

**Björn Stenström**

MD, PhD, is Research Fellow, Department of Gastroenterology, Sir Charles Gairdner Hospital, Perth, Western Australia. bjorn.stenström@hpylori.com.au

Aruni Mendis

PhD, DIC, is Manager, Scientific & Regulatory Affairs, Tri-Med Australia, Perth, Western Australia.

Barry Marshall

FRACP, FAA, FRS, Nobel Laureate, is Clinical Professor of Microbiology, The University of Western Australia.



Helicobacter pylori

The latest in diagnosis and treatment

Background

European and North American guidelines on the management of *Helicobacter pylori* infection were updated in 2007. New diagnostic methods have been introduced and in Australia, the recommended therapy choices in cases of penicillin allergy and for second line treatment are only accessible through the Therapeutic Goods Administration Special Access Scheme.

Objective

The article aims to update general practitioners on recommendations for testing and treating *H. pylori* infection, practical aspects of diagnostic methods, proof of cure testing to prove eradication, and the management of eradication failure and recurrent infection.

Discussion

Urea breath tests are the best way to diagnose current *H. pylori* infection. Serology should primarily be used when UBTs may be false negative, eg. current bleeding ulcer or *H. pylori* suppressing drugs. For children who cannot use UBTs, stool antigen tests may be useful. In case of eradication failure with standard clarithromycin based therapy, bismuth based quadruple therapy is the favoured second line therapy. Preparing the patient for possible side effects is important as poor compliance and antibiotic resistance are the main reasons for eradication failure.

■ ***Helicobacter pylori* is strongly linked to peptic ulcer disease and is classified as a group 1 carcinogen by the World Health Organization's International Agency for Research on Cancer. Socioeconomic level seems to be the major determinant of risk of infection. In Australia, 25–30% of the population is infected, with the prevalence increasing with age. In some indigenous communities, prevalence is 2–3 times higher than in nonindigenous communities.¹**

The American College of Gastroenterology (ACG) and the European Helicobacter Study Group (EHSG) presented updated guidelines on the management of *H. pylori* infection in 2007.^{2,3} A particular problem for Australian doctors managing *H. pylori* infection is restricted access to globally recommended drug therapies. However, commonly recommended alternative drug therapies can be prescribed through the Australian Therapeutic Goods Administration Special Access Scheme (TGA-SAS). Another problem for general practitioners had been the restricted indications for requesting the urea breath tests (UBTs); from November 2006 there are no Medicare restrictions on UBT use.

Indications for diagnosing and treating *H. pylori* infection

Established indications for testing and treating *H. pylori* infection are presented in *Table 1*. For a number of other conditions the evidence is currently insufficient (*Table 2*).

Peptic ulcer disease and ulcer bleeding

There is overwhelming evidence supporting the merits of *H. pylori* eradication in patients with peptic ulcer disease (PUD). Furthermore, a recent Cochrane systematic review demonstrated that maintenance of acid suppression was not routinely necessary to prevent ulcer recurrence after successful *H. pylori* eradication and ulcer healing.⁴

NSAIDs or aspirin

The recommendations for *H. pylori* eradication in nonsteroidal anti-inflammatory drug (NSAID) users are summarised in *Table 3*.



The results of *H. pylori* eradication in NSAID users are conflicting. *Helicobacter pylori* and NSAIDs independently and significantly increase the risk of peptic ulcer bleeding. The risk of ulcer bleeding is further increased when both factors are present. *Helicobacter pylori* eradication seems to have a different effect in chronic and naive NSAID users.^{5,6}

Dyspepsia

A test and treat strategy for *H. pylori* infection is recommended for patients with uninvestigated persistent dyspepsia who are less than 45 years of age without any of the following 'alarm features':

- bleeding
- anaemia
- early satiety
- unexplained weight loss
- progressive dysphagia
- odynophagia
- recurrent vomiting
- family history of gastrointestinal cancer
- previous esophagogastric malignancy.⁷

Helicobacter pylori eradication may be appropriate for patients with investigated nonulcer dyspepsia when *H. pylori* positive. The benefit is modest but significant, and economic modelling suggests that it is cost effective. An estimated 7–15 infected patients need to be treated (NNT) to cure symptoms of one such patient. The relative risk (RR) of remaining symptomatic is 0.91. In areas of low *H. pylori* prevalence (<20%), proton pump inhibitor (PPI) empirical treatment is an equivalent option.^{8,9}

GORD and long term PPI treatment

There is no clear evidence that eradication of *H. pylori* infection causes gastro-oesophageal reflux disease (GORD) or exacerbates GORD. *Helicobacter pylori* eradication therapy should not be withheld due to concerns of creating or worsening GORD. Routine testing for *H. pylori* is not recommended in GORD. However, in patients receiving long term maintenance treatment with PPIs, *H. pylori* testing should be considered. Profound acid suppression affects the pattern and distribution of gastritis favouring corpus dominant gastritis and may lead to atrophic gastritis. *Helicobacter pylori* eradication halts the progression of atrophic gastritis and may reverse the process of atrophy therefore decreasing cancer risk.^{10,11}

Mucosa associated lymphoid tissue lymphoma

In mucosa associated lymphoid tissue (MALT) lymphoma, the most common gastrointestinal lymphoma, *H. pylori* eradication can cure the majority of patients and is now recognised as the treatment of choice for low grade tumours.¹²

Gastric cancer prevention

Stomach cancer is rare in persons who have never had *H. pylori* infection. Conversely, eradication prevents development of pre-

Table 1. Proven indications for the diagnosis and treatment of *H. pylori*

- Peptic ulcer disease (active or confirmed history)
- A test and treat strategy is appropriate for patients with uninvestigated dyspepsia who are <45 years of age and who do not have any 'alarm features'
- Low grade gastric MALT lymphoma
- After endoscopic resection of early gastric cancer
- First degree relatives of patients with gastric cancer

Table 2. Conditions where evidence is inconclusive for diagnosis and treatment of *H. pylori*

- Investigated nonulcer dyspepsia (ie. 'functional dyspepsia': dyspepsia patients who have no ulcer at endoscopy)
- With NSAID use (see Table 3)
- Gastro-oesophageal reflux disease (GORD)
- Populations at higher risk for gastric cancer (Japan and parts of China)
- Unexplained iron deficiency anaemia in adults
- Idiopathic thrombocytopenic purpura

Table 3. NSAID and *H. pylori* eradication

- *H. pylori* eradication is of value in chronic NSAID users but is insufficient to prevent NSAID related ulcer disease completely
- In naive NSAID users *H. pylori* eradication may prevent peptic ulcer and bleeding
- For patients with a history of an ulcer complication who require subsequent therapy with an NSAID or aspirin, PPI maintenance treatment is better than *H. pylori* eradication in preventing ulcer recurrence and/or bleeding. Co-therapy may be an option
- Patients taking long term aspirin and who bleed should be tested for *H. pylori*, and be treated for the infection if positive

neoplastic changes (atrophic gastritis and intestinal metaplasia) of the gastric mucosa. However, definite evidence on whether *H. pylori* eradication can reduce the risk of developing gastric adenocarcinoma is lacking. It is likely that cancer risk persists for several years after the bacterium is gone.¹³

Extra-intestinal disease

Both EHS and ACG guidelines state *H. pylori* infection should be diagnosed and treated in patients with unexplained iron deficiency anaemia. The EHS also recommends diagnosis and treatment for patients with idiopathic thrombocytopenic purpura. However, cause and effect has not been demonstrated. *Helicobacter pylori* has no proven role in other extra-intestinal diseases.



H. pylori infection in children

Recurrent abdominal pain is not a proven indication for a test and treat for *H. pylori* strategy in children. However, if other causes of the symptoms have been excluded it is prudent to treat for *H. pylori* infection. Iron deficiency anaemia refractory to iron supplementation is also an indication to test for and treat *H. pylori* infection if other causes such as coeliac disease and inflammatory bowel disease have been excluded.¹⁴ Referral to a paediatrician is indicated when *H. pylori* is suspected in children.

Diagnosis and treatment

Diagnostic procedures

Several factors, including the need for endoscopy, pretest probability of infection, local availability, and an understanding of the performance characteristics of the individual tests, influence choice of evaluation for an individual patient.

Most diagnostic methods used for detecting *H. pylori* are negatively affected by drugs that suppress the bacterial population. Antibiotics and bismuth should not be used for 4 weeks before a test based on *H. pylori* urease production, such as rapid urease tests (RUT) performed at endoscopy and UBTs. Proton pump inhibitors should be stopped for at least 1 week before performing a diagnostic test.¹⁵

The diagnostic accuracy of UBT is >95%. These are accurate, practical and readily available tests, and are the mainstay of *H. pylori* diagnostics if the patient does not require an endoscopy.¹⁶

Serology has a low diagnostic accuracy of 80–84%.¹⁷ In areas with low *H. pylori* prevalence (such as Australia), this means that the positive predictive value (PPV) will be as low as 50% (half of positive results are false positive). Therefore, positive serology results at least need to be confirmed by other methods. Serology can also remain positive for months to years after successful eradication.¹⁸ However, the negative predictive value (NPV) is excellent and a negative result almost rules out current infection. Therefore, serology is useful when

other diagnostic tests might be false negative, such as in patients with bleeding ulcers, gastric atrophy, MALT lymphoma, past gastric surgery and recent use of PPIs or antibiotics.¹⁹

Culture, requiring an endoscopy, has excellent specificity and is necessary for determination of antibiotic sensitivities. However, culture is difficult to perform, so negative cultures may be falsely reassuring. Several studies have shown that higher eradication rates are obtained when antibiotics are chosen based on susceptibility testing rather than chosen empirically, and this may also be a cost effective approach.²⁰ Strong evidence of infection certainly raises the motivation of the patient and the physician, therefore improving cure rate.

In a systematic review evaluating the stool antigen test, the sensitivity and specificity were 91 and 93%, respectively. However, specimens are sensitive to room temperature and must be immediately frozen after collection. Polyclonal tests are less accurate than monoclonal tests.²¹ This test may be useful in children who are unable to perform a UBT.

Histology has good sensitivity and specificity, but is generally only available in the endoscopy setting.

Serology based near doctor patient tests and detection of specific *H. pylori* antibodies in urine and saliva are generally less accurate than the tests described, and so are less important in the management of *H. pylori* infection.

As no test is 100% accurate, there may be a case for using a concordance of two tests with different mechanisms, ie. urea breath test together with stool test or serology, in order to prove if the patient's *H. pylori* status is negative or positive. Particularly, positive serology tests need to be confirmed by other methods.

Treatment

Based on global recommendations, availability in Australia and practical considerations, suggested eradication therapies are listed in *Table 4*. A number of factors influence how the *H. pylori* infected patient can be

Table 4. Practical options for *H. pylori* eradication in Australia

First and second line therapies	
7 days	PPI standard dose bd*/clarithromycin 500 mg bd/amoxicillin 1000 mg bd
7 days	PPI standard dose bd*/clarithromycin 500 mg bd/metronidazole 500 mg bd
14 days	PPI standard dose bd*/colloidal bismuth subcitrate 120 mg qid**/tetracycline 500 mg qid**#/metronidazole 400 mg qid
10 days	5 days of PPI standard dose bd*/amoxicillin 1000 mg bd followed by 5 days of PPI standard dose bd*/clarithromycin 500 mg bd/ tinidazole 500 mg bd
Third line ('rescue/salvage') therapies	
14 days	PPI standard dose bd*/bismuth subcitrate 120 mg qid**/furazolidone 200 mg bd**/tetracycline 500 mg qid**#
14 days	PPI standard dose bd*/amoxicillin 1000 mg bd/rifabutin 150 mg bd/ciprofloxacin 500 mg bd
* Standard PPI doses: esomeprazole 40 mg/day, lansoprazole 30 mg/day, omeprazole 20 mg/day, pantoprazole 40 mg/day, rabeprazole 20 mg/day	
** Available from supplier once TGA-SAS approval is obtained (see <i>Table 5</i>)	
# Tetracycline cannot be replaced with doxycycline because of different pharmacokinetics	
bd = twice daily, qid = 4 times daily	



Table 5. Obtaining orphan/TGA-SAS drugs

Colloidal bismuth subcitrate (De-Nol), tetracycline and furazolidone are available under the TGA-SAS (SAS-category B). To prescribe or obtain these drugs for treating *H. pylori* infection, follow these three steps:

- obtain the SAS form from the TGA website (www.tga.gov.au/docs/pdf/unapproved/sascata.pdf)
- fax the completed form to the TGA for approval (it will be faxed back to you by the TGA after 1 week)
- deliver the SAS form to the drug supplier to be filled

managed in Australia. *Table 4* lists a number of considerations to keep in mind as checklist when choosing a treatment combination.

General

- Drug availability, through private prescription or Pharmaceutical Benefits Scheme (PBS) subsidy, and orphan drugs that can be acquired following TGA-SAS approval (*Table 5*)
- Treatment regimen should be clinically validated and should have a probability of eradication success of >80%. Therapies listed in *Table 4* are all validated, with the exception of the ciprofloxacin containing third line therapy.

Patient specific

- The most important predictors of treatment failure with *H. pylori* eradication therapy include poor compliance and antibiotic resistance²²
- With any eradication attempt it is important to prepare both doctor and patient for common side effects. This dramatically improves compliance and the probability that the entire course can be completed. 'Coaching' can help most patients complete at least 7 days of therapy. Common side effects are listed in *Table 6*
- Acid secretion inhibition substantially increases the effectiveness of antibiotics used in *H. pylori* eradication. If the patient cannot tolerate a PPI, it can be substituted with a histamine receptor antagonist (H₂RA)²³

- If the first treatment regimen fails, increasing the PPI dose can be beneficial²⁴
- It is advisable to take a detailed history of previous antibiotic use. This increases the chances of eradicating the infection with the first treatment
- Nonspecific drug reactions are not infrequently mislabelled as penicillin allergy, depriving the patient the possible benefits of penicillin treatment. Therefore, investigation of allergic reactions to penicillin is often warranted
- There may be a slight advantage in using rabeprazole over omeprazole due to differences in metabolism.²⁵ This is due to heterogeneity in enzymatic activity, primarily of importance in east Asian populations
- If the patient has previously been treated with clarithromycin (CTM) for any indication, there is a higher risk of primary CTM resistance. Further use of CTM containing therapies should be avoided or CTM sensitivity confirmed through antimicrobial sensitivity testing
- Clarithromycin should be avoided without prior antimicrobial sensitivity testing if local primary CTM resistance exceeds 15–20%. In Australia, resistance is usually below this level at 10–15%
- Metronidazole (MET) resistance is less definitive. If the patient has failed a MET containing regimen, resistance can be overcome by increasing the dose to 1500 mg/day, particularly with bismuth and tetracycline therapy²⁶
- Treatment duration: first eradication attempt – 7 days; subsequent attempts – 10 or 14 days treatment may have a higher chance of success. However, the risk of adverse effects increases
- After two failed eradication attempts, current guidelines advocate antimicrobial sensitivity testing. Culture should be performed in specialised laboratories, as the procedure is technically demanding. Several studies have shown that higher eradication rates are obtained when antibiotics are chosen based on susceptibility testing, and this seems to be a cost effective approach
- Taking food with drugs does not seem to impair eradication results.

Testing to prove eradication

Situations in which posteradication testing is recommended are listed in *Table 7*. We suggest that in Australia, where prescribing a

Table 6. Common side effects

PPIs	Headache and diarrhoea
Clarithromycin	Gastrointestinal (GI) upset, diarrhoea, and altered taste
Amoxicillin	GI upset, diarrhoea, and headache
Metronidazole	Tends to be dose related, a metallic taste, dyspepsia, a disulfiram-like reaction with alcohol consumption
Tetracycline	GI upset, photosensitivity
Bismuth subcitrate	Darkening of the tongue and stool, nausea, and GI upset
Furazolidone	Nausea, vomiting, headache, and malaise in up to a third of patients. Less frequently hypersensitivity, hypotension, a disulfiram-like reaction with alcohol consumption, and mild reversible haemolytic anaemia
Rifabutin	Red discoloration of urine while using the drug. Rash, diarrhoea, nausea, vomiting, dyspepsia. Small but serious risk of myelotoxicity and ocular toxicity. Can select for resistance among mycobacteria

**Table 7. Testing to prove *H. pylori* eradication**

The ACG guidelines include four groups for post-treatment testing to confirm eradication:

- Patients with *H. pylori* associated ulcers
- Patients who have undergone resection of early gastric cancer
- Patients with *H. pylori* associated MALT lymphoma
- Patients with dyspeptic symptoms persisting after the test and treat strategy

suitable treatment can be difficult, routine eradication confirmation may lead to fewer patients being repeatedly treated with inefficient drug combinations and to better overall eradication results. We frequently encounter patients who seek help as they have 'been infected again' and are then treated repeatedly with inadequate drug combinations. However, most people have acquired the infection in childhood, and except in very poor socioeconomic conditions, the risk of reinfection is low. Therefore, the majority of such cases are in fact recurrences where the *H. pylori* infection has been temporarily suppressed by treatment.²⁷

Noninvasive tests should be employed for confirmation of eradication except in cases where repeat endoscopy is indicated, for example in patients with a gastric ulcer.

A urea breath test is the best option. A monoclonal stool antigen test is slightly less accurate, but may be an option especially in children. Testing to prove eradication should be performed no sooner than 4 weeks after completing the antibiotic therapy.

Resource

The Helicobacter Foundation – www.helico.com/.

Conflict of interest: Aruni Mendis is Manager of Scientific & Regulatory Affairs, Tri-Med Distributors P/L. Professor Barry Marshall is the Medical Director of Tri-Med Distributors P/L, a company which specialises in the distribution of *H. pylori* diagnostics and anti-Hp therapeutics.

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