World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i18.5302

World J Gastroenterol 2014 May 14; 20(18): 5302-5307
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

Helicobacter pylori: Management in 2013

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Received: September 30, 2013 Revised: November 25, 2013
Accepted: January 6, 2014
Published online: May 14, 2014

Abstract

Helicobacter pylori (*H. pylori*) is a prevalent, worldwide, chronic infection. Choice of treatment can be modified according to antibiotic-resistance rates of *H. pylori*. The ideal therapeutic regimen for *H. pylori* infection should achieve an eradication rate of ⩾ 80%. In some countries, triple therapy with a proton-pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole is still the best option. Bismuth-containing quadruple therapy consisting of bismuth salts, tetracycline, metronidazole and PPI, may be the preferred option in countries with clarithromycin resistance > 20%. Sequential therapy including a PPI and amoxicillin given for the first 5 d, followed by triple therapy including a PPI, clarithromycin, and nitroimidazole antimicrobial (all twice daily) for the remaining 5 d, can be another option for the first-line treatment of *H. pylori*. Recent data suggest that treatment with PPI, levofloxacin, and amoxicillin for 10 d is a good choice for second-line therapy. Concomitant therapy consisting of PPI, amoxicillin, clarithromycin and metronidazole is another option for second-line treatment. If second-line treatment also fails, it is recommended to culture *H. pylori* from biopsy specimens and perform antimicrobial susceptibility testing. Rescue treatment should be based on antimicrobial susceptibility.

Key words: *Helicobacter pylori*; First-line therapy; Second-line therapy; Rescue therapy

Core tip: *Helicobacter pylori* (*H. pylori*) is a prevalent, worldwide, chronic infection. The ideal therapy regimen for *H. pylori* infection should achieve an eradication rate ⩾ 80%. Triple therapy remains an appropriate first-line therapy in areas of low clarithromycin resistance, and quadruple therapy should be the first-line therapy in areas of high clarithromycin resistance. Sequential therapy can be an alternative. Levofloxacin-containing regimens or concomitant therapies can be good choices for second-line therapy. Choice of treatment regimen for *H. pylori* infection should be done cautiously and antibiotic-resistance rates should be taken into consideration.

Alahdab YO, Kalayci C. *Helicobacter pylori*: Management in 2013. *World J Gastroenterol* 2014; 20(18): 5302-5307 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i18/5302.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i18.5302

INTRODUCTION

The ideal therapeutic regimen for *Helicobacter pylori* (*H. pylori*) infection should achieve an eradication rate of ⩾ 80%. Treatment may depend on the patient, treatment indication, local antibiotic-resistance profile, and whether the patient was treated previously for *H. pylori* infection.

FIRST-LINE THERAPY

Triple therapy

Triple therapy, comprising two antibiotics, amoxicillin and clarithromycin, and a proton pump inhibitor (PPI) for 1 or 2 wk (Table 1), was recommended as the initial

Table 1 Eradication regimens

Name of therapy	Time (d)	Contents of therapy
Triple therapy	7-14	Proton pump inhibitor (PPI) (twice daily) + clarithromycin (500 mg twice daily) + amoxicillin (1 g twice daily) or metronidazole (500 mg twice daily)
Quadruple therapy	10-14	PPI (twice daily) + bismuth subsalicylate (525 mg 4 times daily) + metronidazole (250 mg 4 times daily) + tetracycline (500 mg 4 times daily)
Levofloxacin therapy	7-10	PPI (twice daily) + levofloxacin (250 mg twice daily) + amoxicillin (1 g twice daily)
Sequential therapy	10	PPI (twice daily) + amoxicillin (1 g twice daily) for the first 5 d, followed by PPI + clarithromycin (500 mg twice daily) + nitroimidazole/tinidazole (500 mg twice daily)
Concomitant therapy		PPI (twice daily) + amoxicillin (1 g twice daily) + clarithromycin (500 mg twice daily) + metronidazole
Levofloxacin-containing sequential therapy	10	PPI +amoxicillin (1 g twice daily) for the first 5 d followed by PPI + levofloxacin (500 mg daily) + metronidazole (500 mg twice daily)

treatment of choice at several consensus conferences[1,2]. Eradication rates with triple therapy range between 70% and 85%[3-5]. Most studies support that 1 and 2 wk triple therapy is associated with similar eradication rates[6,7]. In contrast, the superiority of 2-wk triple therapy over 1-wk triple therapy has been confirmed by a recent large randomized single center trial from Italy. In an intention-to-treat analysis, 2-wk triple therapy with omeprazole, amoxicillin and clarithromycin achieved a significantly higher eradication rate than 1-wk triple therapy (70% *vs* 57%, $P = 0.05$)[8]. The most frequently reported side effects include gastrointestinal (GI) upset, diarrhea, and altered taste for clarithromycin, and GI upset, headache, and diarrhea for amoxicillin. However, rates of *H. pylori* eradication using traditional clarithromycin-containing triple therapies have decreased because of increasing clarithromycin resistance[9].

Quadruple therapy

Triple therapy regimens are becoming less effective, therefore, alternative therapies are needed. Quadruple therapy containing PPI, bismuth, metronidazole and tetracycline given for 10-14 d (Table 1) is a good alternative for first-line treatment of *H. pylori* infection[2,10]. Success rates range between 75% and 90%. Side effects of metronidazole include a metallic taste in the mouth, dyspepsia, and a disulfiram-like reaction with alcohol consumption. Side effects of tetracycline include GI upset and photosensitivity. Bismuth compounds have been associated with darkening of the tongue and stools, nausea, and GI upset[11]. According to the Maastricht Ⅲ and Maastricht Ⅳ Consensus, bismuth-containing quadruple therapy is recommended as first-line therapy, especially in areas with a high prevalence (> 20%) of clarithromycin resistance[1,10].

In a meta-analysis comprising 51 trials to 2004, it was reported that quadruple therapy cures > 85% of *H. pylori* infections[12]. These data were supported by another meta-analysis that reported an eradication rate of 82.6% with bismuth-containing quadruple therapy[13].

The success rate of bismuth-containing quadruple therapy is reported as > 90% from different parts of the world[14-16]. In a meta-analysis comprising four randomized control trials (RCTs), eradication rates with bismuth-containing quadruple therapy *vs* clarithromycin-containing triple therapy were reported as 81% *vs* 78% (OR = 0.83; 95%CI: 0.61-1.14; $P = 0.3$)[17]. According to these data, quadruple and triple therapies seem to be equivalent in terms of effectiveness, compliance and side-effect profile when administered as first-line treatment for *H. pylori* infection. Another meta-analysis reported similar eradication rates for quadruple and triple therapies as first-line therapy for *H. Pylori* infection. They reported a quadruple-therapy eradication rate of 78.3%, whereas the eradication rate of triple therapy was 77.0% (RR = 1.002, 95%CI: 0.936-1.073)[18]. A recent meta-analysis showed that eradication rate of quadruple therapy was 77.6%, whereas triple therapy was 68.9% [risk difference (RD) = 0.06, 95%CI: 0.01-0.13]. In the subgroup analysis of treatment duration, the 10-d quadruple therapy achieved eradication rate of 82.5%, whereas triple therapy achieved an eradication rate of 57.7% (RD = 0.25, 95%CI: 0.18-0.32). Thus, 10-d quadruple therapy was shown to be more effective than the 7-d triple therapy[19]. It is suprising that in these reports both therapies yielded overall similar but suboptimal eradication rates, as distinct from the success rate of quadruple therapy trials.

In contrast, there are trials showing that quadruple therapy is better than triple therapy. In a trial consisting of 440 patients, *H. pylori* eradication rate of quadruple therapy in intention-to-treat analysis was 80%, whereas eradication rate of triple therapy was 55% ($P < 0.0001$). *H. pylori* eradication rate of quadruple therapy in per-protocol analysis was 93%, whereas eradication rate of triple therapy was 70% ($P < 0.0001$)[20]. In another study, the intention-to-treat eradication rates in quadruple and triple therapies were reported as 89.4% and 63.5%, respectively ($P < 0.05$). By per protocol analysis, the eradication rates of the two groups were 91.6% and 65.1%, respectively ($P < 0.05$)[21].

Sequential therapy

The sequential regimen is a simple dual therapy including a PPI plus 1 g amoxicillin (both twice daily) given for the first 5 d, followed by triple therapy including a PPI, 500 mg clarithromycin, and a nitroimidazole antimicrobial (all twice daily) for the remaining 5 d (Table 1). Its initial reported success rate was > 90%[22,23]. Initial studies of sequential therapy suggested that its superiority over standard triple therapy might be due to improved eradication of clarithromycin-resistant strains[24,25]. In a recent study comparing sequential and triple therapy, *H. pylori* eradication rates were 77.8% *vs* 62.2%, respectively ($P =$

0.002)[26]. In this study, the reported eradication rate of sequential therapy was lower than in previous studies. In a multicenter study from Latin America comprising 1463 patients, sequential therapy was not significantly better than standard triple therapy. Eradication rates were 82.2% *vs* 76.5% for triple and sequential therapy, respectively[27]. In an other meta-analysis, the overall eradication rate of sequential therapy was reported to 84.3%, and it was not superior to 14-d triple therapy, bismuth-containing quadruple therapy, and non-bismuth quadruple therapy[28].

It has been suggested that levofloxacin rather than clarithromycin can achieve better eradication rates in sequential regimes. Eradication rates of levofloxacin containing sequential therapy were reported as 95.1% and 90% from Taiwan and Turkey, respectively[29,30].

SECOND-LINE THERAPIES

In patients who were treated for *H. pylori* infection, and did not achieve eradication, second-line therapy is required. The Maastricht Ⅳ consensus states that if triple therapy fails, either a bismuth-containing quadruple therapy or levofloxacin-containing triple therapy can be used as second-line therapy[10].

Levofloxacin-containing therapy can be used as second-line therapy in case of triple-therapy failure[31-33] or as second-line therapy in case of failure of bismuth-containing quadruple therapy in areas of high clarithromycin resistance. Levofloxacin-containing therapy consists of PPI, levofloxacin and amoxicillin and is used for 10 d (Table 1). Side effects of levofloxacin consist of anorexia, nausea, vomitting and abdominal discomfort. It may also cause mild headache and dizziness.

In two different meta-analyses it has been shown that levofloxacin therapy was superior to quadruple therapy as second-line treatment of *H. pylori* infection. Meta-analysis also showed that levofloxacin-based triple therapy has fewer adverse effects and is better tolerated than quadruple-therapy regimens. After *H. pylori* eradication failure, levofloxacin triple therapy is more effective and better tolerated than bismuth-containing quadruple therapy[34,35]. In spite of these results, levofloxacin therapy should be used cautiously because of rising rates of levofloxacin resistance.

Levofloxacin therapy can also be good as an alternative after failure of non-bismuth-containing quadruple sequential or concomitant treatment to eradicate *H. pylori* infection[36].

Classical concomitant or non-bismuth-based quadruple therapy consists of PPI, amoxicillin, clarithromycin and metronidazole (Table 1). Eradication rates of 94.9% and 91.4% were obtained with non-bismuth-containing quadruple therapy in studies from Japan and Greece, respectively[37,38]. A meta-analysis comprising 19 studies (2070 patients) revealed a mean *H. pylori* eradication rate of 88% for non-bismuth- containing quadruple therapy. In this meta-analysis, it has been shown that concomitant therapy was more effective than triple therapy with an eradication rate of 90% *vs* 78%, respectively[39].

RESCUE THERAPY

Rifabutin-based rescue therapy constitutes an encouraging strategy after previous eradication failures with key antibiotics such as amoxicillin, clarithromycin, metronidazole, tetracycline and levofloxacin[40]. Rifabutin can be an alternative to bismuth-based quadruple salvage therapy. In trials using rifabutin-based therapy, eradication rates are reported at > 80%[41,42]. Side effects of rifabutin include rash and GI upset such as nausea, vomiting, dyspepsia and diarrhea, and red discoloration of urine. Rarely, rifabutin is associated with myelotoxicity and ocular toxicity[43].

If second-line treatment also fails, it is recommended to culture *H. pylori* from biopsy specimens and perform antimicrobial susceptibility testing[10,44].

PENICILLIN ALLERGIC PATIENTS

PPI, clarithromycin and metronidazole therapy can be first-line treatment for the patients with penicillin allergy living in areas of low clarithromycin resistance[45]. PPI, tetracycline and metronidazole regimens or bismuth-containing quadruple therapy can be used in areas of high clarithromycin resistance[46]. As an alternative treatment PPI, bismuth subcitrate, rifabutin and ciprofloxacin are used for patients with penicillin allergy and this therapy gave an eradication rate of 94.2%[47].

EXPERIMENTAL TREATMENTS

There is some evidence that adding 500 mg vitamin C plus 200 U vitamin E twice daily for 30 d may increase *H. pylori* eradication rate[48,49]. Similarly, adding bovine lactoferrin to *H. pylori* eradication therapy potentially improves *H. pylori* eradication rates without any impact on adverse effects, but available evidence is limited and further research is necessary to confirm the findings[50]. In a study from Turkey, it has been shown that *Saccharomyces boulardii* had no significant affect on the rate of *H. pylori* eradication[51]. In contrast, *S. boulardii* improved antibiotic-therapy-associated diarrhea, epigastric discomfort, and treatment tolerability[51,52]. However, systemic review of five RCTs evaluating addition of *S. boulardii* to triple therapy showed that *S. boulardii* given along with triple therapy significantly increased the eradication rate (4 RCTs, n = 915, RR = 1.13, 95%CI: 1.05-1.21) and reduced the risk of overall *H. pylori* therapy-related adverse effects, particularly of diarrhea (4 RCTs, n = 1215, RR = 0.47, 95%CI: 0.32-0.69)[53].

OTHER FACTORS

There are some factors affecting eradication success. Cytochrome P450 2C19 (CYP2C19) and P-glycoprotein (*MDR1*) gene polymorphisms, which influence the clear-

ance of PPIs, and thus their effect on gastric acid secretion, may affect the therapeutic efficacy of a PPI-based eradication therapy for *H. pylori* infection[54]. In particular, T/T genotype of the MDR1 C3435T polymorphism could be a predictive indicator of the lower eradication rate of a PPI-based eradication therapy[55]. The usage of high-dose PPI instead of standard dose can increase the efficacy of treatment. According to a meta-analysis, high-dose PPI is more effective than standard dose, and increases eradication rate by approximately 8%[56].

Smoking decreases the treatment success rate for *H. pylori* eradication. In a meta-analysis consisting of 22 published studies, it has been reported that the mean difference in eradication rates between smokers and nonsmokers was 8.4%[57].

CONCLUSION

Triple therapy remains an appropriate first-line therapy in areas of low clarithromycin resistance; conversely, quadruple therapy should be the first-line therapy in areas of high clarithromycin resistance. The usage of sequential therapy has become increasingly common, however, more data are needed before recommending sequential therapy as first-line therapy. Levofloxacin-containing regimens or concomitant therapies can be good choices for second-line therapy. Choice of treatment regimen of *H. pylori* should be done cautiously and resistance rates of antibiotics should be taken into consideration.

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ISSN 1007-9327