

Treatment of *Helicobacter pylori*

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Subject headings *Helicobacter pylori*/pathogenicity; *Helicobacter* infections/therapy; peptic ulcer/microbiology

Harris A. Treatment of *Helicobacter pylori*. *World J Gastroenterol*, 2001; 7(3):303-307

INTRODUCTION

Using an evidence-based approach this review discusses the current treatment of *Helicobacter pylori* infection in patients with peptic ulcer disease, functional (non ulcer) dyspepsia or gastro oesophageal reflux disease (GORD). It also briefly addresses the potential role of eradication of *H. pylori* in preventing gastric cancer.

PATIENTS WITH DUODENAL ULCER DISEASE (DU)

In a patient with a well documented DU, who is not taking non steroidal anti-inflammatory drugs (NSAIDs), *H. pylori* may either be assumed to be present (more than 90% prevalence) or may be confirmed at endoscopy by tissue biopsy (for rapid urease test, histology or microbiological culture). *H. pylori* eradication therapy (see below) may then be prescribed. *H. pylori* eradication therapy, if successful, will be effective in healing the ulcer regardless of whether the patient is seen at the initial presentation of the disease, or at a recurrence^[1]. Patients on long-term treatment with histamine-2 receptor antagonists (H₂RAs) or proton pump inhibitors (PPIs) for DU should also be offered *H. pylori* eradication treatment, regardless of whether they are symptom-free, or still experiencing symptoms, because eradication of the bacterium will cure the disease^[1].

DUs heal quickly and completely after eradication of *H. pylori*, so that a separate healing course of anti-secretory therapy is unnecessary in an uncomplicated ulcer^[2,3]. After a course of eradication therapy it may be acceptable to await the clinical outcome, i.e. an improvement in symptoms, rather than to formally test for the presence or absence of *H. pylori*. Recurrence of symptoms signifies either failure of *H. pylori* eradication, or the "unmasking" of some other disease, for example, GORD^[4]. In such cases, further management will not be clear unless the outcome of eradication therapy is known. The best way to determine this is either through the ¹³C-urea

breath test (¹³C-UBT) or possibly, a faecal antigen test, performed no sooner than four weeks after eradication therapy^[5].

COMPLICATED DU

Complications of DU such as bleeding or perforation are associated with appreciable morbidity and mortality, especially in the elderly. There is good evidence that eradication of *H. pylori* decreases the risk of re-bleeding and re-perforation from DU^[6]. In such patients *H. pylori* eradication therapy should be followed by treatment with an H₂RA (such as ranitidine 300 mg at night) for a further four weeks until either repeat upper g.i. endoscopy with biopsies to confirm re epithelialisation of the ulcer crater and to assess *H. pylori* status, or a ¹³C-UBT. If *H. pylori* has been successfully eradicated (and the patient is not taking NSAIDs) anti-secretory therapy is no longer needed. The prevalence of *H. pylori* in patients with complicated DU may be lower than that in patients with simple DU and it is therefore important to confirm that the patient is colonised with the bacterium before prescribing eradication therapy and stopping anti-secretory medication^[7].

GASTRIC ULCER

The main point of difference in the management of a patient with *H. pylori* associated GU is the need to exclude malignancy in an apparently benign GU. Patients with GU should therefore be re-endoscoped about 8 weeks after *H. pylori* eradication therapy to confirm healing, obtain further biopsies if re-epithelialisation is incomplete and to ascertain *H. pylori* status.

Eradication of *H. pylori* leads to healing of GU and markedly decreases the incidence of relapse^[1,8]. The effect of eradication of *H. pylori* on GU complications is unknown at present. Anti secretory maintenance treatment should therefore be started after successful eradication of *H. pylori* in those patients with GU who have a history of haemorrhage or perforation, until complete healing of the ulcer is confirmed at follow up endoscopy.

H. PYLORI AND NSAID-ASSOCIATED ULCER

Despite several studies, no clearly defined guidelines about the relationship between NSAIDs, gastro-duodenal ulceration and *H. pylori* have emerged^[9,10]. NSAIDs and *H. pylori* appear to be independent risk factors for gastro-duodenal ulceration and ulcer bleeding. There is some evidence that *H. pylori* eradication may prevent the development of ulcers in patients starting

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Received 2001-03-20 Accepted 2001-04-15

NSAIDs^[10]. However there is other evidence that *H. pylori* associated gastritis may even be beneficial, because of prostaglandin release protecting against mucosal injury by NSAIDs^[9]. Indeed it appears that NSAID associated ulcers heal more rapidly after treatment with PPI in the presence of *H. pylori*^[9]. In a *H. pylori* positive patient with a history of peptic ulcer disease, *H. pylori* should be eradicated before starting treatment with NSAIDs because the NSAIDs may increase the likelihood of ulcer relapse^[9]. There is no evidence that eradication of *H. pylori* is of benefit in decreasing the dyspepsia associated with treatment with NSAIDs^[9].

H. PYLORI AND GASTRIC CANCER

Infection with *H. pylori* is associated with a three to six fold increase in the risk of developing non-cardiac (body and antrum) stomach cancer^[11]. Although prevention of gastric cancer through eradication of *H. pylori* is potentially extremely important in global terms (750 000 deaths attributable annually to the neoplasm), it must be emphasised that, at present, there is no evidence that eradication of *H. pylori* decreases that risk. Nor is it known at what stage *H. pylori* has to be eradicated to prevent the progression of chronic gastritis to atrophy, intestinal metaplasia, dysplasia and eventually to invasive cancer. Although infection with *H. pylori* is very common, the life-time risk of developing non-cardiac stomach cancer in infected individuals in the developed world is estimated to be less than 1%^[11]. In subjects with other risk factors for stomach cancer, such as one or more first degree relatives with this condition, or the presence of gastric mucosal dysplasia or intestinal metaplasia found at gastroscopy, it seems reasonable to offer *H. pylori* eradication therapy. It is important however to discuss with the patient the possible side effects of the treatment, the lack of evidence to support this practice and the possibility of treatment failure.

PATIENTS WITH FUNCTIONAL DYSPEPSIA AND H. PYLORI INFECTION

Functional dyspepsia is defined as pain or discomfort in the central upper abdomen which originates in the upper gastrointestinal tract, which has been present for at least three months and in the absence of organic disease, such as peptic ulcer or GORD^[12]. This diagnosis accounts for up to 60% of patients with non-NSAID associated dyspepsia^[13]. The evidence for an association between *H. pylori* and functional dyspepsia is uncertain. Several well designed, randomised and controlled trials assessing the efficacy of *H. pylori* eradication treatment in patients with functional dyspepsia have been published in the past three years but have produced discordant results^[13-16]. A recent systematic review has found that eradication of *H. pylori* was

significantly superior to placebo in treating functional dyspepsia (relative risk reduction 9%, 95% confidence interval 4%-14%) suggesting that one case of dyspepsia would be cured for every 15 patients treated^[17]. The mechanism by which eradication of *H. pylori* decreases dyspepsia in these patients is unclear. It is possible that the patients that benefited may have had an ulcer diathesis which was not active at the time of endoscopy.

PATIENTS WITH GORD

There is unequivocal evidence that infection with *H. pylori* is the principal cause of peptic ulcer disease and there appears to be a small, but definite association between the bacterium and functional dyspepsia^[1,17]. The relationship between *H. pylori* and GORD is however still unclear^[18,19].

The prevalence of *H. pylori* is not increased and may actually be decreased in patients with GORD^[20]. Recent studies have reported that significantly fewer patients with GORD are infected with *H. pylori* than healthy, age and sex matched individuals^[20,21]. More importantly, there appears to be a negative correlation between the prevalence of *H. pylori* infection and the severity of oesophagitis; patients with erosive (grade III) oesophagitis or Barrett's columnar lined oesophagus are significantly less likely to be infected with *H. pylori* than patients with either a normal oesophagus or milder degrees of oesophagitis^[22,23]. This inverse relationship has been further assessed according to the subtypes or strains of *H. pylori*; patients with *cagA* positive strains appear to be significantly less likely to develop erosive oesophagitis or Barrett's oesophagus^[24-27]. Furthermore the prevalence of *cagA* positive strains appear to be significantly less frequent in patients with oesophageal adenocarcinoma or dysplasia, conditions which may result from longstanding and severe GORD^[25].

ERADICATION OF H. PYLORI AND GORD

There is no convincing evidence that GORD improves after eradication of *H. pylori*^[18,19]. There is conflicting data regarding the development of GORD following eradication of *H. pylori*. Some studies have found that patients develop endoscopic oesophagitis after eradication of *H. pylori* either for duodenal ulcer disease or functional dyspepsia^[28-30] but these findings were not confirmed in another study^[31]. The prevalence of heartburn does not appear to increase between 6 months and 3 years after eradication of *H. pylori* in patients with either functional dyspepsia, GORD or DU disease^[32-36].

Another reason to carefully evaluate the role of *H. pylori* eradication therapy in patients with GORD is the recent finding that the treatment of GORD may be more effective in the presence of the

bacterium: pantoprazole was significantly more effective at healing the oesophagus in the presence of *H. pylori*^[37]. It was found that healing of oesophagitis (grades II and III) was significantly greater after 4 and 8 weeks treatment with pantoprazole in *H. pylori* positive patients compared with *H. pylori* negative patients. On that point, anti-secretory therapy also appears to more effective in the presence of *H. pylori* in patients with functional dyspepsia^[38]. The exact mechanism for these most interesting findings is unclear at present.

Patients with GORD and *H. pylori* infection who need prolonged treatment with standard or high doses of PPIs, according to one uncontrolled study, may be at increased risk of developing atrophic gastritis^[39]. During profound acid suppression with PPIs *H. pylori* may migrate from the antrum to the more proximal parts of the stomach leading to chronic active corpus gastritis which may progress to atrophic gastritis, which is associated with increased risk of carcinoma^[40]. The latter changes do not occur with profound acid suppression in patients without *H. pylori* infection. It has therefore been recommended that patients with GORD who need prolonged treatment with a PPI should have their *H. pylori* status determined and if positive, eradication therapy should be given. This recommendation is based on hypothesis, rather than on scientific evidence, and it has to be borne in mind that *H. pylori* eradication may render PPIs to be less effective^[37,38]. Further studies are needed before these contradictory considerations can be resolved^[41].

H. PYLORI/ERADICATION TREATMENT

The aim of treatment of *H. pylori* in any therapeutic context is eradication of the organism from the foregut. Eradication is defined as negative tests for the bacterium four weeks, or longer, after the end of antimicrobial therapy^[42]. Failure to detect *H. pylori* on tests done less than four weeks after the end of therapy may give false negative results because clearance, or uppression of *H. pylori* may occur during treatment, followed by rapid recrudescence of the original infection.

Antibacterial treatment of *H. pylori* is difficult because of the very rapid development of resistance to anti microbial agents, especially to nitroimidazoles, such as metronidazole and tinidazole, and clarithromycin^[41]. The prevalence of resistance to these anti-microbial agents varies with gender, ethnic group and country of origin (Table 1)^[41]. It was recently reported from Hong Kong that almost 50% of pre-treatment strains of *H. pylori* were resistant to metronidazole and over 10% to clarithromycin^[42]. The efficacy of treatment for *H. pylori* is significantly decreased in the presence of pre-treatment anti-microbial resistance and the likelihood of this should influence

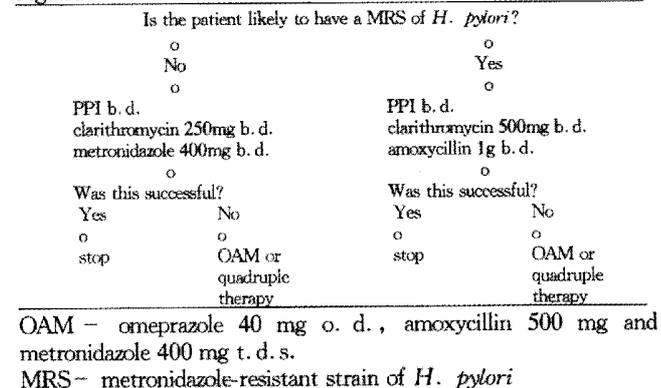
the chosen regimen (Table 1, Figure 1)^[5,41].

Monotherapy or dual therapy (PPI or ranitidine bismuth citrate (RBC) with an antibiotic) cannot be recommended and should not be used because of inconsistent and highly variable results^[5,41].

Table 1 Risk factors for nitroimidazole resistance in *H. pylori*

- Previous use of nitroimidazoles, e.g. gynaecological infections, infective diarrhoeas
- Failed *H. pylori* eradication regimen containing a nitroimidazole
- Urban or inner city areas
- Patients born in emergent countries

Figure 1 How to choose a one week *H. pylori* eradication regimen



LOW-DOSE TRIPLE THERAPY

The most overall effective *H. pylori* eradication regimens reported to date combine either a PPI (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) or RBC with two of the following: amoxycillin, clarithromycin, or a nitroimidazole (metronidazole or tinidazole)^[5,42,43-49] (Table 2). These regimens are commonly prescribed for one week and the tablets are taken twice daily. There are few side effects (the most common are nausea, diarrhoea and taste disturbance). Results from large, randomised and controlled trials have consistently shown *H. pylori* eradication in about 90% of treated patients^[44,46-49].

Table 2 Low dose triple therapy

Therapy	PPI or RBC Amoxycillin Clarithromycin	PPI or RBC Clarithromycin Metronidazole
Dosing	b.d. 1 g b.d. 500 mg b.d.	b.d. 250 mg b.d. 400 mg b.d.
Duration		One week
Side effects	Nausea, diarrhoea,	taste disturbances
<i>H. pylori</i> eradication	90%	90% in MSS 75% in MRS

PPI- proton pump inhibitor; RBC- ranitidine bismuth citrate; b.d.- twice daily;

MSS- metronidazole-sensitive strain of *H. pylori*;

MRS- metronidazole-resistant strain of *H. pylori*

A one week course of omeprazole 40 mg once daily in combination with amoxicillin 500 mg and metronidazole 400 mg three times daily has been shown to be effective even in the presence of pre-treatment metronidazole resistant strains (MRS) of *H. pylori*, with 75% eradication^[50]. Side effects are more common and compliance more complex than with the twice daily regimens, so that this regimen is best reserved for first line treatment failures (Figure 1).

CLASSICAL TRIPLE THERAPY

Bismuth based triple therapy was the first multi drug treatment to be widely investigated and used in clinical practice. Originally, it consisted of 14 days treatment with colloidal bismuth subcitrate 120 mg qds, together with metronidazole 400 mg tds and either amoxicillin, or tetracycline 500 mg qds. Unfortunately side effects are frequent and the regimen is complicated to follow with more than 11 tablets to be taken daily. Furthermore, the efficacy of the triple therapy is dependent on the susceptibility of *H. pylori* to metronidazole, with eradication in only 50% of those patients who are colonised by a metronidazole-resistant strain of *H. pylori*^[5,41].

QUADRUPLE THERAPY

Classical bismuth-based triple therapy has been reported to be more effective when co-prescribed with a PPI. More than 90% *H. pylori* eradication is possible with a combination of omeprazole, colloidal bismuth subcitrate, tetracycline and metronidazole given for 7 days^[5,41,51,52] (Table 3). Efficacy is highly dependent on patient's compliance with the complicated prescription. Furthermore, these quadruple regimens have been shown to work in 75%-80% of patients who failed first line eradication therapy with metronidazole and/or clarithromycin containing regimens^[51,52].

Table 3 Quadruple therapy

Therapy	Omeprazole Colloidal bismuth subcitrate Tetracycline Metronidazole
Dosing	o.d. 120 mg q.d.s. 500 mg q.d.s. 400 mg q.d.s.
Duration	One week
Side effects	Common: nausea, diarrhoea, taste disturbances
<i>H. pylori</i> eradication	>75% in MRS >90% in MSS

o.d.- once daily; q.d.s.- four times daily;
MRS- metronidazole-resistant strains of *H. pylori*;
MSS- metronidazole-sensitive strains of *H. pylori*

FIRST-LINE TREATMENT (FIGURE 1, TABLE 2)

In areas with low (<30%) prevalence of pre treatment metronidazole-resistant strains of *H. pylori*, a one week triple therapy regimen consisting

of a PPI, metronidazole and clarithromycin is recommended at present. Patients' compliance is likely to be good because of twice daily dosing and few side effects. If metronidazole resistance is likely (Table 1), a PPI in combination with amoxicillin and clarithromycin given for one week is preferable (Table 2).

SECOND-LINE TREATMENT (FIGURE 1, TABLES 2,3)

After a proven failure with a regimen containing metronidazole, the patient is likely to be colonised by a metronidazole-resistant strain of *H. pylori*. In this case, a PPI in combination with amoxicillin and clarithromycin given for one week should be used, with around 90% success. If *H. pylori* eradication is unsuccessful after a clarithromycin- and metronidazole-containing regimen or the patient is likely to harbour a pre-treatment metronidazole resistant strain of *H. pylori*, then either omeprazole in combination with amoxicillin and metronidazole^[50] or quadruple therapy are the only logical options (Table 4), with approximately 75% success^[51,52].

Table 4 Current indications for *H. pylori* eradication therapy

Diagnosis	Established evidence-based indications
Non-NSAID DU	+
Non-NSAID GU	+
NSAID DU or GU	-
Functional dyspepsia	+ or ?
GORD	-
Risk of gastric cancer	+ or ?
MALT lymphoma	+

Key: +, good/excellent evidence in favour of treatment;
-, unclear or negative outcome from treatment;
?, equivocal or mild benefit in favour of treatment

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