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The status and progress of first-line treatment against *Helicobacter pylori* infection: a review

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***Abstract*:** *Helicobacter pylori* (HP) is a major causative agent of chronic gastritis and peptic ulcer. HP is also engaged in the development of gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma. It is an important pathogenic factor in various other systemic diseases, such as vitamin B12 deficiency, iron deficiency, and idiopathic thrombocytopenia. The current consensus is that unless there is a special reason, eradication therapy should be implemented whenever HP infection is found, and it is ideally successful the first time. International guidelines recommend that under certain conditions, treatment should be personalized based on drug susceptibility testing. However, drug susceptibility testing is often not available because it is expensive, time-consuming, and difficult to obtain living tissue. Each region has separately formulated guidelines or consensuses on empirical therapy. Owing to an increasing drug resistance rate in various places, the eradication rate of proton pump inhibitor (PPI) triple therapy and sequential therapy has been affected. These regimens are rarely used; the PPI triple especially has been abandoned in most areas. Currently, radical treatment regimens for HP involve bismuth-containing quadruple therapy and concomitant therapy. However, quadruple therapy has its own limitations, such as complex drug administration. To improve the effectiveness, safety, and compliance, many clinical studies have proposed useful modified regimens, which mainly include the modified bismuth-containing quadruple regimen, high-dose dual therapy, and vonoprazan-containing regimens. Studies have shown that these emerging regimens have acceptable eradication rates and safety, and are expected to become first-line treatments in empirical therapy. However, the problem of decline in the eradication rate caused by drug resistance has not been fundamentally solved. This review not only summarizes the effectiveness of mainstream regimens in the first-line treatment of HP infection with the currently increasing antibiotic resistance rates, but also summarizes the effectiveness and safety of various emerging treatment regimens.

Keywords: drug resistance, first-line therapy, *Helicobacter pylori*, quadruple therapy, triple therapy, vonoprazan

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Introduction

Helicobacter pylori (HP) is a Gram-negative bacterium that lives in the stomach of more than half of the world's population.[1] HP is an important pathogenic factor in stomach-related diseases, such as gastritis, peptic ulcer, gastric cancer, and mucosa-associated lymphoid tissue lymphoma, and various systemic diseases, such as vitamin B12 deficiency, iron deficiency, and idiopathic thrombocytopenia.[2] The current consensus is that unless there is a special reason, eradication therapy should be implemented whenever HP infection is found, and it is ideally successful the first time. Immediate success could avoid repeated treatment and testing and reduce costs, anxiety, and negative effects on other intestinal

microflora.[3] However, as the resistance rate of HP to clarithromycin, metronidazole, and levofloxacin continues to increase, decreasing the eradication rate, the effectiveness of mainstream regimens recommended by some guidelines may no longer be satisfactory.[4,5] This review presents the current status of classical HP first-line treatment worldwide and the emergence of effective and safe treatment options that may become first-line treatment.

Treatment guided by drug sensitivity

International guidelines recommend that the first treatment for HP infection should be successful.[6–8] Therefore, personalized treatment programs tailored to patients according to drug sensitivity tests are the preferred choice, which can not only provide a satisfactory eradication rate but also prevent the misuse of antibiotics to avoid further increases in global antibiotic resistance.[9,10] In a prospective study in Korea, the agar-dilution method was used to determine the minimum inhibitory concentration to select the treatment regimen. The study showed that a reliable and excellent eradication rate [intention-to-treat (ITT) analysis, 93.1%; per-protocol (PP) analysis, 100%] could be achieved even in areas with high drug resistance.[11] An open controlled trial, also from Korea, compared the safety and efficacy of customized (TR) eradication strategies based on 23s ribosomal RNA point mutations with empirical bismuth-containing quadruple therapy (BCQT), and concluded that TR strategies had fewer related complications (12.0% *versus* 43.0%; $p < 0.001$).[12]

However, considering the cost, difficulty, and availability of drug sensitivity tests, personalized treatment is difficult to implement, so in practice, first-line treatment is often dominated by empirical treatment. In first-line empirical therapy, the guidelines unanimously recommend the use of BCQT, while concomitant therapy (CT) can also be used in areas where bismuth is not available or where clarithromycin is resistant. The use of PPI-based triple therapy is strictly restricted and can only be used in areas with low drug resistance, so that it cannot be used in most areas. There is no consensus on the use of other first-line treatments, such as sequential therapy (ST) and hybrid therapy (HT), in the guidelines developed by expert groups in Europe, Canada, and the USA for the treatment of HP infection. Clinicians should consider not only the history of drug contact and the prevalence of local drug resistance but also the history of allergy, compliance, cost, availability, and adverse reactions. The effectiveness of the regimen is influenced by all the above factors. Therefore, the best regimen for first-line empirical therapy has not been determined.

Empirical treatment

PPI triple therapy

PPI triple therapy refers to the use of PPI and two antibiotics against HP infection for 7–14 days. The antibiotics used are generally amoxicillin, clarithromycin, metronidazole, and levofloxacin. On the one hand, triple therapy with sufficient treatment duration is still effective in a few areas with low drug resistance; on the other hand, a new antibiotic is used in the first-line treatment of HP in order to improve eradication rates, which are reduced by increasing antibiotic resistance.

In the past few decades, clarithromycin-containing triple therapy [with PPI, ampicillin, and clarithromycin (PAC)] has been the mainstream regimen in the first-line treatment of HP infection. A systematic review and meta-analysis showed that in 7722 patients, the optimal PAC treatment duration was 14 days.[13] The eradication rate of PAC after 14 days was higher than that after 7 days (81.9% *versus* 72.9%). In another study, the eradication rate of PAC after 10 days was only slightly higher than that after 7 days (79.9% *versus* 75.7%).[8] A meta-analysis of 3715 people in Turkey showed that regardless of whether the treatment lasted for 7 days or 14 days, the eradication rate was extremely low (<60%), which may be due to high clarithromycin resistance in the region.[14] This is also the current situation of using clarithromycin-based triple therapy to eradicate HP in most areas; this regimen can no longer meet the criteria for effective eradication. Since the introduction of PPI-based triple therapy in 1990, the eradication rate in first-line treatment has dropped from 90% to less than 70–80%.[15] Resistance to clarithromycin has come to be an independent factor in HP eradication.[16] Therefore, international guidelines recommend that only in areas with low clarithromycin resistance (<15%), can PAC be used as first-line treatment for HP if duration is extended to 14 days.[6–8] However, in a meta-analysis of 27 randomized

controlled trials (RCTs) where 4825 patients were grouped on the basis of resistance to metronidazole and clarithromycin, the results showed that even in the clarithromycin-sensitive group, the PAC regimen did not meet the criteria for successful eradication (80%).[17] This may be explained by the fact that most of the included RCTs were performed with PAC regimens that lasted only 7 days.

Some studies have shown that the global eradication rate of the PPI/amoxicillin/metronidazole (PAM) regimen is comparable with that of the PAC regimen. In recent years, PAM has shown better efficacy, especially in people over 60 years of age. In areas where metronidazole resistance is low and clarithromycin resistance is high, the PAM regimen can achieve eradication rates of 92.5%.[17] In an RCT of young Japanese patients, according to ITT and PP analyses, the eradication rates of PAM were 95.5% and 96.3%, respectively, while those of PAC were 67.0% and 66.7%, respectively.[18] Therefore, it is recommended that in countries such as Japan, where the resistance to metronidazole is very low, metronidazole is used in the first-line treatment of HP infection, while in North America and Chile, where metronidazole resistance is relatively low (<20%), the PAM regimen may be more effective.[19,20]

With the increase of clarithromycin resistance, levofloxacin plays an increasingly important role in first-line treatment. In the past decade, levofloxacin-based triple therapy has achieved acceptable efficacy and safety as a first-line treatment in different clinical trials. Unfortunately however, levofloxacin has also encountered drug resistance. A study has shown that the eradication rate of levofloxacin-based triple therapy is between 72% and 96%.[15] The American Society of Gastroenterology suggests levofloxacin-based triple therapy as the first-line treatment for HP infection.[6] However, in a retrospective observational study carried out in the USA comparing the eradication rate between the three first-line regimens, the eradication rate of levofloxacin-based triple therapy was considerably lower (49.2%) than that of clarithromycin-based triple therapy (78.3%).[21] The difference in effectiveness may be due to differences in drug resistance for adults in different regions, with levofloxacin resistance rates of 14.1% in Europe (Western/Central and Southern Europe >20%; Northern European countries <10%), and 31.3% in North America.[22,23] Therefore, it is particularly important to establish a regional drug resistance database as soon as possible.

It is well known that in recent years, the resistance rates of clarithromycin, metronidazole, and levofloxacin are increasing globally, which greatly reduces the effectiveness of traditional PPI-based triple therapy in first-line treatment. Recently, a new triple therapy in the USA has made significant progress in clinical trials. The efficacy and safety of rifabutin-based triple therapy (RHB-105) were assessed in a three-phase, double-blind, clinical RCT involving 455 people. The experimental group was treated with amoxicillin (3 g), omeprazole (120 mg), and RHB-105 (150 mg) for 14 days, while the control group was treated with the same doses of amoxicillin and omeprazole only. The ITT analysis revealed eradication rates in the RHB-105 and control groups of 83.8% and 57.7%, respectively ($p < 0.001$). The type and incidence of adverse events were similar, which may mean they used a small dose of RHB-105. Moreover, resistance to clarithromycin and metronidazole did not impact the effectiveness of the experimental group.[24] Compared with non-bismuth quadruple therapy, the mode of RHB-105 therapy administration is more concise and can improve patients' compliance to a certain extent. However, it also has some disadvantages: (a) the study did not include Asian patients who have a higher prevalence of poor CYP2C19 metabolizers; (b) serious adverse reactions may occur, such as myelosuppression; (c) with the increase of application, resistance to RHB-105 may be increased. Although it has an eradication rate of 83.8%, attention should also be paid to adverse reaction and drug resistance. If the resistance of RHB-105 increases, the treatment of other diseases, such as tuberculosis, will be affected. Whether the RHB-105 regimen can be used as the first-line regimen in empirical treatment remains to be discussed, and more clinical trials are required, including trials in other regions, with other ethnic groups, and with larger study populations.

Non-bismuth quadruple therapy

Non-bismuth quadruple therapy, which consists of treatment with a PPI and three antibiotics (clarithromycin, amoxicillin, and nitroimidazole) for 10–14 days, was designed to solve the problem of drug resistance. There are three types of non-bismuth quadruple therapy, that is, ST, CT, and HT.[6,25] However, both the therapeutic efficacy of

these treatments and the prominent role of relieving antibiotic resistance in HP treatment have been widely doubted.[26] Resistance to metronidazole or clarithromycin affected the eradication rate of ST, while dual drug resistance decreased the eradication rate of CT. As a result, ST is gradually being abandoned, and the use of CT is also limited. Moreover, quadruple therapy generally has some disadvantages, such as intricate administration, many side effects, high cost, and poor patient compliance. Therefore, improved regimens have been studied.

ST and CT have achieved good results in some areas, which are more satisfactory than the standard triple therapy. Furthermore, the ideal duration of the treatment regimen has been confirmed to some extent. A large RCT in Myanmar has shown that ST and CT are both effective and have the exact same efficacy and safety. According to PP analysis, their eradication rates were 95% and 93%, respectively, and according to ITT analysis results, they were 79% and 82.5%, respectively.[27] Similarly, in Korea, a multicenter RCT involving 1141 people showed that in first-line treatment, the eradication rate of the 10-day CT regimen was significantly higher than that of the 7-day triple therapy regimen (ITT, 81.2% *versus* 63.9%; PP, 90.6% *versus* 71.4%); the eradication rate of the 10-day ST regimen was also better than that of the 7-day triple therapy regimen (ITT, 76.3% *versus* 63.9%; PP, 85.0% *versus* 71.4%), and there was no significant difference in adverse reactions among the three regimens.[28] In Egypt, a prospective study not only compared the efficacy between ST and standard triple treatment but also estimated the optimal duration of ST. Studies have shown that ST is superior to triple therapy, especially when ST lasts for 14 days (96.7% *versus* 90.7% *versus* 63.3%). Cost-benefit analyses showed that although the 14-day ST uses more drugs and lasts longer, it is the most cost effective.[29] A prospective study in Greek adult patients assessed the optimal cycle of CT. It was concluded that 10-day and 14-day continuous treatments were equally effective, and both achieved a high eradication rate (PP, >90%), but the 14-day regimen was more prone to causing side effects.[30] An RCT of 364 people, also in Greece, found that the duration of treatment affected neither efficacy nor safety, and the serious adverse reactions between them were similar (0.5% in the 10-day group *versus* 2.2% in the 14-day group; $p > 0.05$).[31] Overall, they considered that the eradication rate of CT lasting for only 10 days was acceptable, even in areas with high resistance to clarithromycin.

However, a study in India has shown that although the eradication rate of CT was higher than that of standard triple therapy (PP, 77.1% *versus* 58.3%), it still fell short of people's expectations. In first-line treatment, physicians aim to achieve an eradication rate of 90%; eradication rates below 80% are considered unacceptable.[32,33] Similarly, a prospective trial in 228 Chinese children showed that CT and ST were not superior to triple therapy (84.6% *versus* 69.5% *versus* 74.1%).[34] The differences in the above results may be due to the different resistance of microorganisms to antibiotics. Strong evidence has indicated that clarithromycin or metronidazole single resistance affects the efficacy of ST, while it does not affect the efficacy of CT, but dual drug resistance affects the efficacy of the latter.[35–37]

On the premise of ensuring the effectiveness of the regimen, in order to minimize the number of tablets taken by patients every day, the concept of HT was put forward. HT combines the advantages of ST and CT. PPI and amoxicillin were used in the first 7 days, and metronidazole and clarithromycin were added in the latter 7 days. A study in Taiwan showed that in ITT and PP analyses, the eradication rates of combination therapy were 97.4% and 99.1%, respectively.[38] It is as effective as or better than 10-day ST, and similar to bismuth-containing therapy in effectiveness.[39–41] Even in areas with high drug resistance, HT is an efficient first-line therapy (ITT, 85.8%; PP, 90.2%), but clarithromycin and metronidazole dual resistance can significantly reduce the eradication rate (50%).[42] HT also has drawbacks compared with other regimens, for example, a more complicated procedure and the addition of two drugs in the latter 7 days, which can lead to confusion in patients. Therefore, the concept of reverse HT has been put forward, which has proved to be equivalent to HT.[43] A recent RCT showed that the efficacy of reverse HT was similar to that of CT (ITT, 95.2% *versus* 93.5%; $p = 0.582$), but the incidence of adverse reactions was lower (20.2% *versus* 38.7%; $p = 0.001$).[44]

BCQT

International guidelines recommend the use of BCQT that consists of PPI, bismuth salt,

tetracycline, and nitroimidazole for 10–14 days in areas with high resistance to clarithromycin and metronidazole.[8] In recent years, BCQT has played an increasingly important role in first-line therapy because its efficacy is not affected by the resistance to clarithromycin, metronidazole, and levofloxacin, even the double resistance to clarithromycin and metronidazole did not affect the eradication rate.[45,46] Nevertheless, this regimen also has its limitations. First, there are the common problems of quadruple therapy (such as complexity and poor compliance), and second, tetracycline is not widely available in many areas. In order to solve these problems, three-in-one capsules and many modified BCQTs (mBCQTs) have been proposed. Some mBCQTs have excellent efficacy and safety and are very promising as new first-line therapies.

In areas with high clarithromycin resistance, BCQT was more effective than PPI-based triple therapy, and the eradication rate of BCQT for 14 days was higher than that for 10 days.[47] In areas where clarithromycin resistance is high but dual resistance is low, BCQT is similar to CT in safety (56% *versus* 46.3%) and efficacy (>90%).[48] However, an RCT has shown that although the efficacy between them was similar (BCQT was slightly better than CT; ITT, 88.2% *versus* 79.4%), the rates of adverse reactions for BCQT were lower than those for CT (33.8% *versus* 51.5%; $p=0.037$).[49] This may be due to the use of high-dose tetracycline but reduced administration in this study (1000 mg bid). In any case, it is certain that they have a high eradication rate, but both studies have the limitations of small samples. In areas with high double drug resistance rates, the eradication rates of BCQT were higher than those of standard triple therapy, ST, and CT.[34]

In order to simplify the administration procedure of traditional BCQT, a new kind of preparation, pylera, has been developed. Pylera is a three-in-one capsule containing bismuth subcitrate, tetracycline, and metronidazole. Pylera therapy has good efficacy and safety.[50] A systematic meta-analysis of 30 studies (6482 patients) analyzed the efficacy of pylera for different treatment periods. During first-line treatment, the eradication rate in ITT was 90% [95% confidence interval (CI), 87–92%; 21 studies; $I^2=88\%$].[51] A retrospective study of 345 Italian immigrants showed that pylera achieved good eradication rates in different patient populations (except in patients of African descent).[52]

As a supplement to the treatment of HP infection, bismuth can increase the eradication rate, especially of clarithromycin-resistant strains. A meta-analysis of 3990 patients showed a risk ratio of 2.81 (95% CI, 2.03–3.89) for bismuth-containing therapy (excluding the standard BCQT), compared with 1.83 (95% CI, 1.57–2.13) for non-bismuth therapy.[53] Meanwhile, standard BCQT has some shortcomings: (a) the high cost of standard quadruple therapy; (b) complex regimens affecting compliance and eradication rates; (c) the low availability of tetracycline in some areas; (d) the high incidence of adverse reactions; (e) differences in the level of availability of antibiotics. Therefore, there are some mBCQTs which have PPI and bismuth but different types of antibiotics, duration of administration, or drug doses.[54–56] Many studies have shown that these modified therapies are effective and safe (Table 1), and can be even as good as susceptibility-guided therapy. An RCT involving 382 patients in China showed that the eradication rates of susceptibility-guided therapy in ITT and PP analyses were 97.7% and 91.6%, respectively, while those of mBCQT (amoxicillin/metronidazole/PPI/bismuth) were 85.4% and 97.6%, respectively, indicating the former is not superior to the latter.[46] A multicenter RCT showed the eradication rate of mBCQT was not inferior to that of the standard BCQT (ITT, 82.8% *versus* 87.2%). Resistance to clarithromycin and metronidazole did not affect the efficacy of the therapy, and it could be used in areas with high drug resistance.[57] In order to solve the problem that tetracycline is generally difficult to obtain, mBCQT containing clarithromycin has been recommended in China. Since its use, the recommended dose of clarithromycin has been 500 mg, but in this trial, the effects of half doses of clarithromycin were found to be equivalent to those of standard doses (PP, 91% *versus* 91.2%), with a significantly lower incidence of adverse reactions (34.29% *versus* 54.21%; $p=0.004$) and lower cost.[58] In another study, the semisynthetic tetracycline minocycline, which has the same mechanism as tetracycline, was chosen to replace tetracycline. Minocycline and metronidazole or amoxicillin had better eradication rates, and the former caused fewer side effects. The minocycline/amoxicillin regimen achieved higher eradication rates than the amoxicillin/metronidazole regimen (89.5% *versus* 76.8%; $p<0.05$).[59] Other studies have also

Table 1. Studies of modified bismuth-containing quadruple regimens for *H. pylori* eradication published in or after January 2019.

Country	Sample size	PPI	Bismuth	Antibiotics	Treatment duration	Eradication rates	AEs	Reference
China	382	Esomeprazole 20 mg bid	220 mg bid	AMO 1 g tid MET 400 mg tid	14 days	ITT, 97.6% PP, 85.4%	12.5%	Mateo *et al.*[54]
Korea	233	Rabeprazole 20 mg bid	300 mg qid	AMO 1 g tid MET 500 mg tid	14 days	ITT, 87.2% PP, 96.2%	29.9%	Graham and Lee[55]
China	210	Esomeprazole 20 mg bid	600 mg bid	AMO 1 g bid CLR 250 mg bid	14 days	ITT, 86.67% PP, 91%	34.29%	Liang *et al.*[56]
China	360	Rabeprazole 10 mg bid	220 mg bid	MIN 1 g bid AMO 1 g bid	14 days	ITT, 85.7% PP, 89.5%	30.0%	Bang *et al.*[57]
		Rabeprazole 10 mg bid	220 mg bid	MIN 1 g bid MET 400 mg tid	14 days	ITT, 77.1% PP, 84.3%	37.5%	
		Rabeprazole 10 mg bid	220 mg bid	AMO 1 g bid CLR 500 mg bid	14 days	ITT, 71.7% PP, 76.8%	40.0%	
Thailand	100	Rabeprazole 60 mg qid	1048 mg qid	LVX 750 mg qid CLR-MR 1 g qid	7 days	84%	–	Lu *et al.*[58]
		Rabeprazole 60 mg qid	1048 mg qid	LVX 750 mg qid CLR-MR 1 g qid	14 days	94%	–	
China	115	Rabeprazole 10 mg bid	220 mg bid	AMO 1 g bid DOX 100 mg bid	14 days	ITT, 89.8% PP, 93.8%	6.8%	Zhang *et al.*[59]
Italy	40	Esomeprazole 40 mg bid	–	AMO 1 g bid pylera 3 tablets qid	The first 5 days, the second 5 days	ITT, 100% PP, 100%	12.8%	Song *et al.*[60]

AE, adverse event; AMO, amoxicillin; bid, twice a day; CLR, clarithromycin; CLR-MR, clarithromycin-modified release; DOX, doxycycline; ITT, intention-to-treat analysis; LVX, levofloxacin; MET, metronidazole; MIN, minocycline; PP, per-protocol analysis; PPI, proton pump inhibitor; qid, four times a day; tid, three times a day.

obtained similar results, in which the eradication rate of the rabeprazole, minocycline, amoxicillin, and bismuth regimen is 87.5%, and the esomeprazole, minocycline, metronidazole, and bismuth regimen is 85.5%.[60,61] However, there are so few studies on minocycline that the results are not sufficiently convincing and we need further research. In another study, the administration procedure was simplified, and mBCQT (levofloxacin/clarithromycin-modified release) was given once a day. It was found that the eradication rate of the 14-day regimen was 94%, regardless of whether the HP strain was clarithromycin resistant, and a 100% eradication rate was obtained in levofloxacin-sensitive bacteria.[62] The doxycycline/amoxicillin/PPI/bismuth regimen was also considered as the first-line empirical therapy.[63] In a recent prospective trial, a 10-day bismuth-containing hybrid regimen was composed of PPI, amoxicillin, and pylera, which surprisingly achieved an eradication rate of 100% in both ITT and PP analyses.[64]

Dual therapy

Dual therapy, which refers to the use of only PPI and amoxicillin to eradicate HP, has not yet been recognized as first-line therapy and is currently recommended as a rescue regimen in international guidelines.[6] Successful eradication was first reported in 1989, and since then, the regime's effectiveness has been controversial, which may be related to the total dose, the frequency of administration, the duration of amoxicillin treatment, and whether a high pH can be stably maintained in the stomach. In general, high-dose dual therapy (HDDT) can increase the eradication

Table 2. Studies of modified bismuth-containing quadruple regimens for *H. pylori* eradication published in or after January 2019.

Country	Sample Size	PPI	Amoxicillin	Treatment duration	Eradication rates	AEs	Reference
China (Taiwan)	240	Esomeprazole 40 mg tid	750 mg qid	14 days	ITT, 91.7% PP, 95.7%	9.6%	Auttajaroon *et al.*[62]
China	208	Esomeprazole 20 mg qid	750 mg qid	10 days	ITT, 79.8% PP, 81.3%	5.9%	Gu *et al.*[63]
		Esomeprazole 20 mg tid	1000 mg tid	14 days	ITT, 83.5% PP, 86.4%	5.0%	
China	232	Esomeprazole 20 mg qid	750 mg qid	14 days	ITT, 87.9% PP, 91.1%	6.3%	Gao*et al.*[65]
Turkey	150	Rabeprazole 20 mg tid	1000 mg tid	14 days	PP, 91.3%	0%	Tai *et al.*[66]

AE, adverse event; ITT, intention-to-treat analysis; PP, per-protocol analysis; PPI, proton pump inhibitor; qid, four times a day; tid, three times a day.

rate in patients given treatment of sufficient dosage and duration. However, the optimal dosage and course of treatment need to be confirmed.

In contrast to previous meta-analyses, a recent meta-analysis involving 12 RCTs (2249 patients) showed that in first-line treatment, HDDT had the same efficacy (ITT, 83.2% *versus* 85.3%) and compliance (94.3% *versus* 93.5%) as the mainstream therapy recommended in the guidelines, with fewer side effects (12.9% *versus* 28%).[65] In view of the fact that the resistance rate of amoxicillin in various places is still low[5] and HDDT has high eradication rates, few side effects, and a simple mode of drug administration, some recent studies have suggested that HDDT can be used as a first-line treatment. The eradication rate of HDDT (esomeprazole 40 mg bid, amoxicillin 750 mg four times a day (qid) for 14 days) in a prospective RCT in Taiwan was 91.7% in ITT analysis, equivalent to that of non-bismuth quadruple therapy.[66] In another study, the eradication rate of the same regimen was only 79.8% if it lasted for 10 days, while if amoxicillin was changed to 3 g/day three times a day (tid), successful eradication rates could be achieved (ITT, 83.5%).[67] Smoking and bismuth addition could affect the effectiveness of the regimen.[68] A study in China has shown that modified dual therapy is as effective as BCQT (ITT, 87.9% *versus* 89.7%), and the incidence and cost of adverse reactions are lower than those of the latter.[69] Another HDDT with rabeprazole in Turkey also achieved a satisfactory eradication rate of 91.3% (Table 2).[70] More large-scale clinical studies are needed to formally promote HDDT into first-line therapy, especially in different populations, and to determine the types of PPI that can be used, the drug dosages, and the optimal frequency of administration.

Patients with penicillin allergy

As penicillin is the most common drug that can elicit allergic reactions (about 5–10%), a few studies have evaluated the efficacy and safety of first-line HP therapy in patients with penicillin allergy.[71,72] As patients are allergic to penicillin, none of the regimens including amoxicillin can be used, so triple therapy consisting of PPI, clarithromycin, and metronidazole is usually the first choice; another option is the classic BCQT. A European study involving 1048 patients showed that classic BCQT seemed to be the better choice in first-line treatment (91% *versus* 69%; $p < 0.001$);[73] unfortunately we do not know the duration of the two regimens in this study. The number of patients included in other articles was not very large, and most regimens lasted for 7 days, which obviously is considered to be not enough. However, another study has suggested that the incidence of adverse reactions to this regimen is high, especially in women.[74] In order to avoid the problem that tetracycline is not available in some areas, a prospective study proposed a cefuroxime/levofloxacin/PPI/bismuth regimen with satisfactory effectiveness and safety (ITT, 85.5%; adverse events, 21.3%). In this study, the resistance rates of cefuroxime and levofloxacin were 4.6% and 40.0%, respectively.[75]

Vonoprazan

Vonoprazan, a new type of oral acid inhibitor, is an extraordinarily promising drug that was approved for use in Japan in 2015.[76] It is a reversible H^+-K^+ATPase inhibitor with faster, stronger, and longer-lasting acid inhibitory effects than PPIs.[77–79] Most studies on vonoprazan were focused on triple therapy, and most were carried out in Japan. Recently, there have been some studies of vonoprazan-based dual treatment. In order to make better use of vonoprazan, trials need to be conducted outside East Asia and compared with PPIs in different regimens (such as CT, ST, and bismuth-containing therapy).

A meta-analysis that included only RCTs showed that triple therapy using vonoprazan as an alternative to PPI had a significantly higher eradication rate (91.4% *versus* 74.8%) and fewer adverse reactions (32.7% *versus* 40.5%).[80] A large RCT in Japan compared the efficacy and safety between vonoprazan plus low-dose amoxicillin and vonoprazan triple therapy, and reported eradication rates of 84.5% and 89.2%, respectively, in ITT analysis, and 87.1% and 90.2%, respectively, in PP analysis.[81] The regimen of vonoprazan plus low-dose amoxicillin achieved an eradication rate between 80% and 90%, which may be related to the fact that the course of treatment of the regimen lasted only 7 days and the dose of amoxicillin, and further trials are needed to determine a more appropriate course and dose. Clarithromycin may have no additional effect in first-line treatment when using vonoprazan. No significant difference was observed in the eradication rate between vonoprazan and vonoprazan plus clarithromycin regimens (85–90%) or between clarithromycin-resistant and -sensitive strains (ITT, 85% *versus* 87.6%; $p = 0.7272$).[81–83] The use of vonoprazan can increase the eradication rate of HP, but this effect is more obvious in young people; the eradication rate in elderly patients is significantly lower than that in young patients; the efficacy and safety in children are not clear.[84,85]

Conclusion

This review summarizes the current situation and progress of first-line treatment of HP. To overcome the general increase in antibiotic resistance globally, many studies have proposed good improvements on the basis of the treatment recommended by international guidelines. These improved methods often achieve good effectiveness and safety by changing the type of antibiotics and the frequency, sequence, and dose of administration. The most fundamental approach remains personalized treatment based on drug sensitivity tests as studies have shown that triple therapy is effective against sensitive bacteria even in areas of high drug resistance. In order to solve the problem of antibiotic resistance, we not only need to avoid the misuse of antibiotics, develop new drugs, and propose new treatment regimens, but also develop new techniques to detect drug sensitivity.

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