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Who should be treated for *Helicobacter pylori* infection?

CK Ching, BCY Wong

***Helicobacter pylori* infection affects approximately half of the world's population. In Hong Kong, approximately 55% of the population is infected with this organism. But symptoms and clinical disease develop in only a minority of infected individuals during their lifetime. Treatment should thus be appropriately targeted. It is imperative that infected patients who have either a current or past history of peptic ulcer disease, with or without bleeding or a perforation complication, and those with low-grade gastric, mucosa-associated lymphoid tissue lymphoma should all have the organism eliminated. There is evidence that anti–*Helicobacter pylori* therapy reduces the recurrence of gastric cancer after the successful removal of early gastric cancer lesions. Patients with non-ulcer dyspepsia, particularly those with severe symptoms, should also be considered for a trial of eradication therapy. Whether or not eradication therapy should be given to those who require long-term non-steroidal anti-inflammatory drug therapy, but who do not have a history of peptic ulcer disease is still not decided. The use of prophylactic eradication to stop the development of gastric cancer or peptic ulceration in *H pylori*–positive but asymptomatic individuals should be considered only in research settings.**

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Introduction

If only there were a magic bullet that could eliminate the *Helicobacter pylori* bacterium without any patient side effects and be given at a low cost, there would be no need to give anti–*H pylori* therapy to specific patient groups. We could simply treat everyone. Since the discovery of this organism in 1983,[1] evidence has accumulated that confirms its association with certain upper gastro-intestinal tract disorders. However, there are other conditions for which only tenuous evidence is available to support its aetiopathogenetic role. This article reviews the current evidence using the Sackett scoring system[2] (Table 1) to establish in which patients anti–*H pylori* therapy should be imperative or beneficial and which patients who should not be treated.

Table 1. Sackett grading scale for ranking the reliability of clinical trial results[2]

Grade	Definition
A	Large, randomised controlled trial
B	Small, non-definitive randomised trial
C	Non-randomised study

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Natural history of *H pylori* infection

In a study of native American children, Perez-Perez et al[3] showed that once contracted, *H pylori* infection remains lifelong in the majority of infected individuals. Circulating immunoglobulin (Ig) G and IgM anti–*H pylori* antibodies are unable to defend the gastro-duodenal mucosa from the toxic effects of *H pylori.* As a direct or indirect result of this organism, different pathological entities evolve that result in clinical disorders. Some disorders have a significant impact on health and require intervention. However, most infected individuals remain asymptomatic and clinically disease-free. Guidelines have been established recently in North America,[4] Europe,[5] and the Asia-Pacific region[6]; they outline when antibacterial agents should be used to eliminate *H pylori* infection in different gastroduodenal disease subgroups. On the other hand, those who are *H pylori*–positive asymptomatic carriers should not be treated except under special circumstances.

H pylori *infection and associated pathological changes*

Correa[7] performed a cross-sectional and longitudinal follow-up study in Columbia and found that the prevalence of infection was high, at around 80% of the population. Subsequent surveillance of the participants and evaluation of the histopathological features of their gastric biopsies enabled the investigators to construct a hierarchy of pathological changes over a decade in the untreated, infected individuals.[7] It was found that *H pylori* infection continued to colonise the stomach and triggered the development of acute gastritis and then chronic superficial gastritis. In a proportion of the subjects chronic atrophic gastritis developed, with or without intestinal metaplasia, dysplasia, or carcinoma changes.

Numerous cross-sectional, case-control studies have demonstrated that *H pylori* infection is associated with an increased incidence of gastric carcinoma.[8-12] The best evidence for this comes from a number of longitudinal studies.[8-10] The overall increased risk has been estimated to be up to six times that of non-infected individuals. Studies from Scandinavia reveal that *H pylori* infection also increases the risk of peptic ulceration by five- to 15-fold after a mean follow-up period of 10 years.[13,14] It is still unclear whether *H pylori* has a significant clinical role in patients with functional dyspepsia, also commonly known as non-ulcer dyspepsia (NUD).

When is *H pylori* eradication therapy indicated?

H pylori *and peptic ulcer disease*

Approximately one in 10 adults develops peptic ulceration in their lifetime.[15] It is well known that peptic ulcers that are not induced by non-steroidal anti-inflammatory drugs (NSAIDs) or acute stress have a tendency to recur. Acid suppressor or mucosal protective agents have been used to prevent recurrence of peptic ulceration and peptic ulcer bleeding. However, it has been shown that peptic ulcer recurrence and bleeding still occur in 10% to 20% of individuals despite long-term maintenance therapy. Since documentation of the role of *H pylori* in peptic ulcer disease, therapeutic clinical trials have been conducted to evaluate the long-term outcome of eradication therapy in these patients. It has been demonstrated that not only do ulcers (duodenal or gastric) heal after the successful elimination of the organism, but also the relapse rate significantly reduces to approximately 6%.[16,17] A recent meta-analysis of all the well-conducted trials performed in the United States by Laine et al[18] has detected a 20% recurrence rate of peptic ulceration, rather than the reported rate of approximately 6%. In addition, the study confirmed that those who remain infected with *H pylori* have a five-fold increased risk of having a recurrence of peptic ulceration compared with those in whom *H pylori* is successfully eradicated. Patients who have had ulcer bleeding also have a significantly lower rate of relapse and recurrent bleeding when the organism has been cleared.[19-21]

Expert panels have recommended *H pylori*–positive patients with ulceration should have *H pylori* eradication therapy (Table 2).[4-6] The decision was based on numerous level-I randomised controlled trials that demonstrated beneficial effects.[22-27] Maintaining acid suppression after successful *H pylori* eradication therapy, even in those who have had prior bleeding or perforated ulcers, is now considered unnecessary. A recent randomised study by Maier et al[28] reported no recurrent bleeding in the *H pylori* eradication therapy group compared with a 12% rebleeding rate in the ranitidine maintenance therapy (*H pylori*–infected) group within 1 year of follow-up.

It has been repeatedly demonstrated that *H pylori* eradication therapy is significantly more cost-effective than either on-demand or maintenance acid suppression therapy for *H pylori*–infected patients who have a history of previous or current peptic ulcer disease.[29-31]

The development of mucosa-associated lymphoid tissue–type lymphoma

Gastric mucosa-associated lymphoid tissue (MALT)–

Table 2. *H pylori* eradication therapy recommendations for various gastroduodenal disease subgroups[4-6]

Gastroduodenal disease	Recommendation	Sackett grades
Peptic ulcer disease (active or past history)	Imperative	A
Peptic ulcer bleeding (active or past history)	Imperative	A
Low-grade gastric MALT* lymphoma	Imperative	C
Gastritis with severe unresponsive NUD†	Worth a trial	C
Following complete resection of gastric cancer	Worth a trial	C
Previous ulcer history requiring NSAIDs‡	Worth treating	C

* MALT mucosa-associated lymphoid tissue
† NUD non-ulcer dyspepsia
‡ NSAIDs non-steroidal anti-inflammatory drugs

type lymphoma has been shown to be strongly associated with *H pylori* infection.[32] Accordingly, successful eradication of the organism has been proven to cure the majority of cases of early-grade gastric MALT lymphoma.[33-35] Hence, patients with the latter condition should be treated with the appropriate *H pylori* eradication therapy and given appropriate follow-up to assess whether the eradication and elimination of the lymphoma cells has been successful (Table 2).[4-6] Higher-grade gastric MALT lymphomas, however, should receive additional therapy, since the majority cannot be cured by *H pylori* eradication therapy alone.

Patients in whom the eradication of *H pylori* can be beneficial (Table 2)

H pylori *infection and non-ulcer dyspepsia*

This is a grey area and no consensus agreement on the value of eradication of *H pylori* infection exists. A recent survey of gastro-enterologists in the United Kingdom revealed that the majority (69%) would advocate a trial of *H pylori* eradication therapy in patients with NUD despite the fact that 75% of the specialists disagreed that there was a relationship between the two.[36] Epidemiological evidence supports the view that *H pylori* infection and NUD are linked.[37] Therapeutic trials have been criticised for being flawed, which thus has affected the significance of the studies.[38] However, recent studies in the United States[39] and Taiwan[40] confirm that the successful eradication of *H pylori* infection leads to a significant reduction in NUD symptom scores.

Until further guidelines are available, it has been suggested that each case should be considered separately as to whether or not *H pylori* eradication therapy should be instituted. We consider that those who have had long-standing persistent or recurrent NUD symptoms that have not responded to conventional symptomatic therapy, should be given the benefit of such therapy. This approach was also endorsed by the panel of experts who met at the 1998 Asian-Pacific consensus meeting.[41] Although there is very little evidence that eradication of *H pylori* alters the underlying motility disorder, some patients may derive symptomatic improvement. Our own experience shows that the majority of these patients obtain significant symptomatic relief, although the improvements last for less than 6 months only (unpublished data). Approximately 60% of the patients did not require further medication. Of the balance, most patients required fewer medications to control their NUD symptoms.

H pylori *eradication therapy and early gastric cancer recurrence*

Japan is one of the leading countries with a high annual gastric cancer mortality rate. Consequently, mass screening is a common practice for those who are older than 40 years. As a result, early gastric cancers are regularly detected in a subgroup who are thus spared the need to undergo a formal gastrectomy. Instead, mucosectomy has been used to cure these patients. Adjunctive *H pylori* eradication therapy after mucosectomy reduces the recurrence of gastric cancer in patients in whom the organism has been successfully eradicated,[42] compared with those who have a mucosectomy only. Unfortunately, mass gastric cancer screening has not been proven useful or practical outside of Japan, where the incidence is high. Because gastric cancer is usually diagnosed at a late stage of disease, performing a mucosectomy is not a valid therapeutic option. Studies, however, have begun to see if the successful elimination of *H pylori* has any beneficial outcome in terms of survival after gastric cancer resection. The results of these studies are eagerly awaited.

Non-steroidal anti-inflammatory drugs, peptic ulcers, and H pylori *infection*

One of the main causes of ulceration in the stomach and the duodenum is the taking of NSAIDs. At the recent Asia-Pacific consensus meeting,[6] the possible additive harmful effect of NSAIDs and *H pylori* infection were discussed. It was unanimously agreed that routine testing for and treatment of *H pylori* infection is not to be recommended prior to initiating NSAID therapy. Recent preliminary therapeutic studies, however, demonstrate that by rendering patients *H pylori*–negative, there is a significantly lower risk of new or recurrent peptic ulceration and bleeding in patients who use NSAIDs.[43,44] On the other hand, the value of eliminating *H pylori* has also been challenged by others who have shown that *H pylori* and NSAIDs act negatively rather than synergistically to reduce peptic ulcer bleeding.[45]

It is generally accepted that patients who have a history of peptic ulcer, with or without bleeding, should be tested for *H pylori* infection. If the presence of the bacterium is confirmed, patients should be treated accordingly before NSAIDs are given. The Asia-Pacific Consensus Panel[6] decided that patients who require lifelong maintenance NSAID therapy should be tested and treated for *H pylori* infection if they have recent or current dyspepsia. Alternatively, these patients could be given lifelong treatment with omeprazole, which has been shown to be superior to both ranitidine or

misoprostol in healing and preventing the development of NSAID-induced peptic ulcers.[46,47] Lately, alternative NSAIDs, the cyclo-oxygenase (COX)-2 inhibitors, have become available. They are less likely to cause gastro-intestinal adverse effects when compared with the conventional NSAIDs, which are COX-1 inhibitors. It is not yet known if eradication therapy is beneficial for patients who are taking the COX-2 inhibitors.

Other conditions that might benefit from the eradication of *H pylori*

Treating those with premalignant gastric lesions

It has been suggested that premalignant gastric lesions such as dysplasia and intestinal dysplasia may be reversed after *H pylori* eradication therapy.[48,49] This is a very controversial area and many experts are sceptical that these results can be achieved.[50]

It is known that premalignant gastric lesions are associated with chronic *H pylori* infection. These lesions have also been shown to be linked to the gastric cancer prevalence in various regions of the world.[51] Hence, it is thought that *H pylori* plays a vital aetio-pathogenetic role in the malignant transformation of cells in the stomach. Thus, the World Health Organization has categorised *H pylori* as a class-I carcinogen.[52] Definitive proof of the relationship between *H pylori* infection and the development of gastric premalignant and malignant lesions will have to come from the results of current interventional studies in Japan and China. Until it can be shown that the prevalence of gastric premalignant and malignant lesions can be either halted and/or reduced by the successful eradication of *H pylori* from people living in areas with a high incidence of gastric cancer, such as Japan and certain provinces of China, it is inappropriate to treat all infected patients on the grounds that they may one day develop gastric cancer.

Family members of gastric cancer patients may be offered *H pylori* testing and appropriate treatment if they wish, but screening for *H pylori* infection in such individuals should not be recommended.

Should cagA–*positive* H pylori *be eliminated?*

Helicobacter pylori strains that bear the cytotoxin VacA and its associated *cagA* genes are with significant gastrodudoenal pathologies such as peptic ulcer, gastric cancer, and NUD. The presence of these pathogenic strains can now be readily detected by a serological assay[53] instead of the more tedious polymerase chain reaction techniques. Unfortunately, the majority (approximately 70%) of *H pylori* strains in south-east Asia are *cagA*-positive, which makes it difficult to distinguish the subgroups with disease from those who are asymptomatic carriers by using the serological assay alone. In a recent study, we demonstrated that more than 50% of symptomatic patients, were *cagA*-positive, but about 25% of the asymptomatic patients carried the same gene.[53] If we were to screen symptomatic patients with the anti-*cagA* assay and target therapy to those who were positive, we would only miss a small percentage of patients with ulcers (<10%) and approximately 50% of NUD patients. Whether treatment should be given to the latter patients is still undecided at this stage. If we take the extreme view that all *H pylori*–infected NUD patients should be treated, we will have undertreated half of these patients. On the other hand, if none of them should be treated, we will have overtreated half of these patients. Further studies are still required to help clinicians selectively target treatment towards those who most need it.

Patients in whom H pylori *eradication therapy is not indicated*

Helicobacter pylori has been incriminated as one of the possible aetiological factors in a variety of clinical diseases outside of the digestive system—for example, short stature in children, coronary artery disease, and autoimmune disease.[54] The evidence for such claims is weak and the link often is not substantiated by further studies. These patients should not be treated with *H pylori* eradication therapy if they do not have any history of peptic ulcer disease or significant NUD symptoms. Likewise, healthy, asymptomatic individuals and their relatives should not be treated or even tested for *H pylori* infection. However, there are exceptions because recent preliminary evidence suggests that spouses of *H pylori*–positive patients, particularly those who are symptomatic, are at significantly greater risk of being infected by the organism and of having a significant underlying gastroduodenal pathology themselves.[55,56] If the infected spouse of an index patient is not treated, there is a high probability that the patient will be reinfected at a later date and thus exposed to a greater risk of ulcer recurrence.

Conclusion

Table 3 and the Figure outline the approach we use to decide whom to test and treat for *H pylori* infection. Patients with proven gastric and/or duodenal ulcer disease and those with early-grade MALT lymphoma must be given *H pylori* eradication therapy as the

Table 3. Categories of patients who should and should not be tested for *H pylori* infection[4-6]

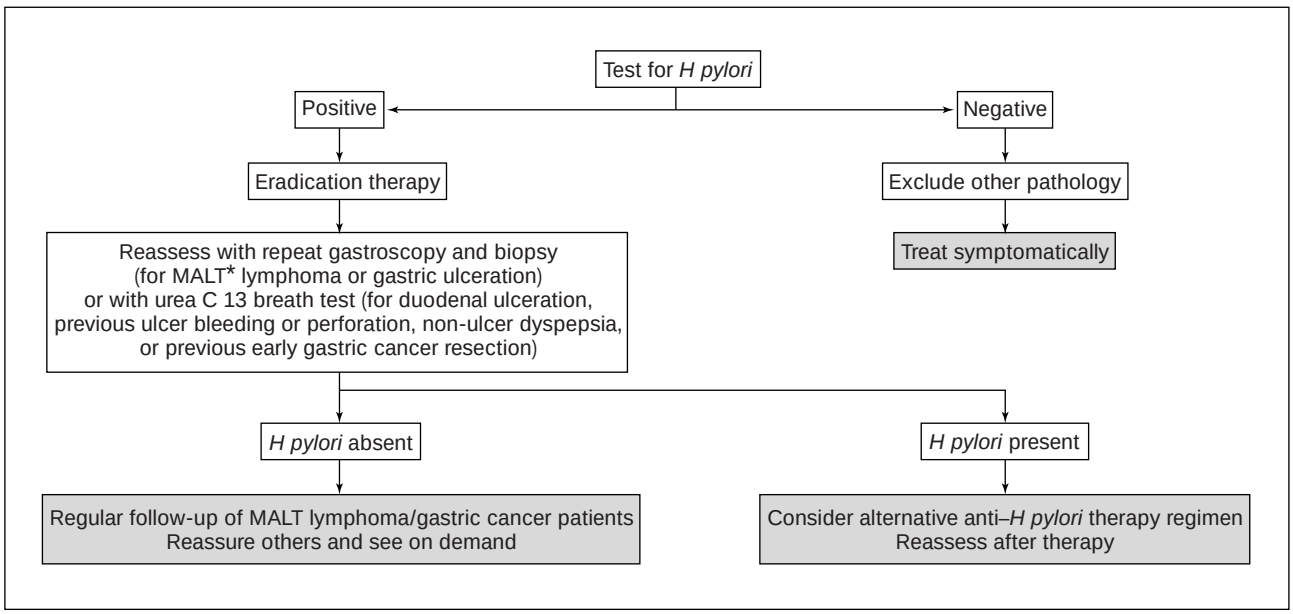
Yes	No
Active peptic ulceration	Asymptomatic individuals
Previous peptic ulcer bleeding or perforation	Family members of *H pylori*–positive patients
Confirmed MALT* lymphoma	
Following resection of early gastric cancer	
Patients with severe NUD†	
Previous peptic ulcer history requiring NSAID‡ therapy	
Current or recent dyspeptic history requiring long-term NSAID therapy	
Spouses of *H pylori*–positive patients	
Patient request after counselling	

* MALT mucosa-associated lymphoid tissue
† NUD non-ulcer dyspepsia
‡ NSAID non-steroidal anti-inflammatory drug

first-choice intervention. Proper follow-up to confirm that eradication and healing have occurred is essential. Failure to cure the infection is associated with a high risk of peptic ulcer recurrence, which in turn is accompanied by the need for further diagnostic tests, additional medication costs, time lost from work, and the risk of a life-threatening ulcer complication (1% annually).[15] Maintenance acid suppression is now outdated and should only be used in exceptional circumstances. The use of *H pylori* eradication therapy in patients with NUD, early gastric cancer, and post–gastric cancer resection subgroups remains controversial. Whether or not a course of anti–*H pylori* treatment is justified in such patients has to be made on an individual basis.

Prophylactic anti–*H pylori* therapy to prevent the development of gastric cancer or peptic ulcer is not justified at this stage but preliminary reports suggest that both gastric cancer[42] and peptic ulcer[57] prevalences have been reduced by eliminating the organism. In addition, the inappropriate use of *H pylori* eradication therapy may lead to the appearance of multidrug resistant strains, which are more difficult to eradicate. For example, it has been shown that in Hong Kong there was an approximately three-fold increase in the number of metronidazole-resistant *H pylori* strains over 5 years (from 1991 to 1995) since the introduction of metronidazole.[58]

Although our knowledge and understanding of the biology, genetics, and virulence of *H pylori* has greatly increased over the past decade, there is still no way of eliminating this organism for good. The solution will most likely come from the development of a vaccine such as the one that has been experimentally used in ferrets.[59] There are also some promising vaccine candidates on the horizon.[60] A vaccine would not only help to eradicate the bacterium, but would also help prevent infection and reinfection.



* MALT mucosa-associated lymphoid tissue

Fig. Management algorithm for patients with *H pylori*–associated pathologies

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