Eradication of *H. pylori* infection: the challenge is on if standard therapy fails

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***Abstract*:** The recommended standard triple therapy for *Helicobacter pylori* infection, consisting of a proton pump inhibitor, clarithromycin and amoxicillin or metronidazole, can reach eradication rates in over 90%. However, in recent years resistance to antibiotics has increased and eradication rates have declined. Approximately one in five patients need a second-line therapy because eradication therapy fails. Second-line treatment with a bismuth-based quadruple therapy leads to satisfactory eradication rates, but bismuth is not available in many countries. Modern second- and third-line treatments can only be successful if they are adapted to the current resistance situation and they need to evolve continuously. Moreover, pharmacodynamic effects due to polymorphisms of the cytochrome P450 system are important. Because therapy adherence is significantly associated with therapy success, modern regimens if possible should be easy to take and well tolerated. In recent years, various novel salvage-therapy regimens have been investigated that significantly improve treatment options.

***Keywords*:** *Helicobacter pylori*, triple therapy, proton pump inhibitor, clarithromycin, metronidazole, amoxicillin, bismuth, cytochrome P450

Introduction

According to the Maastricht III Consensus [Malfertheiner *et al*. 2007] the recommended first-line therapy for *Helicobacter pylori* eradication is a proton pump inhibitor (PPI), clarithromycin and amoxicillin or metronidazole, if the primary resistance to clarithromycin in the area is lower than 15–20%. There is a small advantage in using metronidazole instead of amoxicillin and, therefore, this combination was found to be preferable in areas where the prevalence of metronidazole resistance is lower than 40%. Treatment success of a 14-day treatment may be more effective compared to a 7-day treatment [Ford and Moayyedi, 2003], but a 7-day treatment may be acceptable where local studies have shown high efficacy. When available, bismuth-based quadruple therapies can be used as alternative first-line therapies [Malfertheiner *et al*. 2007].

If first-line therapy with PPI triple therapy fails, according to the Maastricht III Consensus a second treatment with a bismuth-based quadruple therapy is recommended. If bismuth was previously used or if bismuth is not available, PPI plus amoxicillin or tetracycline and metronidazole is recommended as an alternative. For patients who fail second-line treatment, current guidelines suggest an individually tailored case-by-case approach at the specialist care level based on antimicrobial susceptibility testing [Malfertheiner *et al*. 2007].

When the Maastricht III guidelines were made in, 2005, only limited data or studies on retreatment if initial therapy failed were available. Therefore, the recommendations had to be given at a rather low level of evidence (2c, based on noncontrolled cohort studies). In recent years, a number of controlled studies increased our knowledge about *H. pylori* retreatment after failure of initial therapy. These new data have to be taken into account if a salvage therapy is necessary. Although current data are not sufficient for general recommendations, there are a number of new aspects that influence therapy decisions and offer new effective treatment options for an increasing number of patients who fail first-line therapy.

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Why do eradication therapies fail?

Even with the correct use of drug combinations, infection cannot be eradicated in up to 23% of patients that receive first-line eradication therapy [Parente *et al*. 2003]. In patients that receive retreatment, eradication rates further decline. Analysis and elimination of the factors that led to therapy failure in the individual patient is important so as to increase the chance of successful eradication with a subsequent treatment. The key factors that increase the risk of *Helicobacter pylori* eradication therapy failure are as follows:

- discontinuation of therapy because of adverse effects
- poor adherence to therapy
- pretreatment antibiotic-resistant *H. pylori*
- pharmacodynamic effects.

These will now be discussed.

Adverse events

Side-effects are frequent with *H. pylori* eradication therapy and increase with the number of previous therapies [Gisbert *et al*. 2008a]. While first line-therapies lead to approximately one-quarter to one-third of patients reporting adverse advents, this increases to more than half of the patients who receive third-line therapy [Gisbert *et al*. 2008a]. This is especially important because side-effects reduce therapy adherence and decrease efficacy of a therapy [Cheon *et al*. 2006]. Therapy additives, for example probiotics or lactoferrin, can significantly reduce side-effects and improve eradication rates [Tong *et al*. 2007; Tursi *et al*. 2007; Di Mario *et al*. 2006]. In a meta-analysis that included randomized trials with a total of, 1671 patients, supplementation with probiotics was shown to reduce therapy-related side effects by 15% and increase eradication rates by almost 10% [Tong *et al*. 2007]. Therefore, add-on medications provide an excellent tool to minimize side effects and to improve eradication rates in patients that experienced side-effects with previous unsuccessful *H. pylori* treatments.

Poor adherence to therapy

Complicated therapy regimens and high pill burden reduce adherence and therapeutic efficacy [Bartlett *et al*. 2001]. Some of the eradication therapies are rather complex and have a high pill burden. For example, quadruple therapies containing bismuth salts that are currently recommended in second-line therapy can have a pill burden of up to 10 pills per day. Together with a high frequency of side-effects this reduces therapy adherence [Navarro-Jarabo *et al*. 2007]. In recent years, many studies were conducted to look at improving second-line and salvage therapies by making them simpler, and to reduce pill burden as well as side effects. Several of the alternative therapies used in second-line therapy can reach higher eradication rates than conventional quadruple therapy. Currently, the simplest therapy with the lowest pill burden is a once-daily therapy with only three pills per day [Miehlke *et al*. 2008]. Despite the low number of pills, this therapy is highly effective and reaches an eradication rate of 77.7% in pretreated patients with persisting *H. pylori* infection resistant to both metronidazole and clarithromycin.

As well as type of therapy, diagnosis (duodenal ulcer/nonulcer dyspepsia) was demonstrated to be an independent predictor of eradication failure; however, this was not the case in other studies [Chung *et al*. 2007; Gisbert *et al*. 1999]. A potential explanation could be that the patient's diagnosis is linked to therapy motivation. While motivation is difficult to measure, it is without doubt that motivation increases therapy adherence. Therefore, after failure of *H. pylori* eradication, the therapy motivation of the patient should be checked, and improved if necessary, before initiating the next eradication attempt.

Pretreatment antibiotic-resistant H. pylori

Pretreatment antibiotic-resistant *H. pylori* reduces the cure rate of infection by up to 66% [Realdi *et al*. 1999]. Metronidazole resistance reduces effectiveness by an average of 37.7%, whereas clarithromycin resistance reduces it by an average of 55% [Dore *et al*. 2000]. Resistance increases with the number of unsuccessful treatments. After two eradication failures one can assume that almost all patients carry *H. pylori* strains that are resistant to metronidazole and clarithromycin [Cammarota *et al*. 2004]. Resistance to quinolone antibiotics can reach up to 31% [Cammarota *et al*. 2004]. Resistance to rifabutin, tetracycline and amoxicillin is rare [Cammarota *et al*. 2004; Heep *et al*. 2000]. Resistance to clarithromycin is associated with metronidazole resistance in 85–89% [Heep *et al*. 2000].

Eradication rates can be increased significantly by susceptibility-based treatments [Lamouliatte

et al. 2003]; however, in clinical practice susceptibility testing is often not available or is not performed for other reasons. Also, a number of studies showed that empirical second- or third-line therapies may have excellent therapeutic results; however, it must be kept in mind that for some of the patients who were treated empirically susceptibility testing could have predicted therapy failure. This is nicely shown in patients who receive a second-line PPI-based triple therapy containing levofloxacin. Statistically, salvage therapies containing levofloxacin are highly effective empirical therapies because levofloxacin-resistant strains are still rare [Cammarota *et al.* 2004; Heep *et al.* 2000]. However, in the small number of patients who are infected with levofloxacin-resistant *H. pylori*, levofloxacin-containing triple therapy is useless because therapy fails in 67–100% [Perna *et al.* 2007; Wong *et al.* 2006].

If empirical second- or third-line therapies are used, treatment history is critically important. An excellent example is the study of Treiber *et al.* who showed that in patients who failed a standard PPI-based triple therapy containing clarithromycin and metronidazole, second-line quadruple therapy containing tetracycline and metronidazole was successful only in 39% of the patients. In this study, 90% of the patients could be cured if the metronidazole was replaced by furazolidone [Treiber *et al.* 2002].

Pharmacodynamic effects

PPIs undergo extensive hepatic biotransformation by the cytochrome P450 (CYP) isoenzymes CYP2C19 and CYP3A4 [Furuta *et al.* 2005]. Genetic polymorphism of CYP2C19, the so-called extensive metabolizer genotype, can significantly increase the activity of CYP2C19 and thus result in a rapid inactivation of PPIs and in consequence reduces acid inhibition. Effective acid inhibition, however, is crucial for successful *H. pylori* eradication because it increases the bioavailability of antibiotics in the gastric mucus by altering gastric volumes and increasing the stability of some antibiotics. The antibiotic effect of amoxicillin on *H. pylori* depends mainly on the time that drug levels are above the minimum inhibitory concentration (MIC), but not on the area under the curve (AUC) or maximum plasma concentration (C_{max}) of the antibiotic [Furuta *et al.* 2005]. Therefore, a shorter time of sufficient acid suppression due to the extensive metabolizer genotype can have a strong impact on the success of *H. pylori* eradication therapy. To date, systematic studies that evaluate the impact of the extensive metabolizer genotype on *H. pylori* eradication are rare. Studies from Japan show that patients who fail eradication therapy are often extensive metabolizers. In some studies, up to 100% of the patients who fail eradication therapy are homozygous or heterozygous for the extensive metabolizer genotype [Togawa *et al.* 2005; Furuta *et al.* 2003]. Most likely the combination of a resistant strain of *H. pylori* and extensive metabolizer genotype results in therapy failure in these patients. Adapting the PPI dose and dosing scheme to the metabolization rate in patients with therapy failure or changing to a PPI with a different metabolization pattern are useful strategies to increase eradication rates in patients with CYP2C19 polymorphisms who have already failed previous eradication therapies [Miehlke *et al.* 2006; Togawa *et al.* 2005; Furuta *et al.* 2003].

Interleukin-1β or multidrug resistance (MDR) 1 gene polymorphisms are further factors that may influence eradication rates by pharmacodynamic effects; however, these polymorphisms seem to be less important [Furuta *et al.* 2007, 2004; Take *et al.* 2003]. Currently, genotyping of CYP2C19 or other polymorphisms is only a research instrument, but it may become a valuable clinical tool to improve eradication rates in *H. pylori* salvage therapy.

In an expert setting where methods like susceptibility testing and CYP2C19 genotyping are available, eradication therapies can be individually tailored and therapy regimens adjusted to the individual needs of the patient. However, to reach the wide majority of *H. pylori*-infected patients it is important to have treatment strategies that can be done by primary care physicians who usually do not have these specialized methods available. Therefore, for primary care, clear treatment strategies are important that are simple and do not depend on specialized methods. In recent years, various novel salvage-therapy regimens have been evaluated that significantly improve the treatment options.

New developments in bismuth-containing therapies

Bismuth-based quadruple therapy has proven to be an effective second-line therapy

[Boixeda *et al*. 2002; Dore *et al*. 2002]. Currently, the recommended second-line quadruple therapy is a PPI, together with bismuth, tetracycline and metronidazole; however, other combinations of antibiotics may be effective as well. Recently three quadruple-therapy regimens were compared in a randomized study. All regimens contained bismuth subcitrate and lansoprazole plus two antibiotics. The combination with metronidazole and tetracycline as well as the combination with tetracycline and amoxicillin, with eradication rates of 82.1% and 81.5% respectively, were slightly more effective than a third quadruple therapy containing metronidazole and amoxicillin that resulted in an eradication rate of 74.7% [Uygun *et al*. 2008]. A culture-guided third-line quadruple regimen including omeprazole, bismuth, doxycycline and amoxicillin was effective in 91% even in subjects with resistance to multiple antibiotics [Cammarota *et al*. 2004]. Quadruple therapy with esomeprazole, bismuth, amoxicillin, and levofloxacin was inferior to the recommended second-line quadruple therapy with the combination of PPI, bismuth, tetracycline and metronidazole in a controlled study with an intention-to-treat eradication rate of 56% *versus* 90%, respectively [Yee *et al*. 2007]. In patients who failed PPI-based first-line triple therapy containing clarithromycin and metronidazole, second-line quadruple therapy according to the Maastricht consensus containing metronidazole and tetracycline was ineffective with eradication rates of only 39%. This may be explained by the likelihood of metronidazole resistance in those patients. In consequence, substitution of metronidazole by furazolidone increases the eradication rate to 90% [Treiber *et al*. 2002].

Despite good treatment results, bismuth-based quadruple therapy also has disadvantages. Efficacy of quadruple therapies containing bismuth salts are often limited by poor patient compliance due to side-effects, and number of tablets per day [Cheon *et al*. 2006; Perri *et al*. 2001]. Moreover, bismuth is not available in all countries. Therefore, PPI-based triple therapies that have less pill burden, are easier to take and are believed to have fewer side-effects have been evaluated as alternative treatment options. There are several randomized head-to-head studies that compare conventional quadruple second-line therapy containing omeprazole, bismuth citrate, tetracycline and metronidazole with PPI-based triple therapy containing a PPI and two antibiotics. Generally, these studies show that novel second-line triple-therapies have higher eradication rates and are superior with respect to side-effects [Kang *et al*. 2007; Cheon *et al*. 2006; Wong *et al*. 2006; Nista *et al*. 2003; Perri *et al*. 2001]; however, there are also individual studies that show the opposite results [Navarro-Jarabo *et al*. 2007] or have comparable results for both therapy regimens [Kang *et al*. 2007; Wong *et al*. 2003]. Good results for PPI-based triple therapies in randomized head-to-head studies were found for the combinations of amoxicillin plus rifabutin [Perri *et al*. 2001], moxifloxacin plus amoxicillin [Kang *et al*. 2007; Cheon *et al*. 2006], levofloxacin plus amoxicillin [Saad *et al*. 2006; Wong *et al*. 2006], and rifabutin plus levofloxacin [Wong *et al*. 2003].

Another option to reduce pill burden and make bismuth-based therapy simpler is to use ranitidine bismuth citrate instead of a PPI and bismuth. A randomized study that compared a 7-day course of second-line therapy with omeprazole, bismuth, tetracycline and metronidazole *versus* ranitidine bismuth citrate, tetracycline and metronidazole showed a significantly better eradication rate in those patients who received ranitidine bismuth citrate (83% *versus* 57%, respectively). Surprisingly, the authors stated that adverse effects were infrequent and mild with both regimens [Gisbert *et al*. 1999]. A second controlled study comparing ranitidine bismuth citrate, tetracycline and metronidazole with a PPI-based triple therapy containing omeprazole, levofloxacin and amoxicillin showed similar results in both groups for cure rates, side-effects and adherence [Gisbert *et al*. 2007]. Ranitidine bismuth citrate, amoxicillin and tinidazole resulted in comparable eradication rates to a quadruple-therapy regimen [Perri *et al*. 2003].

New combinations of antibiotics in PPI-based triple therapies that can be used after failure of standard therapy

PPI, levofloxacin and amoxicillin

Triple therapy containing a PPI, levofloxacin, and amoxicillin has been proven to be effective as empirical second-line and third-line therapies [Gisbert *et al*. 2008a, 2008b; Perna *et al*. 2007; Watanabe *et al*. 2003]. A treatment for 10 days resulted in eradication rates of 77% in patients in whom a first treatment with PPI, clarithromycin

and amoxicillin had failed [Gisbert *et al.* 2008b]. Therapy duration of 7 days seemed to be inferior to 10-days therapy [Saad *et al.* 2006]. Eradication therapy with PPI, levofloxacin and amoxicillin is not effective in levofloxacin-resitant *H. pylori* strains [Perna *et al.* 2007; Wong *et al.* 2006]; thus, pretreatment testing for levofloxacin resistance is recommended [Wong *et al.* 2006].

PPI, moxifloxacin and amoxicillin

Empirical second-line therapies with PPI, moxifloxacin and amoxicillin result in eradication rates of 71.9% to 75.6% [Kang *et al.* 2007; Cheon *et al.* 2006]. In head-to-head comparison PPI-based triple therapy with moxifloxacin and amoxicillin was at least equal in terms of eradication rate and superior in terms of side-effects to bismuth containing quadruple therapy [Kang *et al.* 2007; Cheon *et al.* 2006].

PPI, moxifloxacin and rifabutin

Currently, PPI-based triple therapy with moxifloxacin and rifabutin is the only once-daily eradication therapy with proven efficacy even in pretreated patient with persistent *H. pylori* infection resistant to both metronidazole and clarithromycin. The regimen resulted in an eradication rate of 77.7% in the intention-to-treat analysis [Miehlke *et al.* 2008]. To date, however, there are no head-to-head studies for this regimen. Also, the therapy could be problematic in patients with the extensive metabolizer genotype.

PPI, levofloxacin and rifabutin

Second-line triple therapy with levofloxacin and rifabutin has been shown to be equally effective to quadruple therapy with eradication rates of 91% for both regimens [Wong *et al.* 2003].

PPI, amoxicillin and rifabutin

Triple therapy consisting of standard-dose PPI, amoxicillin and rifabutin twice daily for 10 days successfully eradicates *H. pylori* in 72% of patients (intention-to-treat analysis) [van der Poorten and Katelaris, 2007]. This can be increased to intention-to-treat eradication rates of 90% with 12 days therapy and three times daily administration of amoxicillin and PPI [Borody *et al.* 2006], or by increasing the rifabutin daily dosage from 150 to 300 mg [Perri *et al.* 2001]. Rifabutin 150 mg daily is not recommended [Navarro-Jarabo *et al.* 2007; Perri *et al.* 2001]. If PPI-based triple-therapy with amoxicillin and rifabutin is used as a third-line therapy (i.e. after failure of the standard first-line therapy and consecutive quadruple-therapy), efficacy can drop to a cure rate of only 45% [Gisbert *et al.* 2006b]; however, there may be regional differences that have to be further evaluated [Miehlke *et al.* 2006; Gisbert *et al.* 2003; Perri *et al.* 2000]

Other interesting antibiotics and novel treatment strategies

Faropenem is the first orally-active carbapenem antibiotic. It has been available under the trade name Farom in Japan since, 1997. In a Japanese study, a second-line therapy with rabeprazole, amoxicillin and faropenem reached an intention-to-treat eradication rate of 91.3% [Togawa *et al.* 2005]. Morover, the faropenem-containing treatment regimen was effective despite the fact that all patients in the study were homozygous or heterozygous for the extensive metabolizer genotype.

Other interesting antibiotics for salvage therapy are tinidazole [Nista *et al.* 2003; Watanabe *et al.* 2003] and nitrofuran [Ebrahimi-Dariani *et al.* 2003; Isakov *et al.* 2002; Treiber *et al.* 2002]. A new sequential first-line treatment strategy was shown to achieve higher eradication rates compared to the standard regimen [Zullo *et al.* 2003]. Until now, there have been no studies that evaluated sequential treatments in patients that already failed one or more eradication therapies.

Conclusion

The authors recommend the following steps in treating patients who have already failed eradication therapy:

- Carefully analyse the individual reasons that led to eradication failure(s).
- Use susceptibility testing whenever possible.
- Do not use antibiotics previously used with potential post-therapeutic resistance.
- Ensure sufficient acid suppression.
- Motivate the patient in order to increase therapy adherence.

Conflict of interest statement

Peter Malfertheiner receives research grants from AstraZeneca. Speakers bureau with AstraZeneca, Nycomed, Abbott.

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