

Treatment of *Helicobacter pylori*

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Abstract

Since the discovery of *Helicobacter pylori* in the early 1980s many treatment regimes have been developed to effectively treat this infection. International guidelines have allowed consensus on the best management and improved eradication rates. In recent years, increasing antimicrobial resistance has resulted in falling eradication rates with standard therapies. In this article, we review the most recent studies and guidelines in the treatment of *H. pylori*. Currently, the first-line treatment remains clarithromycin, amoxicillin or metronidazole and proton pump inhibitor twice daily, but a number of recent studies have shown low eradication rates with this treatment. Increased duration of therapy has been recommended to overcome the falling eradication rates. However, conflicting findings have been reported on the benefits of extending the length of traditional therapy. Sequential therapy may be an effective alternative to standard triple therapy in regions of increased antimicrobial resistance. Probiotics reduce side-effects from traditional regimens and may improve eradication rates. A quinolone-based second-line triple therapy appears to be effective and well tolerated. Bismuth-based quadruple therapy is also an effective alternative if available. In the future, regional antimicrobial resistance and eradication rates will determine the best treatment for *H. pylori*.

The treatment of *Helicobacter pylori* remains a challenging clinical problem despite extensive research over the last 25 years. Increasing antimicrobial resistance and falling eradication rates are the result of the widespread use of antibiotics. The third Maastricht Consensus Report agreed that effective treatment for *H. pylori* should achieve an intention-to-treat (ITT) eradication rate of over 80% [1]. However, in clinical practice eradication rates are lower than 80% for many of the standard treatment regimes. A number of factors such as duration of treatment, choice of antibiotics, new drug combination, improved patient compliance, and novel agents may help to improve eradication rates.

Antimicrobial Resistance

Antibiotic resistance is a major cause of treatment failure [2]. The prevalence of antimicrobial resistance in *H. pylori* shows regional variation both within and between countries. Alternative antibiotics based on local resistance rates may improve eradication rates. Clarithromycin resistance has a greater effect on treatment efficacy than nitroimidazole resistance [3]. The widespread and

sometimes indiscriminate use of antibiotics in developing countries has resulted in a higher prevalence of resistance than in industrialized countries [4]. Clarithromycin resistance rates in the USA have a prevalence of 10–12.5% [5,6]. In Canada, clarithromycin resistance is estimated to be less than 4% [7]. In Europe, there is a significant difference between clarithromycin resistance rates in Northern, Eastern, and Southern Europe with resistance rates of 4.2%, 9.3%, and 18%, respectively [8]. The prevalence of secondary clarithromycin resistance, i.e. after failure of a treatment including this drug, is extremely high, up to 60% [7]. Resistance to metronidazole is much more common than resistance to macrolides. In developed countries about 35% of *H. pylori* strains are resistant to nitroimidazoles, whereas in developing countries the resistance rates are even higher [4]. However, metronidazole resistance in vitro does not always predict treatment failure. There is poor correlation between different methods of metronidazole resistance detection and this may explain differing resistance rates between institutions. As with macrolides, the essential risk factor for resistance is the previous consumption of the drug. Metronidazole is more commonly used in developing countries for the treatment

Regimen	Country	Eradication rate 7 days	Eradication rate 14 days	Reference
PAC	Italy	57% (n = 117)	70% (n = 126)	13
PAM	Italy	52% (n = 122)	56% (n = 121)	
PAC	Croatia	74% (n = 122)	93% (n = 58)	14
PAM	Croatia	75% (n = 122)	95% (n = 58)	
PAC	Italy	80% (n = 301)	82% (n = 301)	15
PAC	Korea	71% (n = 337)	76% (n = 261)	16

P, proton pump inhibitor; A, amoxicillin; C, clarithromycin; M, metronidazole.

Table 1 *Helicobacter pylori* eradication rate according to length of treatment in proton pump inhibitor-amoxicillin-based triple therapies

of parasitic infections. In developed countries, it is mainly used for dental and gynecological infections, and in some studies resistance is more commonly found in females [7]. The prevalence of amoxicillin resistance is low (< 1%). In areas where penicillin is available without prescription, it may be higher. Tetracycline resistance is estimated to be less than 1%. Fluoroquinolones are being increasingly prescribed in recent years and thus has led to increasing resistance rates.

A recent Italian study showed very high primary resistance to antibiotics. *H. pylori* resistance rate was 16.9% for clarithromycin, 29.4% for metronidazole, and 19.1% for levofloxacin. Clarithromycin resistance was significantly higher in patients with non-ulcer dyspepsia than in patients with peptic ulcer (19.1% vs. 0%, $p = .02$). Metronidazole resistance was higher in foreign than in Italian patients (50% vs. 22.9%, $p = .0004$), and levofloxacin resistance was higher in older than in younger patients (28.4% vs. 14.4%, $p = .048$). Levofloxacin resistance was also more frequent in strains with either clarithromycin or metronidazole resistance [9]. Another study suggested that *H. pylori* resistance to fluoroquinolones is already high in Belgium (17%) [10]. In comparison a Dutch study highlights the European regional differences in antibiotic resistance rates. In this study, mean rates of primary resistance to metronidazole and clarithromycin were 14.4% and 1.0%, respectively. Primary metronidazole resistance was stable over the 6-year period (1997–2002), and primary clarithromycin resistance showed a decreasing trend. Patients of foreign descent and from secondary care had a higher chance of harboring primary metronidazole-resistant *H. pylori*. Patients with failed *H. pylori* eradication had a higher chance of harboring multi-resistant *H. pylori* than untreated patients [11]. In the Netherlands, sales of antibiotics are lower than in any other European Union country and four times lower than in some Mediterranean countries. A meta-analysis proved that drug resistance is a strong predictor of efficacy across triple therapies for the eradication of *H. pylori* in adults [3]. These findings suggest that regional specific treatment regimes based on local

antibiotic resistance may improve eradication rates. The third Maastricht guidelines recently recommended local reference centres to measure antibiotic resistance rates within countries to improve eradication [1].

First-Line Treatment

Proton pump inhibitor (PPI)-based triple therapy has been used as first-line treatment of choice for over a decade [12]. A combination of PPI, clarithromycin 500 mg, and amoxicillin 1 g or metronidazole 400 or 500 mg, all given twice a day, is still recommended by the European Helicobacter Study Group [1]. There is some controversy over the most effective length of treatment for this regime. The European guidelines acknowledged that a 14-day treatment course may be more effective than a 7-day course. A number of recent studies continue to provide conflicting evidence in regard to the length of treatment course (Table 1).

A Croatian study comparing 7-, 10-, and 14-day treatment courses of PPI, amoxicillin, and clarithromycin (PAC) or metronidazole (PAM) demonstrated that an eradication rate (ITT analysis) exceeding 80% was achieved only by a 14- and 10-day course of PAC and only by a 14-day course of PAM. This study failed to achieve an adequate eradication rate with a 7-day treatment course [13]. A northern and central Italian study also showed that a 14-day PAC therapy achieved a significantly higher eradication rate than 7-day or 14-day regimes with metronidazole (70% vs. 52%, $p < .01$) and the same therapy for 7 days (70% vs. 57%, $p = .05$). At per-protocol (PP) analysis, a 14-day therapy with omeprazole, amoxicillin, and clarithromycin showed a significantly higher eradication rate than a 7-day therapy with amoxicillin and metronidazole (77% vs. 62%; $p = .03$) but no difference with 1-week of the same regime (66%) [14]. This study concluded that 2-week therapies, independently of antibiotic combination, lead to a significant increase in *H. pylori* eradication rate compared to 1-week therapies. The compliance and tolerability were similar for 1-week and 2-week treatment groups.

Table 2 Efficacy of different first-line treatment regimens to eradicate *Helicobacter pylori*

Country	Regimen (twice daily)	Duration (days)	Patient no.	Eradication rate		Reference
				ITT	PP	
Italy	CAE	7	100	75%	79%	18
	CME	7	100	72%	77%	
	CLE	7	100	87%	91%	
Italy	CRE	7	24	58%		20
	LRE	7	24	42%		
Germany	CAE	7	31	84%	84%	19
	LEA	7	30	87%	93%	
Spain	BAL	10	64	84%	89%	21
Italy	EBMT	10	95	91%	95%	22
Spain	CAO	7	171	86%	77%	23
	OBMT (t.d.s.)	7	168	89%	83%	

C, clarithromycin; A, amoxicillin; E, esomeprazole; L, levofloxacin; R, rifaximin; B, ranitidine bismuth citrate; M, metronidazole; T, tetracycline; O, omeprazole. ITT, intention to treat; PP, per protocol.

Eradication rates for both 1 and 2 weeks were, however, inadequate and this study questions the efficacy of this therapy in this region in Italy.

However, another Italian study comparing 1 and 2 week regimes led to similar results in terms of efficacy, safety and patient compliance with ITT eradication rates of 79.9% and 81.7%, respectively [15]. A Korean study again failed to show a benefit in the longer duration of treatment [16]. Again neither the 7-day or the 14-day course of PAC achieved acceptable eradication rates on an ITT analysis.

These conflicting findings may reflect varying resistance rates within the populations studied and confirm the need for more local reference centres to determine the best treatment regimes. In these studies it is also noticeable that the eradication rate for standard triple therapy is not adequate and is often less than 80%.

Eradication rates have decreased in recent years and increased duration of therapy may not overcome increasing bacterial resistance. A Turkish study that determined eradication rates over a 10-year period showed a marked decrease in eradication after year 2000. Pooled eradication rates each year from 1996 through 2005 were 79.4%, 83.7%, 81.8%, 81.8%, 75.1%, 61.3%, 65.6%, 65.1%, 55.3%, and 61.1%, respectively. In this study, eradication rates were not affected by the duration of treatment, choice of PPI, or indication for treatment [17]. In this era of increasing clarithromycin use, the effectiveness of standard triple-therapy regimen for *H. pylori* eradication needs reassessment. The most promising alternatives include sequential therapy and quinolone-based therapy.

Levofloxacin has proven very effective in the treatment of *H. pylori* infection in a number of studies. In a comparative study in Italy, the eradication rate achieved with levofloxacin-based triple therapy as a first-line treatment was significantly higher than that with standard therapies in either ITT or PP analysis (Table 2). The incidence of side-effects was similar with both standard and levofloxacin treatment [18]. In a study of patients with known antimicrobial sensitivity in a German population, a 7-day levofloxacin treatment had an eradication rate of 92.2% and 86.7% on a PP and ITT analysis, respectively [19]. In contrast, rifaximin-based triple therapy was not effective as first-line treatment in Italy [20]. Quadruple therapies comprising PPI, metronidazole, tetracycline, and bismuth are effective alternative first-line treatments which may be advocated in areas of high antibiotic resistance [22,23]. A meta-analysis confirmed this regimen's effectiveness as a first-line treatment [3].

Sequential Therapy

In Italy, a substantial decline in *H. pylori* cure rates with standard triple therapy has led to the use of sequential therapy. Sequential therapy in which PPI plus amoxicillin are given for 5 days followed by PPI plus clarithromycin and tinidazole also for 5 days has eradication rates close to or greater than 90%. This sequential therapy has proved superior to standard triple therapy in a number of Italian studies (Table 3). The incidence in side-effects was similar with both regimes in these trials. This treatment regimen appears to overcome clarithromycin resistance. Further international study is required for this promising approach.

Table 3 Comparative studies of sequential and standard therapy for first-line treatment of *Helicobacter pylori*

Patient no.	Year	Eradication rate % (ITT)		Reference
		Sequential therapy	Triple therapy	
300	2007	89%	77%	24
213	2006	94%	76% (7 days) 82% (10 days)	25
179	2005	94%	80%	26
342	2004	94%	71% (7 days) 80%	27

ITT, intention to treat.

Treatment after One or More Eradication Failures

Following first-line treatment failure, a number of options are available for second-line treatment that may overcome bacterial resistance. Triple therapy, quadruple therapy and more recently levofloxacin-based therapy have been studied as second-line therapies.

A large French study using a combination of PPI, amoxicillin, and metronidazole for 14 days achieved an eradication rate of 81% and 59% for metronidazole-susceptible and metronidazole-resistant strains, respectively. The overall eradication rate was 69% [28]. Clarithromycin should be avoided in second-line treatment in most areas unless resistance tests confirm the *H. pylori* strain to be susceptible. In Japan, the PPI-amoxicillin-metronidazole regime used as second-line treatment has been more successful with a number of trials showing eradication rates of over 90%.

Bismuth-based quadruple therapy is the second-line treatment of choice in many countries. Bismuth salt reduces the bacterial load of *H. pylori* in the stomach. Several studies have obtained good results with the regimen of PPI, ranitidine bismuth citrate, metronidazole, and tetracycline [31]. However, this regime requires the administration of four drugs with a complex scheme and is associated with a high incidence of side-effects [32]. Also bismuth salts are not universally available due to toxicity. This bismuth-based regime still fails to eradicate *H. pylori* in up to 30% of patients. In a Taiwan study of quadruple therapies PPI, bismuth, metronidazole, and tetracycline had an eradication rate of 77% similar to a quadruple therapy where clarithromycin replaced bismuth [33]. Quadruple therapy with PPI, metronidazole, clarithromycin, and amoxicillin was effective in first-line treatment according to a meta-analysis [3].

Levofloxacin-based triple therapies are now the second-line treatment of choice in some European countries. A meta-analysis showed a mean eradication rate of 80%

with levofloxacin-based rescue regimes. *H. pylori* cure rates were higher with a 10-day than a 7-day regime. This suggests that a 10-day regime of levofloxacin 250 mg b.d., amoxicillin 1 g b.d., and PPI twice daily should be chosen as the second-line treatment. Levofloxacin is generally well tolerated and most adverse events associated with its use are mild to moderate and transient. The most frequent adverse effects affect the gastrointestinal system. In this meta-analysis, levofloxacin-based treatments had a lower incidence of adverse events than quadruple therapy (19% and 44%, respectively) [32].

A study comparing levofloxacin, amoxicillin, and omeprazole versus ranitidine bismuth citrate, tetracycline, and metronidazole after treatment failure found comparable eradication rates. The incidence of side-effects with these two regimes was also comparable [34].

Patients who are not cured following two consecutive treatments including clarithromycin and metronidazole are most likely to have a strain resistant to one if not both antibiotics. Eradication therapy after two failures should be based on susceptibility testing [1]. Empirical treatment regimes following two treatment failures depend on initial treatment administered. Levofloxacin therapy had an eradication rate of 60% in patients with two failed treatments with standard triple therapy and bismuth-based quadruple therapy, respectively. Rifabutin has been used with some degree of success in the treatment of *H. pylori*; however, in a one study it had poor eradication results [35]. Levofloxacin-based therapy is more effective than rifabutin-based therapy in third-line treatment [36]. Widespread use of rifabutin could induce resistance in mycobacteria and so it should be used with caution.

Adjuvant Therapy

Bacterial resistance and poor patient compliance are believed to be the primary factors in *H. pylori* treatment failure. The occurrence of side-effects can reduce the compliance of patients with treatment regimens and lead to the development of bacterial resistance [37]. This has led to the development of alternative treatment options in *H. pylori*. Adjuvant therapy with probiotics, bovine lactoferrin, and curcumin have been studied in recent years.

A probiotic is defined as a living microbial species that, on administration, may have a positive effect on bowel microecology and improve health conditions [38]. The most studied probiotics are lactic acid-producing bacteria, particularly *Lactobacillus* species [39]. Probiotics play a role in the stabilization of the gastric barrier function and decrease of mucosal inflammation [40]. Some probiotic species such as lactobacilli and bifidobacteria release bacteriocins that may inhibit *H. pylori* growth and its adherence to gastric epithelial cells [39].

Table 4 Studies of adjuvant therapy

Regimen	Adjuvant	Eradication rate (ITT)%		Significant reduction in side-effects	Compliance	Reference
		Placebo	Adjuvant			
CAE	bLF and Pbs	73%	89%	Diarrhea $p = .001$ Nausea $p = .005$	No difference	37
EBATi	Lactoferrin	89%	94%	Overall $p = .05$	No difference	41
CTiE	Lactoferrin	77%	90%	Not significant	No difference	42
CTiR	Lactobacillus	80%	76%	Taste $p = .0027$	No difference	43
	<i>Saccharomyces boulardii</i>	80%	81%	Diarrhea $p = .018$		
CAR	<i>Lactobacillus</i> and bifidobacteria	80%	86%			
	<i>Bacillus clausii</i>	71%	72%	Overall $p < .05$	No difference	44

C, clarithromycin; E, esomeprazole; A, amoxicillin; Ti, tinidazole; R, rabeprazole.

Bovine lactoferrin is an iron-binding glycoprotein that is found in body fluids and secretions of humans and bovines. It appears to play a role in the hosts defense against bacteria and has a bacteriostatic and bactericidal effect [42]. It inhibits adherence and iron uptake by *H. pylori*. A number of studies have compared triple therapy with and without adjuvant therapy (Table 4). Eradication rates may or may not improve with adjuvant therapy but the incidence of side-effects especially diarrhea, nausea, and taste disturbance is reduced significantly. A large scale meta-analysis in *H. pylori* treatment has shown a significant reduction in side-effects with adjuvant therapy. Tong et al. showed that eradication rates of combining probiotics with standard triple therapy were slightly higher in both ITT and PP analysis [45]. De Bartoli et al. showed a significant increase in eradication rates with a combination of standard triple therapy, probiotics, and bovine lactoferrin. There was also a significant reduction in side-effects such as diarrhea, nausea, and taste disturbance [37]. The addition of bovine lactoferrin 200 mg (b.i.d.) and a probiotic may improve eradication rates and reduce side-effects.

Factors Related to Eradication Failure

A number of other factors have been studied in *H. pylori* eradication. Smoking is an independent risk factor for *H. pylori* treatment failure [46,47]. In a Finnish study, smoking and coffee drinking reduced the efficacy of therapy [48]. In contrast, alcohol consumption may facilitate elimination of *H. pylori* infection among adults [49]. A number of studies have shown a positive effect of alcohol consumption on the success of eradication therapy [50]. In a Polish study nonsmokers who drink alcohol had the highest eradication rate of 92% with standard triple therapy. There is some controversy on the role of the CYP2C19 phenotype on eradication therapy. A number of

studies have failed to show any significance of this genetic polymorphism in eradication therapy [47].

Conclusion

Increasing evidence suggests that standard triple therapy may no longer be the most effective first-line treatment in certain regions. Two-week therapy may be more effective than 1 week but may not overcome bacterial resistance. Sequential therapy appears to be an effective alternative. Adjuvant therapy with probiotics and bovine lactoferrin can reduce side-effects and may improve eradication rates. Local reference centres are required to monitor antibiotic resistance and eradication rates and determine the best treatment regimes.

Conflicts of interest

The authors have declared no conflicts of interest.

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