Helicobacter pylori Treatment Regimens: A US Perspective

Jonathan J. C. Ho, MD,[1] Erick A. Argueta, MD,[2] and Steven F. Moss, MD[2]

[1]Department of Internal Medicine, Warren Alpert School of Medicine, Brown University, Providence, Rhode Island

[2]Division of Gastroenterology, Warren Alpert School of Medicine, Brown University, Providence, Rhode Island

Corresponding author:
Dr Steven F. Moss
Rhode Island Hospital
Division of Gastroenterology
593 Eddy Street
Physicians Office Building #240
Providence, RI 02903
Tel: (401) 444-5679
Fax: (401) 444-8751
E-mail: steven_moss@brown.edu

Abstract: *Helicobacter pylori* infects nearly one-third of the US population. *H pylori* is a significant cause of gastroduodenal disease, including peptic ulcers and cancers. However, rising antibiotic resistance has complicated management of *H pylori*. This article provides a practical review of management strategies, including first-line empiric therapies and how to treat patients when prior therapies fail. Bismuth-based quadruple therapy remains the standard initial empiric regimen, although a rifabutin-based triple regimen is another approach for empiric therapy in the United States. Clarithromycin and levofloxacin therapies should be avoided except when treating a strain of known susceptibility. When therapies fail, resistance should be tested with molecular or culture-based methods. Knowing local resistance patterns and/or using practice-based eradication rates is important for devising logic-based clinical choices. Ultimately, shared decision-making, patient counseling, and careful attention to drug type and dosage are essential for refractory cases.

Keywords
Helicobacter pylori, antibiotics, management, treatment, resistance

Helicobacter pylori is a highly prevalent organism, infecting more than one-half of the global population. Within the United States, the estimated prevalence is around 35% with significant variance by location and socioeconomic factors.[1] Because *H pylori* infection is a strong risk factor for peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric cancer, it should be eradicated whenever detected.[2] Many guidelines review the management of *H pylori*, but most relevant for the United States are those from the American College of Gastroenterology and the Maastricht consensus of international *H pylori* experts, which is updated approximately every 5 years.[3,4] Growing concerns about increasing antibiotic resistance, coupled with new modalities for resistance testing and new regimens, are changing the approach to the management of *H pylori*. This article highlights current and emerging treatment regimens for practitioners in the United States, based on the available evidence and guidelines.

Table 1. Empiric First-Line Therapies for *Helicobacter pylori* Infection

Therapy	Agents	Frequency	Duration
Standard bismuth-based quadruple therapy	PPI	BID	14 days
	Bismuth	QID	
	Metronidazole 250 mg or 500 mg	QID TID to QID	
	Tetracycline 500 mg	QID	
Branded bismuth-based quadruple therapy	PPI	BID	10 days
	Combination bismuth subcitrate potassium + metronidazole + tetracycline, 3 capsules	QID	
Rifabutin-based triple therapy	PPI	BID	14 days
	Rifabutin 150 mg	Daily	
	Amoxicillin 750 mg	TID	
Branded rifabutin-based triple therapy	Combination omeprazole magnesium + amoxicillin + rifabutin, 4 capsules	TID	14 days

BID, twice daily; PPI, proton pump inhibitor; QID, 4 times daily; TID, 3 times daily.

Empiric Treatment With Bismuth-Based Quadruple Therapy

Despite recent advances in susceptibility testing, as well as the recognition that the principles of antibiotic stewardship should apply to *H pylori* infection, the treatment of *H pylori* infection remains empiric for most patients.[5] Multiple factors should be taken into consideration prior to making an antibiotic regimen selection for *H pylori,* but most important is choosing a regimen that achieves reliably high cure rates. However, unlike for other infections, there is very little knowledge of current local, regional, and national *H pylori* success rates, or of resistance patterns. In a recent meta-analysis of a limited number of published US studies, resistance rates for clarithromycin, metronidazole, and levofloxacin have been found to be higher than 30% for each.[6] Based upon these limited data, such high resistance rates for clarithromycin and levofloxacin are not compatible with their use with proton pump inhibitors (PPIs) and amoxicillin in the triple regimens that had been the standard for many years. Instead, clarithromycin and levofloxacin should be used only in refractory cases in which the *H pylori* strain is proven to be susceptible, based on resistance testing for that individual patient.[7] In contrast, amoxicillin, tetracycline, and rifabutin offer better options for empiric treatment of first-line or refractory cases, given their low rates of resistance (Table 1).

Several national and international guidelines have coalesced around 14 days of bismuth-based quadruple therapy containing tetracycline and metronidazole as first-line therapy for the empiric treatment of *H pylori* infection.[3,4,8] Although more complex than traditional clarithromycin-based triple therapy, this regimen has reliably achieved higher eradication rates.[9] Despite these recommendations, clarithromycin continues to be prescribed in nearly 80% of all eradication attempts, based on prescription claims data.[10] As an alternative to prescribing the individual components of bismuth-based quadruple therapy, a branded option (Pylera, AbbVie) significantly simplifies this regimen by decreasing the total pill burden to a single capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline.[11] However, its widespread use has been cost prohibitive, and the standard prescription is for a 10-day course vs the 14-day optimal duration of bismuth-based quadruple therapy.[12]

The overall efficacy of empiric bismuth-based quadruple therapy is limited primarily by metronidazole-resistant *H pylori*. However, metronidazole resistance is a complex issue, as in vitro resistance is only weakly predictive of failure in bismuth-based quadruple therapy.[13] Indeed, metronidazole resistance can be partially or almost completely overcome by increasing the total daily dosage to 1.5 to 2 g divided into 3 or 4 doses throughout

Table 2. Therapies for Refractory *Helicobacter pylori* Infection[a]

Therapy	Agents	Frequency	Duration
Levofloxacin-based quadruple therapy	High-dose PPI	BID	10-14 days
	Bismuth	QID	
	Levofloxacin 500 mg	Daily	
	Tetracycline 500 mg or metronidazole 500 mg	QID TID to QID	
Concomitant therapy	PPI	BID	10-14 days
	Clarithromycin 500 mg	BID	
	Amoxicillin 1 g	BID	
	Metronidazole 500 mg	BID	
Clarithromycin-based triple therapy	PPI	BID	14 days
	Clarithromycin 500 mg	BID	
	Metronidazole 500 mg or amoxicillin 1 g	TID BID	
Levofloxacin-based triple therapy	High-dose PPI	BID	14 days
	Amoxicillin 750 mg	TID	
	Levofloxacin 500 mg	Daily	

BID, twice daily; PPI, proton pump inhibitor; QID, 4 times daily; TID, 3 times daily.

[a]Choice should be based on knowledge of antibiotic susceptibility.

the day and increasing the total duration of therapy.[14] If unsuccessful despite this attempt, alternative forms of bismuth-based quadruple therapy could be considered, such as substituting metronidazole with amoxicillin, although this has not been studied much outside East Asia.

High-Dose Dual Therapy

Given its simplicity, high-dose dual therapy consisting of high-dose amoxicillin (2-3 g daily) and PPIs is an attractive option for *H pylori* treatment. Eradication success with high-dose dual therapy has been shown to be comparable with bismuth-based quadruple therapy in some studies from East Asia.[15,16] However, results from studies outside East Asia have demonstrated less success. For example, with treatment of 3 g of amoxicillin and 120 mg of omeprazole daily for 14 days, eradication rates in a US multicenter trial were only 58%.[17] However, emerging evidence supports the potential use of vonoprazan, a drug from a new and more potent class of acid-suppressing agents, instead of a PPI in dual therapy. In a recent phase 3 clinical trial from the United States and Europe, vonoprazan-based dual and triple therapy (with clarithromycin) achieved similar eradication rates (77.2% and 80.8%, respectively).[18] For the primary endpoint in strains not resistant to amoxicillin or clarithromycin, both dual and triple therapies with vonoprazan were noninferior to lansoprazole-based triple therapy (78.5% and 84.7% vs 78.8%, respectively). For the secondary endpoint in strains with clarithromycin resistance, both dual and triple therapies with vonoprazan were significantly superior to lansoprazole-based triple therapy (69.6% and 65.8% vs 31.9%, respectively).[18]

Rifabutin-Based Triple Therapy

Rifabutin-based triple therapy has generally been considered an appropriate regimen after patients fail 1 or more therapies against *H pylori*. However, a recent study from the United States found evidence suggesting a role for rifabutin-based triple therapy in the first line, leading to its US Food and Drug Administration approval.[17] In a clinical trial of treatment-naive patients, rifabutin-based triple therapy (with omeprazole and amoxicillin in a single capsule [Talicia, RedHill]) produced a greater eradication rate (83.8%) than high-dose dual therapy with

omeprazole and amoxicillin (57.7%).[17] There were higher rates of diarrhea in the rifabutin group but similar rates of headache, nausea, and vomiting between groups. Some concerns remain regarding whether widespread rifabutin use will promote resistance to rifamycin and its derivatives among tuberculosis strains, and regarding myelotoxicity as a rare but potentially important adverse effect. Thus far, neither has emerged as a significant issue in *H pylori* therapy.

Treatment Regimens for Refractory *Helicobacter pylori*

When deciding among regimens for refractory *H pylori* infection, providers should first consider patient tolerance, ability to adhere to treatment, prior antibiotic exposure, and the presence or absence of a true penicillin allergy. If available, local *H pylori* resistance patterns to the most commonly prescribed antibiotics should also be reviewed and used to help guide selection (Table 2). Additionally, a bismuth-based quadruple therapy or a rifabutin-based triple therapy could be used empirically as a second-line therapy if it had not been used as the initial treatment regimen. Finally, a thorough review of the patient's medical record and detailed shared decision-making with the patient can help determine the best next course of action.[7,19]

When an initial therapy fails, providers should avoid antibiotics that were previously used, particularly clarithromycin and levofloxacin, for which resistance is very likely. However, as resistance to amoxicillin, tetracycline, and rifabutin is low in the United States, these antibiotics can generally be used in subsequent treatment regimens.

If a patient declares a penicillin allergy, testing should be performed because most patients will not exhibit a true allergy. If testing reveals no evidence of penicillin allergy, there are several treatment options. First, empiric rifabutin-based triple therapy can be considered because *H pylori* is rarely resistant to the drugs in this combination. Rifabutin-based triple therapy includes twice-daily high-dose PPI, rifabutin 150 mg once daily, and amoxicillin 750 mg 3 times daily for a total of 14 days. The combination omeprazole, amoxicillin, and rifabutin pill simplifies this regimen and contains omeprazole 10 mg, amoxicillin 250 mg, and rifabutin 12.5 mg in each capsule, and the treatment involves taking 4 capsules 3 times daily for 14 days. The other option for patients who are not allergic to penicillin depends on antibiotic susceptibility data. If levofloxacin or clarithromycin resistance locally is known to be less than 15% (unlikely in the United States) or the strain is known to be sensitive to levofloxacin or clarithromycin, either antibiotic could be used in a triple therapy with high-dose PPI twice daily and amoxicillin 750 mg 3 times daily, or in a quadruple therapy with high-dose PPI, bismuth, levofloxacin 500 mg daily, and amoxicillin 750 mg 3 times daily. For patients allergic to penicillin and in a region with low levofloxacin resistance or with a known levofloxacin-sensitive *H pylori* strain, a regimen with PPI, bismuth, levofloxacin, and tetracycline or a regimen with PPI, bismuth, levofloxacin, and metronidazole can also be considered, bearing in mind that there are very little to no data on these combinations in US patients. In general, if a strain is sensitive to both clarithromycin and levofloxacin, clarithromycin is preferred, given that fluoroquinolones may have potential adverse effects such as tendonitis and cardiac arrhythmia.[20]

Testing for Resistance

Antimicrobial resistance testing is recommended after a patient has failed 1 or more empiric therapies. In the United States, culture-based approaches using agar dilution or an epsilometer test have been available in a very limited number of hospitals or via a send-out service to a small number of commercial laboratories. Owing to its fastidious properties, culturing *H pylori* from gastric biopsy samples is not easy and in some cases fails because of problems with specimen handling and processing leading to a loss of viability during shipping. As a result, most gastroenterologists have underutilized resistance testing despite declining eradication rates.

H pylori resistance testing has entered a new era in which awareness of its necessity has increased and molecular techniques are commercially available using fresh or formalin-fixed gastric biopsies or stool samples (Table 3).[21] For endoscopists, molecular approaches are easier because sample processing is simpler and specimen recovery is greater. Polymerase chain reaction (PCR) assays, including real-time PCR, digital PCR, and PCR enzyme immunoassay, with sequencing of amplified segments are faster than culture-based methods with a turnaround time of a few days.[13] However, they are limited to identifying known regions of mutation, cannot determine minimum inhibitory concentrations, and cannot distinguish between live organisms and the presence only of *H pylori* DNA.

Molecular susceptibility testing can also be performed using next-generation sequencing (NGS) of gastric biopsies (using fresh or formalin-fixed paraffin-embedded tissues) and now even with stool samples.[22,23] This approach utilizes knowledge of the molecular underpinnings of phenotypic resistance to assess for the presence of gene mutations to the 6 most commonly prescribed antibiotics in *H pylori* regimens: clarithromycin, amoxicillin, tetracycline, metronidazole, rifabutin, and levofloxacin. The test

Table 3. Laboratories in the United States Offering *Helicobacter pylori* Susceptibility Testing

Culture-Based Resistance Testing	Catalog Code
ARUP Laboratories	2006686
Mayo Clinic Laboratories	HELIS
Labcorp	18085
Quest Diagnostics	369949
Microbiology Specialists Inc	058, 238
Molecular Resistance Testing	**Catalog Code**
Mayo Clinic Laboratories (stool PCR)	HPFRP
American Molecular Laboratories (next-generation sequencing of gastric biopsies or stool specimens)	PyloriAR/AmHPR

Adapted from Graham DY, Moss SF.[21]

PCR, polymerase chain reaction.

has been commercialized with proprietary methodology to offer a turnaround time of 24 to 72 hours. However, full prospective evaluation of NGS with phenotypic methods and, more importantly, outcome measures is awaited because the correlation between resistance prediction by NGS and phenotypic resistance and eradication rates in US populations is not yet clear. The test appears highly predictive for levofloxacin or clarithromycin in triple therapy, but perhaps less predictive for metronidazole-containing regimens.[24,25]

Optimizing Proton Pump Inhibition

PPIs are essential components of current eradication therapies. PPIs synergize with antibiotics by suppressing gastric acidity, increasing the proportion of bacteria in the dividing and growing state, and allowing for better antibiotic efficacy.[26] PPIs also inhibit urease, which helps *H pylori* adapt to and survive the acidity of the gastric environment. Standard PPI doses are pantoprazole 40 mg, omeprazole 20 mg, lansoprazole 30 mg, esomeprazole 20 mg, and rabeprazole 20 mg. PPIs administered at twice the standard dosage in *H pylori* eradication regimens are typically referred to as high-dose PPIs.[27] Some studies demonstrate that high-dose PPIs may allow for improved eradication rates, overcoming variances in PPI metabolism.[27]

The variability in how PPIs are metabolized can contribute to differences in treatment efficacy owing to polymorphisms in the *CYP2C19* and *CYP3A4* genes that create inactive metabolites. Poor PPI metabolism has been found in a larger percentage of East Asian patients than White patients (15%-20% vs 3%, respectively).[28] Eradication rates are higher in poor metabolizers as a result of greater acid suppression.[29,30] The pharmacokinetics, and to a lesser extent pharmacodynamics, of the earlier generation of PPIs (omeprazole, lansoprazole, and pantoprazole) are significantly impacted by *CYP2C19* polymorphisms. This is much less of an issue for rabeprazole and esomeprazole.[26] Vonoprazan, a drug in the class of potassium-competitive acid blockers (PCABs), may have advantages over PPIs in combination with antibiotics for improved *H pylori* eradication success. Compared with PPIs, PCABs are faster-acting and are not significantly affected by *CYP2C19* polymorphisms.[31] Vonoprazan has shown considerable promise in Japan, where it was first approved for use.[32,33] As discussed previously, US clinical trials have recently been completed and the final results are awaited.[18]

Probiotics

Probiotic adjuncts have been studied in an effort to improve eradication rates and/or reduce the adverse effects of current *H pylori* therapies. A network analysis of studies predominantly from Asia reported that the use of probiotics slightly improved eradication with triple therapy (intent-to-treat, 81.5% vs 71.6%).[34] The probiotic arms of these studies had approximately one-half the rate of antibiotic side effects compared with the placebo group. Similarly, a recent randomized controlled trial from Greece using probiotics as an adjunct to concomitant therapy reported greater eradication rates with the addition of a probiotic compared with placebo (92.0% vs 86.8%).[35] However, given the significant heterogeneity between studies in the meta-analysis and concerns over the quality of many of the studies, the use of probiotics should still be considered experimental.

Patient and System-Related Risk Factors for Failure

Antibiotic resistance is the most common reason that *H pylori* therapies may fail, but many other factors can also contribute. For example, socioeconomic status in

childhood is known to affect acquisition of *H pylori* and its transmission. A crowded household, unstable housing situation, and parents' occupation as unskilled rather than skilled workers have all been associated with increased *H pylori* infection risk.[36] Although relatively few studies have attempted to directly assess possible correlations between such socioeconomic factors and *H pylori* eradication success, 1 study reported that annual household income less than $54,000 was associated with a decreased probability of eradication.[37] Higher odds of therapy failure noted in studies performed outside the United States include body mass index greater than 30 and smoking.[38-40] Further, nonadherence can be a significant issue. Adherence to greater than 60% of the course of antibiotics is considered necessary for successful eradication in primary treatment.[41] A high pill burden, increased regimen complexity, high drug costs, and poor patient-provider communication can each hinder medication adherence.[7] Many of these issues can be addressed with shared physician-patient decision-making and are particularly important to consider in treating refractory *H pylori* infections.

Conclusion

Treating *H pylori* infection remains a common issue for gastroenterologists and has become more challenging during the past 20 years because of increased antimicrobial resistance. Practitioners should aim to prescribe antibiotics based on the local *H pylori* resistance pattern wherever possible. However, as these data are generally not available, bismuth-based quadruple therapy containing tetracycline and metronidazole for 14 days is now the preferred empiric choice. If this therapy fails, rifabutin-based triple therapy is recommended. If a patient is concerned about a possible penicillin allergy, prompt referral to an allergist should be made in order to enable the use of amoxicillin. Because clarithromycin resistance and levofloxacin resistance are now common among US *H pylori* strains, these antibiotics should generally be avoided and used only when strains are known to be susceptible to them, as determined by resistance testing. Providers should also appreciate the essential role of acid suppression and consider doubling the PPI dosage, especially in refractory cases or when their rates of primary treatment with empiric regimens are suboptimal. When the treatment choice is unclear, several commercial laboratories now offer antimicrobial susceptibility testing to guide regimen selection. Finally, effective communication with patients and consideration of potential demographic, social, cultural, and financial barriers to treatment adherence can help increase the success of *H pylori* eradication efforts.

Disclosures

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References

1. Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. *Gastroenterology*. 2017;153(2):420-429.
2. Sugano K, Tack J, Kuipers EJ, et al; Faculty members of Kyoto Global Consensus Conference. Kyoto global consensus report on Helicobacter pylori gastritis. *Gut*. 2015;64(9):1353-1367.
3. Malfertheiner P, Megraud F, O'Morain CA, et al; European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection—the Maastricht V/Florence Consensus Report. *Gut*. 2017;66(1):6-30.
4. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of Helicobacter pylori infection. *Am J Gastroenterol*. 2017;112(2):212-239.
5. Graham DY, Liou JM. Primer for development of guidelines for Helicobacter pylori therapy using antimicrobial stewardship. *Clin Gastroenterol Hepatol*. 2022;20(5):973-983.e1.
6. Ho J, Elfanagely Y, Moss S. S1400 Helicobacter pylori antibiotic resistance in the United States over the last 10 years: a systematic review and meta-analysis [abstract]. *Am J Gastroenterol*. 2021;116:S643.
7. Shah SC, Iyer PG, Moss SF. AGA clinical practice update on the management of refractory Helicobacter pylori infection: expert review. *Gastroenterology*. 2021;160(5):1831-1841.
8. Fallone CA, Chiba N, van Zanten SV, et al. The Toronto consensus for the treatment of Helicobacter pylori infection in adults. *Gastroenterology*. 2016;151(1):51-69.e14.
9. Alsamman MA, Vecchio EC, Shawwa K, Acosta-Gonzales G, Resnick MB, Moss SF. Retrospective analysis confirms tetracycline quadruple as best Helicobacter pylori regimen in the USA. *Dig Dis Sci*. 2019;64(10):2893-2898.
10. Howden CW, Sheldon KL, Almenoff JS, Chey WD. Pitfalls of physician-directed treatment of Helicobacter pylori: results from two phase 3 clinical trials and real-world prescribing data [published online December 4, 2021]. *Dig Dis Sci*. doi:10.1007/s10620-021-07323-5.
11. Malfertheiner P, Bazzoli F, Delchier JC, et al; Pylera Study Group. Helicobacter pylori eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. *Lancet*. 2011;377(9769):905-913.
12. Tursi A, Franceschi M, Allegretta L, et al. Effectiveness and safety of Pylera® in patients infected by Helicobacter pylori: a multicenter, retrospective, real life study. *Dig Dis*. 2018;36(4):264-268.
13. Tshibangu-Kabamba E, Yamaoka Y. Helicobacter pylori infection and antibiotic resistance—from biology to clinical implications. *Nat Rev Gastroenterol Hepatol*. 2021;18(9):613-629.
14. Ji Y, Lu H. Meta-analysis: high-dose vs. low-dose metronidazole-containing therapies for Helicobacter pylori eradication treatment. *PLoS One*. 2018;13(1):e0189888.
15. Tai WC, Liang CM, Kuo CM, et al. A 14 day esomeprazole- and amoxicillin-containing high-dose dual therapy regimen achieves a high eradication rate as first-line anti-Helicobacter pylori treatment in Taiwan: a prospective randomized trial. *J Antimicrob Chemother*. 2019;74(6):1718-1724.
16. Zhu YJ, Zhang Y, Wang TY, et al. High dose PPI-amoxicillin dual therapy for the treatment of *Helicobacter pylori* infection: a systematic review with meta-analysis. *Therap Adv Gastroenterol*. 2020;13:1756284820937115.
17. Graham DY, Canaan Y, Maher J, Wiener G, Hulten KG, Kalfus IN. Rifabutin-based triple therapy (RHB-105) for *Helicobacter pylori* eradication: a double-blind, randomized, controlled trial. *Ann Intern Med*. 2020;172(12):795-802.
18. Chey WD, Mégraud F, Laine L, et al. S1382 Vonoprazan dual and triple therapy for Helicobacter pylori eradication [abstract]. *Am J Gastroenterol*. 2021;116:S634.
19. Argueta EA, Moss SF. How we approach difficult to eradicate Helicobacter pylori. *Gastroenterology*. 2022;162(1):32-37.
20. Yarrington ME, Anderson DJ, Dodds Ashley E, et al. Impact of FDA black

box warning on fluoroquinolone and alternative antibiotic use in southeastern US hospitals. *Infect Control Hosp Epidemiol*. 2019;40(11):1297-1300.
21. Graham DY, Moss SF. Antimicrobial susceptibility testing for Helicobacter pylori is now widely available: when, how, why. *Am J Gastroenterol*. 2022;117(4):524-528.
22. Saracino IM, Pavoni M, Zullo A, et al. Next generation sequencing for the prediction of the antibiotic resistance in *Helicobacter pylori*: a literature review. *Antibiotics (Basel)*. 2021;10(4):437.
23. Moss SF, Dang LP, Chua D, Sobrado J, Zhou Y, Graham DY. Comparable results of Helicobacter pylori antibiotic resistance testing of stools vs gastric biopsies using next-generation sequencing. *Gastroenterology*. 2022;162(7):2095-2097.e2.
24. Argueta EA, Alsamman MA, Moss SF, D'Agata EMC. Impact of antimicrobial resistance rates on eradication of Helicobacter pylori in a US population. *Gastroenterology*. 2021;160(6):2181-2183.e1.
25. Hulten KG, Genta RM, Kalfus IN, Zhou Y, Zhang H, Graham DY. Comparison of culture with antibiogram to next-generation sequencing using bacterial isolates and formalin-fixed, paraffin-embedded gastric biopsies. *Gastroenterology*. 2021;161(5):1433-1442.e2.
26. Scott DR, Sachs G, Marcus EA. The role of acid inhibition in Helicobacter pylori eradication. *F1000Res*. 2016;5:F1000 Faculty Rev-1747.
27. Ierardi E, Losurdo G, Fortezza RFL, Principi M, Barone M, Leo AD. Optimizing proton pump inhibitors in *Helicobacter pylori* treatment: old and new tricks to improve effectiveness. *World J Gastroenterol*. 2019;25(34):5097-5104.
28. El Rouby N, Lima JJ, Johnson JA. Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. *Expert Opin Drug Metab Toxicol*. 2018;14(4):447-460.
29. Morino Y, Sugimoto M, Nagata N, et al. Influence of *Cytochrome P450 2C19* genotype on *Helicobacter pylori* proton pump inhibitor-amoxicillin-clarithromycin eradication therapy: a meta-analysis. *Front Pharmacol*. 2021;12:759249.
30. Kuo CH, Lu CY, Shih HY, et al. CYP2C19 polymorphism influences Helicobacter pylori eradication. *World J Gastroenterol*. 2014;20(43):16029-16036.
31. Scarpignato C, Hunt RH. Editorial: acid suppression with potassium-competitive acid blockers dismissing genotype concerns. *Aliment Pharmacol Ther*. 2021;53(1):187-188.
32. Oshima T, Miwa H. Potent potassium-competitive acid blockers: a new era for the treatment of acid-related diseases. *J Neurogastroenterol Motil*. 2018;24(3):334-344.
33. Shinozaki S, Kobayashi Y, Osawa H, et al. Effectiveness and safety of vonoprazan versus proton pump inhibitors for second-line Helicobacter pylori eradication therapy: systematic review and meta-analysis. *Digestion*. 2021;102(3):319-325.
34. Shi X, Zhang J, Mo L, Shi J, Qin M, Huang X. Efficacy and safety of probiotics in eradicating Helicobacter pylori: a network meta-analysis. *Medicine (Baltimore)*. 2019;98(15):e15180.
35. Viazis N, Argyriou K, Kotzampassi K, et al. A four-probiotics regimen combined with a standard Helicobacter pylori-eradication treatment reduces side effects and increases eradication rates. *Nutrients*. 2022;14(3):632.
36. Moayyedi P, Axon AT, Feltbower R, et al; Leeds HELP Study Group. Relation of adult lifestyle and socioeconomic factors to the prevalence of Helicobacter pylori infection. *Int J Epidemiol*. 2002;31(3):624-631.
37. Singh H, Chung H, Awan I, et al. Designing strategies for eradication of Helicobacter pylori based on prevalence patterns of infection and antibiotic resistance in a low-income, medically underserved community in the United States. *Helicobacter*. 2021;26(1):e12769.
38. Pan K-f, Zhang L, Gerhard M, et al. A large randomised controlled intervention trial to prevent gastric cancer by eradication of Helicobacter pylori in Linqu County, China: baseline results and factors affecting the eradication. *Gut*. 2016;65(1):9-18.
39. Abdullahi M, Annibale B, Capoccia D, et al. The eradication of Helicobacter pylori is affected by body mass index (BMI). *Obes Surg*. 2008;18(11):1450-1454.
40. Suzuki T, Matsuo K, Ito H, et al. Smoking increases the treatment failure for Helicobacter pylori eradication. *Am J Med*. 2006;119(3):217-224.
41. Graham DY, Lew GM, Malaty HM, et al. Factors influencing the eradication of Helicobacter pylori with triple therapy. *Gastroenterology*. 1992;102(2):493-496.