Re-eradication of *Helicobacter pylori* Infection following Initial Treatment Failure: Treatment Options in Clinical Practice

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Helicobacter pylori is the major causative factor in the pathogenesis of gastritis and peptic ulcer disease. Eradication of the organism results in ulcer healing and reduces the risk of ulcer recurrence and complications [1]. During the last decade researchers tested many different antibiotic combinations in the search for the most effective regimen for eradicating *H. pylori*. The current recommended first-line therapy, which was also proposed by the European *Helicobacter Pylori* Study Group, is a proton pump inhibitor combined with clarithromycin and amoxicillin, or metronidazole. However, controlled studies have shown that even with this treatment there is a significant failure rate of about 10–25%; this rate is even higher in clinical practice [2]. In these cases, repeated courses of antibiotic therapy will be needed to achieve eradication once a decision to treat has been made. In contrast to first-line eradication regimes, there is relatively little data reporting the efficacy of second-line therapy. In this review we describe the current policy in the re-treatment of *H. pylori* infection following an initial treatment failure.

First-line therapy

Selection of a first-choice treatment regimen should be based on effectiveness, since efficacy has been shown to be the single most important determinant of cost-effectiveness. It will also minimize development of secondary resistance to metronidazole and clarithromycin. Currently, the treatment regimes that were shown in randomized controlled trials to be most effective consist of two antibiotics combined with a proton pump inhibitor. The PPI-based triple therapies include: one week of a PPI twice daily, together with amoxicillin (2 x 1,000 mg daily) and clarithromycin (2 x 500 mg daily) (P-AC); or alternatively, one week of a PPI in standard dose twice daily, together with metronidazole (2 x 400 mg daily) and clarithromycin (2 x 250 mg daily) (P-CM).

In a systematic review that included 561 studies and 770 treatment arms involving 39,614 patients, Houben et al. [3] summarized the eradication rates of *H. pylori* with various triple therapies; the results of PPI-based triple therapies are summarized in Table 1. As seen in this Table, an initial attempt at eradicating *H. pylori* with these regimes failed in approximately 10–20% of patients. Incomplete treatment due to poor compliance or side effects, and antimicrobial resistance are the most important reasons for treatment failure. The prevalence of metronidazole resistance varies from 10% to 90% in different countries. Since triple therapy is reported to be significantly less effective against metronidazole-resistant strains of *H pylori*, it is advisable not to include metronidazole in the treatment regimen in localities where the prevalence of metronidazole resistance is high. Primary resistance to clarithromycin is much less common than metronidazole resistance, ranging from 7% to 14%, and there is a trend of rising resistance due to the widespread use of clarithromycin in the treatment of upper respiratory tract infections. Acquired (secondary) resistance to clarithromycin frequently develops in individuals after initial treatment failure, due to the decreased affinity of the drug for the point mutated 23 S rRNA of the bacterial ribosome. In a recent study from Israel, Samra and colleagues [4] found that resistance to metronidazole and clarithromycin was much higher in the isolates from previously treated than from untreated patients: 60.7% and 38.2% for metronidazole (minimal inhibitory concentration = 8 mg/L) and 46.4% and 8.2% for clarithromycin. Thus, when designing an anti-*H. pylori* treatment strategy, it should be thought of as a "treatment package" and the results of both first-line and second-line treatments together should be considered. In light of this principle, the European *Helicobacter Pylori* Study Group recommended that the combination of PPI with clarithromycin and amoxicillin (P-CA) should be preferred as first-line therapy rather than the use of clarithromycin and metronidazole (P-CM). This recommendation is based on the fact that initial regimens containing both clarithromycin and metronidazole were associated with significantly worse results overall, with lower eradication rates after logically chosen second-line therapy and sensitivity-directed third-line therapy.

Second-line therapy

As mentioned above, the choice of second-line treatment depends on which treatment was used initially. In principle, if the initial regimen that was given to patients contained clarithromycin or metronidazole, there are mainly two options: a) prescribing a second course of PPI-based triple therapy and avoiding antimicrobial agents against which prior therapy may have induced resistance, for example, replacement of clarithromycin with

Table 1. Eradication rate of various PPI-based triple therapies

Treatment code	No. of arms	No. of patients	Eradication rate (%) ITT	Eradication rate (%) PP
P-AC-1	113	6,839	81	84
P-AC-2	59	2,823	85	91
P-CM-1	119	6,990	86	90
P-CM-2	23	872	83	90

A = amoxicillin, M = metronidazole, T = tetracycline, P = PPI, C = clarithromycin, 1 = 1 week, 2 = 2 weeks, ITT = intention to treat, PP = per protocol

PPI = proton pump inhibitor

Table 2. Efficacy of second-line regimens for *H. pylori* eradication

Regimen	No. of studies	No. of patients	No. eradicated	Eradication rate (%)
PAM	8	167	125	74.9
PAC	6	159	126	79.2
PBMTc	24	597	444	74.4
BAM	3	201	157	78.1

P = proton pump inhibitor, A = amoxicillin, M = metronidazole, C = clarithromycin, Tc = tetracycline, B = bismuth

metronidazole or vice versa, or b) quadruple therapy with PPI, bismuth, tetracycline, and high dose of metronidazole (P-BMT), or a combination of ranitidine bismuth citrate plus tetracycline, clarithromycin or metronidazole. Table 2 shows the results of a pooled analysis performed by Hojo et al. [5], which summarizes the eradication rates with various second-line anti-*H. pylori* treatments. Concerning the first option, eradication rates were found to be higher when two antimicrobials were added than rates from studies with none or only one new antimicrobial added [5].

The quadruple therapy has shown relatively good results. A recent meta-analysis of 10 studies involving 255 patients who had received quadruple therapy (P-BTM) as second-line therapy demonstrated a mean eradication rate of 77.2% (95% confidence interval, 72–82%). In this regimen, the PPI should be given twice daily, colloidal bismuth citrate at a dose of 120 mg four times daily, tetracycline 500 mg four times daily, and metronidazole at a high dose of 500 mg three times a day [6]. Some authors recommended that the second-line treatments be given for a longer period of 10–14 days. Although this seems feasible, it has not yet been proven in controlled studies.

Other ''rescue'' regimens

Several alternative approaches to second-line therapies have been reported recently and one of the combinations – a rifabutin-based rescue therapy – is encouraging. Rifabutin is a spiropiperidyl derivative of rifamycin that is currently used to cure or prevent *Mycobacterium avium* complex disease in patients with human immunodeficiency virus infection. This drug, which is chemically stable over a wide pH range, has been shown to have an extremely high anti-*H. pylori* activity *in vitro*. Several rifabutin-based therapies consisting of PPI at a standard dose twice a day, rifabutin 300 mg once a day, and amoxicillin 1 g twice a day for 7–14 days have been reported to cure *H. pylori* infection in 70–79% of patients who failed eradication after standard PPI-based triple therapies; moreover this therapy had an excellent compliance and infrequent side effects [7]. The use of rifabutin should be restricted to second or third-line *H. pylori* therapy regimens, as a broader use of this drug might lead to the development of multiresistant strains of *M. tuberculosis*.

Is it necessary to perform susceptibility tests in cases of treatment failure?

It has been suggested that antibiotic susceptibility data should be collected to guide the choice of antibiotics in the event of primary treatment failure. There are several problems with this approach: *H. pylori* culture is not always available on a routine basis, the antimicrobial susceptibility cannot be obtained in all cases, and even when the susceptibility of the bacteria is known there is no correlation between the *in vivo* susceptibility and the treatment success. In a controlled study, Avidan et al. [8] found that the culture results did not influence the outcome of treatment. It seems, therefore, that performing routine pretreatment susceptibility tests is not a cost-effective option and clinicians should choose the appropriate combination of drugs based on sensitivity patterns provided by a local reference center. Nonetheless, several authors suggest that in cases of recurrent treatment failures, susceptibility testing should be performed to guide further therapy [9].

Conclusion

The choice of second-line anti-*H. pylori* treatment depends on the initial treatment. First-line treatment should not combine clarithromycin and metronidazole because of the problem of resistance to both antibiotics. For second-line, re-treatment with the same regimen even for a longer period is not recommended, and avoiding antimicrobial agents against which prior therapy may have induced resistance is suggested. Quadruple therapy containing bismuth has been suggested as the optimal second-line therapy, and rifabutin-based therapy was recently reported to be a promising strategy for eradication failures. Assessment of *H. pylori* antimicrobial susceptibility is recommended only after recurrent treatment failures.

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