Treatment of *Helicobacter pylori* infection

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The availability of clinic-based diagnostic tests means that screening for and the eradication of *Helicobacter pylori* can be done by primary care physicians. However, confusion still exists regarding the indication and treatment regimens. It is universally accepted that patients with *Helicobacter pylori* infection and peptic ulcer disease require eradication therapy. But the benefits of *Helicobacter pylori* eradication in gastro-oesophageal reflux disease, non-steroidal anti-inflammatory drug–related peptic ulceration, and non-ulcer dyspepsia remain unclear. There is no evidence that the elimination of *Helicobacter pylori* is beneficial for asymptomatic patients or in preventing gastric cancer. One-week triple therapy with a proton pump inhibitor or ranitidine bismuth citrate in combination with clarithromycin/metronidazole and amoxycillin is the recommended first-line treatment for *Helicobacter pylori* infection. Problems with patient compliance and the development of antibiotic resistance are the two most important factors to consider when choosing the treatment regimen. The optimal retreatment therapy for treatment failure is still unknown, and quadruple therapy is best reserved for these cases.

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Introduction

The discovery of *Helicobacter pylori* in the early 1980s revolutionised the management of many gastroduodenal diseases. Our understanding of *H pylori* infection and its associated gastroduodenal diseases continues to evolve, with new indications for anti–*H pylori* treatment being constantly added. The availability of simple, accurate, and non-invasive diagnostic tests, such as the urea breath test and serological analysis, facilitates the screening and eradication of *H pylori* by primary care physicians. However, confusion still exists regarding the indication and treatment regimens. This review aims to clarify some issues in the treatment of *H pylori* infection.

Who needs to be given *H pylori* eradication treatment?

Guidelines on who should receive *H pylori* eradication therapy were first published by the National Institutes of Health (NIH) Consensus Development Panel on *Helicobacter pylori* in 1994.[1] The panel concluded that patients with *H pylori* infection and peptic ulcer disease, regardless of disease stage (first presentation or recurrent ulceration) or use of non-steroidal anti-inflammatory drugs (NSAIDs), require eradication therapy. But whether or not *H pylori* infection in those with non-ulcer dyspepsia should be treated was unclear. The routine detection of *H pylori* in the absence of an ulcer was not recommended. The NIH Consensus Panel did not give a definite recommendation on the need for *H pylori* eradication in patients with complicated peptic ulceration, peptic ulcer disease in children, or as a preventive measure against gastric cancer. Two years later, in 1996, the European *Helicobacter pylori* Study Group formulated further guidelines on the management of *H pylori* infection.[2] This group confirmed that all *H pylori*–positive patients with peptic ulcer disease, whether the condition is active or not, should receive anti–*H pylori* therapy. The most remarkable feature was that it recommended that dyspepsia be screened for and treated at the primary care level. This European Consensus suggested that screening for *H pylori* followed by eradication therapy should be given to all dyspeptic patients younger than 45 years with no alarm symptoms. The group suggested that therapy should also be extended to patients with mucosa-associated lymphoid tissue (MALT) lymphoma, gastritis with severe intestinal metaplasia (or gastric atrophy), and those who have had early gastric cancer resected. It should be pointed out that some

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of these recommendations were based on relatively weak scientific evidence, but more by voting of the participants.

In 1998, the Asia-Pacific Consensus established guidelines for use in this region.[3] The consensus statement shares much with the European guidelines. It extends recommendations regarding the treatment of *H pylori* infection to patients with complicated ulcer disease. For patients requiring long-term NSAIDs, prophylactic *H pylori* eradication therapy is recommended for patients who have a history of ulcers or dyspepsia. Routine screening and eradication in asymptomatic patients is still not implemented. The role of *H pylori* eradication in patients with premalignant lesions such as intestinal metaplasia was not addressed by the Asia-Pacific Consensus despite the high incidence of gastric cancer in the region. To date, there is no evidence that suggests intestinal metaplasia can be reversed by *H pylori* eradication.[4]

The benefits of *H pylori* eradication in gastro-oesophageal reflux disease, NSAID-related peptic ulcer and non-ulcer dyspepsia remain unclear. Whether or not *H pylori* is a hindrance to the host in these conditions is unclear. It should also be noted that the eradication of *H pylori* infection in an asymptomatic patient is not recommended in any of the consensus statements. Table 1 summarises the recommendations of three consensus groups.

Which is the best treatment regimen for effective *H pylori* eradication?

Most gastro-enterologists would agree that the best regimen should be effective (ie more than a 90% success rate in curing *H pylori* infection), simple, and safe.

Bismuth-based triple therapy

Bismuth compounds have been used for decades to treat dyspepsia and peptic ulceration—even before the anti–*H pylori* action of the compounds was known. The classic triple therapy of bismuth (colloidal bismuth subcitrate or bismuth subsalicylate), metronidazole, and either amoxycillin or tetracycline is the most common regimen. Tetracycline-containing triple therapy achieves a greater cure rate than the amoxycillin alternative. With a 1-week course of triple therapy, both duodenal and gastric ulcers heal—even without acid suppression by H_2-receptor antagonists or proton pump inhibitors (PPIs).[5,6] Unfortunately, the efficacy of bismuth-based triple therapy is significantly reduced when given to patients infected with metronidazole-resistant bacteria. Although bismuth-based triple therapy is inexpensive, it is poorly tolerated and significant side effects are experienced in up to 40% of patients.[7,8] The many tablets, frequent doses, and long duration of therapy also affect patient compliance. Both the side effects and complexity of treatment have made bismuth-based triple therapy a less popular choice in recent years.

Dual therapy

Dual therapy refers to the combination of PPIs or ranitidine bismuth citrate (RBC) and one antibiotic, usually amoxycillin or clarithromycin. Inhibition of acid secretion with a PPI or H_2-receptor antagonist

Table 1. *H pylori* eradication guidelines as contained in various consensus statements

Disease	NIH* (1994)	EHPSG† (1997)	AP‡ (1998)
Peptic ulceration			
gastric ulceration	+	+	+
duodenal ulceration	+	+	+
bleeding	Inconclusive	+	+
perforation	-	-	+
NSAID§ user			
ulceration	+	+	+
prophylaxis	Inconclusive	Advisable	+ (If dyspepsia present)
Dyspepsia			
uninvestigated	-	+ (If <45 years)	+ (Regional variation)
non-ulcer dyspepsia	Not recommended	Advisable	+ (If *H Pylori* present)
Malignancy			
MALTxx	-	+	+
early cancer	-	+	+
family history	-	+	+
gastrectomy surgery	-	Advisable	-

* NIH National Institutes of Health Consensus Development Panel on *Helicobacter pylori*[1]
† EHPSG European *Helicobacter pylori* Study Group[2]
‡ AP Asia-Pacific Consensus Conference on the management of *H pylori* infection[3]
§ NSAID non-steroidal anti-inflammatory drug
xx MALT mucosa-associated lymphoid tissue
+ signifies recommendation; - signifies that there was no information available

increases the intragastric acid level to pH5 or more and acts synergistically with amoxycillin and clarithromycin. These regimens are better tolerated and simpler to follow than bismuth-based triple therapy. The first dual therapy combining omeprazole with amoxycillin had unpredictable efficacy ranging from 20% to 90% and thus credibility with most gastroenterologists.[9,10] The results of dual therapy are more reproducible when amoxycillin is replaced by clarithromycin. The PPI and clarithromycin combination, however, requires frequent dosing of clarithromycin (up to 500 mg three times daily for 2 weeks to achieve an efficacy of 63% to 81%.[11-13] The high doses of PPI and clarithromycin have substantially increased the cost of this regimen. Although it is one of the United States Food and Drug Administration (FDA)–approved regimens for *H pylori* eradication, this course of therapy is not widely used outside of the United States. Dual therapy with the RBC 400 mg and clarithromycin 500 mg twice daily for 2 weeks is another FDA-approved regimen and achieves eradication rates up to 80%.[14] However, the long duration of treatment and subsequent reduced compliance remain a problem.

Triple therapy

To date, the most popular treatment regimen for the cure of *H pylori* infection consists of an acid-suppressant (PPI or RBC) and two antimicrobial agents (Box).

The Metronidazole, Amoxycillin, Clarithromycin, *Helicobacter* (MACH)-1 study tested omeprazole in combination with various antimicrobials (amoxycillin, tetracycline, and metronidazole) and confirmed the efficacy of this 1-week regimen.[15] The best results were obtained from the therapies of omeprazole, clarithromycin, and amoxycillin or metronidazole. Their side effects are much milder than the original bismuth-based triple therapy and patient compliance is expected to improve. The role of omeprazole in these non–bismuth-based triple therapies has been substantiated by the MACH-2 study; the role appears to be a class effect of PPI.[16] Trials of regimens using other PPIs such as lansoprazole and pantoprazole showed no significant difference in their efficacy of *H pylori* eradication.[17,18] On the other hand, the choice of antibiotics decides the efficacy of PPI-based triple therapy. The inclusion of clarithromycin in the triple therapy ensures high efficacy and reproducible results. However, the effectiveness of clarithromycin cannot be generalised to other macrolides. The use of roxithromycin and azithromycin in PPI-based triple therapy has not been as successful as the clarithromycin combination.[19]

There have been attempts to shorten the treatment period of PPI-based triple therapy to less than 1 week, but the cure rates were markedly decreased.[20] Longer treatment times of 10 to 14 days do not give superior results either.[21,22]

Ranitidine bismuth citrate is a new amalgamated compound of ranitidine and bismuth; it combines the antisecretory activity of ranitidine with the mucoprotective and anti–*H pylori* effects of bismuth. Because of its high solubility, RBC-triple therapy has proven to be highly effective in eradicating *H pylori*, with cure rates ranging from 80% to 96%.[23,24] In a head-to-head comparison of RBC-triple therapy with PPI-triple therapy, no difference in the cure rate of *H pylori* infection and duodenal ulcer was found.[25] One-week RBC-based triple therapy is now increasingly considered as an effective regimen for *H pylori* eradication. Commonly used eradication therapies are summarised in Table 2.

Quadruple therapy

Quadruple therapy combines an acid-suppressive drug, usually a PPI, with three antimicrobial agents. Typical quadruple therapy includes omeprazole, tetracycline, metronidazole, and a bismuth salt. Newer quadruple therapy may comprise another PPI, amoxycillin, clarithromycin, and metronidazole. Studies have been done to evaluate the possible role of quadruple therapy in shortening the duration of treatment or improving the efficacy of eradication. Currently, quadruple therapy is mainly reserved as a second-line regimen for use in cases of treatment failure.

Recommended triple therapy regimen to eliminate *H pylori*

PPI* twice daily				Amoxycillin 1 g twice daily
or	+	Clarithromycin‡ twice daily	+	or
RBC† 400 mg twice daily				Metronidazole 400 mg twice daily

* PPI proton pump inhibitor: omeprazole 20 mg, lansoprazole 30 mg, or pantoprazole 40 mg
† RBC ranitidine bismuth citrate
‡ Clarithromycin 500 mg (with amoxycillin) or 250 mg (with metronidazole)

Table 2. Dosage schedules for 1-week triple therapy regimens

Treatment regimen	Frequency	Duration of treatment	Efficacy*	Side effects
Tripotassium dicitratobismuthate 120 mg + tetracycline 500 mg + metronidazole 400 mg	4 times daily	1 week	74% to 80%	Nausea, diarrhoea, taste disturbance, stool discolouration, efficacy may be affected by metronidazole resistance
Omeprazole 20 mg† + amoxycillin 1 g + clarithromycin 500 mg	twice daily	1 week	90%	Nausea, diarrhoea
Omeprazole 20 mg* + metronidazole 400 mg + clarithromycin 500 mg	twice daily	1 week	85% to 90%	Nausea, diarrhoea, taste disturbance, efficacy may be affected by metronidazole resistance
Ranitidine bismuth citrate 400 mg + amoxycillin 1 g + clarithromycin 500 mg	twice daily	1 week	85% to 90%	Nausea, diarrhoea
Ranitidine bismuth citrate 400 mg + metronidazole 400 mg + clarithromycin 500 mg	twice daily	1 week	90%	Nausea, diarrhoea, taste disturbance

* Efficacy is evaluated by intention-to-treat (rather than per-protocol) analysis
† Lansoprazole 30 mg and pantoprazole 40 mg would achieve a similar efficacy

Why does treatment sometimes fail?

The most important causes of treatment failure are poor compliance on the part of patients and the development of bacterial resistance to antimicrobial agents. Patient compliance can only be improved by choosing a simple and well-tolerated treatment regimen. The importance of the prescribing physician giving detailed instruction and explaining any possible side effects cannot be overstated.

Resistance to metronidazole is caused by a failure of bacterial reduction; consequently, the nitro-imidazole compound is not reduced to the active form of the drug. The prevalence of metronidazole resistance varies from 10% to 90% in different countries. In Hong Kong, up to 60% of *H pylori* strains are resistant to metronidazole and their prevalence appears to be rising.[26] Triple therapy is reported to be significantly less effective against metronidazole-resistant strains of *H pylori*, with most eradication results falling between 30% to 70%.[16,27-29] It is advisable not to include metronidazole in the treatment regimen in localities where the prevalence of metronidazole resistance is high. Primary resistance to clarithromycin is much less common than metronidazole resistance, ranging from 0% to 15%.[30] Unlike metronidazole resistance, the resistance to clarithromycin is less common in Asia. Nevertheless, there is a trend of rising resistance due to the widespread use of clarithromycin in the treatment of upper respiratory tract infections. Acquired (secondary) resistance to clarithromycin frequently develops in individuals after initial treatment failure, due to the decreased affinity of the drug for the point-mutated 23 S rRNA of the bacterial ribosome.[31]

Performing routine pretreatment susceptibility tests is not a cost-effective option. Clinicians should choose the appropriate combination of drugs based on sensitivity patterns provided by a local reference centre. However, when treatment fails, susceptibility testing should be performed to guide further therapy.

What is the best regimen in cases of treatment failure?

No antimicrobial regimen can cure 100% of infected patients. Even the best therapies fail in 5% to 10% of cases.[15,25] If the initial regimen that was given to patients who have been compliant to treatment contained clarithromycin or metronidazole, then second-line treatment could replace clarithromycin with metronidazole or vice versa. If the first-line therapy contained both clarithromycin and metronidazole, quadruple therapy consisting of a PPI, bismuth, tetracycline, and metronidazole would offer optimal 'salvage' therapy. Uncontrolled trials have reported variable eradication rates ranging from 50% to 87% for this regimen.[32,33] Ideally, the antibiotic sensitivity pattern of the organism should be established before the second-line therapy is chosen.

Conclusion

One-week triple therapy with a PPI or RBC in combination with clarithromycin/metronidazole and amoxycillin is the recommended first-line treatment for *H pylori* infection. Compliance and antibiotic resistance are the two most important factors to

consider in choosing the treatment regimen. Data on optimal retreatment therapy for treatment failures is still lacking. Until further studies are available, quadruple therapy is best reserved for these cases.

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