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. Usually acquired in childhood, it colonises the gastric mucosa of about 50% of the world’s population at some time in their life. In westernised countries, H. pylori infection has a prevalence of approximately 30%. H. pylori was first identified and isolated from a gastric biopsy specimen in 1983. 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. 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.

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. 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. 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%, which is somewhat less than
the risk of \textit{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.\textsuperscript{1}

\section*{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 \textit{H. pylori} colonisation. The reason by their general practitioner (GP).\textsuperscript{5} Fortunately, as understanding of the natural history of gastric and duodenal ulcers grows, \textit{H. pylori} testing has become more common over the last decade. An \textit{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.\textsuperscript{6} It is also important to screen for \textit{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.\textsuperscript{7}

It would not be appropriate to investigate for \textit{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.\textsuperscript{4} In this context, investigations should first be directed at excluding malignancy, for example with a gastroscopy.

Investigations for \textit{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 \textit{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.

\begin{table}[h]
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\begin{tabular}{|l|l|l|}
\hline
\textbf{Test} & \textbf{Mechanism} & \textbf{Notes} \\
\hline
\textbf{Invasive} & & \\
\hline
\textbf{Rapid urease test} & \begin{itemize}
\item Biopsy specimen is combined with urea and pH is measured
\item \textit{H. pylori} converts urea to ammonia (NH$_3$) + CO$_2$
\item Test is positive for \textit{H. pylori} if pH of the medium becomes more alkaline, indicated by colour change
\end{itemize} & \begin{itemize}
\item Quick and inexpensive
\item Highly sensitive and specific
\item Not suitable for monitoring post-eradication because that would entail further gastroscopy
\end{itemize} \\
\hline
\textbf{Culture} & \begin{itemize}
\item Culturing the organism allows determination of antibiotic sensitivities
\end{itemize} & \begin{itemize}
\item Expensive
\item Not widely available
\item Highly specific, low sensitivity
\end{itemize} \\
\hline
\textbf{Histology} & \begin{itemize}
\item Offers additional information on degree and pattern of inflammation
\end{itemize} & \begin{itemize}
\item Expensive
\item Highly sensitive and specific
\item Requires gastroscopy
\item Can detect early changes of MALT lymphoma
\end{itemize} \\
\hline
\textbf{Non-invasive} & & \\
\hline
\textbf{Serology} & \begin{itemize}
\item Presence of \textit{H. pylori}-specific IgG antibodies
\end{itemize} & \begin{itemize}
\item Inexpensive and widely available.
\item Positive in low titre indicates past exposure to \textit{H. pylori} and not necessarily active colonisation
\item Positive in high titre reflects active colonisation
\item Not suitable for monitoring post-eradication because successful treatment does not alter IgG levels immediately
\end{itemize} \\
\hline
\textbf{Urea breath test} & \begin{itemize}
\item Uses principle of urea metabolism by \textit{H. pylori}
\item Patient ingests radio-labelled (13c) urea followed by a measurement of the concentration of isotope-labelled CO$_2$ exhaled
\item Positive for \textit{H. pylori} if isotope-labelled CO$_2$ present
\end{itemize} & \begin{itemize}
\item High positive predictive value
\item High negative predictive value
\item Suitable and recommended as the post-eradication monitoring test
\item Not widely available
\end{itemize} \\
\hline
\textbf{Stool antigen test} & \begin{itemize}
\item Presence of \textit{H. pylori} antigen in the stool
\end{itemize} & \begin{itemize}
\item Suitable for pre-treatment diagnosis and post-treatment monitoring
\item Unpleasantness associated with the means of specimen collection
\end{itemize} \\
\hline
\multicolumn{3}{|l|}{IgG, immunoglobulin G; MALT, mucosa-associated lymphoid tissue} \\
\end{tabular}
\caption{Commonly used diagnostic tests for \textit{H. pylori}}
\end{table}

\textit{H. pylori} and duodenal ulcers grows, testing has become more common over the last decade. Additional therapies have emerged to address the failures of \textit{H. pylori} eradication with bismuth-based therapies.

The eradication regimens for \textit{H. pylori} have continued to evolve over the past 20 years. Initially, mainstay therapy included histamine H$_2$ receptor blockers with an antibiotic. The rate of successful eradication was 73–84%.\textsuperscript{5} 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 became the most effective means of achieving \textit{H. pylori} eradication.
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. 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 (Table 2).

These guidelines quote pre-treatment clarithromycin resistance in Australia to be 5–7%, and indicate they are likely to rise. 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. However, bismuth is only available in Australia under the Special Access Scheme.

The efficacy of triple therapy has been widely tested and has not proved superior to regimens employed two decades ago. Standard PPI-based triple therapy appears to have a success rate of 70–85%. 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. Comparable findings were reached in an extensive Swedish pooled analysis which compared PPI-based triple therapy to various other traditional therapies for H. pylori. 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, growing resistance to antibiotics used in this treatment is of concern. This has led to a resurgence of interest of late 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.

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. This trial also tested 14-day sequential therapy, which proved even more efficacious with a 90.7% success rate.

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%. If this data series is expanded to per protocol analysis, sequential therapy portends a 93.7% H. pylori eradication rate.

### 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.

The limited evidence-based data currently available in Australia suggests salvage therapy is achieving high success rates. The ACG reports that salvage treatment is 76% effective when implemented after a failed sequential regime. 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. 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.

<table>
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<tr>
<th>Table 2. Currently recommended eradication regimens</th>
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<td><strong>Eradication therapy</strong></td>
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<td>PPI-based triple therapy</td>
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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. 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. 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. Although evidence points towards lower treatment failure rates with newer therapies, it is likely that they too will experience a similar phenomenon. 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, rather consideration be given to trials of sequential or salvage therapy.

Addressing compliance

Good patient compliance is also a vital predictor of outcome. 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.

Side effects are a major cause of non-compliance with eradication regimens. Although they occur in some 5–20% of patients, 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.

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.

**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.

### Table 3. Side effects of common medications used in eradication regimens

<table>
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<tr>
<th>Antimicrobial agent</th>
<th>Side effects</th>
<th>Frequent</th>
<th>Infrequent</th>
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| Proton pump inhibitor (PPI) | ● Cough  
● Pharyngitis  
● Abdominal pain  
● Diarrhoea | ● Paraesthesia  
● Alopecia  
● Haemolytic anaemia |          |
| Clarithromycin       | ● Abdominal pain  
● Altered taste sensation | ● Arrhythmia  
● Anaphylaxis |          |
| Amoxicillin          | ● Rash  
● Diarrhoea | ● Crystalluria  
● Anaphylaxis |          |
| Metronidazole        | ● Thrombophlebitis  
● Nausea  
● Headache  
● Vaginal discharge | ● Optic nerve toxicity  
● Pancreatitis  
● Hepatitis  
● Thrombocytopenia |          |
| Bismuth salts        | ● Dark discolouration of stool, tongue, teeth  
● Diarrhoea  
● Nausea  
● Vomiting | ● Dizziness  
● Headache  
● Neurotoxicity |          |
| Tetracycline         | ● Photosensitivity | ● Azotemia |          |
| Tinidazole           | ● Altered taste sensation  
● Candida vaginitis | ● Confusion  
● Agitation  
● Seizure |          |
| Levofloxacin         | ● Diarrhoea  
● Headache  
● Nausea | ● Arrhythmia  
● Hypoglycaemia  
● Hypersensitivity reaction  
● Tendinitis |          |

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### References


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