AN UPDATE ON THE TREATMENT OF *HELICOBACTER PYLORI* INFECTION

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ABSTRACT

Helicobacter pylori treatment is becoming a challenge in light of increasing antimicrobial resistance and falling eradication rates. This is a cause for concern based on the complications of *H. pylori* infection, which include gastric and peptic ulcers, gastric cancer, and mucosa-associated lymphoid tissue lymphoma. This review discusses recent data assessing the current treatment options for *H. pylori* infection and the importance of considering the prevalence of antibiotic resistance at a regional level when choosing an appropriate therapy. Alternatives to the standard first-line treatment, such as bismuth and non-bismuth quadruple therapies, are outlined and rescue therapies involving levofloxacin and rifabutin are also reviewed.

Keywords: *Helicobacter pylori,* triple therapy, bismuth quadruple therapy, sequential therapy, concomitant therapy, hybrid therapy, antibiotic resistance.

INTRODUCTION

Helicobacter pylori is a gram-negative bacterium that specifically colonises the stomachs of approximately 50% of the global population.[1] Infection is usually acquired in early childhood and, despite triggering a vigorous immune response, *H. pylori* persists for life if left untreated. The prevalence of *H. pylori* infection varies throughout the world and is associated with older age and with lower socioeconomic conditions.[1] Although most infected individuals do not develop any significant symptoms, *H. pylori* is causally linked to a number of gastrointestinal disorders; peptic ulcers develop in 1–10% of those infected, while gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma present in 0.1–3% and <0.01% of infected individuals, respectively.[2] The World Health Organization's International Agency for Research on Cancer has classified *H. pylori* as a definite (Group 1) carcinogen.[3] *H. pylori* infection has also been linked to unexplained iron-deficiency anaemia and idiopathic thrombocytopenic purpura, with recent guidelines on the management of these conditions recommending *H. pylori* eradication where present.[4,5]

Consensus guidelines on the management of *H. pylori* infection recommend a standard first-line triple therapy that consists of an acid-suppressing proton pump inhibitor (PPI; 20–40 mg) together with the antibiotics clarithromycin (500 mg) and amoxicillin (1,000 mg) taken twice daily for 7–14 days (Table 1).[6-8] Metronidazole (500 mg) is used instead of amoxicillin in penicillin-allergic individuals. Unfortunately, the success rate of first-line triple therapy has fallen in many countries, with eradication rates of just 55–57% reported from countries in Western Europe.[9,10] A number of factors contribute to treatment failure, including high bacterial load, low gastric pH, and impaired mucosal immunity,[11] although the main reasons for *H. pylori* treatment failure are thought to be poor compliance and antimicrobial resistance.[6,11-13] Several strategies have been shown to improve the efficacy of standard triple therapy. A recently published meta-analysis has shown that increasing the duration of triple therapy involving a PPI, amoxicillin, and clarithromycin from 7 to 10 days results in a significantly higher eradication rate (76.2% versus 80.5%, respectively).[14] Fourteen days was found to provide the most effective eradication rate (85.8%).[14] Increasing the dose of PPIs also has

a positive effect on treatment outcome, as PPIs increase gastric pH, reduce gastric juice volume, and delay gastric emptying, thus preventing acid-related antibiotic degradation and increasing gastric levels of antibiotics.[15,16] If initial therapy fails, however, a levofloxacin-based rescue therapy is recommended.[6,13] If subsequent treatment is required, rifabutin-based regimens may be prescribed,[6,17] but treatment should be guided by antimicrobial susceptibility testing.[6]

H. PYLORI ANTIBIOTIC RESISTANCE

The antibiotics used for eradication of *H. pylori* target pathways that disrupt bacterial homeostasis or replication. The use of more than one antibiotic in each treatment regimen enables targeting of *H. pylori* viability through multiple pathways, thereby increasing the likelihood of successful eradication. Amoxicillin is included in most treatment regimens as resistance to this antibiotic is low. Amoxicillin is a β-lactam antibiotic that acts by interfering with bacterial peptidoglycan synthesis, in particular by blocking transporter proteins called penicillin-binding proteins. Mutations in the *pbp-1a* gene have been reported to confer amoxicillin resistance.[18,19] Clarithromycin is a macrolide antibiotic that binds to the 23S ribosomal subunit of *H. pylori*, thus preventing bacterial protein synthesis. Single point mutations (most commonly A2146C, A2146G, and A2147G) within the *H. pylori rrl* gene that encodes the 23S ribosomal subunit confer clarithromycin resistance.[19] Levofloxacin belongs to the fluoroquinolone family of antibiotics that target the DNA gyrase enzyme involved in DNA strain relief during bacterial replication. The most significant mutations conferring quinolone resistance are located at positions 87 (N87K) and 91 (D91N, D91G, D91Y) of the *H. pylori gyrA* gene, which encodes the A subunit of the DNA gyrase enzyme.[20] Metronidazole is a nitroimidazole antibiotic that functions as a pro-drug that is non-enzymatically reduced to a molecule that destabilises bacterial DNA, resulting in bacterial cell death.[19] In terms of metronidazole resistance, a definitive panel of resistance-associated point mutations has not yet been characterised, although mutations in the *H. pylori rdxA* and *frxA* genes have been implicated.[19] Although the mutations mediating tetracycline and rifabutin resistance have been described, resistance to these antibiotics is low in most regions.[21-23] The mechanism of action of tetracycline is interference with protein synthesis at the ribosomal level. Tetracycline resistance is associated with mutations in the 16S rRNA gene.[18,19]

Table 1: *Helicobacter pylori* treatment regimens.

Therapy	Description
Standard triple therapy	PPI*, 500 mg clarithromycin, and 1,000 mg amoxicillin (twice daily for 7–14 days)
Bismuth quadruple therapy**	PPI* (twice daily), 120–600 mg bismuth salt, 250–500 mg metronidazole, and 250–500 mg tetracycline (up to four times daily for 7–14 days)
Sequential therapy	PPI* and 1,000 mg amoxicillin (twice daily for 5–7 days) followed by PPI*, 500 mg clarithromycin, and 500 mg metronidazole (twice daily for 5–7 days)
Concomitant therapy	PPI*, 1,000 mg amoxicillin, 500 mg clarithromycin, and 500 mg metronidazole/tinidazole (twice daily for 7–14 days)
Hybrid therapy	PPI*, 1,000 mg amoxicillin (twice daily for 14 days) with 500 mg clarithromycin and 500 mg tinidazole (twice daily for the final 7 days)
Levofloxacin-based triple therapy	PPI*, 250 mg levofloxacin, and 1,000 mg amoxicillin (twice daily for 7–14 days)
Levofloxacin-based sequential therapy	PPI* and 1,000 mg amoxicillin (twice daily for 5 days) followed by PPI*, 250 mg levofloxacin, and 500 mg metronidazole (twice daily for 5 days)
Rifabutin-based triple therapy	PPI*, 1,000 mg amoxicillin, and 150 mg rifabutin (twice daily for 7–14 days)

*PPI dose: 20 mg omeprazole, 20 mg rabeprazole, 30 mg lansoprazole, 40 mg esomeprazole, or 40 mg pantoprazole; **Variations in the dose of bismuth quadruple therapy have been reported.
PPI: proton pump inhibitor.

Table 2: Recent data on the prevalence of *Helicobacter pylori* antibiotic resistance.

Region	Resistance rate Clar	Resistance rate Met	Resistance rate Lev	Reference
China, Beijing	37.2%**	63.9%**	50.3%**	26
China, south-east coastal region	21.5%**	95.4%**	20.6%**	27
Europe, northern countries	7.7%*	28.6%*	7.7%*	21
Europe, southern countries	21.5%*	29.7%*	13.1%*	21
Europe, western and central countries	18.7%*	43.8%*	18.6%*	21
Japan	38.8%* 55.6%**	ND ND	34%* 38.6%**	28
Latin America	12%*	53%*	15%*	29
Senegal	1%*	85%*	15%*	30
Thailand	3.7%*	36%*	7.2%*	23
USA	16.4%**	20.3%**	31.3%**	24

*Primary resistance rate; **Overall resistance rate.
Clar: clarithromycin; Met: metronidazole; Lev: levofloxacin; ND: not determined.

Table 3: *Helicobacter pylori* treatment strategies based on local clarithromycin resistance patterns.

Treatment	Option	Low clarithromycin resistance (<15–20%)	High clarithromycin resistance (>15–20%)
First-line	A	Clarithromycin-based triple therapy*	Bismuth quadruple therapy
	B	Bismuth quadruple therapy	Non-bismuth quadruple therapy (sequential**, concomitant, or hybrid)
Second-line	A	Levofloxacin-based triple therapy†	
	B	Bismuth quadruple therapy‡	
Subsequent	A	Guided by antimicrobial susceptibility testing	
	B	Rifabutin-based triple therapy	

*14 days triple therapy with high-dose proton pump inhibitor (e.g. 40 mg esomeprazole twice daily) demonstrates the best eradication rates; **Not suitable in areas with high rates of dual clarithromycin and metronidazole resistance; †Unless local data indicate high rates of quinolone resistance; ‡Unless already used in first-line therapy.

Rifabutin is a spiro-piperidyl-rifamycin antibiotic that targets the β subunit of the DNA-directed RNA polymerase encoded by the *rpoB* gene; mutations in this gene confer rifabutin resistance.[19]

H. pylori antibiotic resistance is thought to develop due to the outgrowth of a small existing population of resistant organisms. Primary antibiotic resistance refers to *H. pylori* antibiotic resistance in individuals with no previous *H. pylori* eradication therapy. Secondary antibiotic resistance results when a susceptible strain acquires resistance during the course of a treatment. In both cases, resistance is thought to occur due to inappropriate antibiotic use. There exists a clear link between *H. pylori* antibiotic resistance and previous antibiotic use. Analysis of cumulative and yearly outpatient antibiotic consumption in Europe revealed a significant association between the use of long-acting macrolides and resistance of *H. pylori* to clarithromycin, and between previous quinolone use and levofloxacin resistance.[21]

Studies on the prevalence of antibiotic resistance in the UK and USA have also shown previous antibiotic use increases the risk of harbouring resistant strains of *H. pylori*.[22,24]

The most recent assessment of primary antibiotic resistance in Europe reported overall resistance rates for clarithromycin, levofloxacin, and metronidazole of 17.5%, 14.1%, and 34.9%, respectively, with a prevalence ≤1% for tetracycline, rifampicin, and amoxicillin.[21] Almost 8% of strains isolated had combined resistance to metronidazole and clarithromycin. The rate of clarithromycin resistance had almost doubled since the previous European survey,[25] which is a cause for concern as clarithromycin resistance decreases the efficacy of standard first-line triple therapy by up to 70%.[6] Metronidazole resistance was high at 34.9%,[21] but the level had not changed significantly since the previous Europe-wide study.[25] The impact of metronidazole resistance on *H. pylori* eradication is less than that of clarithromycin resistance, and can be overcome by increasing the dose and duration of treatment or by prescription of bismuth-containing quadruple therapy.[9]

Interestingly, variations in the prevalence of antibiotic resistance across European countries were observed (recent data summarised in Table 2).[26-30] The resistance rate for clarithromycin was <10% in northern European countries, while most countries in the rest of Europe (except Spain and Germany) had a resistance rate of >15%.[21] Such variations in antibiotic resistance have also been reported at a local level within countries. For example, a recent study in the UK indicated that the resistance rates to clarithromycin, metronidazole, and quinolones in Wales were 18%, 43%, and 13%, respectively, but in England were 3%, 22%, and 1%, respectively.[22] Differences in resistance rates have also been reported outside Europe (Table 2). For example, although the overall resistance rates for clarithromycin, metronidazole, and levofloxacin in Thailand were 3.7%, 36%, and 7.2%, respectively, metronidazole resistance was more prevalent in southern Thailand than north-eastern Thailand (66.7% versus 33.3%).[23] Such diversity in the prevalence of antibiotic resistance has important consequences when it comes to choosing the appropriate therapy for successfully eradicating *H. pylori* in a given population. According to the Maastricht IV guidelines, standard triple therapy should now only be prescribed in regions where the prevalence of clarithromycin resistance is known to be <15–20% (Table 3).[6]

While no new drug has been developed as a direct replacement, recent trials have assessed the efficacies of therapies involving different combinations of known antibiotics, the results of which are discussed below.

BISMUTH QUADRUPLE THERAPY

Bismuth quadruple therapy (Table 1) has been recommended as a first-line therapy in regions of high clarithromycin resistance, and in areas with low clarithromycin resistance as an alternative to standard triple therapy or as a rescue regimen.[6] A recent meta-analysis reported eradication rates of 77.6% and 68.9% for bismuth quadruple therapy and standard triple therapy, respectively.[31] Compliance and adverse events were similar across the two treatment groups and bismuth quadruple therapy did not appear to be affected by metronidazole resistance. Variations in the bismuth therapy treatment regimens were described in terms of antibiotic dose and treatment duration. A sub-analysis of the data showed that, although bismuth therapy for 10 days was more effective than 7 days of triple therapy, the two therapies given for the same length of time yielded similar eradication rates.[31] In keeping with the idea that the duration of bismuth quadruple therapy affects eradication success, a 95% eradication rate for a 14-day bismuth therapy regimen has been described.[32]

In terms of rescue therapy, a meta-analysis by Marin et al.[13] indicated that when bismuth-containing quadruple therapy was prescribed following failure of standard clarithromycin-based triple therapy, the eradication rates were 76%, 77%, and 82% for 7, 10, and 14 days, respectively. In addition, high *H. pylori* eradication rates with bismuth therapy have been described in patients who did not respond to previous therapies, including those with metronidazole resistance.[33-35] Taken together, these findings support a role for bismuth quadruple therapies as both first-line and rescue regimens. However, due to the unavailability of tetracycline and bismuth salts in several countries, bismuth quadruple therapy may not always represent an accessible treatment option.[13,36]

NON-BISMUTH QUADRUPLE THERAPY

Sequential Therapy

Non-bismuth quadruple therapy has been proposed as an alternative to bismuth quadruple

therapy for first-line treatment in regions with high clarithromycin resistance.[6] The efficacy of sequential therapy (Table 1) compared with triple therapy, however, depends on the treatment durations under comparison and the study population. A systematic review and meta-analysis performed by Gatta et al.,[37] which compared 46 randomised controlled trials, indicated that sequential therapy was superior to 7-day triple therapy, marginally superior to 10-day triple therapy, but not superior to 14-day triple therapy. Geographic variations in the prevalence of antibiotic resistance appear to be a key factor affecting the lack of difference between sequential therapy and 14-day triple therapy, as a meta-analysis by Losurdo et al.[38] reported that sequential therapy was superior to 14-day triple therapy in areas with high clarithromycin resistance, but sequential and triple therapy were similar in areas of high metronidazole resistance. Of note, the Gatta study[37] described an overall eradication rate of just 37% for sequential therapy in patients infected with *H. pylori* strains resistant to both clarithromycin and metronidazole resistance, indicating that dual antibiotic resistance significantly impacts the efficacy of sequential therapy.

Concomitant Therapy

Standard triple therapy can be converted to concomitant therapy (Table 1) by the addition of 500 mg of metronidazole or tinidazole twice daily. A meta-analysis of the randomised controlled trials comparing concomitant with standard triple therapy revealed eradication rates of 90% and 78% for concomitant and triple therapy, respectively, by intention-to-treat analysis.[39] The analysis indicated that clarithromycin resistance may impact the efficacy of concomitant therapy, but to a lesser extent than standard triple therapy.[39] A recent multicentre trial in Spain comparing 14-day triple therapy with 14-day concomitant therapy revealed that the extended concomitant therapy achieved significantly higher cure rates (>90%) compared with 14-day triple therapy, with milder adverse events and no effect on compliance.[15] Evidence to date suggests similar eradication rates when concomitant therapy is compared with sequential therapy, with no significant differences in terms of compliance or adverse events.[36,37,40,41] Therefore, while the eradication rates for concomitant and sequential therapy appear similar, both appear superior to standard triple therapy as a first-line treatment option.

Hybrid Therapy

The recently described hybrid therapy represents a combined version of sequential and concomitant therapy, comprising a PPI (20–40 mg) with amoxicillin (1,000 mg) for 14 days plus clarithromycin (500 mg) and a nitroimidazole derivative (500 mg) for the final 7 days (Table 1). Hsu et al.[42] initially reported eradication rates of >90% for hybrid therapy. However, it is unclear whether hybrid therapy has any significant advantage over sequential or concomitant therapy, as recent meta-analyses of trials to date demonstrated similar eradication rates across all three therapies.[43,44] Further studies in additional countries are required in order to determine whether hybrid therapy exhibits improved efficacy over sequential or concomitant therapy as a first-line therapy.

SECOND-LINE AND SUBSEQUENT *H. PYLORI* ERADICATION THERAPIES

Following failure of standard triple therapy, a levofloxacin-based rescue therapy (Table 1) is recommended unless local data indicate high rates of quinolone resistance.[6,13] Meta-analyses have shown that 10 days of levofloxacin triple therapy is superior to bismuth quadruple therapy, but not 7 days of levofloxacin therapy.[45,46] The inclusion of levofloxacin in sequential therapy has also been shown to be effective for patients who have failed either sequential or triple therapy.[47] Indeed, an analysis of three studies comparing sequential therapy with sequential therapy containing levofloxacin (instead of clarithromycin) demonstrated increased eradication success using the modified sequential therapy.[32] Combining levofloxacin and bismuth in patients who have previously failed *H. pylori* treatment has also been demonstrated to be a successful strategy for *H. pylori* eradication.[48] As levofloxacin resistance is emerging in many countries,[21] rifabutin-based triple therapy has been suggested as an alternative rescue therapy. Primary *H. pylori* rifabutin resistance is low[49] and rifabutin is effective in patients with dual metronidazole and clarithromycin resistance.[17] As a fourth-line therapy, Gisbert et al.[50] have provided a rationale for the use of rifabutin-based therapy as a valid rescue strategy following multiple eradication failures.

TAILORING THERAPY BASED ON ANTIBIOTIC RESISTANCE DATA

Given that antibiotic resistance impacts treatment outcome and rates of resistance vary between different regions, surveillance of antibiotic resistance represents a key strategy in choosing the appropriate first-line *H. pylori* treatment regimen in a given population. Culture of *H. pylori* from gastric biopsy specimens and antimicrobial susceptibility testing by means of minimum inhibitory concentration determination has been considered the gold standard for assessing *H. pylori* antibiotic resistance to date. However, *H. pylori* is a fastidious bacterium and culture is time-consuming and often challenging, with low sensitivity values.[51] Molecular testing for *H. pylori* antibiotic resistance offers an attractive alternative to culture and allows for analysis of *H. pylori* DNA directly from biopsy samples, providing a key opportunity for same-day diagnosis. In addition, molecular tests have been used to analyse stool samples,[52,53] potentially enabling *H. pylori* antimicrobial susceptibility testing through non-invasive procedures. In addition to surveillance, evidence from numerous studies provides a rationale for tailoring treatment based on antimicrobial susceptibility testing to improve the efficacy of both first-line[54-56] and rescue therapies.[57,58] Cost-effectiveness of tailored therapy is a genuine consideration, but it is thought to be economically viable, especially in areas of high clarithromycin resistance.[54,55]

SUMMARY

H. pylori antibiotic resistance exhibits regional variations and is constantly evolving. As such, local resistance data is imperative in guiding efficacious treatment choices (summarised in Table 3). In regions where high clarithromycin resistance has been detected, evidence supports the use of both bismuth and non-bismuth quadruple therapies as first-line alternatives to standard triple therapy. Levofloxacin-based rescue therapies are useful in areas of low quinolone resistance, while rifabutin offers a promising alternative if levofloxacin resistance is detected or following multiple treatment failures. Treatment duration is a key factor in *H. pylori* eradication success, with studies demonstrating that increasing the treatment duration improves the efficacy of all of the therapies discussed above. However, longer treatment durations may affect compliance, and therefore adherence should be strongly emphasised for the first and any subsequent *H. pylori* eradication therapies.

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