

## How to Proceed in *Helicobacter pylori*-Positive Chronic Gastritis Refractory to First- and Second-Line Eradication Therapy

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### Key Words

*Helicobacter pylori* infection · Chronic gastritis · Eradication therapy · Peptic ulcer disease

### Abstract

*Helicobacter pylori* is a widespread disease causing most of the peptic ulcer diseases and low-grade mucosa-associated lymphoreticular tissue (MALT) lymphoma. Moreover, *H. pylori* is a proven environmental risk factor for gastric carcinoma and it has been recognized as a type 1 carcinogen factor. A combination of drugs has been proposed, using a proton pump inhibitor (PPI), amoxicillin, clarithromycin, metronidazole and tetracycline to treat the infection. Since 1996, according to the European guidelines, the first-line approach using PPI, amoxicillin and clarithromycin or metronidazole has been suggested. Seven days of quadruple therapy with PPI (or ranitidine), tetracycline, bismuth salts and metronidazole has been reserved as second-line treatment. To improve the eradication rate of the triple therapy, a different combination of the available antibiotics has been proposed, consisting of a 10-day sequential regimen. A second-line levofloxacin-amoxicillin-based triple therapy given for 10 days has been proposed, obtaining a high eradication rate, suggesting this regimen to be a suitable retreatment option in eradication failure. A third-line treatment with rifabutin-based regimen has been proposed.

*Helicobacter pylori* infection is a cause of peptic ulcer disease, gastric mucosa-associated lymphoreticular tissue (MALT) lymphoma and gastric cancer [1]. Standard treatments for *H. pylori* that have been endorsed by US and European authorities rely on clarithromycin or metronidazole in conjunction with other antibiotics and acid inhibitors [2, 3]. The prevalence of clarithromycin and metronidazole resistance has increased significantly in recent years and there has been a corresponding decline in the eradication rate for *H. pylori* [4]. Eradication rates in most Western countries have declined to unacceptable values with approximately 1/5 patients failing eradication therapy [5]. A simple, short treatment regimen that would return eradication levels to the high values seen at the advent of *H. pylori* treatment is urgently needed [5]. Such a treatment regimen should have high efficacy against clarithromycin- and metronidazole-resistant strains of *H. pylori* as these strains are increasingly encountered in routine clinical practice.

Triple therapy with a proton pump inhibitor (PPI), clarithromycin, and either amoxicillin or metronidazole is the most popular treatment regimen to cure *H. pylori* infection among primary care physicians and gastroenterologists in the USA and Europe [6–8]. However, two double-blind, US multicenter studies recently found disappointingly low eradication rates with this regimen. In one study, 75.6% of 402 patients and in the other, 77.2%

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of 307 patients were cured of *H. pylori* infection following a 10-day triple regimen [9, 10]. Low eradication rates have also been reported with this regimen in Europe, and Australia and Asia [11].

A novel 10-day sequential therapy consisting of a 5-day dual (PPI + amoxicillin) therapy followed by a 5-day triple (PPI, clarithromycin and tinidazole) therapy has had a good eradication success in unblinded trials in adult and pediatric patients [12–14]. Recently, a double-blind controlled trial against conventional therapy demonstrated that sequential therapy has high eradication rates, good tolerability, and high patient compliance [15].

The outcome of *H. pylori* therapy depends to a significant degree on compliance with the regimen and the presence of antibiotic resistance [16]. Clarithromycin resistance is a major problem in many Western countries, and its prevalence is 12.9% (varying from 6.1 to 14.5%) in the USA, and as high as 24% in some European countries [17–19]. A systematic review of *H. pylori* therapy reported a 53% decrease in eradication rates if clarithromycin resistance was present and a clarithromycin-containing regimen was used [16]. The reasons why the sequential regimen is more effective than the standard therapy on clarithromycin-resistant strains have been previously reported [20]. Briefly, the first course of sequential therapy is based on amoxicillin's ability to destroy the bacterial wall impairing the transmembrane efflux system which acts contrasting the intracellular clarithromycin entrapment in the resistant strains [20]. In agreement with previous studies, we suggest that the role of metronidazole resistance is less important for treatment success with clarithromycin-based triple therapy [21].

Cost is a major consideration in many countries. In Europe the cost of the sequential regimen is similar to that of the standard regimen making it an attractive alternative to current triple therapy. Tinidazole has recently become available in the USA and the cost of sequential therapy based on retail cost is lower than that of triple therapy. Sequential therapy may therefore be a reasonable alternative to standard therapy.

In 1996, the first European guidelines for *H. pylori* management were drawn up, and they were updated and substantially confirmed in 2000 [22]. The guidelines advise the use of a 7-day triple therapy, comprising a PPI (or ranitidine bismuth citrate), clarithromycin and amoxicillin or metronidazole as first-line therapy, whilst a 7-day quadruple therapy (PPI, bismuth salts, tetracycline, and metronidazole) should be reserved for eradication-failure patients.

Numerous clinical trials have been published since the last Maastricht conference. In susceptible strains the combination of PPI-clarithromycin-metronidazole is more successful than the combination of PPI-clarithromycin-amoxicillin. In the case of clarithromycin resistance alone, the eradication rates are also higher with PPI-clarithromycin-metronidazole than with PPI-clarithromycin-amoxicillin (50 vs. 18%, respectively). In metronidazole resistance, when a PPI-clarithromycin-metronidazole regimen is used, there is a 25% decrease in eradication rate (72 vs. 97%). The predicted eradication rates for the PPI-clarithromycin-metronidazole combination show a better efficacy than PPI-clarithromycin-amoxicillin which is nullified only when metronidazole resistance reaches 40% [23].

### Second-Choice Therapy

According to the recent Consensus report [23], bismuth-based quadruple therapy is a preferred option as second-choice therapy if not previously used. However, PPI triple therapies have been tested as second-choice treatment. Clarithromycin should not be used unless phenotypic or genotypic tests show that the strain is susceptible. The eradication rate obtained with the combination of PPI-amoxicillin-metronidazole was 89 and 64% for metronidazole-susceptible and -resistant strains, respectively. In a clinical trial using this combination as a second-choice therapy, the global eradication rate was 64%.

Recently, a 10-day levofloxacin-based triple therapy has been shown to be safe and effective, achieving an eradication rate in almost 80% of the patients [24]. Similar results have been confirmed in two recent meta-analyses [25, 26].

### Third-Choice Therapy

Two other classes of antibiotics have emerged in the treatment of *H. pylori* infection: a fluoroquinolone, levofloxacin, and a rifamycin, rifabutin. These antibiotics have been evaluated for the most part in first-choice therapies with PPI and amoxicillin rather than rescue therapies with a good success rate. However, rifabutin is an antibiotic which can select resistance among *Mycobacterium*, so it must be used cautiously. *H. pylori* resistance to rifabutin may occur but is rare.

Culture for the management of *H. pylori* infection has been neglected for a long time, despite the fact that several studies have shown that higher eradication rates are obtained when antibiotics are chosen based on susceptibility testing versus choosing empirically. This may be a cost-effective approach. The high impact of clarithromycin resistance led to the proposal to perform culture and

antimicrobial susceptibility testing when the resistance rate reaches 15–20%. Culture and sensitivity may help in decision-making after failure of second-choice therapy. It has to be recommended that monitoring of primary antibiotic resistance be carried out in different regions in order to appreciate the risk of failure linked to antimicrobial resistance [23].

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