Received: 7 July 2021 | First decision: 28 July 2021 | Accepted: 4 October 2021

DOI: 10.1111/apt.16652

AP&T Alimentary Pharmacology & Therapeutics WILEY

Treatment considerations in *Helicobacter pylori* management

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1 | INTRODUCTION

Helicobacter pylori (*H pylori*) infection is one of the most prevalent diseases in the world. It is also an important cause of several gastric pathologies including chronic atrophic gastritis, gastroduodenal ulcers, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. The World Health Organization (WHO) classified *H pylori* as a class I carcinogen in 1994. There is strong evidence that, by eradicating *H pylori*, the recurrence of peptic ulcers can be substantially reduced while minimising the risk of gastric malignancies.[1]

2 | KEY TREATMENT CONSIDERATIONS IN THE KYOTO CONSENSUS REPORT

While *H pylori* is linked to multiple upper GI conditions, the clearest indication for *H pylori* eradication therapy is peptic ulcer disease. Nearly three decades after the discovery of *H pylori* by Barry Marshall and Robin Warren, the management of gastritis in the Kyoto Consensus Report was finally published in 2015 and highlighted several key treatment considerations in the management of gastritis associated with *H pylori* infection.[2]

First, there is consensus that chronic gastritis is considered an infectious disease and general principles for the management of infections should be followed. These include the need to collect antibiotic sensitivity profiles (if possible) before treatment, and to prescribe tailored therapy (precise treatment), while understanding that the current standard of using first-line therapies (empiric treatment) is more practical with real-life clinical scenarios. Second, due to the strong association between *H pylori* infection and the development of chronic gastritis and gastric malignancies, it is highly recommended that all individuals infected with *H pylori* undergo eradication therapy, including those without GI symptoms. Third, infected individuals with advanced lesions, such as atrophic gastritis and intestinal metaplasia, are at increased risk of gastric malignancies despite successful *H pylori* eradication.

Some other international consensus statements have also been published on the treatment of *H pylori* from Europe, the United States, Asia-Pacific and other regions of the world that are tailored to local clinical practices and antibiotic resistance profiles.[3-6]

3 | FACTORS THAT AFFECT THE EFFECTIVENESS OF *H PYLORI* ERADICATION THERAPY

The management of *H pylori* infection in the first few decades after its discovery was perhaps less complicated since the most used clarithromycin-based triple therapy was, initially, highly effective with an estimated clarithromycin-resistance of <15%.[3-5] However, in the current era of rising clarithromycin resistance of >20%, practitioners should be aware that one out of every four patients will fail *H pylori* eradication therapy.[7] Thus, treating physicians must be made aware of potential factors that limit the effectiveness of *H pylori* eradication regimens which include, (a) poor tolerance and compliance due to a large number of pills prescribed, (b) insufficient dosing of medications throughout the treatment period, (c) gastric luminal environments such as gastric pH and anatomical alterations causing malabsorption of drugs, (d) medication allergies, and (e) *H pylori* antibiotic resistance. The first three factors can be optimised by treating physicians. For instance, it is important to counsel patients regarding the importance

The Handling Editor for this article was Dr Colin Howden, and it was accepted for publication after full peer-review.

of completing the treatment course as prescribed and asking them to call if anti-emetics are needed. Regarding medication dosing, using higher doses of antibiotics and proton pump inhibitors (PPIs) may be required, especially in those who failed lower dose regimens in the past. Physicians should also be aware of the differential metabolism according to CYP2C19 genotype among different PPIs and the potential benefit of prescribing a low acid diet[8]. The fifth factor, antibiotic resistance, is perhaps the most critical in determining the likelihood of treatment success but may be less predictable. However, some additional considerations below may help to minimise its impact on treatment success. Before prescribing a salvage regimen, clinicians should consider local data on *H pylori* primary antibiotic resistance and inquire about a patient's prior antibiotic exposure and treatment regimens to avoid using antibiotics that are likely to fail.

A probable mechanism linking most of the aforementioned factors that affected treatment success is the subtherapeutic luminal concentration of antibiotics leading to a failure to exceed the minimal bactericidal concentration (MBC). There are several potential causes of a subtherapeutic antibiotic luminal level. First is poor compliance due to intolerance to antibiotics or caused by the complexity of the therapeutic regimen. Other reasons may include the daily work schedule of the patient leading to missing the mid-day dose. It has been estimated that 11.5% of patients stopped their course of *H pylori* treatment prematurely, of whom two-thirds stopped due to side effects, and an inverse relationship was observed between poor compliance and *H pylori* eradication rates.[9] Thus, physicians should forewarn their patients regarding potential side effects of the treatment regimen and emphasise the importance of not stopping treatment prematurely[3-5] to motivate patients to complete the course. Second, the development of antibiotic resistance can lead to the inability to achieve the MBC required to eradicate *H pylori* with the recommended antibiotic dosing. *H pylori* gene mutations that affect drug resistance result in an increased minimal inhibitory concentration (MIC) and MBC values that cannot be reached in the gastric mucosa. Third, another important determinant of an antibiotic's MIC and MBC against *H pylori* is intragastric pH. The acidic gastric luminal environment can affect the optimal pharmacological activity of most antibiotics by decreasing their stability thus reducing their bactericidal properties.[10] Thus, effective acid suppressants, such as the PPIs, play an important role in anti-*H pylori* therapy as evident in PPI/amoxicillin dual therapy.[11] In fact, metabolism of PPI by CYP2C19 was found to significantly impact the eradication rates of *H pylori*.[12] Fourth, other host factors causing ineffective antibiotic activities may include a high *H pylori* colonisation density, non-proliferative *H pylori* state (e.g., in coccoid form), and high body mass index.[13,14]

4 | TREATMENT OPTIONS CONSIDERING FACTORS THAT IMPACT SUCCESSFUL *H PYLORI* ERADICATION

Given the above-mentioned factors leading to a lower luminal concentration and MBC of antibiotics, three therapeutic strategies can be considered: (a) continue empiric therapy based on established guidelines, (b) develop new highly efficacious regimens that can avoid the influence of drug resistance and (c) use tailored therapy based on antibiotic sensitivity profiles.

5 | EMPIRICAL THERAPY BASED ON ESTABLISHED GUIDELINES

In recent years, many treatment guidelines for *H pylori* infection have been reported from different geographic areas, such as Europe, the United States, Canada and Asia[3-6] (Table 1). Non-bismuth-containing triple therapies and quadruple therapies are commonly recommended first-line. Bismuth-containing quadruple therapy (BQT) has been recommended in most treatment guidelines as a first-line and as a rescue regimen for *H pylori* eradication. Fluoroquinolone-containing regimens are only recommended to be used as second-line treatment. However, the main issue with continuing empirical treatment based on international treatment guidelines is the lack of updated local *H pylori* resistance patterns. In particular, there is a paucity of data on clarithromycin resistance across different regions of the world.

The efficacy of treatment for *H pylori* infection has decreased steadily because of the increase in antibiotic resistance, especially to clarithromycin, metronidazole and levofloxacin.[15] However, not all antibiotic resistance is treated equally; resistance to some cannot be overcome by increasing the dose or frequency (e.g., macrolides, quinolones)[15] while others (e.g., metronidazole) may be partially overcome by increasing the dose and duration of treatment.[15,16]

Other empiric therapies include sequential therapy which was initially reported to be more efficacious than standard triple therapy in those with clarithromycin resistance.[17] Its efficacy, however, is significantly reduced in patients with clarithromycin/metronidazole dual resistance as well as those with mono-resistance to clarithromycin or metronidazole.[3,18] Furthermore, the dosing schedule of sequential therapy is more complex than other empiric therapies. Therefore, most updated international guidelines do not recommend sequential therapy.[3,5] Concomitant therapy, another empiric therapy, contains four drugs with a full dosing schedule that would, in theory, be more effective than the other bismuth-free regimens. (Figure 1) Thus current guidelines prefer the use of concomitant therapy as the representative regimens of the bismuth-free quadruple option.[3-5] Another empiric approach is hybrid therapy. It can also be affected by clarithromycin/metronidazole dual resistance but this regimen is also more complex due to its dual-step dosing schedule. However, a simplified dosing method reversing the dosing sequence of hybrid therapy (i.e., reverse hybrid therapy) has attracted growing attention. Two studies from Taiwan showed that the efficacy of reverse hybrid therapy is equivalent to that of BQT and concomitant therapy in the first-line treatment of *H pylori* infection.[19,20] Similar to sequential and concomitant therapies, reverse hybrid therapy is also impacted by dual resistance to clarithromycin and metronidazole.[3,5]

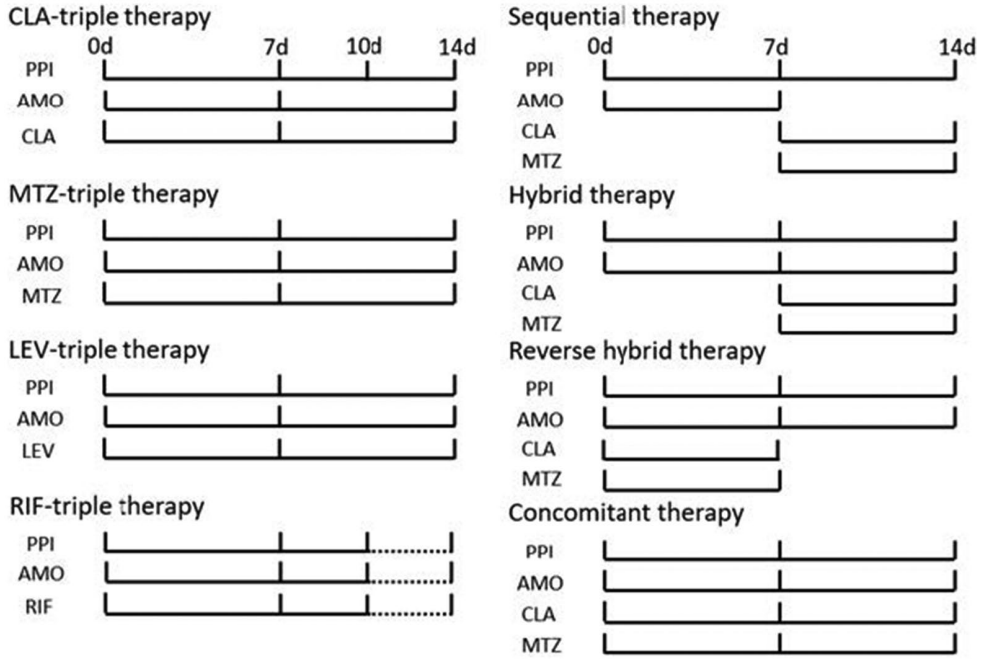

FIGURE 1 Dosing schedules of current non-bismuth triple and quadruple regimens. AMO: amoxicillin; CLA: clarithromycin; LEV: levofloxacin; MTZ: metronidazole; PPI: proton pump inhibitor; RIF: rifabutin. The dotted line represents dosing schedule for low-dose rifabutin-containing triple therapy recently approved by the FDA.

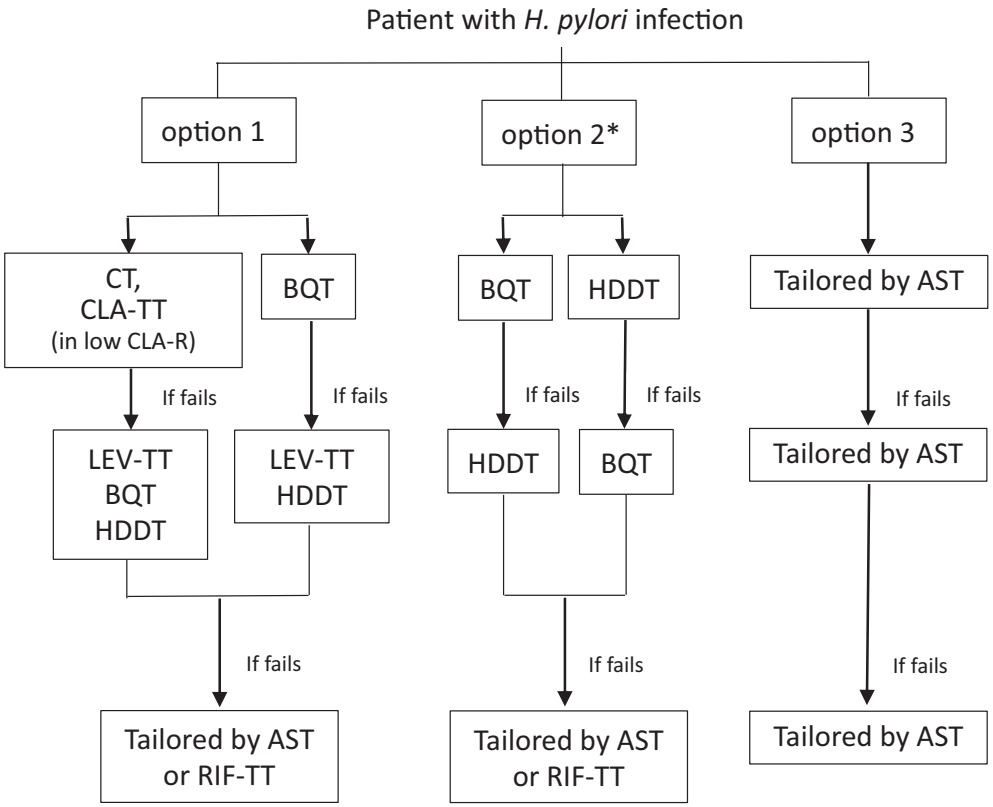

FIGURE 2 Treatment options for *H. pylori* eradication in the era of increasing antibiotic resistance. Option 1: empirical therapy based on established guidelines; Option 2: developing new regimens to avoid the influence of drug resistance; Option 3: tailored treatment based on antimicrobial susceptibility test; AST: antimicrobial susceptibility testing; BQT: bismuth-containing quadruple therapy; CLA-R: clarithromycin-resistant; CLA-TT: clarithromycin-containing triple therapy; CT: concomitant therapy; HDDT: high-dose dual therapy; LEV-TT: levofloxacin-containing triple therapy; RIF-TT: rifabutin containing triple therapy (* Low-dose rifabutin-containing triple therapy is FDA approved and can be used as a first-line treatment in Option 2).

TABLE 1 Regimens used for *H pylori* eradication by current international guidelines

Guidelines	2017 Europe	2017 USA	2016 Canada	2009 Asia-Pacific region
First-line	Low CLA-R CLA-TT, 14 d High CLA-R BQT, 14 d unless 10 d proven	CLA-TT, 14 d BQT, 10-14 d	BQT, 14 d CT, 14 d	CLA-TT, 7-14 d
Alternative	Low CLA-R BQT, 14 d unless 10 d proven High CLA-R CT, 14 d unless 10 d proven		Low CLA-R CLA-TT, 14 d	BQT, 7-14 d
Second-line	Low CLA-R BQT, 14 d unless 10 d proven LEV-TT, 14 d High CLA-R LEV-TT, 14 d	BQT, 10-14 d LEV-TT, 10-14 d	BQT, 14 d LEV-TT, 14 d	BQT, 7-14 d LEV-TT, 10 d
Alternative	HDDT, 14 d	HDDT, 14 d	HDDT, 14 d	
Refractory	Guided by AST or RIF-TT	Guided by AST or RIF-TT, 10 d	Guided by AST or RIF-TT, 10 d	Guided by AST or RIF-TT, 10 d

Abbreviations: AST, antimicrobial susceptibility testing; BQT, bismuth-containing quadruple therapy; CLA-R, clarithromycin-resistant; CLA-TT, clarithromycin-containing triple therapy; CT, concomitant therapy; HDDT, high-dose dual therapy; LEV-TT, levofloxacin-containing triple therapy; RIF-TT, standard-dose rifabutin containing triple therapy.

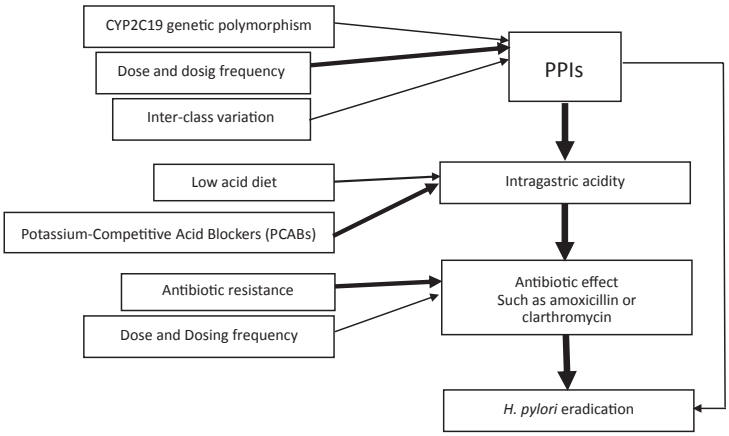

FIGURE 3 Flow chart of factors influencing the treatment outcome of *H. pylori* eradication. Thickness of arrows indicates the relative contribution of the various factors. PPIs: proton pump inhibitors

Thus, it is anticipated that the efficacy of these bismuth-free quadruple regimens will decline as mono- or dual-resistance strains continue to increase, particularly as salvage therapy.

6 | DEVELOPING NEW REGIMENS TO AVOID THE INFLUENCE OF DRUG RESISTANCE

BQT has been recommended as a standard first-line or rescue regimen as to it is minimally impacted by antibiotic resistance, and as it can be used in patients with penicillin allergy. While the mechanism of action of bismuth is still not well understood, we have observed that the addition of bismuth compounds to strong acid suppression may independently increase the treatment efficacy. Commercialised capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline is available in several countries. A large multi-centre trial showed good performance with this capsule and omeprazole.[21] However, as with any BQT, compliance is a major limitation given the large number of pills and more frequent adverse events. Moreover, bismuth and/or tetracycline are unavailable in several countries.

Another regimen not frequently affected by antibiotic resistance is high-dose dual therapy with PPI and amoxicillin.[18] Amoxicillin has been used as a key component in both first line and rescue anti-*H pylori* therapies for more than two decades since the global prevalence of primary and secondary resistance to amoxicillin is still very low.[3,7] Amoxicillin is normally prescribed thrice-daily since the blood concentration is expected to exceed MIC for a longer duration with more frequent dosing than if used twice daily. In addition to increasing the frequency, amoxicillin's MIC is influenced by intragastric pH as the rate constant of amoxicillin degradation is decreased at higher pH.[10] In fact, most patients with successful *H pylori* eradication using amoxicillin-based dual therapy had a mean intragastric pH greater than 5.5.[22] Given the negative impact of intraluminal gastric acidity, it is important to consider the impact of CYP2C19 genotype as poor metabolisers, found only in a small proportion of the western population,[23] might achieve a sufficiently high intragastric pH with standard rather than high PPI doses and a higher dose PPI is generally recommended. Moreover, a study in Japan showed the advantage of more frequent PPI dosing by demonstrating that, given the same total daily dose, rabeprazole four times daily achieved a higher and more stable intragastric pH than once or twice daily dosing.[24]

Besides using higher and more frequent doses of a PPI, the choice of PPI is an important consideration to achieve higher intraluminal pH. Most treatment guidelines suggest the use of

esomeprazole or rabeprazole.[3-6] Besides a higher pKa less value, rabeprazole is affected by CYP2C19 genotype and lowers antibiotic MIC level against *H pylori*.[23,25] Consistent with these concepts, the cure rate with HDDT, comprising rabeprazole 20 mg four times daily and amoxicillin 750 mg four times daily for 14 days, was superior to currently standard first-line or rescue therapy.[18]

A recent meta-analysis found that HDDT was superior to standard first-line therapies[26] but consisted of mostly Asian populations thus raising concerns regarding the generalisability to the western population that has a larger parietal cell mass and a higher prevalence of CYP2C19 extensive metaboliser genotype than Asian populations.[23] Other confounding factors include a higher body mass index, which is associated with treatment failure,[14] and dietary habits with highly acidic foods, which are frequently noted in western countries. In fact, a high acid diet significantly reduced the efficacy of HDDT by 13%.[8] A summary of the factors influenncing the efficacy of HDDT is given in Table 2.

The potassium-competitive acid blocker (P-CAB) vonoprazan, whose metabolism is not affected by CYP2C19 genotype, was shown to have superior efficacy than lansoprazole in clarithromycin-containing triple therapy (93% vs 76%) even in patients with clarithromycin resistance (82% vs 40%).[27] Recently, two studies from Japan indicated that vonoprazan-based dual therapy performs comparably to vonoprazan-based triple therapy, suggesting that the use of vonoprazan may obviate the need for a second antibiotic.[28,29] Thus, vonoprazan-amoxicillin dual therapy is a promising approach able to overcome most of the factors impacting the success of HDDT as listed in Table 2.

In an era with rising antibiotic resistance to clarithromycin and metronidazole, rifabutin-containing triple therapy should be considered when patients fail triple therapy or BQT, an approach recommended by most treatment guidelines since the prevalence of rifabutin resistance is still very low or non-existent.[3-5] In the U.S., a low-dose (50mg TID) rifabutin-containing triple therapy was recently approved by the Food and Drug Administration (FDA) with superior efficacy vs HDDT[30] but its use has not been included in most practice guidelines. However, HDDT has the advantage of being simpler than rifabutin-based triple therapy but more studies are needed to inform clinical decisions.

7 | TAILORED TREATMENT BASED ON ANTIMICROBIAL SUSCEPTIBILITY TEST

Several studies using tailored treatments based on *H pylori* susceptibility to antibiotics, in comparison with standard empirical triple therapy, have shown higher eradication rate and may be cost-effective.[3-5] However, data regarding antibiotic resistance among *H pylori* strains from North America and other areas remain scarce.[3-5] A recent meta-analysis indicated that the prevalence of *H pylori* antibiotic resistance has reached an alarming level worldwide with primary and secondary resistance rates to clarithromycin, metronidazole, and levofloxacin estimated at >15% in almost all WHO regions.[31] A similar study from the Asia-Pacific region showed that the prevalence of primary *H pylori* resistance was 17% for clarithromycin, 44% for metronidazole, 18% for levofloxacin, 3% for amoxicillin and 4% for tetracycline.[7]

TABLE 2 Factors related to low efficacy of PPI/amoxicillin high-dose dual therapy

1.	Suboptimal selection of PPI (e.g., omeprazole vs rabeprazole/esomeprazole)
2.	Suboptimal frequency of PPI dosing (bid/tid vs qid)
3.	Suboptimal frequency of amoxicillin dosing (bid/tid vs qid)
4.	Suboptimal duration of treatment (7-day vs 14-day)
5.	Suboptimal diet control (frequent acid or spicy foods: Yes vs No)
6.	Suboptimal patient compliance (good communication and education: No vs Yes)

Abbreviations: bid, twice daily; PPI, proton pump inhibitor; qid, four times daily; tid, three times daily.

Although current treatment guidelines have emphasised the importance of culture and standard antimicrobial susceptibility testing (AST) in the treatment of *H pylori* infection, culture is technique-dependent and not always readily available. Molecular testing with genotyping can be used as an alternative method if *H pylori* culture is not available. Molecular testing offers several advantages compared to culture, including the potential for rapid and non-invasive (e.g., applied to faecal specimens) susceptibility testing, and may be suitable for the application of the "test and treat" strategy. However, up to now, molecular testing has mostly been applied tot the detection of clarithromycin and levofloxacin resistance only. Because the role of each mutation site is still not well investigated for some antibiotics, it is difficult to extend the use of the genotypic test to other antibiotics that are commonly used for the eradication of *H pylori* in clinical practice. Moreover, the genotypic testing does not provide MIC values for each antibiotic. A study was conducted to investigate the reliability of genotypic testing for clarithromycin resistance in clinical practice.[32] Although a concordance between the phenotypic and genotypic testing was present in about 92% of patients, the wide MIC distribution in genotypic-resistant strains indicates that genotyping was unable to accurately predict its MIC value and the grade of resistance. In the phenotypic-resistant patients, genotyping was falsely negative in about one-third, many of whom had MIC of ≥16 mg/L, leading to unnecessary treatment failure in about 60%.[32]

Table 3 summarises the limitations of genotypic testing. A major weakness of genotypic testing is the lack of MIC determination. Physicians treating patients with other bacterial infections typically depend on the MIC value obtained from culture and sensitivity testing. In the era of increasing drug resistance, it is expected that multiple drug resistance, not only to clarithromycin or levofloxacin, will continue to increase and impair our ability to eradicate *H pylori*. Further research is needed to understand better the impact of *H pylori* genetic mutations that lead to the development of antibiotic resistance with the hope of identifying new targets to combat *H pylori* antibiotic resistance. *H pylori* has been identified by the WHO

TABLE 3 Limitations and weaknesses of genotypic testing for antibiotic resistance

1.	The role of each mutation site for some commonly used antibiotics is still not well clarified.
2.	Genotypic testing can only detect the presence of mutations. It cannot provide the MIC value, and cannot predict the grade of resistance (e.g., high or low MIC value).
3.	Genotypic testing cannot distinguish the potency of different antibiotics with in the same family
4.	Some factors may cause false-negative results: other mutation sites (e.g., T2182C for clarithromycin) other mechanisms causing antibiotic resistance.
5.	The frequency of false-negative results is about 20%–30% in clinic practice, and may lead to about 20% of patients with clarithromycin resistance being treated inappropriately.
6.	The methodology of genotypic testing is still not standardised.

as one of 16 antibiotic-resistant bacteria with the greatest threat to human health.[33]

In an ideal practice setting where clinicians can obtain *H pylori* culture and sensitivity testing results, selection of treatment regimen should be based on the following priorities: (a) use antibiotic(s) with the best MIC profiles, (b) use simpler regimens to improve compliance and minimise side effects, and (c) choose the most cost-effective strategies. The treatment strategies based on these three options described above are summarised in Figure 2.

8 | CONCLUSION

The factors influencing treatment outcomes of *H. pylori* infection are summarised in (Figure 3). In the past three decades, a wealth of information has accumulated and has been summarised in international consensus guidelines. These offer practical algorithms to help clinicians navigate the road map of managing *H pylori* infection using empiric therapies which used to have relatively high efficacy. Emerging data and clinical experience indicate an alarming trend of increasing clarithromycin and levofloxacin resistance which corresponds to the decreased efficacy of first-line clarithromycin-containing triple therapy and rescue levofloxacin-containing triple therapy. Considerations for *H pylori* management are no longer simply to obtain information regarding a patient's history of medication allergies. Given the growing number of persistent *H pylori* infections despite first- and second-line therapies, physicians are faced with decisions on which antibiotics had not been tried without subjecting patients to repeated courses of ineffective therapies and the risk of antibiotic-associated complications such as C. difficile infection. New considerations will need to include choosing antibiotics by performing antibiotic sensitivity testing, being aware of the influence of gastric acidity by choosing optimal acid suppressants, patient education to increase compliance, and choosing the correct dosage to exceed the MBC. The concepts presented here will require further validation through rigorous clinical evaluation to assess which strategies are most effective. Meanwhile, by knowing the possible factors influencing outcomes of *H pylori* therapies, physicians facing desperate patients with persistent *H pylori* infection should be able to develop a stronger rationale for recommending the next course of treatment instead of blindly choosing another course hoping for a better outcome.

ACKNOWLEDGEMENTS

Declaration of personal interests: JYK serves as a consultant for Phathom Pharmaceuticals and RedHill Biopharma. JCY has no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

No data is available.

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How to cite this article: Yang J-C, Kao JY. Treatment considerations in *Helicobacter pylori* management. *Aliment Pharmacol Ther*. 2022;55(Suppl. 1):S22–S28. https://doi.org/10.1111/apt.16652