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REVIEW

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Treatment of *Helicobacter pylori* infection: A clinical practice update

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Abstract

Background: *Helicobacter pylori* infection is still frequent in the community and all infected subjects should be offered an eradication therapy. Nowadays physicians have to face the challenge of antibiotic resistance in treating *Helicobacter pylori*-infected individuals.

Aim: This review provides an overview of current international guidelines and reports recent evidence from systematic reviews and clinical trials on the treatment of *Helicobacter pylori* infection and should help physicians to better treat their patients.

Results: General rules to optimize the management of *Helicobacter pylori* infection include: (i) considering previous patient's exposure to antibiotics; (ii) using high dose of proton-pump inhibitors; and (iii) avoiding repeating the same regimen, if it has already failure. Bismuth quadruple therapy and concomitant therapy are the best first-line empirical treatments in areas with high clarithromycin resistance and in individuals with previous use of macrolides; otherwise, the 14-day clarithromycin-containing triple therapy is a valid regimen. The sequential therapy is no longer a suggested treatment by international guidelines.

Conclusions: Current international guidelines are consistent in defining treatment strategies for *Helicobacter pylori* infection. The use of national registries to monitor the efficacy and tolerability of different regimens in the real world of clinical practice is now needed.

KEYWORDS
Helicobacter pylori, infection, treatment

1 | INTRODUCTION

Despite the decreasing prevalence of *Helicobacter pylori* (*H. pylori*) infection, this bacteria still infects 30%-50% of the general population in Western countries.[1] *Helicobacter pylori* causes active chronic gastritis in all infected subjects and may cause complications, such as dyspepsia, peptic ulcer, gastric malignancies and extragastric diseases. The eradication of *H. pylori* leads to the healing of gastritis and prevents complications; thus, all subjects with known *H. pylori* infection should be offered eradication treatment.[2]

However, bacterial antibiotic resistance is still challenging the outcome of *H. pylori* eradication treatment. The "key" antibiotics in the treatment of *H. pylori* infection are clarithromycin and levofloxacin, and the prevalence of *H. pylori* strains resistant to these antibiotics has been increasing over the last decades.[3] Several international guidelines have been published over the last years pointing out new recommendations for the treatment of *H. pylori* infection, with particular attention to the issue of antimicrobial resistance.

This review provides an overview of current international guidelines and reports recent evidence from

systematic reviews and clinical trials on the treatment of *H. pylori* infection. This review should help physicians to choose the most adequate treatment for their patients with *H. pylori* infection.

2 | GENERAL RULES

To optimize the treatment of *H. pylori* infection, physicians should take into account three basic rules: (i) investigating previous patient's exposure to antibiotics; (ii) using high doses of proton-pump inhibitors (PPIs); and (iii) avoiding repeating the same regimen, if it has already failed.

2.1 | Investigating previous patient's exposure to antibiotics

If a subject with *H. pylori* infection had used in the past macrolides or quinolones for any reasons, such as infections of the genito-urinary tract or respiratory tree, there is an increased chance that *H. pylori* had become resistant to those antibiotics.[4] Therefore, patients with previous use of macrolides and quinolones should be considered as potential carriers of *H. pylori* strains resistant to these antibiotics, and in these patients, clarithromycin- or levofloxacin-containing triple therapies should be avoided.[5-7] In their clinical practice, doctors should ask patients about previous treatments with antibiotics and should take this information into account when choosing the *H. pylori* treatment regimen.

2.2 | Using high doses of proton-pump inhibitors

International guidelines recommend to use the PPIs at a standard dose twice daily to increase the efficacy of antimicrobial regimens.[5-7]

A systematic review and meta-analysis reported significantly higher *H. pylori* eradication rates when a standard dose of PPI, ie omeprazole 20 mg, esomeprazole 40 mg, pantoprazole 40 mg, lansoprazole 30 mg or rabeprazolo 20 mg, was given twice daily compared to single dose.[8] There are several explanations for this finding. First, higher intragastric pH values reduce both the bacterial load of *H. pylori* and the minimal inhibition concentration of antibiotics in the gastric mucosa increasing the antibacterial effect of antibiotics.[9] In addition, high doses of PPIs would increase *H. pylori* eradication rates in subjects who are extensive metabolizers of PPIs. There is evidence that CYP2C19 polymorphisms can affect the efficacy of eradication therapy driving the capacity of the patient to metabolize PPIs,[10] and in Europe and North-America, more than half of subjects seem to be high metabolizers of PPIs.[11]

Thus, physicians should always use high doses of PPIs in the treatment of *H. pylori* infection.[5-7]

2.3 | Avoiding repeating the same antimicrobial regimen

A general rule in the empirical treatment of any infectious diseases is to avoid repeating the same antibiotic regimen that is already failed. In the treatment of *H. pylori* infection, the failure of clarithromycin-containing triple therapy is commonly related to *H. pylori* primary or acquired resistance to clarithromycin.[12] A meta-analysis of 8 studies reported a very low eradication rate of 46% after repeating a clarithromycin-containing therapy.[13] Therefore, repeating the same antimicrobial regimen in the treatment of *H. pylori* infection should be avoided.[5-7]

3 | FIRST-LINE TREATMENT

Several regimens have been proposed over the last decades as first-line treatment of *H. pylori*. The most common regimens are the clarithromycin-containing triple therapy extended for more than 7 days and the non-bismuth (sequential and concomitant) and bismuth quadruple therapies.

3.1 | Clarithromycin-containing triple therapy for more than 7 days

A systematic review and meta-analysis of 45 randomized controlled trials (RCTs), including a total of 7722 patients, provided evidence that 14 days is the optimum duration for the clarithromycin-containing triple therapy (PPI, clarithromycin and amoxicillin or metronidazole/tinidazole).[14] This regimen given for 14 days provided a pooled eradication rate significantly higher than 7 days (81.9% vs 72.9%). On the other hand, increasing the duration from 7 to 10 days had just a little benefit on the eradication rate (75.7% vs 79.9%). All international guidelines agree that clarithromycin-containing triple therapy may still be used in the first-line treatment of *H. pylori* infection, providing that its duration is extended for 14 days.[5-7]

3.2 | Non-bismuth quadruple therapies

Non-bismuth quadruple therapies are regimens including a PPI and three antibiotics, which are clarithromycin, amoxicillin and metronidazole or tinidazole. There are two types of non-bismuth quadruple therapies: the sequential therapy, where the three antibiotics are given sequentially—amoxicillin for 5 days then replaced by clarithromycin and metronidazole for additional 5 days; the concomitant therapy, where the three antibiotics are given all together.

Notably, both sequential and concomitant regimens were designed to overcome the issue of clarithromycin resistance. However, the therapeutic performance of these regimens, in particular their efficacy in patients with *H. pylori* strains resistant to antibiotics, has been largely debated.

Several studies have been recently published providing new insight on the performance of these regimens. A recent large randomized controlled trial assessed the efficacy of a 10-day sequential therapy in comparison with a 14-day clarithromycin-containing triple therapy.[15] In this study, both regimens performed well with clarithromycin-susceptible strains, showing eradication rates higher than 90%, whereas their efficacy dropped to 70% or lower when *H. pylori* strains were clarithromycin-resistant. Thus, clarithromycin resistance undermined the efficacy of both sequential and 14-day clarithromycin-containing triple therapies. There is consistent evidence that sequential therapy is affected also by metronidazole resistance.[5] Moreover, a recent systematic review and meta-analysis, including 8 RCTs and 3831 patients, reported that sequential therapy was not better than 14-day clarithromycin-containing triple therapy, with similar pooled eradication rates (81.4% for sequential therapy and 80.3% for 14-day triple therapy, risk difference = 2% (95% confidence interval (CI), −2% to 6%), in the first-line treatment for *H. pylori* infection.[16]

On the other hand, concomitant therapy seems not to be affected by clarithromycin resistance providing eradication rates around 80% in patients with *H. pylori* clarithromycin-resistant strains.[5] Different from sequential, concomitant therapy is also able to overcome the issue of metronidazole single resistance. Indeed, in a head-to-head comparison study, concomitant therapy achieved an eradication rate of 97% in patients with metronidazole single-resistant strain, whereas sequential therapy yields a significantly lower eradication rate of 79%.[17]

A meta-analysis of 14 RCTs showed that concomitant therapy was significantly better than sequential therapy with a risk difference in eradication rate of 6% (95% CI, 3%-9%, $P < .0001$).[6]

However, also the concomitant therapy has a weak point; it loses efficacy in the presence of *H. pylori* strains with dual resistance to clarithromycin and metronidazole. Indeed, a randomized clinical trial performed in a high clarithromycin resistance area reported an eradication rate of 75% with concomitant therapy in patients with dual resistance to clarithromycin and metronidazole.[17]

3.3 | Bismuth quadruple therapy

The bismuth quadruple therapy is a 20-year-old regimen that consists of PPIs plus bismuth salt, tetracycline and metronidazole.[18] This regimen was recommended in the past only as second-line treatment, as it was more complex than the standard triple therapy.[19] However, the bismuth quadruple therapy is a "strong weapon" for antibiotic resistance as it does not contain either clarithromycin or levofloxacin. Thus, there has been over the last decade a coming back to bismuth quadruple therapy that is now recommended also as first-line treatment.[20]

As expected, this regimen is highly effective in naive patients. A multicenter randomized controlled trial compared bismuth quadruple therapy with concomitant and 14-day clarithromycin-containing triple therapies in the first-line treatment of *H. pylori* infection.[21] This study showed that bismuth quadruple therapy was significantly more effective than 14-day triple therapy (intention to treat eradication rate: 90.4% vs 83.7%, $P = .001$), and also slightly better than concomitant therapy (85.9%). Bismuth quadruple therapy was not affected either by clarithromycin resistance, yielding an intention to treat eradication rate of 89%, or by dual clarithromycin and metronidazole resistance (eradication rate: 94%). This study confirmed that clarithromycin resistance affected the efficacy of the 14-day clarithromycin triple therapy (eradication rate: 48%) and that dual clarithromycin and metronidazole resistance affected concomitant therapy (eradication rate: 59%).

Two randomized controlled trials in the USA[22] and Europe[23] have shown the good performance of bismuth quadruple therapy also with the new formulation of "3-in-1 capsule" of bismuth sub-citrate, tetracycline and metronidazole. This new formulation was essentially designed to overcome the complexity of the classic bismuth quadruple therapy and thus improve patient's compliance. In the European trial, the new formulation "3-in-1 capsule" of bismuth quadruple therapy achieved an overall eradication rate higher than 90% and was highly effective in subjects infected by clarithromycin, metronidazole or dual clarithromycin- and metronidazole-resistant strains achieving eradication rates of 91%, 91% and 92%, respectively.[23] This new formulation has been on the market in Europe only from a few years; thus, data on its efficacy and safety in the daily clinical practice are still scarce. A recent study reported data on a series of 131 consecutive outpatients who were given the new formulation "3-in-1 capsule" in the real world of clinical practice in Italy, both in first- and second-line.[24] The new formulation of bismuth quadruple therapy showed a good performance, achieving an eradication rate higher than 90%, with only a quarter of patients reporting mild or moderate side effects; only 3% of patients discontinued the treatment because of adverse events.

3.4 | What is the treatment of choice?

All international guidelines agree that the choice of the first-line regimen should be based on the prevalence of

H. pylori clarithromycin-resistant strains in the population and on the previous patient's exposure to macrolides (clarithromycin/azithromycin).

Bismuth quadruple therapy and concomitant therapy, given for at least 10 days according to European[5] and North American guidelines[7] and for 14 days according to the Canadian guidelines,[6] are the recommended regimens in areas with high prevalence of clarithromycin resistance (>15%). In areas with high dual clarithromycin and metronidazole resistance, bismuth quadruple therapy is the recommended regimen (Figure 1).[5-7] The clarithromycin-containing triple therapy is still recommended in areas with low prevalence of clarithromycin resistance (<15%) and in patients without previous exposure to macrolides[5-7]; all guidelines underline that this regimen should be given for 14 days to optimize its efficacy (Figure 1). Notably, current guidelines discourage the use of sequential therapy.[5-7] In areas with high prevalence of clarithromycin resistance, the sequential therapy would be less effective than concomitant or bismuth quadruple therapies, whereas in areas with a low prevalence of clarithromycin resistance, it would not be superior to a 14-day clarithromycin-containing triple therapy, which is a simpler regimen containing one antibiotic less.

However, data on the local prevalence of *H. pylori* antibiotic resistance are conflicting or lacking in most areas. For example, in Italy, only a few studies with a small sample size reported rates of clarithromycin resistance varying from 10% to 35%.[25] Thus, the choice of the first-line regimen is not always simple, and these areas should be driven by the local efficacy of the different regimens and the previous patient's exposure to antibiotics.[5–7,25] For example, a 14-day clarithromycin-containing triple therapy may be used in regions where this regimen has been proven to achieve high eradication rates in clinical practice and in those patients without a previous use of macrolide; otherwise, a concomitant or bismuth quadruple therapy, using the new formulation of "3-in-1 capsule" when available, should be the preferred option. National registries reporting eradication rates and side effects with the different regimens in clinical practice are strongly encouraged to improve the treatment of *H. pylori* infection.

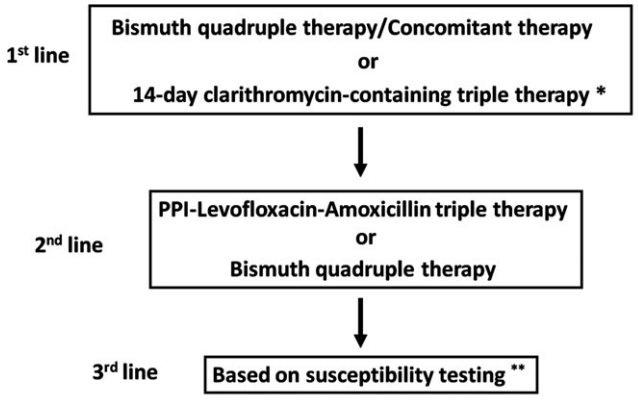

FIGURE 1 Algorithm for eradication therapies of *Helicobacter pylori* infection

4 | SECOND-LINE AND RESCUE THERAPIES

After the failure of an empirical first-line treatment, physicians should use a levofloxacin triple therapy (PPI + levofloxacin + amoxicillin) or a bismuth quadruple therapy[5-7] (Figure 1). In particular, levofloxacin triple therapy should be the treatment of choice after the failure of bismuth quadruple therapy. Two recent meta-analyses showed that these two regimens have similar performances as second-line treatment for *H. pylori* infection.[5,26] A meta-analysis of 25 RCTs assessed the outcome of levofloxacin triple therapy in second-line reporting a pooled eradication rate of 74.5% (95% CI: 70.9-77.8).[26] Similarly, a pooled analysis of 38 RCTs, assessing the efficacy of bismuth quadruple therapy as second-line treatment, reported an eradication rate of 78% (95% CI, 75%-81%).[5]

After the failure of second-line treatment, the third-line regimen should be based on culture with susceptibility testing or molecular determination of genotype resistance (Figure 1).[5-7] However, susceptibility testing is not widely available[7]; international guidelines finally recognized that this is a real issue in clinical practice and provided recommendations for an empirical third-line treatment. It is recommended to use in third-line the eradication regimen that was not used in first- and second-line among clarithromycin containing therapies, levofloxacin triple therapy and bismuth quadruple therapy.[5] A bismuth-based levofloxacin quadruple therapy and a rifabutin-containing triple therapy (PPI + rifabutin + amoxicillin) may be a valid alternative for third- or fourth-line treatments.[5-7,27]

5 | CONCLUSIONS

Helicobacter pylori gastritis is still a highly prevalent infectious disease, and eradication therapy should be offered to all infected subjects. Investigating previous patient's exposure to antibiotics, using high doses of proton-pump inhibitors and avoiding repeating the same antimicrobial regimen are basic rules to optimize the eradication treatment. Recent international guidelines are consistent in defining treatment strategies for *H. pylori* infection. Bismuth quadruple therapy is the best empiric regimen in areas with high

antibiotic resistance, in subjects with previous use of macrolides or quinolones or after the failure of either clarithromycin- or levofloxacin-based regimens. Clarithromycin-containing triple therapy is still recommended in patients who are less likely to carry a clarithromycin-resistant strain, and it should be given for 14 days. The use of sequential therapy is discouraged. Application of guidelines and the use of registries to monitor treatment efficacy and safety in the real world of clinical practice are strongly recommended.

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