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The future of Helicobacter pylori *eradication: a personal perspective*

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SUMMARY

Future changes in the use of *Helicobacter pylori* eradication therapy first will involve a decision-making process to determine which individuals require testing. Clearly, only persons who require therapy need to be diagnosed and, at present, the indications for therapy are constantly expanding. The author takes the view that everyone with *H. pylori* would be better off without the bacterium, but accepts that in many countries resources are inadequate to achieve this goal.

Where antibiotic therapy for *H. pylori* fails due to a resistant organism, second treatment must include a different class of antibiotic. When a third therapy is contemplated, antibiotic sensitivity studies are usually necessary.

In developing counties where reinfection with *H. pylori* is common, lesser goals than permanent cure might be appropriate. Thus, selected patients could have *H. pylori* suppressive therapy to prevent full expression of *H. pylori*-associated disease, or to prevent reinfection after an initial eradicative therapy.

After considering all these alternatives, one must conclude that a vaccination strategy, if safe and cost effective, is the ideal future therapy.

INTRODUCTION

In 1997 it is widely accepted that antimicrobial therapy for *H. pylori* is necessary and beneficial in patients with known peptic ulcer disease. In some persons with upper gastrointestinal symptoms but no ulcer, *H. pylori* eradication may also lead to clinical improvement. Currently, there is no method which can identify responsive patients from those with incidental dyspepsia due to other conditions.

Independent of ulcer symptoms, there are good data at present to indicate a causative role for *H. pylori* in gastric adenocarcinoma. Therefore, persons with a family history of gastric cancer or high-risk ethnic groups, also require investigation and treatment of *H. pylori*.

In Western countries, the current therapies are cost effective, especially in an environment where long-term H_2 receptor antagonists have been used for peptic ulcer prevention. As *H. pylori* eradication therapy for non-ulcer dyspepsia has not been universally accepted, the issue becomes one of cost, i.e. is it worth carrying out invasive investigations in order to select out a few patients who actually have an ulcer crater? Alternatively, is it worth treating all *H. pylori*-positive patients with antibiotics in order to cure a few (10–20%) who actually have the peptic ulcer diathesis? The answers to these questions are determined by the relative costs of investigation and of therapy.

In developing countries the environment is often contaminated with *H. pylori* so that a high reinfection rate makes cure of *H. pylori* a temporary event. Therefore, three possible management strategies might be chosen, two of which are currently available. In the first strategy, therapy is prescribed only in severe cases of recurrent peptic ulcer or in gastrointestinal symptoms not responding well to alternative remedies. As so many people have *H. pylori* and are symptomatic already, this strategy is especially useful when medical resources are limited. Reinfections, when they occur, are re-treated in the same manner as primary infections.

In a second strategy, chronic inhibitory therapy could be given in order to prevent reinfection with *H. pylori* rather than to treat or suppress an active infection. In the third strategy, new infections are prevented and current infections are cured with an oral vaccine.

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WHERE ARE WE IN 1997?

The author's current indications for *H. pylori* therapy are listed in Table 1. Although many possible scenarios exist, the only widely accepted indications are those directly related to peptic ulcer or gastric malignancy.

In the case of peptic ulcer disease, numerous studies have confirmed that *H. pylori* eradication protects patients from ulcer relapse.[1–3] This was recognized by the NIH consensus panel, which in 1994 recommended that patients with peptic ulcer disease be tested for *H. pylori* and be treated for the infection if it is present.[4]

The NIH panel recommended that even patients with a known past history of peptic ulcer disease (inactive) should be tested for *H. pylori* and treated. They reasoned that ulcer relapse was almost inevitable in *H. pylori*-positive ulcer patients so that nearly all *H. pylori*-positive patients in remission would ultimately benefit from eradication.

Widespread implementation of the NIH recommendations will mean that most patients with significant recurring peptic ulcer disease will be cured over the next 5 years. Most of these patients have already been investigated and shown to have a duodenal or gastric ulcer. Therefore, no further investigation is necessary, other than the detection of *H. pylori*. Detection may be performed non-invasively using either a breath test or a serological test.

After treatment the necessity for follow-up to confirm cure is controversial. As the cure rate is high ($> 80\%$ with most therapies), we can expect that asymptomatic patients after therapy, who have ceased maintenance H_2 receptor antagonists, are free of *H. pylori*. In fact this has been born out by both the ulcer relapse studies and a recent paper by Phull *et al.*[5] Logically, patients with persisting symptoms must have a higher chance of failed *H. pylori* eradication. In these patients a urea breath test may be the simplest way to determine the effectiveness of therapy. If the detection rate of *H. pylori* is at least 30% in this group then the urea breath test may be cost effective. If these patients can be shown to have persistent lesions detectable by endoscopy, then EGD may also be an efficient follow-up method.

ANALYSIS OF PATIENTS WITH NON ULCER DYSPEPSIA

The importance of *H. pylori* in patients with non-ulcer dyspepsia is widely debated. Some studies have shown a benefit of *H. pylori* suppression,[6] others have not seen any benefit.[7] Talley *et al.*[8] remarked that most of the double-blind studies lacked sufficient power or had significant methodological errors which made it unlikely that they would detect an effect of *H. pylori* eradication, even where one existed. Taking into account the epidemiology of *H. pylori*, the author speculates that there must be at least three subgroups in any collection of patients with *H. pylori*-positive non-ulcer dyspepsia.

H. pylori-*positive non-ulcer dyspepsia–Group 1*

These are patients in whom acid secretion and mucosal damage are sufficient to produce duodenal or gastric ulcer but in whom an ulcer was not present on the day of endoscopy. Clearly these patients will have a relapsing and remitting clinical course similar to proven ulcer patients and would benefit from *H. pylori* eradication. As there is no perfect way of detecting these patients invasively or non-invasively, there is a case for giving all patients with non-ulcer dyspepsia a trial of *H. pylori* eradication to see if a clinical response occurs. Physiological studies of acid secretion and gastrin release[9] might be done to help select this responsive group but such studies are impractical in routine patient management.

H. pylori-*positive non-ulcer dyspepsia–Group 2*

These may be patients with symptomatic gastritis in whom a peptic ulcer will never occur. Individuals in the true non-ulcer dyspepsia group are sometimes very symptomatic and are expensive to investigate and treat. Examples are some patients with chronic nausea who have been noted to respond to *H. pylori* eradication.[10] Clearly, if *H. pylori* is causing symptoms, only *H. pylori* eradication will offer a cure. Most of these patients have already been investigated elsewhere and no treatable cause has been found. While irritable bowel and psychosomatic overlays are also common in gastroenterology patients, these conditions do not have a definitive diagnostic test or a curative therapy, so they will always be at the end of the diagnostic algorithm.[11]

As pointed out by Talley *et al.*,[6] double-blind studies to date have had inadequate power to exclude the possibility that a subgroup of patients with non-ulcer dyspepsia do respond to *H. pylori* eradication. Until this subgroup has been precisely defined or absolutely excluded, there will always be a case for a trial of eradication therapy for *H. pylori*, in patients with non-ulcer dyspepsia.

Table 1. Clinical situations in which therapy for *H. pylori* has been used and/or proposed

Indications	Action	Comments
Active peptic ulcer	Test for *H. pylori*, treat if present	Patient is symptomatic, compliance is high
Inactive (past) peptic ulcer	As for active ulcer	Patient asymptomatic, probably on H_2RA
Non-ulcer dyspepsia (implies absence of peptic ulcer at endoscopy)	If investigation has ruled out an ulcer, treatment of *H. pylori* is optional. Alternatively, if ulcer symptoms are present clinically, investigation is optional	Patients with non-ulcer dyspepsia have not been proven to benefit from eradication of *H. pylori* but clinical trials so far have been inadequate
Gastric adenocarcinoma	Eradication of *H. pylori* may protect the patient from future adenocarcinoma if the initial lesion is completely resected	*H. pylori* eradication is worthwhile when curative resection of cancer has been performed (e.g. lesions detected in surveillance programmes)
Atrophic gastritis (intestinal metaplasia)	As for resected gastric cancer (see above)	Proof that eradication of *H. pylori* in patients with atrophic gastritis will prevent adenocarcinoma is not available
Family history of gastric cancer	Implies that the patient has been exposed to both genetic risk and possibly also a 'carcinogenic' strain of *H. pylori*	Eradicate *H. pylori* regardless of symptoms
Proton pump inhibitors	As for atrophic gastritis (above). *H. pylori* may need to be treated before long–term therapy with a proton pump inhibitor is undertaken	Proton pump inhibitors may accelerate the development of atrophic gastritis when *H. pylori* is present[27]
MALT lymphoma	When the lymphoma is confined to the stomach and of low grade, eradication of *H. pylori* is the initial goal of therapy	Expect at least 50% of patients to have clinical cure. Endoscopic follow-up is recommended for 5 years
Incidental *H. pylori*	Patients are tested for *H. pylori* only when there is a clinical indication for therapy	Once *H. pylori* has been detected, the physician is probably obliged to offer the patient eradicative therapy
Immigrants	Immigrants from Mediterranean countries, Eastern Europe, Latin America and Asia have more than 50% prevalence of *H. pylori* and are likely to maintain a level of *H. pylori* associated disease in their adopted country. Screening for *H. pylori* in these persons would have a high detection rate and therapy for detected *H. pylori* would be an option	Many practical difficulties exist in the diagnosis and treatment of *H. pylori* in asymptomatic persons
Adopted children	Adopted children from Eastern Europe and Asia, are likely to be infected with *H. pylori*. They may carry the infection into immunologically naive families. Children may 'amplify' the infectivity of *H. pylori* in families[28]	Diagnosis and treatment of *H. pylori* in asymptomatic children is also likely to be problematic
Rosacea	Anecdotal reports of benefit in some patients await confirmation in properly designed studies	In any chronic disease of unknown aetiology, this author believes that proven *H. pylori* should be eradicated if therapy is convenient
Coronary artery disease	In several studies *H. pylori* was associated with increased risk of myocardial infarction.[29] *H. pylori* has also been linked to chronic elevation of C-reactive protein,[30] a known risk factor for atheroma	Declining prevalence of *H. pylori* in developed countries parallels a decline in myocardial infarction over the past 20 years. At present a mechanism has not been defined and the association could be related to lower socioeconomic status in persons with *H. pylori*
Halitosis	Anecdotal evidence from several independent investigators describes resolution of halitosis in patients treated for *H. pylori*	Therapy for *H. pylori* is likely to benefit periodontal and oropharyngeal disease as both metronidazole and clarithromycin are effective against anaerobes and are secreted in saliva

H. pylori-*positive non-ulcer dyspepsia–Group 3*

Depending on the prevalence of *H. pylori* in the general population, the proportion of patients with coincidental asymptomatic *H. pylori* gastritis will vary. For example, in Latin America as many as 80% of patients attending any clinic will have *H. pylori* infection. It follows, therefore, that in a group of patients with non-ulcer dyspepsia, many will have *H. pylori* by sheer coincidence. In a developed country, a similar scenario might exist in a public hospital clinic where patients from lower socio-economic groups predominate.

For example, we noted that the seroprevalence of *H. pylori* infection in the University of Virginia General Medical Clinic was approximately 50% regardless of age, gender or ethnicity (Marshall BJ, unpublished 1992). In contrast, *H. pylori* prevalence was only 25% in blood donors, who tended to be middle-class individuals.[12] It appears that greater power to detect any effect on non-ulcer dyspepsia would occur in a study of patients from the latter group in whom the chance of 'coincidental asymptomatic' *H. pylori* would be low.

WHO WILL WE DIAGNOSE?

An algorithm for the treatment and follow-up of *H. pylori* therapy is shown in Figure 1. Initially patients are suspected of having *H. pylori* on the basis of a clinical presentation of upper gastrointestinal symptoms. For example, if peptic ulcer is in the differential diagnosis, then the patient is a candidate for *H. pylori* testing. Most patients with peptic ulcer will already carry the diagnosis from previous investigations and therefore will not require further invasive or barium studies. Moreover, if the physician intends to confirm all new cases of peptic ulcer before proceeding he must recognize that symptomatic therapy prescribed while waiting for endoscopy will encourage ulcer healing and decrease the chance of detecting an ulcer. Thus, unless the patient agrees not to take H_2 receptor antagonists, and the endoscopy is very soon, the bona-fide ulcer patient may be labelled as 'non-ulcer dyspepsia' after a negative endoscopy.

In the 1990s, therefore, it is natural to allow mostly clinical diagnosis of peptic ulcer and to offer antibiotic therapy to all patients with a positive test for *H. pylori*. Doctors who choose to treat *H. pylori* on clinical grounds must accept, however, that many of the *H. pylori*-positive 'ulcer patients' do not actually have ulcer disease and will not see the excellent clinical response reported in trials of duodenal ulcer.

OUTCOME OF INITIAL THERAPY IN PROVEN ULCER PATIENTS

The expected effect of treating 100 patients with duodenal ulcer is shown in Figure 2. The proportions reflect a therapy in 100 patients all of whom have *H. pylori* initially, but in whom only 80 are cured of the infection.

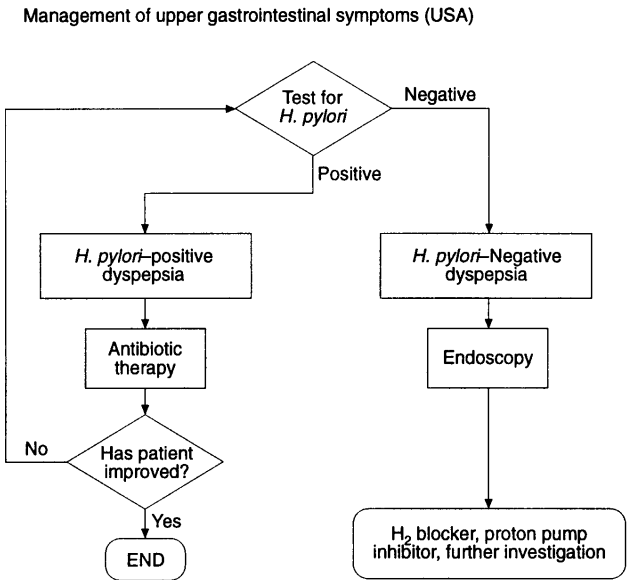

Figure 1. Treatment and follow-up of *H. pylori*.

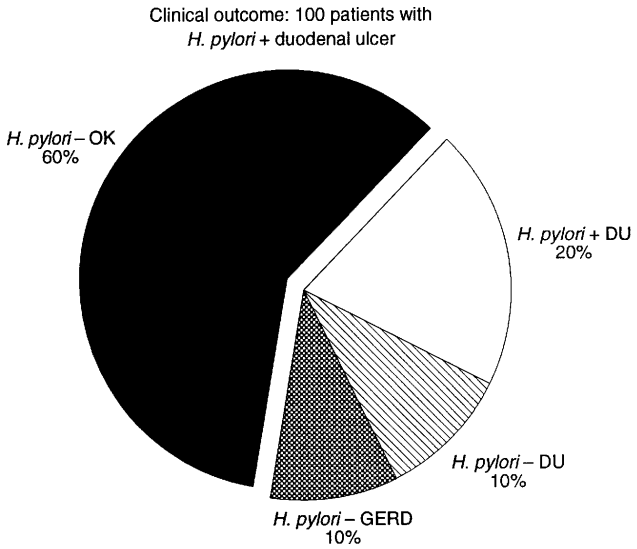

Figure 2. Likely outcome of patient with duodenal ulcer after cure of *H. pylori*.

Thus, 20 patients who are still *H. pylori*-positive will have continuing peptic ulcer disease and will eventually relapse. Of the remaining 80, up to 10% will have continuing *H. pylori*-negative ulcer disease[13, 14] and 10% will have continuing need for acid reduction because of gastroesophageal reflux disease (GERD). Thus, after typical therapy, one third of patients will require follow-up because of continued presence of *H. pylori* and/or other gastrointestinal disorders. This symptomatic state will require a test to confirm cure of the *H. pylori* triggering further investigation of patients who are *H. pylori*-negative.

CHOICE OF SECOND THERAPY

When *H. pylori* is still present, the patient will probably require further therapy to eradicate the bacterium. The therapy chosen will depend on what antibiotic exposure the patient has had in the past. For example, a previous treatment with metronidazole would make this antibiotic relatively useless in a second combination because metronidazole therapy almost always leads to metronidazole resistance in surviving Helicobacters. Similarly, initial therapy with clarithromycin alone results in at least a 50% conversion to a macrolide resistant strain[15] leading to poor cure rates with a second course. If patients have been given both these antibiotics in an initial therapy then the organism might be twice as resistant after just one course of treatment.

WHEN ALL ELSE FAILS

Possible options in patients with multiply resistant H. pylori

Ultimately a few patients will have *H. pylori* which is impossible to eradicate. If the symptoms are mild then acid reduction or other symptomatic therapy will leave these patients no worse off than the average ulcer patient treated before 1995. If symptoms are severe or complications have occurred then suppression of *H. pylori* might be a useful addition to H_2 receptor antagonist therapy. For example, phenoxymethyl penicillin (Penicillin V) has been shown to maintain ulcer remission,[16] and persons with rheumatic fever have taken this drug long term without ill effects. Similarly, chronic therapy with doxycycline has been used in dermatology clinics for acne and this type of once daily therapy is convenient to take. While doxycycline does not usually eradicate *H. pylori*, it is secreted in bile so would be particularly effective in patients with bile reflux such as patients with past partial gastric resection.[17] Other options for chronic therapy include furazolidone which has been shown to suppress *H. pylori* with frequent small doses.[18] Because these patients are uncommon, clinical trial data for suppressive therapy is presently unavailable.

OPTIONS FOR PREVENTION OF REINFECTION WITH *H. PYLORI*

When patients fail therapy, it is worthwhile to evaluate the sensitivity of the organism. Continuing infection with an organism sensitive to metronidazole probably indicates that reinfection has occurred from the patient's spouse or other family member. In this circumstance the author screens for *H. pylori* in immediate family members and treats both the patient and infected family members simultaneously.

In developing countries such as Peru, attempts to eradicate the organism may fail because of rapid reinfection from environmental sources such as the water supply.[19] Although not proven to be of use, there may be a role for prophylactic therapy with low-dose bismuth or antibiotic to prevent re-colonization of the patient. Small amounts of antibiotics such as penicillin or tetracycline might be used to protect susceptible patients from *H. pylori* reinfection. Obviously this would only be considered in patients with severe complicated peptic ulcer disease who do not respond to acid reduction and the potential benefit of *H. pylori* suppression would have to be weighed against disadvantages. For example, low-dose antibiotics will generate a resistant bacterial flora in the gut, cause antibiotic side-effects and, in the case of bismuth therapy, could cause toxicity from heavy metal accumulation.

OPTIONS FOR PROTECTION FROM IATROGENIC INFECTION

In some areas where endoscope washing machines and sterilizing solutions are too expensive or unavailable, reinfection at follow-up endoscopy is possible.[20] In these circumstances the author has used a single dose of antibiotic or bismuth immediately after endoscopy. An example of such a therapy is 500 mg of a bismuth salt (bismuth subsalicylate or colloidal bismuth subcitrate). Ampicillin, nitrofurantoin or tetracycline could also

be used. In clinical trials of therapy, the urea breath test would be a first choice for follow-up rather than endoscopy.

PROGRESS TOWARDS A VACCINE TO PREVENT AND CURE *H. PYLORI* INFECTION

If it proves to be impossible to eliminate *H. pylori* organisms from the environment, a vaccine might be the best way to prevent new infections and reinfections. Once the population has been vaccinated, eradication of *H. pylori* would again bring about permanent cure of peptic ulcer, even in a developing country.

The pessimist's view is that life-long chronic infection with *H. pylori* causes high antibody levels, but fails to protect against reinfection. Therefore, artificial *H. pylori* infection (a vaccine), would also be unlikely to affect the chance of reinfection.

The optimist's view is that animal models of *H. pylori* infection have already shown that it is possible to prevent new infections and cure some established infections. The simplest animal model is the *H. felis*-infected mouse of Adrian Lee's group at the University of New South Wales.[21] In this model, mice are infected with a spiral Helicobacter from cat stomach by oral inoculation. A stable infection develops with antibody production and chronic gastritis. The infection is not transmitted between animals so is quite easy to study in mice housed together. Protection can be demonstrated when the animals are fed urease together with cholera toxin as a mucosal adjuvant. In addition, immunization of already infected animals can cause eradication of established infection.[22]

Some toxin-producing strains of *H. pylori* can also infect mice, and lead to a type of active chronic gastritis.[23] Again, when *H. pylori* antigens are administered with cholera toxin adjuvant, mice can be protected and the infection can be cured. So far, relatively large doses of cholera toxin adjuvant have been used in mice, so these experiments may not translate to effective regimens for humans. One approach is to use an engineered cholera toxin subunit which provides antigenicity, but avoids toxicity.

At present very few data have been presented on the use of these vaccines in humans. It appears that antibody does develop after oral ingestion,[24] but therapeutic and prophylactic trials in infected patients have not yet been reported. This strategy for *H. pylori* control may take another 5–10 years to develop.

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