**New strategies for *Helicobacter pylori* eradication**

Michael Selgrad and Peter Malfertheiner

*Helicobacter pylori* infection is highly prevalent worldwide and is a major cause of diseases occurring in the upper gastrointestinal tract. Successful eradication therapy improves *H. pylori*-related symptoms in functional dyspepsia, cures peptic ulcer disease and may prevent gastric cancer. During the past decade, the success rate of recommended eradication regimens declined from over 90% to about 80%, a critical threshold for effectiveness of the therapy according to the current guidelines. This is mainly because of the rising antimicrobial resistance and underlines that it is imperative to develop new treatment approaches. The prevention of the initial infection by a suitable vaccination might be the new therapeutic strategy for the future.

**Address**
Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University Magdeburg, Magdeburg, Germany

Corresponding author: Malfertheiner, Peter (peter.malfertheiner@med.ovgu.de)

**Current Opinion in Pharmacology** 2008, 8:593–597
This review comes from a themed issue on Anti-infectives
Edited by Harald Labischinski and Helga Ruebsamen-Waigmann
Available online 12th June 2008
1471-4892/– see front matter © 2008 Elsevier Ltd. All rights reserved.
DOI 10.1016/j.coph.2008.04.010

**Introduction**
The recognition of *Helicobacter pylori* as the key pathogen in gastroduodenal diseases with a variety of clinical manifestations ranging from mild dyspeptic symptoms to severe complications has posed an increasing demand for therapeutic interventions. The development of effective treatment options for *H. pylori* infection has resulted in an immense change in the clinical management of upper gastrointestinal diseases with curative antibiotic therapeutic strategies for low-grade gastric-mucosa-associated lymphoid tissue lymphomas and *H. pylori*-related peptic ulcers.

The wide use of antibiotic therapies for *H. pylori* infection has also increased the number of therapeutic failures. Recent data show a decreasing efficacy of these therapies worldwide [1**,2,3]. This has necessitated the request to improve current therapeutic strategies and to develop new drugs.

Indications for therapies have always been a matter of debate. Even the indication for *H. pylori*-associated peptic ulcer therapy has struggled almost for a decade despite of strong scientific evidence that *H. pylori* eradication provides permanent cure for peptic ulcer disease. First guidelines that recommended *H. pylori* eradication for peptic ulcer disease appeared 10 years following the discovery of the bacterium and first reports of effective treatment by *H. pylori* eradication versus acid inhibition. The first consensus guideline with the extension of indications for *H. pylori* treatment was recommended in 1996 (Maastricht I) [4], and the current updated consensus report extended the indications even for some selected conditions outside the gastroduodenal pathologies (Table 1) [5].

**Current treatment standards for *H. pylori* eradication**

**First choice treatment**
The initial treatment of *H. pylori* has not been changed significantly in the past decade. As already recommended in the original Maastricht Consensus Report, treatment regimens should be simple, well tolerated, easy to comply and cost-effective. The first-line therapy should be a proton pump inhibitor (PPI) triple therapy, consisting of PPI, clarithromycin and amoxicillin/or metronidazole in populations with less than 15–20% clarithromycin resistance rate. As stated by the recent Maastricht III Consensus Report standard triple therapy is more effective if extended to more than seven-day treatment [5]. A single meta-analysis of controlled trials analysing the optimal duration of PPI triple therapy found lower eradication rates with 7-day regimen compared to 14-day regimen (relative risk reduction = 12%; 95% CI 7–17%) [6]. The recently published European HYPER study however reported no difference between one-week and two-week triple treatment for *H. pylori* eradication in terms of efficacy, safety and patient compliance [7**]. At this point of time, according to the Maastricht criteria seven-day treatment is sufficient where local studies show acceptable efficiency.

The increase of clarithromycin resistance varies significantly in different regions. It displays the main risk factor for treatment failure [8,9]. In areas with high clarithromycin resistance rates, metronidazole may be substituted for clarithromycin.

An alternative option for the first-line treatment is bismuth-containing quadruple therapy. A large, randomised, controlled trial compared seven-day bismuth-containing quadruple therapy with seven-day PPI triple and 14-day...
bismuth triple therapy [10]. The study demonstrated comparable eradication rates for PPI triple and quadruple therapy, and both regimens were superior to 14-day bismuth triple. Furthermore the two-week bismuth triple therapy was less well tolerated than both one-week regimens. Bismuth-containing quadruple therapy should be considered as the treatment option in areas with low metronidazole resistance, high clarithromycin resistance, and in populations where cost considerations are of prime importance. But it has to be considered that bismuth is not currently available in many countries.

### Treatment after the failure of first-line options

In case of failure, bismuth-based quadruple therapy is the primary recommended treatment option for second-line therapy if not used as first-line. The main problem of the quadruple regimen is the need of a larger number of tablets and the more complex regimen compared to the other available first-line regimens. Recently a single tablet has been developed containing bismuth biskalci-trate, metronidazole, and tetracycline given with omeprazole. In two multicentre, randomised, active-controlled trials, this therapy was comparable with the PPI triple therapy slightly superior in efficiency (eradication rate: 87.7% versus 83.2%) and patient compliance (adverse events: 58.5% versus 59.0%). Although the amount of capsules was reduced, still a large number of tablets need to be taken per day (three tablets four times a day, plus PPI twice a day) [11,12]. Currently this therapy is available only in North America. In countries where bismuth-based therapies are not available, the combination PPI-amoxicillin—metronidazole has been suggested to be the alternative treatment option.

### Third-choice treatment (salvage regimens)

According to the European Guidelines following second failure, rescue treatment should be based according to antimicrobial susceptibility testing, if available. Regimens tested to be effective are either combinations that include a fluoroquinolone or rifabutin (Table 2).

### Reasons for the failure of current eradication therapy regimens

Several factors are responsible for *H. pylori* eradication failure and there is a strong relationship between therapy failure and the bacteria, the host and/or the administered therapy.

Recent data suggest a decreasing therapy efficacy of the seven-day triple therapy as recommended in the European guidelines. The success rate in most European, Asian and North American countries is constantly declining and low cure rates with 20–45% have been recently reported [13,14].

A major cause for this phenomenon is the increasing antimicrobial resistance seen in many countries, in particular against clarithromycin [15]. The *H. pylori* resistance to clarithromycin in Europe displays important regional differences with higher rates in southern (more than 20%) than in northern (less than 5%) Europe [16,17]. In North America, it is estimated to be between 4% and 12% [18]. Clarithromycin is the key antibiotic in the *H. pylori* treatment and a good correlation between bacterial resistance to clarithromycin and eradication failure does exist. A systematic review reported a 56% decrease in eradication rates if clarithromycin resistance was present. Another analysis found even a 70% decline in eradication rates if clarithromycin resistance was detected and a clarithromycin-containing regimen was used [16,19].

### Table 1

**Recommendations for *Helicobacter pylori* eradication according to the Maastricht III Consensus Report**

<table>
<thead>
<tr>
<th>Reason for failure</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninvestigated dyspepsia for populations with a prevalence of <em>H. pylori</em> &lt;20%</td>
<td>Bismuth triple therapy</td>
</tr>
<tr>
<td>Duodenal and gastric ulcer</td>
<td>Bismuth triple therapy</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>Bismuth triple therapy</td>
</tr>
<tr>
<td>Gastric MALT lymphoma</td>
<td>Bismuth triple therapy</td>
</tr>
<tr>
<td>After gastric cancer resection</td>
<td>Bismuth triple therapy</td>
</tr>
<tr>
<td>First-degree relatives of patients with gastric cancer</td>
<td>Bismuth triple therapy</td>
</tr>
<tr>
<td>Unexplained iron-deficiency anaemia and idiopathic thrombocytopenic purpura</td>
<td>Bismuth triple therapy</td>
</tr>
<tr>
<td>Patients on long-term NSAIDs therapy, who have gastrointestinal bleeding and/or peptic ulcer</td>
<td>Bismuth triple therapy</td>
</tr>
<tr>
<td>Patients wishes (after explanation of risks and benefits)</td>
<td>Bismuth triple therapy</td>
</tr>
</tbody>
</table>

### Table 2

**Efficacy of levofloxacin-based or rifabutin-based rescue regimens after two or more *H. pylori* treatment failures**

<table>
<thead>
<tr>
<th>Study (country)</th>
<th>Ref. no.</th>
<th>No. of previous eradication failures</th>
<th>Third-line therapy</th>
<th>% eradication (no. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gatta et al. (Italy)</td>
<td>[44]</td>
<td>2</td>
<td>Levofloxacin triple therapy</td>
<td>76% (115/151)</td>
</tr>
<tr>
<td>Gisbert et al. (Spain)</td>
<td>[45]</td>
<td>2</td>
<td>Levofloxacin triple therapy</td>
<td>67% (37/55)</td>
</tr>
<tr>
<td>Zullo et al. (Italy)</td>
<td>[46]</td>
<td>2–3</td>
<td>Levofloxacin triple therapy</td>
<td>83.3% (30/36)</td>
</tr>
<tr>
<td>Bilardi et al. (Italy)</td>
<td>[47]</td>
<td>1–6</td>
<td>Levofloxacin triple therapy</td>
<td>70% (31/44)</td>
</tr>
<tr>
<td>Coelho et al. (Brazil)</td>
<td>[48]</td>
<td>≥2</td>
<td>Levofloxacin triple therapy</td>
<td>83% (10/12)</td>
</tr>
<tr>
<td>Qasim et al. (Ireland)</td>
<td>[49]</td>
<td>2</td>
<td>Rifabutin triple therapy</td>
<td>76% (143/181)</td>
</tr>
<tr>
<td>Perri et al. (Italy)</td>
<td>[50]</td>
<td>≥2</td>
<td>Rifabutin triple therapy</td>
<td>71% (29/41)</td>
</tr>
<tr>
<td>Canducci et al. (Italy)</td>
<td>[51]</td>
<td>≥2</td>
<td>Rifabutin triple therapy</td>
<td>70% (7/10)</td>
</tr>
<tr>
<td>Gisbert et al. (Spain)</td>
<td>[52]</td>
<td>2</td>
<td>Rifabutin triple therapy</td>
<td>79% (11/14)</td>
</tr>
</tbody>
</table>
The estimated prevalence of *H. pylori* resistance to metronidazole is very high in developing countries (ranging from 50% to 80%) [20], compared to Europe and USA (around 15–40%) [21]. In Japan, antibiotic resistance rates were described to be lower with 9–12% [22]. A drop in efficacy of up to 50% was found for bismuth-based triple and proton pump inhibitor based triple therapies, if nitroimidazole resistance was present [19]. Interestingly, the majority of patients in whom the first-line therapy fails develops secondary resistance to the recommended antibiotics. In an Irish study, after failure of first-line therapy, the clarithromycin resistance rate increased from 3.4% to 58.3% leading to a significant cause of treatment failure [23]. Pilotto *et al.* described that 70% of patients who failed first-line therapy developed antibiotic resistance, with resistance rates to clarithromycin and metronidazole of 64% and 35% [24]. A recent meta-analysis by Fischbach *et al.* showed that drug-resistance is a strong predictor for therapy efficacy of triple therapies [1]. The authors further reported that resistance to either clarithromycin or metronidazole, but not both simultaneously, may be fortunately overcome by using quadruple therapy.

Levofloxacin has recently become an important part of *H. pylori* treatment in case of therapy failure. However, this antibiotic drug has a wide use for other infections, and thus the resistance rate is already relatively high (around 15%) [25]. The prevalence of resistance to amoxicillin and tetracycline has remained low over the years. Most studies show low rates with less than 2% [26,27].

Other factors affecting *H. pylori* eradication have been suggested. For example, a meta-analysis of various studies reported that smoking increases the treatment failure rate for *H. pylori* eradication [28]. 22 studies have been analysed and the summary OR for eradication failure among smokers relative to non-smokers was 1.95 (95% confidence interval [CI]: 1.55–2.45; *P* < .01). Poor patient adherence/compliance is one of the most important issues in therapy failure. Several studies reported that frequent dosing (three or four times a day) or too many tablets per day and long duration of therapy are associated with reduced compliance [29]. The occurrence of adverse events such as diarrhoea with amoxicillin, metallic taste with metronidazole, and taste perversion with clarithromycin may also play a role [30]. Another important factor influencing the success of eradication is the underlying disease state of the treated patient. It has been suggested that eradication rates are lower in patients affected by non-ulcer dyspepsia compared to patients with ulcer dyspepsia [31].

PPIs are a substantial part of most of the current treatment regimens and the increase of gastric pH induced by PPIs is crucially important to allow antibiotics exerting their best activity [8]. Several PPIs are metabolized by the cytochrome P450 system in the liver, and genetic polymorphisms of the cytochrome (CYP)2C19 can affect *H. pylori* eradication. Genetic-determined poor metabolic activity leads to high plasma concentrations of the PPI with a subsequently prolonged effect of the drug associated with decreased treatment failure [32].

**New treatment options for *H. pylori***

**Sequential therapy for *H. pylori***

An innovation for *H. pylori* therapy is the sequential therapy. The sequential regimen is a dual 10-day therapy consisting of a PPI and amoxycillin 1 g (both twice daily) given for the first five days followed by a triple therapy including a PPI, clarithromycin 500 mg, and tinidazole 500 mg (all twice daily) for the remaining five days [33]. Series of studies have been carried out in Italy showing excellent eradication rates with the sequential therapy. Zullo *et al.* performed a pooled-data analysis reporting *H. pylori* eradication in 1687 out of 1805 treated patients, with an overall eradication rate of 93.5% at intention to treat (ITT) analysis [34**]. A head-to-head comparison of sequential therapy with standard 10-day triple therapy found that 10-day sequential regimen had a significantly higher eradication rate compared with the 10-day triple therapy (91% versus 78% by modified ITT analysis) [35].

Another head-to-head analysis has been performed between the sequential regimen and seven-day triple therapy. The infection was cured in 93.7% of the patients treated with sequential therapy compared to 75.9% in patients with seven-day triple therapy (ITT analysis; *P* < .0001). More importantly, the sequential therapy also seems to be effective in patients with clarithromycin-resistance. In patients with clarithromycin-resistant strains eradication rates of 89% were achieved by sequential therapy compared to 29% with standard triple therapy. At this point, most of the studies about sequential therapy have been performed in Italy, and if the promising results can be confirmed in other countries as well, sequential therapy may be considered as a new option for first-line treatment. However, more experience in different world-regions needs to be gathered, as in a recent paper by Shehada *et al.* the sequential therapy was shown to be unsuccessful as a therapy for children and young adults who have failed previous treatment regimen [36].

Among new antibiotics, finafloxacin a novel fluoroquinolone has been developed as a monotherapy for *H. pylori* eradication. After promising *in vitro* and animal study data, the new drug is ready for clinical testing [37].

**Vaccination**

Prophylactic vaccination would bias the potential to prevent *H. pylori*-related complications and as suggested by pharmacoeconomic studies a prophylactic vaccine would be of major cost-effectiveness in developed countries. It has been estimated that a 10-year vaccination programme in the USA could decrease the *H. pylori* prevalence to 0.07% by the end of the 21st century [38].
H. pylori infection is typically acquired during childhood and thus infants can be considered as the targeted population for a prophylactic immunisation. Animal vaccination experiments have proven that vaccines have a therapeutic effect and that the concept of vaccination is possible [39–41]. Whether infected adults would benefit from a therapeutic vaccination is uncertain. However, the exact mechanism of vaccine-induced protection is so far poorly understood, because several factors such as various cytokines (i.e. IL-4, IL-5, IL-12, IL-13, IL-18, TNF-α) and immunoglobulins do not contribute to vaccine-induced protection. For a more detailed discussion about this topic, we refer two recent reviews [42,43]. The safety and effectiveness of different H. pylori-vaccines have been tested in a few clinical trials. At this point, considerable knowledge has been developed over the past decade about the pathogenesis and immunology of H. pylori infection. The concept of H. pylori vaccination deserves full attention.

Conclusion
H. pylori is the major pathogen for gastroduodenal diseases worldwide and causes a high morbidity and mortality. The development of an effective antibiotic treatment has changed remarkably the management of peptic ulcer disease and other H. pylori-related diseases. Current first-line treatment regimens are effective and safe, but over the past decade they are declining in efficacy, mainly because of an increasing antibiotic resistance. Novel therapeutic strategies have provided promising results and new developments are ongoing. The global challenge is on for the development of a safe vaccine.

References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:


7. Zagari RM, Bianchi-Porro G, Fiocca R, Gasbarrini G, Roda E, Bazzoli F: Comparison of 1 and 2 weeks of omeprazole, amoxicillin and clarithromycin treatment for Helicobacter pylori eradication: the HYPER Study. Gut 2007, 56:475-479. Analysing 909 H. pylori-positive patients with duodenal ulcer, the authors showed that one-week and two-week triple treatments (containing both omeprazole, amoxicillin, clarithromycin) are similar in terms of efficacy, safety and patient compliance.


New strategies for *Helicobacter pylori* eradication

Selgrad and Malfertheinier 597


35. The authors performed a pooled-data analysis of all studies on the sequential therapy regimen. More than 1800 patients have been treated with this regimen and eradication rates constantly higher than 90% at ITT analysis have been achieved. In this analysis the sequential regimen achieved higher eradication rates than standard triple therapies.


43. Kabir S: The current status of *Helicobacter pylori* vaccines: a review. *Helicobacter* 2007, 12:89-102. This is a state-of-the-art review about the current status of *H. pylori* vaccine development.


