DR JOHN Y KAO (Orcid ID : 0000-0003-1238-8324)

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Jyh-Chin Yang[1*] and John Y. Kao[2*].

[1]Departments of Internal Medicine, Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan

[2]Division of Gastroenterology, Department of Internal Medicine, Michigan Medicine, University of Michigan, Ann Arbor, Michigan 48109, USA

[*]**Correspondence:**

Jyh-Chin Yang, M.D. Ph.D.

Department of Internal Medicine

Hospital and College of Medicine

National Taiwan University

No. 7, Chung-Shan South Road, Taipei 10002, Taiwan

TEL: +886-2-937018088

Fax: +886-2-23930258

E-mail: jcyang47@ntu.edu.tw

John Y. Kao, M.D.

Division of Gastroenterology

Department of Internal Medicine

University of Michigan Health System

6520 MSRB I, SPC 5682

1150 West Medical Center Drive

Ann Arbor, Michigan 48109

Telephone: (734) 647-2964

Fax: (734) 763-2535

E-mail: jykao@umich.edu

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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 other

malignancies such as gastric mucosa-related lymphoma (MALToma), thus the World Health Organization (WHO) classified human *H. pylori* as a class I carcinogen in 1994. There is strong evidence by eradicating *H. pylori,* the recurrence of peptic ulcers can be significantly reduced while minimizing the risk of gastric malignancies[1].

Key treatment considerations in the Kyoto consensus report

While *H. pylori* is linked to multiple GI and non-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 including the need to collect antibiotic sensitivity profiles if possible before treatment to prescribe tailored therapy (precise treatment), but understanding that the current standard guideline 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 even in those without associated 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].

Factors that affect the effectiveness of *H. pylori* eradication therapy

The management of *H. pylori* in the first few decades since its discovery was perhaps less complicated since the most used clarithromycin-based triple therapy was 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 made aware that one out of every four patients will fail *H. pylori* eradication therapy.[7] Thus the treating physicians must be made aware of potential factors that limit the effectiveness of *H. pylori* eradication regimens which include, 1) poor tolerance and compliance due to a large number of pills prescribed, 2)insufficient dosing of medications throughout the treatment period, 3) gastric luminal environments such as gastric pH and anatomical alterations causing malabsorption of drugs, 4) medication allergies, and 5) *H. pylori* antibiotic resistance. The first three factors can be optimized by the treating physicians. For instance, it is important to counsel the patients regarding the importance 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 may be required especially in those failing lower dose regimens in the past. The physicians should also be aware of the differential metabolism of CYP2C19 genotype amongst different proton-pump inhibitors and the potential benefit of prescribing a low-acid diet[8] (Figure 2). The fifth factor, or 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 minimize its impact on the success of eradicating *H. pylori*. Before prescribing a salvage therapy regimen, the clinicians should consider the local data on *H. pylori* primary antibiotic resistance and inquire about the patient's prior antibiotic exposure and treatment regimens to avoid using antibiotics that are likely to fail.

A likely mechanism linking most of the aforementioned factors that impacted treatment success is the subtherapeutic luminal concentration of antibiotics leading to a failure to exceed the minimal bactericidal concentration (MBC). 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 early of which two-thirds were due to side effects and an inverse relationship was observed between poor compliance and *H. pylori* eradication rates.[9] Thus, it was suggested that treating physicians should forewarn their patients regarding potential side effects of the treatment course and emphasize the importance of not stopping the treatment early as a longer duration of therapy is more effective (e.g., 14 days vs 7-10 days)[3-5] as a way to motivate patients to complete the course of therapy. Second, the development of antibiotic resistance by *H. pylori* can lead to the inability to achieve the MBC required to eradicate *H. pylori* with the recommended antibiotic dosing. *H. pylori* gene mutations that impact drug resistance to antibiotics 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 gastric pH. The acidic gastric luminal environment can affect the optimal pharmacological activity of most antibiotics by decreasing the stability of

antibiotics thus reducing their bactericidal properties.[10] Thus, effective acid-suppressants, such as proton pump inhibitors (PPIs), play an important role in anti-*H. pylori* therapy as evident in dual PPI/amoxicillin 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* colonization density, non-proliferative *H. pylori* state (e.g., in coccoid form), and high body mass index.[13-14]

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: 1) continue empiric therapy based on established guidelines, 2) develop new highly efficacious regimens that can avoid the influence of drug resistance, and 3) use tailored therapy based on antibiotic sensitivity profiles (Figure 3).

Empirical therapy based on established guidelines

In recent years, many treatment guidelines for *H. pylori* infection have been reported from different geographic areas worldwide, such as Europe, United States, Canada, and Asia[3-6] (Table 1). Non-Bismuth-containing triple therapies and quadruple therapies are commonly recommended as the first-line regimens.

Bismuth-containing quadruple therapy (BQT) has been recommended in most treatment guidelines as a first-line or rescue regimen for *H. pylori* eradication. Fluoroquinolone-containing regimens are recommended to be used in the second-line treatment only. However, the main issue with continuing empirical treatment based on international treatment guidelines is the lack of updated local *H. pylori* resistance patterns, particularly 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 as some antibiotic resistance are absolute in that it cannot be overcome by increasing the dose or frequency (e.g., macrolides, quinolone)[15] while others (e.g., metronidazole) may be partially overcome by increasing the dose and duration.[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 rather complex than other empiric therapies thus most updated international guidelines do not recommend the use of sequential therapy.[3, 5] Concomitant therapy, another empiric therapy, contains four drugs with a full dosing schedule 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 can also be affected by clarithromycin/metronidazole dual resistance and 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 (a.k.a., reverse hybrid therapy) has attracted growing attention. Two studies from Taiwan showed the efficacy of reverse hybrid therapy is equivalent to the efficacy 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] 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.

Developing new regimens to avoid the influence of drug resistance

BQT has been recommended as a standard first-line or rescue regimen owing to it being minimally impacted by antibiotic resistance and can be used in patient with penicillin allergy. While the mechanism of action of bismuth is still not well understood, we have observed that the addition of bismuth compounds in addition to strong acid suppression may independently increase the treatment efficacy. In the recent decade, a commercialized capsule (Pylera) containing bismuth subcitrate potassium, metronidazole, and tetracycline is available in several countries. A large multi-centre trial showed good performance of BQT with Pylera capsule and omeprazole.[21] However, as with any BQT, compliance is a major limitation given a 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 the first line and rescue anti-*H. pylori* therapies for more than 2 decades given that the global prevalence of primary and secondary resistance to amoxicillin is still very low.[3,7] Frequently prescribed as twice-daily dosing in anti-*H. pylori* regimens, amoxicillin pharmacokinetics is normally prescribed as thrice-daily dosing thus the blood concentration is expected to exceed MIC with a longer duration with more frequent dosing than that used twice daily. In addition to increasing the frequency, amoxicillin MIC is impacted 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 were found to have 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 metabolizers, found only in a small proportion of the western population[23], would be expected to achieve a sufficiently high intragastric pH with standard PPI dose 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 4 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 PPI, the choice of PPI is an important consideration to achieve higher intraluminal pH. Most treatment guidelines suggested the use of esomeprazole or rabeprazole[3-6]. Besides a higher pKa value, rabeprazole was shown to be less affected by CYP2C19 genotype and lowers antibiotic MIC level against *H. pylori*.[23, 25] Consistent with these concepts, a study shows the cure rate of HDDT, which consisted of rabeprazole 20 mg 4 times daily and amoxicillin 750 mg 4 times daily for 14 days, is superior to currently standard first-line or rescue therapy.[18]

A recent meta-analysis found that HDDT is superior to standard first-line therapies[26] but the study consists of mostly Asian populations thus raising concerns regarding the generalizability of this finding to the western population that has a larger parietal cell mass and a higher prevalence of CYP2C19 extensive metabolizer genotype than Asian populations.[23] Other confounding factors include a higher body mass index which is associated with treatment failure[14] and diet habits with high acid food which are frequently noted in western countries. In fact, a diet containing high acid foods was shown to significantly reduced the efficacy of HDDT by 13%.[8] A

summary of the factors impacting the efficacy of HDDT is listed in Table 2.

Emerging data from Japan where a novel potassium-competitive acid blocker (PCAB), vonoprazan, whose metabolism is not affected by the CYP2C19 genotype was shown to have superior efficacy compared to 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, indicating 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 failed triple therapy or QBT, an approach recommended by most treatment guidelines since the prevalence of rifabutin resistance is still quite rare[3-5]. However, HDDT still has the advantage of being a simpler regimen and potentially better tolerated than rifabutin-based triple therapy but more studies are needed to inform clinical decisions.

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 a better 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 indicates 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, except primary clarithromycin resistance in the Americas (10%) and South-East Asia region (10%), and primary levofloxacin resistance in the European region (11%).[30] A similar study from the Asia-Pacific region showed the prevalence of primary *H. pylori* resistance were 17% for clarithromycin, 44% for metronidazole, 18% for levofloxacin, 3% for amoxicillin, and 4% for tetracycline.[7]

Although current treatment guidelines have emphasized the importance of culture and standard antimicrobial susceptibility testing (AST) in the treatment of *H. pylori* infection, the *H. pylori* culture is technique-dependent and is not readily available. Molecular testing with genotyping can be used as an alternative method if *H. pylori* culture is not available. Molecular testing does offer several advantages compared to cultures, including the potential for rapid and noninvasive (e.g., applied on faecal specimens) susceptibility testing, and may be suitable for the application of the "test and treat" strategy. However, up to now, the molecular test is mostly applied for the detection of clarithromycin and levofloxacin resistance only. Because the role of each mutation site is still not well investigated in some antibiotics, it is difficult to extend the use of the genotypic test to other antibiotics that are also commonly used in 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.[31] The authors found that 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 the 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 of patients, many of them had MIC of ≥ 16 mg/L, leading to an unnecessary treatment failure in about 60% of these patients.[31]

Table 3 summarizes the limitations of genotypic testing. A major weakness of genotypic testing is the lack of MIC determination as physicians treating patients with a bacterial infection (e.g., pneumonia, urinary tract infection, etc) 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 resistant to clarithromycin or levofloxacin, will continue to increase and significantly impact 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 druggable targets to combat *H. pylori* antibiotic resistance, which has been listed by WHO as one of 16 antibiotic-resistant bacteria that have the greatest threat to human health in Feb 2017.[32]

In an ideal practice setting where clinicians can obtain the *H. pylori* culture and sensitivity testing results, selection of treatment regimen should be based on the following priorities: 1) use most antibiotic(s) with best MIC profiles, 2) use simpler regimen to improve compliance and minimize side effects, and 3) choose most cost-effective strategies. The treatment strategies based on these three options described above are summarized in Figure 3.

Conclusion

In the past three decades of managing *H. pylori* infection, a wealth of information has accumulated and summarized in several international consensus guidelines offering practical clinical algorithms to help clinicians navigate the road map of

managing *H. pylori* infection using empiric therapies which used to have relatively high efficacy in the decades past. Emerging data and clinical experiences indicate an alarming trend of increasing clarithromycin and levofloxacin resistance which corroborated with decreased efficacy of first-line clarithromycin-containing triple therapy and rescue levofloxacin-containing triple therapy. Considerations for *H. pylori* management is no longer simply obtain the patient's medication allergy but with a growing number of persistent *H. pylori* infections despite first- and second-line therapies, treating physicians are faced with decisions that are based on which ones have not been tried thus 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 sensitive antibiotics by performing antibiotic sensitivity testing, being aware of the influence of gastric acidity by choosing optimal acid suppressants, and ensuring adequate drug bioavailability by patient education to increase compliance, and choosing the correct dosage to exceed the MBC. The concepts presented here will require further clinical validations through rigorous clinical evaluation to assess which strategies are more effective. Meanwhile, by knowing the possible factors impacting treatment 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 than previous.

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Figure legend

Figure 1. Dosing Schedules of currently non-bismuth triple and quadruple regimens. AMO: amoxicillin; CLA: clarithromycin; LEV: levofloxacin; MTZ: metronidazole; PPI: proton pump inhibitor; RIF: rifabutin.

Figure 2. Flow chart of factors influencing the treatment outcome of *H. pylori* eradication. PPIs: proton pump inhibitors; PCABs: potassium-competitive acid blockers.

Figure 3. Treatment options for the *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.

Figure 1.

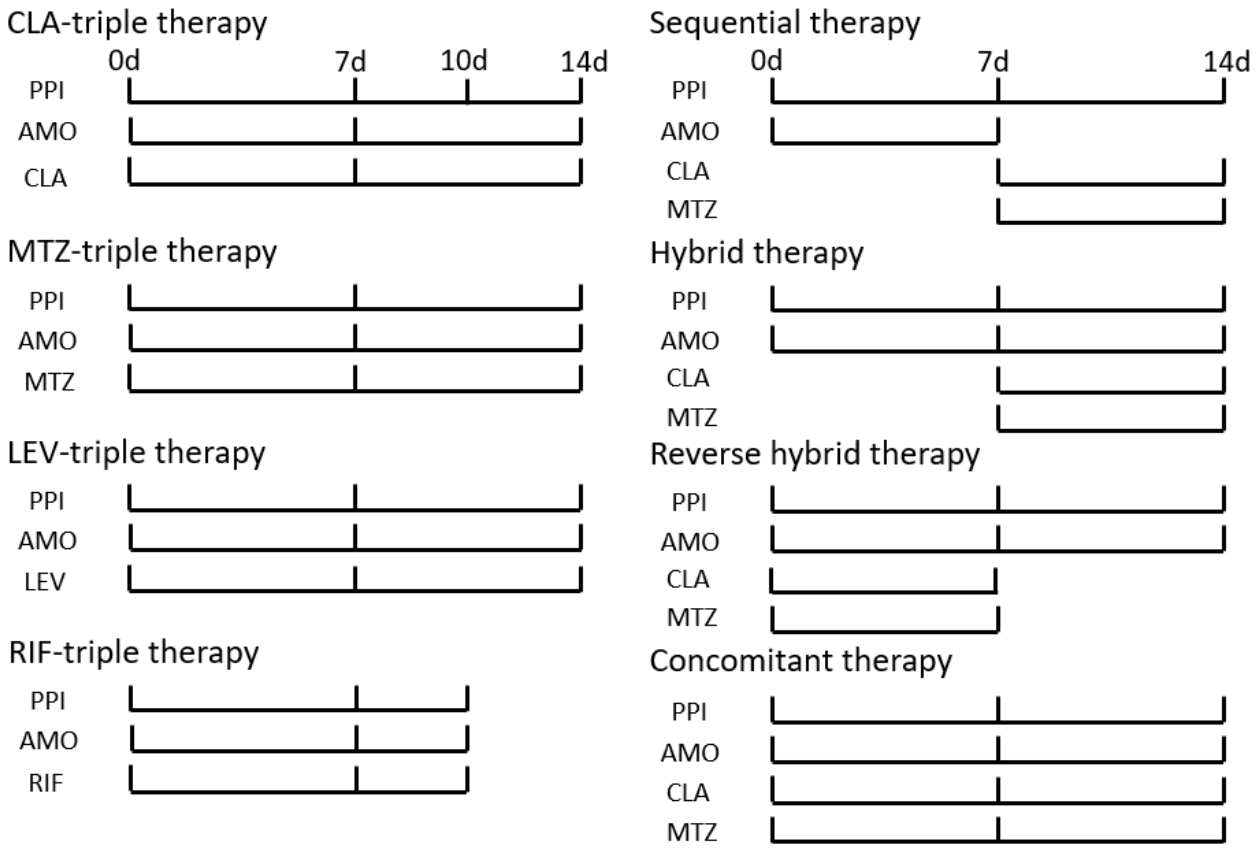
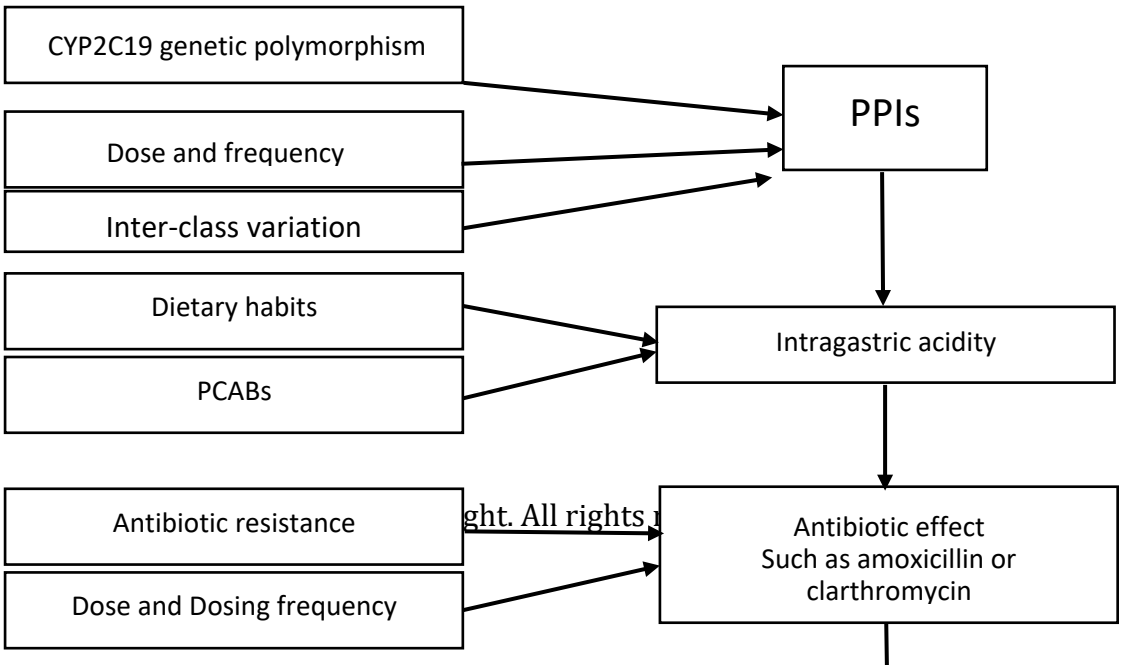
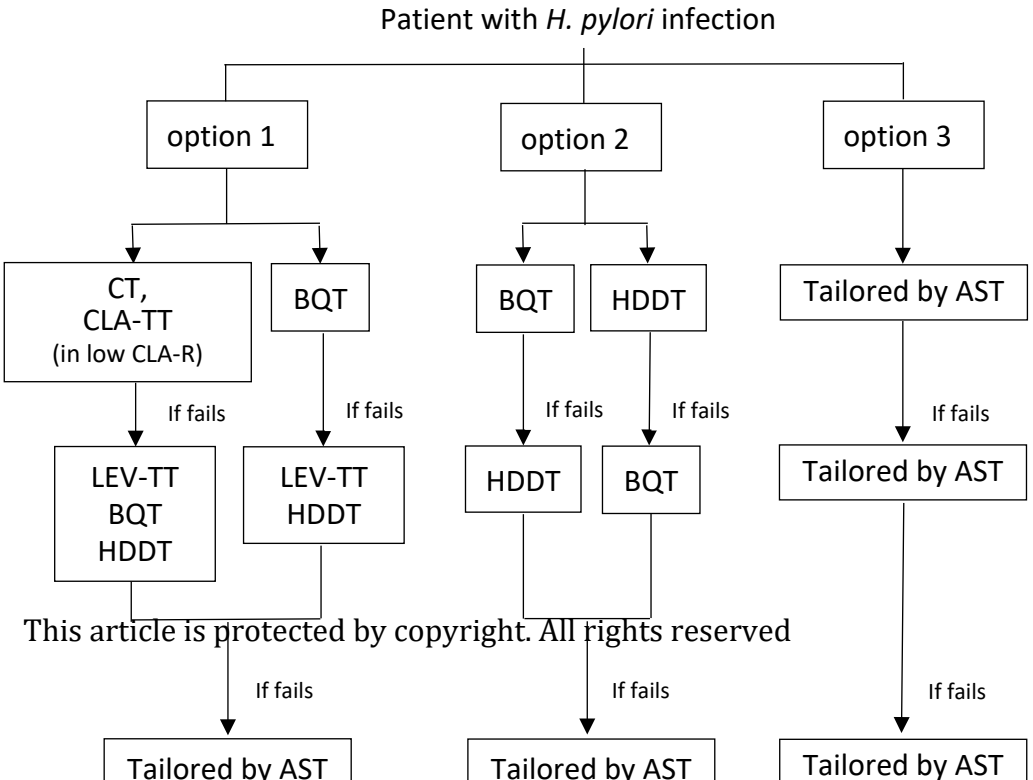


Figure 2.



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		Low CLA-R CLA-TT, 14 d	BQT, 7-14 d

Figure 3.



	10 d proven High CLA-R CT, 14 d unless 10 d proven			
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 RIF-TT	Guided by AST RIF-TT, 10 d	Guided by AST RIF-TT, 10 d	Guided by AST RIF-TT, 10 d

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

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.

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

1. Suboptimal selection of PPI (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 (well communication and education: No vs. Yes)

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

Table 3. Limitations and weaknesses of genotypic testing for antibiotic resistance

1. The role of each mutation site in some commonly used antibiotic is still not well clarified.
2. Genotypic testing can detect the presence of mutation only, it cannot provide the MIC value, and cannot predict the grade of resistance. (e.g., high MIC value or low MIC value)
3. Genotypic testing cannot distinguish the potency of different antibiotics in the same family. (e.g., Sensitive to clarithromycin but resistant to erythromycin, sensitive to sitafloxacin but resistant to ciprofloxacin)
4. Some factors may cause false negative results:
    a. other mutation sites (e.g., T2182C for clarithromycin)
    b. other mechanism causing antibiotic resistance
5. The frequency of false negative results is about 20-30% in clinic practice, and may render about 20% of patients with clarithromycin resistance be treated inappropriately.
6. The methodology of genotypic testing is still not standardized.