



Julian Yaxley  
Bhaskar Chakravarty

# *Helicobacter pylori* eradication – an update on the latest therapies

## Background

The eradication of *Helicobacter pylori* (*H. pylori*) can be challenging in certain circumstances. There is no current first-line therapy that is curative in all patients.

## Objective

This article summaries the role of emerging novel therapies in the treatment of *H. pylori*. Known as sequential therapy and salvage therapy, these new therapeutic strategies are thought to produce eradication rates superior to currently recommended first-line therapies. This article outlines the growing body of evidence supporting their efficacy.

## Discussion

Sequential therapy and salvage therapy have emerged recently as alternative regimens for the eradication of *H. pylori*. Although current guidelines continue to recommend established therapies for first-line management of *H. pylori*, general practitioners should be aware of these new strategies such that these options could be applied when traditional therapy fails.

## Keywords

*Helicobacter pylori*; disease eradication

The link between *Helicobacter pylori* (*H. pylori*) and peptic ulcers is now well-established. Colonisation by *H. pylori* is the main recognised risk factor for peptic ulcer disease (PUD), and its eradication has revolutionised the modern management of peptic ulcers. Until approximately 15 years ago, the mainstay of therapy was short-term ulcer healing and symptomatic relief without eradication of the organism. This necessitated long-term maintenance therapy and fostered high rates of recurrence.

Today, newer eradication regimens are altering peptic ulcer natural history and offering long-term cure with increasing frequency. Nonetheless, the ever-changing face of *H. pylori* therapy, necessitated by the organism's

resistance to various antibiotics, continues to pose a challenge for physicians.

## Pathogenesis of *H. pylori* induced disease

*H. pylori* is a gram negative bacillus that has naturally colonised the human stomach for at least 50,000 years.<sup>1</sup> Usually acquired in childhood, it colonises the gastric mucosa of about 50% of the world's population at some time in their life.<sup>1</sup> In westernised countries, *H. pylori* infection has a prevalence of approximately 30%.<sup>1</sup>

*H. pylori* was first identified and isolated from a gastric biopsy specimen in 1983.<sup>2</sup> The discovery was made in Australia by Marshall and Warren, who realised almost all patients they observed between 1979 and 1984 with gastric or duodenal ulcers were infected with the same organism.<sup>3</sup> *H. pylori* has since emerged as an important pathogen associated with the gastroduodenal region, playing a major role in the pathogenesis of most cases of PUD.<sup>2</sup>

Infection with *H. pylori* induces a persistent immune response. Because the organism has numerous adaptations to prevent immune detection, clearance by the body is never complete. The resulting sustained inflammatory processes in the stomach cause a reduction in the population of somatostatin-producing D cells.<sup>1</sup> This causes a subsequent rise in gastrin secretion followed by an increase in gastric acid release which may lead to peptic ulceration in some patients.

Worldwide, more than 80% of duodenal ulcers and more than 60% of gastric ulcers are associated with *H. pylori*.<sup>1</sup> Most patients colonised with the organism do not develop peptic ulcers, although the majority will develop a gastritis. The lifetime risk of gastric or duodenal ulcers is only 10%,<sup>4</sup> which is somewhat less than

the risk of *H. pylori* colonisation. The reason only some develop ulcers remains unresolved, although a combination of bacterial strain differences, host susceptibility and environmental factors are likely to play a role.<sup>1</sup>

## Investigations and diagnosis of infection

A retrospective study from California in 1998 concluded that fewer than half of patients diagnosed with PUD were screened for *H. pylori*

by their general practitioner (GP).<sup>5</sup> Fortunately, as understanding of the natural history of gastric and duodenal ulcers grows, *H. pylori* testing has become more common over the last decade. An *H. pylori*-related peptic ulcer should be considered in patients with epigastric pain or dyspepsia. Colonisation should also be suspected and screened for in patients with family history of gastric cancer or gastric mucosa-associated lymphoid tissue (MALT) lymphoma.<sup>6</sup> It is also important to screen for *H. pylori* infection in any patient about to undergo short-term or lengthy non-steroidal anti-inflammatory drug (NSAID) therapy, since eradication reduces the incidence of ulcer disease in these patients.<sup>7</sup>

It would not be appropriate to investigate for *H. pylori* initially in the presence of alarm symptoms such as weight loss, bleeding, dysphagia or symptoms in a patient above the age of 55 years.<sup>4</sup> In this context, investigations should first be directed at excluding malignancy, for example with a gastroscopy.

Investigations for *H. pylori* are broadly divided into invasive and non-invasive methods. Each method has its own benefits and drawbacks (Table 1). The most widely used non-invasive test in general practice is the serology test. If the patient demonstrates high titre this is suggestive of active infection, whereas low titre may simply reflect previous exposure to *H. pylori*. The urea breath test is the best test for monitoring eradication success after treatment, although it may not be available to all general practitioners.

## Traditional eradication regimens

The eradication regimens for *H. pylori* have continued to evolve over the past 20 years. Initially, mainstay therapy included histamine H<sub>2</sub> receptor blockers with an antibiotic. The rate of successful eradication was 73–84%.<sup>5</sup> With time, this therapy was used less frequently as newer regimens with better outcomes emerged. Approximately 15 years ago, bismuth-based triple therapy and proton pump inhibitor (PPI)-based dual therapy were introduced. These became the most widely used therapies for the next decade or so, until they were supplanted by newer alternatives. PPI-based dual therapy lacked adequate success rates, while the bismuth-based triple and quadruple therapies

**Table 1. Commonly used diagnostic tests for *H. pylori***

Test	Mechanism	Notes
<b>Invasive</b>		
<b>Rapid urease test</b>	<ul style="list-style-type: none"> <li>Biopsy specimen is combined with urea and pH is measured</li> <li><i>H. pylori</i> converts urea to ammonia (NH<sub>3</sub>) + CO<sub>2</sub></li> <li>Test is positive for <i>H. pylori</i> if pH of the medium becomes more alkaline, indicated by colour change</li> </ul>	<ul style="list-style-type: none"> <li>Quick and inexpensive</li> <li>Highly sensitive and specific</li> <li>Not suitable for monitoring post-eradication because that would entail further gastroscopy</li> </ul>
<b>Culture</b>	<ul style="list-style-type: none"> <li>Culturing the organism allows determination of antibiotic sensitivities</li> </ul>	<ul style="list-style-type: none"> <li>Expensive</li> <li>Not widely available</li> <li>Highly specific, low sensitivity</li> </ul>
<b>Histology</b>	<ul style="list-style-type: none"> <li>Offers additional information on degree and pattern of inflammation</li> </ul>	<ul style="list-style-type: none"> <li>Expensive</li> <li>Highly sensitive and specific</li> <li>Requires gastroscopy</li> <li>Can detect early changes of MALT lymphoma</li> </ul>
<b>Non-invasive</b>		
<b>Serology</b>	<ul style="list-style-type: none"> <li>Presence of <i>H. pylori</i>-specific IgG antibodies</li> </ul>	<ul style="list-style-type: none"> <li>Inexpensive and widely available.</li> <li>Positive in low titre indicates past exposure to <i>H. pylori</i> and not necessarily active colonisation</li> <li>Positive in high titre reflects active colonisation</li> <li>Not suitable for monitoring post-eradication because successful treatment does not alter IgG levels immediately</li> </ul>
<b>Urea breath test</b>	<ul style="list-style-type: none"> <li>Uses principle of urea metabolism by <i>H. pylori</i></li> <li>Patient ingests radio-labelled (13c) urea followed by a measurement of the concentration of isotope-labelled CO<sub>2</sub> exhaled</li> <li>Positive for <i>H. pylori</i> if isotope-labelled CO<sub>2</sub> present</li> </ul>	<ul style="list-style-type: none"> <li>High positive predictive value</li> <li>High negative predictive value</li> <li>Suitable and recommended as the post-eradication monitoring test</li> <li>Not widely available</li> </ul>
<b>Stool antigen test</b>	<ul style="list-style-type: none"> <li>Presence of <i>H. pylori</i> antigen in the stool</li> </ul>	<ul style="list-style-type: none"> <li>Suitable for pre-treatment diagnosis and post-treatment monitoring</li> <li>Unpleasantness associated with the means of specimen collection</li> </ul>
IgG, immunoglobulin G; MALT, mucosa-associated lymphoid tissue		

had considerable side effects. These adverse effects often saw elderly patients presenting to hospital in the anecdotal experience of one of the authors.

Today, PPI-based triple therapy is the most commonly used method worldwide.<sup>8</sup> This regimen includes use of a PPI in combination with amoxicillin and clarithromycin. Current Therapeutic Guidelines in Australia, revised in July 2013, recommend PPI-based triple therapy as the first-line measure for eradication of *H. pylori*<sup>9</sup> (Table 2).

These guidelines quote pre-treatment clarithromycin resistance in Australia to be 5–7%, and indicate they are likely to rise.<sup>9</sup> Therefore, to evade treatment failure, it would be reasonable to consider the American College of Gastroenterology (ACG) recommendation that in areas of known high clarithromycin resistance, bismuth-based quadruple therapy may be preferable.<sup>10</sup> However, bismuth is only available in Australia under the Special Access Scheme.<sup>9</sup>

The efficacy of triple therapy has been widely tested and has not proved superior to regimens employed two decades ago.<sup>11,12</sup> Standard PPI-based triple therapy appears to have a success rate of 70–85%.<sup>1</sup> Additionally, a recent randomised study of 169 patients who trialled quadruple therapy after failed triple therapy showed that quadruple therapy, the recommended treatment in a setting of clarithromycin resistance, also fails in 20–25% of cases.<sup>13</sup> Comparable findings were reached in an extensive Swedish pooled analysis which compared PPI-based triple therapy to various other traditional therapies for *H. pylori*.<sup>14</sup> These included quadruple therapy, bismuth-based therapy and PPI-based dual therapy. Across all treatment groups the rate of successful eradication was similar. The conclusion to be drawn from the Swedish study is that in all traditionally prescribed regimens, eradication is only partially successful.

## Evidence for newer therapies

### Sequential therapy

While standard triple therapy remains the first-line protocol for *H. pylori* infection,<sup>15</sup> growing resistance to antibiotics used in this treatment

is of concern. This has led to a resurgence of interest in novel therapeutic strategies, one of which is sequential therapy.

Evidence for sequential therapy is encouraging, with a number of studies reporting eradication rates superior to any current widely used treatment. Sequential therapy is a two-step, 10-day program consisting of administration of a PPI with amoxicillin for the first 5 days, followed by triple therapy that includes a PPI, clarithromycin and tinidazole for another 5 days.

An example regimen would be esomeprazole 20 mg twice daily combined with amoxicillin 1 g twice daily, prescribed for 5 days. This must then be followed by a triple therapy of esomeprazole 20 mg twice daily, clarithromycin 500 mg twice daily and tinidazole 500 mg twice for the next 5 days.<sup>16</sup>

The *Lancet* published a randomised controlled trial in January 2013 that compared sequential therapy with PPI-based triple therapy. It found that the sequential treatment arm yielded superior eradication rates compared to standard therapy, 87.0% and 82.3% respectively.<sup>17</sup> This trial also tested 14-day sequential therapy, which proved even more efficacious with a 90.7% success rate.<sup>15</sup>

Sequential therapy has proven to be highly effective in other studies. A recent intention-to-treat analysis of 22 randomised trials testing

sequential therapy, involving 2388 patients, showed eradication rates in the order of 91.3%.<sup>18</sup> If this data series is expanded to per protocol analysis, sequential therapy portends a 93.7% *H. pylori* eradication rate.<sup>18</sup>

### Salvage therapy

Despite the high efficacy of sequential therapy, some patients do fail to respond. There is some data available on a second-line option for this cohort, termed salvage therapy. Salvage therapy is a triple therapy comprising a PPI, amoxicillin and levofloxacin administered for 10 days. A suggested prescription would include esomeprazole 20 mg twice daily, amoxicillin 500 mg twice daily, and levofloxacin 500 mg twice daily.<sup>18</sup>

The limited evidence-based data currently available in Australia suggests salvage therapy is achieving high success rates.<sup>9</sup> The ACG reports that salvage treatment is 76% effective when implemented after a failed sequential regime.<sup>8</sup> A small prospective pilot study, by Zullo and others, has also insinuated that salvage therapy is a valid alternative in the event of eradication failure with sequential therapy.<sup>19</sup> The trial included 35 patients, who received a 10-day triple therapy of rabeprazole, levofloxacin and amoxicillin after sequential therapy failure. At intention-to-treat analysis, this treatment was successful in 85.7% of cases.<sup>19</sup>

**Table 2. Currently recommended eradication regimens<sup>9</sup>**

Eradication therapy	Components	Notes
PPI-based triple therapy	<ul style="list-style-type: none"> <li>• Esomeprazole 20 mg twice daily, OR omeprazole 20 mg twice daily</li> <li>• Amoxicillin 1 g twice daily</li> <li>• Clarithromycin 500 mg twice daily<sup>9</sup></li> </ul>	<ul style="list-style-type: none"> <li>• First-line recommendation in Australian guidelines<sup>9</sup></li> <li>• Drugs prescribed in a 7-day course</li> <li>• Combination prescriptions include Nexium Hp7 and Probitor Hp7</li> </ul>
Quadruple therapy	<ul style="list-style-type: none"> <li>• Omeprazole 20 mg once daily</li> <li>• Bismuth subsalicylate 120 mg four times daily</li> <li>• Metronidazole 400 mg three times daily</li> <li>• Tetracycline 500 mg four times daily<sup>9</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Uncommonly used</li> <li>• Prescribed as a 7- or 14-day course</li> <li>• First-line choice under ACG guidelines for areas with known clarithromycin resistance</li> </ul>

ACG, American College of Gastroenterology

## Solving the problem of antibiotic resistance

Antimicrobial resistance to antibiotics is a concern for eradication therapy. Treatment failure is said generally to be due to the rise of antimicrobial drug resistance. Several studies have found that *H. pylori* eradication is more successful when sensitivity testing is performed prior to treatment.<sup>6</sup> This allows selection of antibiotics according to organism susceptibility.

It is also important to ask patients about previous medications. Evidence suggests that previous patient exposure to metronidazole or macrolide antibiotics lowers eradication success.<sup>9</sup> If they have such past exposure, drugs of substitute classes should be selected to avoid treatment failure.

A decline in efficacy has been noted with standard triple therapy over the past 10 years.<sup>17</sup>

Although evidence points towards lower treatment failure rates with newer therapies, it is likely that they too will experience a similar phenomenon.<sup>17</sup> Since the evolution of drug resistance will remain a problem, newer therapies must be implemented sooner rather than later. Thus, it is important to emphasise that following initial failure with standard triple therapy this regimen should not be repeated,<sup>9</sup> rather consideration be given to trials of sequential or salvage therapy.

## Addressing compliance

Good patient compliance is also a vital predictor of outcome.<sup>10</sup> Therefore, it is important to emphasise its relevance to patients. Poor compliance not only contributes to antibiotic resistance, but patients who do not complete their full course of antibiotics are also more

likely to fail treatment. In Australia, incomplete adherence is the most common reason for eradication failure.<sup>9</sup>

Side effects are a major cause of non-compliance with eradication regimens. Although they occur in some 5–20% of patients,<sup>10</sup> it would be prudent to advise patients of possible adverse effects before initiating treatment. Important side effects are listed in *Table 3*. The side effect profiles of sequential therapy and standard triple therapy are similar.<sup>16</sup>

The financial cost of sequential and salvage therapy is also an issue guiding patient compliance. As the 10-day sequential therapy yields results only marginally inferior to that of a 14-day sequential regime, it is cost-effective to recommend the shorter treatment.<sup>9,16</sup>

## Conclusion

*H. pylori* infection remains a significant cause of morbidity worldwide. To date, a completely successful therapeutic strategy remains elusive, however sequential therapy and salvage therapy are becoming accepted as effective first-line and second-line alternatives. While it is premature to recommend their routine use in all cases, these newer options should be considered for the management of *H. pylori* infection when standard triple therapy fails.

## Authors

Julian Yaxley is a medical student, Griffith University, Gold Coast, QLD. [julianyaxley@yahoo.com.au](mailto:julianyaxley@yahoo.com.au)

Bhaskar Chakravarty MBBS, FRACP, PhD (Newcastle), PhD (Cambridge), is a gastroenterologist at Southcoast Digestive Diseases Centre, Gold Coast, QLD

Competing interests: None.

Provenance and peer review: Not commissioned; externally peer reviewed.

## References

1. Long D, Fauci A, Kasper D, et al. Harrison's Principles of Internal Medicine. New York City: McGraw Hill Companies; 2012.
2. Fennerty M, Lieberman D, Vakil N, et al. Effectiveness of *Helicobacter pylori* therapies in a clinical practice setting. *Arch Intern Med* 1999;159:1562–66.
3. Warren J, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983;1:1273–75.
4. Ramakrishnan K, Salinas R. Peptic ulcer disease. *Am Fam Physician* 2007;76:1005–12.

Table 3. Side effects of common medications used in eradication regimens <sup>21,22</sup>		
Antimicrobial agent	Side effects	
	Frequent	Infrequent
Proton pump inhibitor (PPI)	<ul style="list-style-type: none"> <li>• Cough</li> <li>• Pharyngitis</li> <li>• Abdominal pain</li> <li>• Diarrhoea</li> </ul>	<ul style="list-style-type: none"> <li>• Paraesthesia</li> <li>• Alopecia</li> <li>• Haemolytic anaemia</li> </ul>
Clarithromycin	<ul style="list-style-type: none"> <li>• Abdominal pain</li> <li>• Altered taste sensation</li> </ul>	<ul style="list-style-type: none"> <li>• Arrhythmia</li> <li>• Anaphylaxis</li> </ul>
Amoxicillin	<ul style="list-style-type: none"> <li>• Rash</li> <li>• Diarrhoea</li> </ul>	<ul style="list-style-type: none"> <li>• Crystalluria</li> <li>• Anaphylaxis</li> </ul>
Metronidazole	<ul style="list-style-type: none"> <li>• Thrombophlebitis</li> <li>• Nausea</li> <li>• Headache</li> <li>• Vaginal discharge</li> </ul>	<ul style="list-style-type: none"> <li>• Optic nerve toxicity</li> <li>• Pancreatitis</li> <li>• Hepatitis</li> <li>• Thrombocytopenia</li> </ul>
Bismuth salts	<ul style="list-style-type: none"> <li>• Dark discolouration of stool, tongue, teeth</li> <li>• Diarrhoea</li> <li>• Nausea</li> <li>• Vomiting</li> </ul>	<ul style="list-style-type: none"> <li>• Dizziness</li> <li>• Headache</li> <li>• Neurotoxicity</li> </ul>
Tetracycline	<ul style="list-style-type: none"> <li>• Photosensitivity</li> </ul>	<ul style="list-style-type: none"> <li>• Azotemia</li> </ul>
Tinidazole	<ul style="list-style-type: none"> <li>• Altered taste sensation</li> <li>• Candida vaginitis</li> </ul>	<ul style="list-style-type: none"> <li>• Confusion</li> <li>• Agitation</li> <li>• Seizure</li> </ul>
Levofloxacin	<ul style="list-style-type: none"> <li>• Diarrhoea</li> <li>• Headache</li> <li>• Nausea</li> </ul>	<ul style="list-style-type: none"> <li>• Arrhythmia</li> <li>• Hypoglycaemia</li> <li>• Hypersensitivity reaction</li> <li>• Tendinitis</li> </ul>

5. Peura D. Helicobacter pylori: rational management options. *Am J Med* 1998;105:424–30.
6. Stenstroem B, Mendis A, Marshall B. Helicobacter pylori: the latest in diagnosis and treatment. *Aust Fam Physician* 2008;37:608–12.
7. Talley N, Vakil N. Guidelines for the management of dyspepsia. *Am J Gastroenterol* 2005;100:2324–37.
8. Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of helicobacter pylori infection: the Maastricht III Consensus Report. *Gut* 2007;56:772–81.
9. Antibiotic Expert Group. Eradication of *Helicobacter pylori* and ulcer healing In: eTG Complete [Internet] Melbourne. Therapeutic Guidelines Ltd. 2013. Available at [www.tg.org.au](http://www.tg.org.au) [Accessed 15 March 2013].
10. Chey W, Wong B. American College of Gastroenterology guidelines on the management of Helicobacter pylori infection. *Am J Gastroenterol* 2007;102:1808–25.
11. Laine L, Fennerty M, Osato M, et al. Esomeprazole-based Helicobacter pylori eradication therapy and the effect of antibiotic resistance: results of three US multicenter, double-blind trials. *Am J Gastroenterol* 2000;95:3393–98.
12. Vakil N, Lanza F, Schwartz H, Barth J. Seven day therapy for Helicobacter pylori in the United States. *Aliment Pharmacol Ther* 2004;20:99–107.
13. Yoon J, Baik G, Kim Y, et al. Comparison of the eradication rate between 1-week and 2-week bismuth-containing quadruple rescue therapies for Helicobacter pylori eradication. *Gut Liver* 2012;6:434–39.
14. Unge P. What other regimens are under investigation to treat Helicobacter pylori infection? *Gastroenterol* 1997;113:131–48.
15. Edwards P. Eradicating Helicobacter pylori: what is the latest recommended therapy? *Curr Ther* 1996;Jan:49–54.
16. Crowe S. Treatment regimens for Helicobacter pylori. San Diego: UpToDate; 2013.
17. Liou J, Chen C, Chen M, et al. Sequential versus triple therapy for the first-line treatment of Helicobacter pylori: a multicenter, open-label, randomised trial. *Lancet* 2013;381:205–13.
18. Vaira D, Zullo A, Hassan C, Fiorini G, Vakil N. Sequential therapy for Helicobacter pylori eradication: the time is now! *Ther Adv Gastroenterol* 2009;2:317–22.
19. Zullo A, Francesco V, Hassan C, Panella C, Morini S, Ierardi E. Second-line treatment for Helicobacter pylori eradication after sequential therapy failure: a pilot study. *Future Med* 2006;3:251–54.
20. Di Caro S, Franceeschi F, Mariani A, et al. Second-line levofloxacin-based triple schemes for Helicobacter pylori eradication. *Dig Liver Dis* 2009;41:480–85.
21. Micromedex 2.0. 2013 [updated 13 March 2013] Available at: <http://healthcare.thomsonreuters.com/micromedexMobile/> [Accessed 26 March 2013].
22. Australian Medicines Handbook. Adelaide: Pharmaceutical Society of Australia; 2010.

correspondence [afp@racgp.org.au](mailto:afp@racgp.org.au)