the most serious complication of treatment—is very rarely reported. The final decision rests with the patient.

As to the choice of therapy, there is a good consensus that a proton pump inhibitor or ranitidine bismuth citrate, in combination with clarithromycin/metronidazole and amoxycillin for 1 week, is recommended for eradicating *H pylori*.^{1,4} In areas of high *H pylori* resistance to metronidazole, such as Hong Kong, inclusion of this drug should be avoided. Whether we

can shorten the duration or frequency of drug intake during the therapy awaits further studies.

The seminar paper on *H pylori* and gastric cancer by Wong et al⁶ describes the data on the epidemiology and pathophysiology of *H pylori* infection and its association with gastric carcinogenesis. The authors discuss whether eliminating *H pylori* can reduce the incidence of gastric cancer. Large-scale randomised studies are underway worldwide and the results are much awaited. However, one has to look ahead. Even if *H pylori* reduces the incidence of gastric cancer, the total screening and treatment of the infected population would be impractical. The identification of the high-risk population would be preferable—in other words, selective eradication. The timing of intervention would also be crucial, because the present evidence indicates that eradication of *H pylori* does not reverse atrophy and metaplasia. Cancer risk is significantly higher among younger patients who are infected with the bacterium¹² (odds ratios, 9.29 to 1.05). Furthermore, how to identify infected patients non-invasively—that is, without the use of the endoscope—is uncertain. An elevated serum pepsinogen level, which correlates with gastric atrophy, is a possible test but more studies are needed. Recent reports of the induction of gastric cancer and the enhancement of glandular gastric carcinogenesis by *H pylori* in Mongolian gerbils^{13,14} lend support to the important role of *H pylori* in carcinogenesis. Animal models provide a new area of study of the intervention of and multiple environmental factors involved in gastric carcinogenesis.

Helicobacter pylori seropositivity has been found to be associated with cardiovascular, respiratory, neurological, skin, autoimmune, and growth disorders.⁴ However, epidemiologists remind us that a statistical association between two factors does not imply a causal connection, especially when so many diseases are reported to be associated. Causality would depend on the consistency, strength, specificity, temporality, and coherence of the association. Consistency implies that *H pylori* is consistently demonstrated to be present in different populations and by using different methods of study. The strength of the evidence indicates that the risk factor is large and the specificity means that *H pylori* is present in most patients studied. Temporality means *H pylori* infection should consistently precede the occurrence of the disease. Coherence indicates that the basic pathogenetic factors and biology should lend support to the association and that eradication of *H pylori* should reduce or eliminate the occurrence of the disease. None of the diseases mentioned above fulfil these stringent criteria. More

studies are certainly needed before any useful clinical recommendations can be made.

Helicobacter pylori has excited both scientists and clinicians. Discovery of the organism has radically changed treatment strategies for diseases of the stomach. Although we now know how to treat the infection, the understanding of the biology of the infection and its long-term sequelae are yet to come in the next millennium.

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