

Treatment of *Helicobacter pylori*

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ABSTRACT

The efficacy of established *Helicobacter pylori* regimens needs to be reviewed. In view of drug resistance, side effects, and compliance and expense of therapy, treatment failure is increasing and second-line treatment strategies need to be developed. A simulation model suggested by the Cochrane review group showed that *H. pylori* eradication is cost-effective for duodenal and gastric ulcer long-term. The duration of eradication therapy continues to be controversial. In Europe and other parts of the world, 7-day triple regimens are used, whereas guidelines from the United States recommend 10–14 days of therapy. Antibiotic resistance is a major factor affecting the outcome of eradication therapy.

New modified eradication regimens involve substitution of antibiotics used in conjunction with other drugs. The newer generation fluoroquinolones have shown some promise as part of an eradication regimen. Quadruple therapy (bismuth, proton pump inhibitor [PPI] and two antibiotics and sequential treatment [PPI with three antibiotics]) are promising first-line treatments. Novel agents have been tried, but with disappointing results. New drugs and administration forms have been reported but their efficacy needs confirmation.

Keywords. *Helicobacter pylori*, antibiotics, eradication, antibiotic resistance, clarithromycin.

Treatment of *Helicobacter pylori* infection is relatively successful with usually in excess of 80% of patients eradicated of the organism. The principle of successful treatment are both patient and physician compliance to treatment guidelines. The most successful and universal treatment is triple therapy, three drugs twice a day for 1 week (proton pump inhibitor [PPI], amoxicillin and clarithromycin). However, there is still an argument of increasing the duration of treatment to 10 or even 14 days. Increasing problems with drug resistance, ecological considerations, side effects, and expense of antimicrobial therapy have stimulated a search for new treatments. The most fruitful is the substitution of different antibiotics used in combination with other drugs.

Efficacy of Established Regimens

Eradication therapy has been recommended as the most cost-effective option for peptic ulcer disease by experts and international guidelines

for more than a decade. Until recently, this recommendation was based on evidence from individual clinical trials whereas a formal comprehensive Cochrane meta-analysis was lacking. Ford et al. from the Cochrane Upper Gastrointestinal and Pancreatic Diseases Review Group in UK conducted a systematic review and economic analysis based on 52 trials from 1966 onwards in which they compared eradication therapy with ulcer healing drugs or no treatment. The data were included into a Monte Carlo simulation model that incorporated any uncertainties in the estimates. In duodenal, but not in gastric ulcer healing, eradication therapy was superior to ulcer healing drugs. In preventing duodenal ulcer recurrence, eradication therapy was not superior to maintenance therapy with acid suppressants but the simulation model suggested that *H. pylori* eradication is cost-effective for duodenal ulcer over 1 year and for gastric ulcer over 2 years [1].

A meta-analysis based on six studies in 862 patients confirmed that triple eradication therapy for 7 days is sufficient to heal peptic ulcer; however, prolonging PPI therapy for 2–4 weeks did not improve healing rates (91% vs. 92%) [2].

The duration of eradication therapy continues to be controversial. In Europe and other parts of

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the world [3–6], 7-day triple regimens are used, whereas guidelines from the United States recommend 10 to 14 days of therapy. In a sufficiently powered and well-designed multicenter, double-blind, randomized trial, Vakil et al. compared the efficacy of 3-, 7- and 10-day therapies in 803 patients with and without peptic ulcer disease. Amoxicillin (1000 mg bid) and clarithromycin (500 mg bid) were combined with either rabeprazole or omeprazole (20 mg bid). The eradication rates for the rabeprazole-based regimens were: 3-day, 27% (95% CI: 21–34%); 7-day, 77% (71–83%); and 10-day, 78% (72–84%). There was no statistical difference between the 7-day and the 10-day regimens and there was no difference in eradication rates between patients with and without ulcer disease [7]. In contrast, studies from Mexico and India reported superior cure rates with prolonged therapy using triple regimens. Triple therapy with rabeprazole, amoxicillin, and ofloxacin for 14 days achieved an eradication rate of 92.3%, which was significantly superior to 1 week therapy (62.2%) [8]. In the study by Chaudhary et al., 64 patients with *H. pylori*-associated duodenal ulcer disease were randomized to 1, 2, or 3 weeks of therapy with lansoprazole, amoxicillin, and tinidazole. Eradication rates increased significantly with increasing length of therapy (47.6% vs. 80% vs. 91.3%) [9].

Two studies from Turkey reported on the efficacy of PPI-based triple therapy with amoxicillin and clarithromycin for 7 or 14 days, respectively. Both studies reported excellent patient compliance but low eradication rates, 63.6% in the study by Sivri et al. [10] and 45% in the study by Altintas et al. [11]. Antibiotic resistance was blamed, but not measured, in these studies. More acceptable eradication rates were reported from a Greek randomized study, which compared a triple regimen combining amoxicillin and clarithromycin with either esomeprazole (40 mg once or twice daily) or omeprazole (20 mg twice daily) for 7 days. *H. pylori* was eradicated in 96%, 81%, and 71% of the patients, respectively [12]. In line with this, cure rates of 78%, 81%, and 91% were reported from a randomized trial in 342 patients, which compared three triple therapies (lansoprazole, amoxicillin, and metronidazole; ranitidine bismuth citrate, clarithromycin, and tetracycline; lansoprazole, amoxicillin, and clarithromycin) for 7 days [13].

Clinical trials of eradication therapy in children are difficult to conduct. As a consequence, guide-

lines for the management of the infection are often based on data from trials in adults. An Italian multicenter study randomized 43 children, median age 11 years, to 1 week dual therapy with amoxicillin and tinidazole or triple therapy with the same antibiotics combined with lansoprazole. Eradication rates after 6 months did not differ, 71% and 72.7%, respectively [14]. This is in keeping with previous studies that showed a lower eradication rate in children compared to adults.

Second-Line Treatment

Consensus publications, including the Maastricht 2–2000 report, have recommended a PPI-based triple treatment with clarithromycin and either metronidazole or amoxicillin as first-line therapy. However, over time the efficacy of these regimens has decreased because of antibiotic resistance problems. A preferred second-line therapy for eradication failure consists of a PPI, a bismuth compound, and two antibiotics (quadruple therapy). In an important paper, Fischbach et al. analyzed the efficacy and safety of quadruple therapies as first-line treatment. They identified 98 clinical trials with 145 treatment arms and 7151 subjects [15]. Quadruple therapy with omeprazole, bismuth, metronidazole and tetracycline (PPI-BMT) for 10–14 days eradicated *H. pylori* in more than 85% of cases. The safety and adherence profile of this regimen was comparable to PPI-based triple therapy with clarithromycin and amoxicillin. The authors suggest that PPI-BMT quadruple therapy should be recommended as a first-line treatment option for *H. pylori* infection.

In Japan, only PPI-based triple therapies are approved. The cure rate of a PPI-amoxicillin-metronidazole regimen used as second-line therapy for 10 days in 151 patients, who had failed a clarithromycin-based triple therapy, was 87.5% to 93.5% and was highest in the subset of patients, who had susceptibility testing performed [16].

Antibiotic Resistance

Antibiotic resistance is a major factor affecting the outcome of eradication therapy for *H. pylori*. A systematic review of the data on antibiotic resistance published in the last 5 years highlighted regional differences in resistance patterns for clarithromycin and metronidazole [17]. These differences are not trivial as they have a major effect on the success rate of eradication therapy. Eradication rates of 87.8% were found when

strains are clarithromycin susceptible compared to only 18.3% when strains are clarithromycin resistant. When considering nitroimidazole resistance alone, there was a 25% decrease in the success rate from 97% in susceptible strains to 72.6% in resistant strains [17]. In another paper by Mégraud, the prediction of success according to level of resistance was presented. It was shown that metronidazole gave better eradication rates compared to amoxicillin when used in triple therapy regimens [18].

Recent studies have confirmed that the prevalence of resistance to metronidazole varies in different parts of the world and that there is no simple association between metronidazole resistance and eradication failure [19–25]. Published data from the past year have shown that primary metronidazole resistance varies between 20% (New Zealand, [24]), and 38% (Finland, [20]) in industrialized countries. In a clinical study on eradication therapy in Vietnam, primary resistance to metronidazole was found in 76% of the isolates. Eradication rates were negatively affected only at high-level resistance ($\text{MIC} \geq 256 \mu\text{g/ml}$) and when using a once-daily dosing regimen [21].

In North India, metronidazole resistance was present in 41.9% of the isolates, but this was unrelated to the treatment success, and based on eradication rates of only 42% to 65%, Bhatia et al. concluded that imidazole-based eradication regimens should not be recommended in their region [19]. As shown in previous studies, metronidazole resistance was associated with female gender, ethnicity (African American in the USA), young age, and previous use of antibiotics for gynecological infections [20,22,23].

Primary resistance to clarithromycin also varies with rates between 0% to 12.8% in the recently published literature [20–25]. The highest rate was reported from USA [22] and the lowest from New Zealand (0%, [24]), Vietnam (1%, [21]), and Finland (2%, [20]). Only 4% of *H. pylori* isolated from children in Egypt were resistant [25]. In UK, there was a significant decrease in the prevalence of primary resistance to clarithromycin in 1991–2001 from 10.3% to 3.8% [23]. Factors associated with clarithromycin resistance were previous use of antibiotics for respiratory and dental infections [20] and a diagnosis of non-ulcer dyspepsia (as compared to duodenal ulcer) [5]. Branca et al. examined 67 isolates from patients, who had been unsuccessfully treated with amoxicillin, clarithromycin, metronidazole, and levofloxacin. They found that 91% of the

isolates were resistant to clarithromycin and that 77.6% were resistant also to metronidazole [26]. Clarithromycin resistance was also the major cause (83.9% of 62 patients) of failed first-line therapy in a north Japanese population [27].

In a recently published Japanese study, Watanabe et al. tested the sensitivity of 648 *H. pylori* strains isolated from 1985 to 2003 and found an increase in the prevalence of strains with intermittent resistance to amoxicillin. No isolate from the period 1985–1996 was resistant to amoxicillin, while the rate of resistance after 1997 varied between 0% and 8.8% [28]. Other reports on amoxicillin resistance confirm that this is still a rare event [19,21,22,24,26,29].

Factors Contributing to Treatment Failure

Several other factors apart from antibiotic resistance and poor compliance may contribute to treatment failure. According to a controversial theory, pretreatment with a PPI may be associated with low eradication rates by inducing transition of the bacteria into a dormant state. The influence of pretreatment with a PPI was evaluated in a meta-analysis that included nine randomized, comparative trials with a total of 773 patients. Pooled eradication rates were 81.3% for patients pretreated with a PPI compared to 81.2% for patients without pretreatment. Janssen et al. concluded that pretreatment with a PPI does not influence eradication success [30].

Low salivary secretion may contribute to eradication failure according to a study which involved 90 subjects in whom saliva was collected before antibacterial treatment began. In subjects treated with omeprazole, amoxicillin and tinidazole low salivary secretion predicted eradication failure [31].

New and Modified Eradication Regimens

The newer generation fluoroquinolones have shown some promise as part of an eradication regimen. Gatifloxacin is well absorbed from the GI tract and in vitro susceptibility studies have not suggested any resistance problems so far. Sharara et al. evaluated the efficacy of gatifloxacin in combination with amoxicillin and rabeprazole (once or twice daily) for 7 days in 104 patients. The infection was cured in 48 of 52 patients (92%) treated with the twice daily rabeprazole regimen [32].

A simplified regimen might improve compliance in children and this was tested in a randomized

and double-blind trial in Sweden. A total of 131 children, mean age 14 years, were randomized to once daily azithromycin and tinidazole with or without lansoprazole for 6 days. Unfortunately, cure rates were only 67% and 58% in the two groups and the authors concluded that a traditional 7-day PPI-based triple therapy should remain the treatment of choice in children [33].

A small American study suggested that minor adjustments in the timing and formulations of quadruple therapy might improve outcome [34].

A novel 10-day sequential regimen was recently introduced in an attempt to improve eradication rates. In an open label study, 162 infected patients with non-ulcer dyspepsia were treated with rabeprazole and amoxicillin for the first 5 days followed by rabeprazole, tinidazole, and – in a randomized manner – either to low dose (250 mg bid) clarithromycin or high dose (500 mg bid) clarithromycin for a further 5 days. Both regimens were successful with high eradication rates (93% vs. 94%, respectively) and no major side-effects [35]. The high dose clarithromycin sequential regimen was compared with 7- and 10-day triple therapies in another randomized study in 342 patients by the same group from Italy. The authors concluded that the sequential regimen achieved significantly higher eradication rates compared to both 7- and 10-day triple therapies [36].

Patients, who fail both first- and second-line therapies, are a difficult clinical challenge. Experience with a culture guided treatment approach in 94 patients was reported by Cammarota et al. Based on susceptibility analysis, patients were treated with a 1-week quadruple regimen including omeprazole, bismuth, doxycycline, and amoxicillin (89 patients) or a 1-week triple regimen with omeprazole, amoxicillin, and levofloxacin (5 patients). *H. pylori* eradication was obtained in 90% of the subjects [29].

Novel Agents

Alternative modes of treatment, particularly non-toxic, natural, and inexpensive products are attractive. Unfortunately, these experimental therapies rarely, if ever, achieve cure of the infection but for some may temporarily suppress the bacteria.

Some studies have reported on the antibacterial properties of vegetables and plant extracts. Galan et al. tested the effects of oral broccoli sprouts in a small, uncontrolled study of only nine infected patients. Consumption of broccoli sprouts (14, 28, or 56 g daily for 7 days) was associated with

a temporary suppression of *H. pylori* in three of nine patients as assessed by stool antigen testing immediately after therapy [37]. The anti-*H. pylori* activities of six plants were determined against isolates, using a disk susceptibility assay. Two extracts, a flavonoid and a xanthanolate, were superior to the disk antibiotic susceptibility profile and may have potential in eradication regimes [38]. In a similar set-up, Funatogawa et al. isolated 36 polyphenols and four terpenoids from medicinal plants and tested their antibacterial activity in vitro. Hydrolyzable tannins demonstrated promising antibacterial activity against *H. pylori* without affecting the viability of cells derived from human gastric epithelium [39].

Probiotic agents are live microbial supplements that may have beneficial effects in the GI tract and they have been proposed to improve eradication of *H. pylori* by reducing side effects to conventional therapy [40]. Linsalata et al. tested the properties of *Lactobacillus brevis* in 22 *H. pylori*-positive dyspeptic patients in a randomized, placebo-controlled set-up. After 3 weeks of therapy, they found no evidence of eradication but a reduction of the intragastric bacterial load, as suggested by urea breath testing (UBT) [41]. In a placebo-controlled, but not randomized study, 59 infected subjects were treated with a probiotic-enriched yogurt twice daily for 6 weeks. Eleven subjects took an unfermented milk placebo. Serial UBT was performed on all 70 subjects before, during, and after treatment. The study suggested that regular intake of a yogurt containing *Lactobacillus acidophilus* and *Bifidobacterium lactis* can suppress but not eradicate *H. pylori* [42].

The antibacterial activity of bismuth is well established. The therapeutic potential of other metal ions against *H. pylori* was tested in standard broth culture media. Cobalt chloride had a marked and specific activity against the bacteria and this effect was not directed towards the nickel-dependent urease enzyme. The minimum inhibitory concentration for cobalt was similar to some antibiotics [43].

Melanoidins are polymerized products resulting from a chemical reaction between amino acids and reducing sugars. They are found in heat-treated foods and may inhibit the adherence of urease to gastric mucin and therefore may have anticolonization effects against *H. pylori*. This hypothesis was tested by Hiramoto et al. They found that 8 weeks daily intake of 3 g melanoidin reduced the bacterial density assessed by UBT and fecal antigen testing [44].

Cranberry juice reduces the incidence of urinary tract infections, probably by preventing bacteria from adhering to the epithelium in the urinary tract. A similar mechanism has been proposed for *H. pylori* adherence to gastric mucosa and in support of this a high molecular weight, nondialysable material, which inhibits adherence of *H. pylori* in a gastric cell line model, was recently identified in cranberry juice [45]. The clinical effects of cranberry juice were tested in a Chinese study [46]. They randomized 189 *H. pylori*-infected adults to oral cranberry juice or placebo. After 90 days, 14 of 97 subjects treated with cranberry juice had negative UBT results compared to five of 92 subjects in the placebo group ($p < .05$). The investigators concluded that regular consumption of cranberry juice can suppress *H. pylori* infection. If these results can be reproduced in another setting and with a proper follow-up, this novel approach may be a promising alternative or adjunct to antibiotic therapy.

New Drugs and Administration Forms

Iwao et al. from Japan reported on the properties of a novel benzimidazole compound with no activity against common aerobic and anaerobic bacteria other than *H. pylori*. The minimum inhibitory concentration was nearly equal to that of amoxicillin and clarithromycin and exposure of *H. pylori* to the drug did not lead to induction of drug-resistant mutants. The drug was tested on infected Mongolian gerbils and was effective in eradication, even in the treatment of a clarithromycin-resistant strain [47]. This novel benzimidazole might be a useful alternative for eradication therapy, but human studies are needed.

Cetraxate is an anti-ulcer drug that increases gastric mucosal blood flow [48]. Wu et al. compared the efficacy of a pantoprazole–amoxicillin–clarithromycin group with a cetraxate-based triple therapy in 58 infected patients. Cetraxate-based triple therapy was significantly less effective (70.4% vs. 93.5%, $p = .03$) but had a lower frequency of side effects compared to the traditional PPI-based triple regimen [49].

In a small study on eight infected volunteers, the effects of acetazolamide, a carbonic anhydrase inhibitor that has been used as antiulcer therapy, was tested by Shahidzadeh et al. After 4 days of therapy there was a trend for the UBT value to increase and the investigators concluded that acetazolamide had no inhibitory effect on *H. pylori* growth in vivo [50].

Access of antimicrobial drugs to the site of *H. pylori* infection is restricted from the luminal site owing to the mucous gel layer on the gastric mucosa. Targeted drug delivery systems may partly overcome this barrier. In a recent paper, Indian researchers describe a new hybrid vesicle system, which consists of a lipid bilayer shell anchored on the surface of a hydrogel polymer core. Pretreatment of *H. pylori* with these lipobeads bearing acetohydroxamic acid inhibited the adherence of the bacteria to human stomach cells in an in vitro experiment [51]. In another paper from the same group, mucoadhesive nanoparticles bearing amoxicillin were able to eradicate *H. pylori* in infected Mongolian gerbils [52].

Conclusion

Treatment for *H. pylori* infection in a majority of cases is highly effective. Regimes need to be re-evaluated in view of emerging resistance to antibiotics. The most promising treatments are the use of alternative antibiotics. Increasing the duration of triple treatment to 10 or 14 days may increase their efficacy. Quadruple therapy (bismuth-based PPI with two antibiotics) and sequential treatment (PPI with two antibiotics) have given excellent results. Therapy for treatment failure may be improved by assessing antimicrobial sensitivity. Novel agents at best only suppress *H. pylori* infection. The elusive monotherapy seems a distant reality.

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