The Ideal *Helicobacter pylori* Treatment for the Present and the Future

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Keywords

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Abstract

Background: *Helicobacter pylori* eradication treatments are widely performed to improve gastric mucosal inflammation, promote ulcer healing, and reduce the incidence of gastric cancer. However, there are several issues associated with *H. pylori* eradication treatment. First, various treatment regimens are currently used worldwide, and the standard treatment varies with region and country. Second, the antimicrobial resistance of *H. pylori* is increasing due to indiscriminate antibiotic use. Finally, gut microbiota dysbiosis is potentially induced by *H. pylori* treatment. **Summary:** Based on current international guidelines and a network meta-analysis comparing the effects of various treatment regimens, nonbismuth quadruple therapies for 10–14 days and vonoprazan-based triple therapy for 7 days are the currently recommended *H. pylori* treatment regimens. These regimens show good eradication rates of approximately 90%, even in areas where antimicrobial-resistant strains are highly prevalent. However, these regimens still have inherent drawbacks that may

promote further increases in antimicrobial resistance and induce gut microbiota dysbiosis because of the empiric use of multiple antibiotics. **Key Message:** The ideal concept for the present and future *H. pylori* eradication treatment involves “a simple, cost-effective strategy that fosters compliance without having a negative impact on the gut microbiota or contributing to future antimicrobial resistance.” One interesting possibility that may fulfill this concept is a dual therapy involving vonoprazan and amoxicillin. This is the simplest treatment regimen that provides acceptable eradication rates, improves safety and tolerability, and minimizes the potential for increasing antimicrobial resistance or causing gut microbiota dysbiosis.

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Introduction

Helicobacter pylori are Gram-negative, flagellated, spiral bacteria that commonly infect humans, with an estimated 4.4 billion individuals infected worldwide [1]. *H. pylori* infection causes gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric cancer [2]. *H. pylori* eradication treatments are widely

performed to improve gastric mucosal inflammation, promote ulcer healing, and reduce the incidence of gastric cancer and the associated mortality.

Various *H. pylori* eradication treatment regimens are used worldwide, with the standard treatment regimen varying with region and country owing to differences in drug availability and antimicrobial resistance of *H. pylori*. Further, eradication of *H. pylori* is becoming increasingly challenging because of new issues including metabolic changes and gut microbiota changes after treatment. We therefore review the recent literature on *H. pylori* treatment regimens and consider the current recommended regimens to propose the ideal treatment regimen for the future.

Current Standard H. pylori Treatment Regimens

Guidelines on *H. pylori* treatment have been published in many regions. *H. pylori* eradication regimens recommended as the first-line treatment by current international guidelines are shown in Table 1. The Maastricht V/Florence Consensus Report [3] (Europe), Toronto Consensus [4], and American College of Gastroenterology Clinical Guideline [5] (North America) recommend bismuth quadruple therapy or nonbismuth concomitant quadruple therapy for 10–14 days as the first-line treatment for patients in areas with high *H. pylori* clarithromycin resistance. Bismuth quadruple therapy consists of a proton pump inhibitor (PPI), bismuth, and 2 types of antibiotics. Traditionally, the included antibiotics were metronidazole and tetracycline; recently, other agents such as amoxicillin, clarithromycin, and tinidazole have also been included. Concomitant quadruple therapy consists of a PPI and 3 types of antibiotics, typically including amoxicillin, clarithromycin, and metronidazole. Large-scale observational studies have reported sufficient eradication outcomes (>90%) for both therapy types in real clinical practice in Europe [9, 10]. The earlier referenced guidelines recommend clarithromycin-containing triple therapy only in areas with low clarithromycin resistance and only in patients who have not received macrolide antibiotics.

In Asia, the Chinese guideline [6] also recommends 10- to 14-day bismuth quadruple therapy as an empiric treatment. On the other hand, the Korean [7] and Japanese [8] guidelines still recommend the standard triple therapy, containing clarithromycin, as the first-line treatment. The Korean guideline recommends longer (14 days) treatment duration for the triple therapy and that the nonbismuth quadruple therapy (concomitant and sequential therapies) should be used as an empiric first-line

treatment. In Japan, a new gastric acid suppressant, vonoprazan, was launched in 2015; a 7-day vonoprazan-based triple therapy, involving the use of vonoprazan, amoxicillin, and clarithromycin, achieves remarkable eradication success rates. This regimen as the first-line treatment reportedly provided eradication rates of 89–93% in its first randomized control trial [11] and in real clinical practice [12]; moreover, the success rate was >80% even for clarithromycin-resistant strains [13, 14]. A triple-drug (vonoprazan, amoxicillin, and clarithromycin/metronidazole) blister package drug was launched in 2016 in Japan and showed improved patient adherence [15]. Thus, this 7-day, vonoprazan-based triple therapy is currently the primary therapy used in Japan [16].

H. pylori eradication regimens currently used worldwide and their eradication rates are shown in Table 2. Direct comparison of the effectiveness of each regimen to determine the “best” regimen is difficult because the commonly used regimens differ according to region/country due to differences in medical insurance coverage and drug availability. A network meta-analysis, published in 2021, compared the effects of the various regimens currently in use [25]. It analyzed 68 randomized clinical trials, involving 22,975 patients, and compared *H. pylori* eradication rates for first-line empiric treatments involving 8 regimens, namely, bismuth quadruple therapy, concomitant quadruple therapy, sequential therapy, reverse hybrid therapy, levofloxacin-containing therapy, high-dose PPI-amoxicillin dual therapy, PPI-based standard triple therapy, and vonoprazan-based triple therapy. The study determined vonoprazan-based triple therapy to have the best eradication performance, followed by concomitant quadruple therapy and reverse hybrid therapy, in the comparative effectiveness ranking results. Based on that study, vonoprazan-based triple therapy is the best regimen and should be used as the first-line treatment in regions where vonoprazan is available. Where vonoprazan is not available, nonbismuth quadruple therapy including concomitant quadruple therapy or reverse hybrid therapy is recommended as the first-line treatment.

Issues with the Current Standard Treatments

Current standard *H. pylori* eradication treatments, including vonoprazan-based triple therapy and nonbismuth quadruple therapy, have some limitations even though they provide sufficient eradication effect. The primary issue related to *H. pylori* eradication treatment is the increasing prevalence of antimicrobial-resistant strains. Indiscriminate use of antibiotics for medical and veterinary purposes is widespread in many countries, and such

Table 1. First-line *H. pylori* treatment regimens recommended in current guidelines [3–8]

Guideline	Regimen(s)	Treatment duration, days
Maastricht V/Florence Consensus Report [3]	In areas of low (<15%) CLA resistance Standard triple therapy (PPI + CLA + AMO) (PPI + CLA + MET)	14
	In areas of high (>15%) CLA resistance Bismuth quadruple therapy (PPI + bismuth + 2 kinds of antibiotics) Concomitant quadruple therapy (PPI + AMO + CLA + MET/TIN)	14
Toronto Consensus [4]	In areas of low (<15%) CLA resistance Standard triple therapy (PPI + CLA + AMO) (PPI + CLA + MET) (PPI + AMO + MET)	14
	In areas of high (>15%) CLA resistance Bismuth quadruple therapy (PPI + bismuth + TET + MET) Concomitant quadruple therapy (PPI + AMO + CLA + MET)	14
ACG Clinical Guideline [5]	In areas of low (<15%) CLA resistance and in patients without previous macrolide exposure Standard triple therapy (PPI + CLA + AMO) (PPI + CLA + MET)	14
	In areas of high (>15%) CLA resistance or in patients with previous macrolide exposure Bismuth quadruple therapy (PPI + bismuth + TET + MET) Concomitant quadruple therapy (PPI + AMO + CLA + MET)	10–14
Fifth Chinese National Consensus Report [6]	Bismuth quadruple therapy (PPI + bismuth + 2 kinds of antibiotics)	10–14
Korean Guideline 2020 [7]	Standard triple therapy (PPI + CLA + AMO)	14
	Sequential therapy (PPI + AMO/5 days followed by PPI + CLA + MET/5 days) Concomitant quadruple therapy (PPI + AMO + CLA + MET)	10
Japanese Guideline 2016 [8]	Standard or vonoprazan triple therapy (PPI/P-CAB + AMO + CLA/MET)	7

ACG, American College of Gastroenterology; AMO, amoxicillin; CLA, clarithromycin; MET, metronidazole; P-CAB, potassium-competitive acid blocker (vonoprazan); PPI, proton pump inhibitor; TIN, tinidazole; TET, tetracycline.

Table 2. Currently used first-line *H. pylori* treatment regimens and their eradication rates [17–24]

Regimen	PPI/P-CAB	Antibiotics	Treatment duration, days	Eradication rates	
				ITT	PP
Bismuth quadruple therapy	Lansoprazole (30 mg bid)	MTZ (500 mg tid) TET (500 mg qid) Bismuth (300 mg qid)	10	74% [17]	93% [17]
Concomitant quadruple therapy	Esomeprazole (20 mg bid)	AMO (1,000 mg bid) CLA (500 mg bid) MET (500 mg bid)	14	87% [18]	94% [18]
Sequential therapy	Rabeprazole (20 mg bid)	AMO (1,000 mg bid) for 5 days followed by CLA (500 mg bid) for 5 days TIN (500 mg bid) for 5 days		82% [19]	95% [19]
Hybrid therapy	Esomeprazole (40 mg bid)	AMO (1,000 mg bid) for 14 days CLA (500 mg bid) for last 7 days MET (500 mg) for last 7 days		83% [20]	95% [20]
Reverse hybrid therapy	Dexlansoprazole (60 mg qd)	AMO (1,000 mg bid) for 14 days CLA (500 mg bid) for initial 7 days MET (500 mg) for initial 7 days		95% [21]	96% [21]
PPI-based standard triple therapy	Lansoprazole (30 mg bid)	AMO (1,000 mg bid) CLA (500 mg bid)	14	56% [22]	63% [22]
High-dose PPI-amoxicillin dual therapy	Esomeprazole (20 mg qid)	AMO (750 mg qid)	14	87% [23]	92% [23]
Vonoprazan-based triple therapy	Vonoprazan (20 mg bid)	AMO (750 mg bid) CLA (200 mg bid)	7	89% [24]	90% [24]
Vonoprazan-amoxicillin dual therapy	Vonoprazan (20 mg bid)	AMO (750 mg bid)	7	85% [24]	87% [24]

AMO, amoxicillin; bid, twice daily; CLA, clarithromycin; ITT, intention-to-treat; MET, metronidazole; P-CAB, potassium-competitive acid blocker (vonoprazan); PP, per-protocol; PPI, proton pump inhibitor; qd, once daily; qid, 4 times daily; TET, tetracycline; tid, 3 times daily; TIN, tinidazole.

broad antibiotic consumption leads to resistance in various bacterial species, including *H. pylori* [26]. The antimicrobial resistance of *H. pylori* has reached an astonishing level worldwide and considerably affects treatment effectiveness [27]. The WHO recently published a list of antimicrobial-resistant “priority pathogens,” cataloging 12 bacterial families that pose the greatest threat to human health [28]; the list was divided into 3 priority statuses: critical, high, and medium. Clarithromycin-resistant *H. pylori* was classified as a high-priority species, in the same class as vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus*. In addition, strains of *H. pylori* resistant to metronidazole and fluoroquinolones, which are commonly used in *H. pylori* eradication treatments, have also increased to alarming levels (in excess of 15%) in many parts of the

world [27]. As shown in Table 2, all triple or quadruple therapy regimens currently used contain 2 or 3 types of antibiotics. The currently recommended regimens vonoprazan-based triple therapy and nonbismuth quadruple therapy also contain clarithromycin and/or metronidazole, which have major problems with increasing antimicrobial resistance. The use of multiple antibiotics in empiric *H. pylori* treatment can still increase the risk of emerging antimicrobial resistance. Therefore, the increased resistance of *H. pylori* to clarithromycin and other families of antibiotics must be addressed through the proper use of antibiotics in *H. pylori* treatments. Antimicrobial susceptibility testing is the most effective method for optimizing and reducing antibiotic use in *H. pylori* eradication treatment regimes, as is commonly done for other infections. Moreover, tailored therapies based on

the antimicrobial susceptibility test have been reported to dramatically improve eradication rates [29]. However, antimicrobial susceptibility testing is not a routine clinical practice due to the invasiveness of endoscopy; further, it is time-consuming and requires appropriate laboratory culturing facilities, which increases cost considerations.

Another potential issue is gut microbiota dysbiosis induced by *H. pylori* eradication treatments. The human gut microbiota plays an important role in human health due to its contribution to energy metabolism, immune modulation, and host defense [30]. *H. pylori* eradication treatment involves the use of multiple antibiotics and gastric acid-suppressing agents, such as PPIs. Unfortunately, both antibiotics and PPIs may have significant impact on the gut microbiota through their antibacterial effects (antibiotics) and ability to reduce gastric acidity (PPIs). As a result, *H. pylori* eradication treatments can contribute to gut microbiota dysbiosis and has been linked to many digestive diseases and metabolic changes [31, 32]. The resultant gut microbiota disturbances may differ according to the *H. pylori* treatment regimen used because of associated differences in the types and doses of antibiotics and PPIs included. One study compared long-term gut microbiota changes associated with 3 different *H. pylori* treatment regimens (triple therapy, concomitant quadruple therapy, and bismuth quadruple therapy) using fecal samples [33]. The study showed that alpha diversity indexes were lower at 2 weeks after all 3 treatment regimens, but only patients receiving triple therapy possessed baseline levels of alpha diversity at 8 weeks; the baseline values in the other 2 groups were not restored even within the first year after therapy. In addition, several studies also investigated the impact of vonoprazan-based triple therapy on the gut microbiota. One study showed that the alpha diversity significantly reduced, and the beta diversity significantly differed at 1 and 8 weeks, respectively, after vonoprazan-based triple therapy compared with the baseline [34]. Another study showed that significant changes in the gut microbiota persisted 2 months after vonoprazan-based triple therapy in several patients, although the diversity indexes recovered to statistically similar levels [35]. Further studies are needed to verify and establish *H. pylori* eradication regimens that have minimal impact on the gut microbiota while providing sufficient eradication effects.

What Is the Ideal Regimen for the Future?

In the future, new ideal treatment regimens for *H. pylori* infection must be developed to overcome the issues of *H. pylori* antimicrobial resistance and impact on gut

microbiota. To prevent the increasing antimicrobial resistance and lower the effect on gut microbiota, reducing the consumption of antibiotics while maintaining the eradication effect is necessary. In that respect, dual therapy, which combines a PPI with amoxicillin, may be the ideal regimen for the future. A dual therapy consisting of a PPI and amoxicillin was first reported in the 1990s as a first-line *H. pylori* eradication treatment. High-dose and high-frequency dual therapy, defined as administration of both amoxicillin (≥ 2.0 g/day) and PPI (at least twice daily) for 14 days, has excellent *H. pylori* eradication efficacy as a first-line therapy. However, its side effects and poor patient compliance due to the high dose, high frequency of administration, and long treatment duration are the main drawbacks. Thus, this high-dose, high-frequency dual therapy has been used as a rescue/salvage treatment. One interesting possibility is the substitution of conventional PPIs with vonoprazan in dual therapies. Vonoprazan and amoxicillin dual therapy could be an alternative treatment for *H. pylori* eradication. Several comparative studies have reported that 7-day vonoprazan and amoxicillin dual therapy, consisting of 20 mg vonoprazan and 750 mg amoxicillin twice daily for 7 days, achieves *H. pylori* eradication rates of 85–93%, similar to the results of 7-day vonoprazan triple therapy in regions with high clarithromycin resistance [24, 36]. In addition, the vonoprazan-amoxicillin dual therapy has less impact on gut microbiota compared with the vonoprazan triple therapy. The diversity and relative abundance of the gut microbiota components were not significantly altered after 1 and 8 weeks of vonoprazan-amoxicillin dual therapy, compared with the baseline [34]. Moreover, the eradication effect of vonoprazan-amoxicillin dual therapy can be improved by adjusting the dose and/or frequency of amoxicillin. Maintaining steady amoxicillin plasma concentrations above the minimal inhibitory concentration level for its bactericidal effect against *H. pylori* is important for a successful dual therapy regimen. Amoxicillin dose or frequency administered and patient's body size are 2 potential factors that affect the minimal inhibitory concentration level. One study in which the dual therapy consisted of 20 mg vonoprazan twice daily and 500 mg amoxicillin 3 times daily for 7 days as the first-line treatment provided a higher eradication rate of 93% [37]. Another study reported that smaller patient body size, including lower body mass index and lower body surface area, was associated with higher eradication success of the vonoprazan-amoxicillin dual therapy [38]. These study results suggest that vonoprazan-amoxicillin dual therapy with proper adjustment of amoxicillin dose based on pa-

tient body size is expected to be the ideal treatment in the future for minimizing both *H. pylori* antibiotic resistance development and posttreatment gut microbiota dysbiosis while also providing sufficient *H. pylori* eradication. However, currently, there are limited reports on this dual therapy. Further studies from many regions are warranted to establish the dual therapy as the new first-line *H. pylori* eradication treatment.

Conclusion

In this review, we outlined the current standards for *H. pylori* treatment, referencing the latest international guidelines and research data. Nonbismuth quadruple therapy for 10–14 days and vonoprazan-based triple therapy for 7 days are the currently recommended *H. pylori* treatment regimens that are supported by an abundance of evidence. These regimens show good eradication rates of approximately 90%, even in areas with high levels of antimicrobial-resistant strains. However, these regimens have inherent drawbacks that need to be overcome. The empiric use of clarithromycin and metronidazole in these regimens may promote further increases in *H. pylori* antimicrobial resistance. The treatment regimens may also induce gut microbiota dysbiosis and potentially result in digestive diseases and metabolism disorders. The ideal *H. pylori* eradication concept traditionally involves “a simple, well-tolerated regimen that fosters patient compliance and is cost effective.” We believe that this concept

should be further modified by indicating that the ideal therapy should also have “minimal negative impacts on future levels of antimicrobial resistance and on gut microbiota dysbiosis.” One interesting possibility that seems to fulfill this concept is a dual therapy consisting of vonoprazan and amoxicillin. This is the simplest treatment regimen that may provide sufficient eradication rates and improve safety and tolerability, while also minimizing any contribution to future antimicrobial resistance levels and any significant impact on the gut microbiota. We hope that this dual therapy will become widely used in many countries, and that much knowledge on this dual therapy will be accumulated in the future.

Conflict of Interest Statement

All authors have no conflicts of interest to declare.

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References

- Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. *Gastroenterology*. 2017;153(2):420–9.
- McCull KE. Clinical practice. *Helicobacter pylori* infection. *N Engl J Med*. 2010 Apr 29;362(17):1597–604.
- Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, et al. Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report. *Gut*. 2017;66(1):6–30.
- Fallone CA, Chiba N, van Zanten SV, Fischbach L, Gisbert JP, Hunt RH, et al. The Toronto Consensus for the treatment of *Helicobacter pylori* infection in adults. *Gastroenterology*. 2016 Jul;151(1):51–69.e14.
- Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2017 Feb;112(2):212–39.
- Liu WZ, Xie Y, Lu H, Cheng H, Zeng ZR, Zhou LY, et al. Fifth Chinese National Consensus Report on the management of *Helicobacter pylori* infection. *Helicobacter*. 2018 Apr;23(2):e12475.
- Jung HK, Kang SJ, Lee YC, Yang HJ, Park SY, Shin CM, et al. Evidence-based guidelines for the treatment of *Helicobacter pylori* infection in Korea 2020. *Gut Liver*. 2021 Mar 15;15(2):168–95.
- Kato M, Ota H, Okuda M, Kikuchi S, Satoh K, Shimoyama T, et al. Guidelines for the management of *Helicobacter pylori* infection in Japan: 2016 revised edition. *Helicobacter*. 2019 Aug;24(4):e12597.
- Nyssen OP, Bordin D, Tepes B, Pérez-Aisa Á, Vaira D, Caldas M, et al. European Registry on *Helicobacter pylori* management (Hp-EuReg): patterns and trends in first-line empirical eradication prescription and outcomes of 5 years and 21,533 patients. *Gut*. 2021;70(1):40–54.
- Nyssen OP, Perez-Aisa A, Castro-Fernandez M, Pellicano R, Huguet JM, Rodrigo L, et al. European Registry on *Helicobacter pylori* management: single-capsule bismuth quadruple therapy is effective in real-world clinical practice. *United European Gastroenterol J*. 2021;9(1):38–46.
- Murakami K, Sakurai Y, Shiino M, Funao N, Nishimura A, Asaka M. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for *Helicobacter pylori* eradication: a phase III, randomised, double-blind study. *Gut*. 2016 Sep;65(9):1439–46.
- Suzuki S, Gotoda T, Kusano C, Iwatsuka K, Moriyama M. The efficacy and tolerability of a triple therapy containing a potassium-competitive acid blocker compared with a 7-day PPI-based low-dose clarithromycin triple therapy. *Am J Gastroenterol*. 2016 Jul;111(7):949–56.

- 13 Li M, Oshima T, Horikawa T, Tozawa K, Tomita T, Fukui H, et al. Systematic review with meta-analysis: vonoprazan, a potent acid blocker, is superior to proton-pump inhibitors for eradication of clarithromycin-resistant strains of *Helicobacter pylori*. *Helicobacter*. 2018 Aug;23(4):e12495.
- 14 Okubo H, Akiyama J, Kobayakawa M, Kawazoe M, Mishima S, Takasaki Y, et al. Vonoprazan-based triple therapy is effective for *Helicobacter pylori* eradication irrespective of clarithromycin susceptibility. *J Gastroenterol*. 2020;55(11):1054–61.
- 15 Nishida T, Tsujii Y, Okamoto A, Tomita R, Higaki Y, Osugi N, et al. A triple-drug blister-packaged drug with vonoprazan improves first-line eradication of *Helicobacter pylori* in elderly patients: a retrospective propensity score-matched cohort study. *Digestion*. 2020; 101(5):608–14.
- 16 Deguchi H, Uda A, Murakami K. Current status of *Helicobacter pylori* diagnosis and eradication therapy in Japan using a nationwide database. *Digestion*. 2020;101(4):441–9.
- 17 Kim YI, Lee JY, Kim CG, Park B, Park JY, Choi JJ. Ten-day bismuth-containing quadruple therapy versus 7-day proton pump inhibitor-clarithromycin containing triple therapy as first-line empirical therapy for the *Helicobacter pylori* infection in Korea: a randomized open-label trial. *BMC Gastroenterol*. 2021;21(1):95.
- 18 Apostolopoulos P, Ekmektzoglou K, Georgopoulos S, Chounta E, Theofanopoulou A, Kalantzis C, et al. 10-day versus 14-day quadruple concomitant nonbismuth therapy for the treatment of *Helicobacter pylori* infection: results from a randomized prospective study in a high clarithromycin resistance country. *J Clin Gastroenterol*. 2020 Jul;54(6):522–7.
- 19 Myint NPST, Zaw TT, Sain K, Waiyan S, Danta M, Cooper D, et al. Sequential *Helicobacter pylori* eradication therapy in Myanmar: a randomized clinical trial of efficacy and tolerability. *J Gastroenterol Hepatol*. 2020 Apr;35(4): 617–23.
- 20 Mestrovic A, Perkovic N, Bozic J, Pavicic Ivelja M, Vukovic J, Kardum G, et al. Randomised clinical trial comparing concomitant and hybrid therapy for eradication of *Helicobacter pylori* infection. *PLoS One*. 2020;15(12): e0244500.
- 21 Hsu PI, Tsay FW, Kao JY, Peng NJ, Tsai KW, Tsai TJ, et al. Equivalent efficacies of reverse hybrid and concomitant therapies in first-line treatment of *Helicobacter pylori* infection. *J Gastroenterol Hepatol*. 2020 Oct;35(10): 1731–7.
- 22 Farhoud NS, Ibrahim OM, Ezzat SE. Efficacy and cost-effectiveness comparison of 10-day, 14-day sequential versus 14-day triple therapies for treating *Helicobacter pylori* infection in Egyptian patients. *J Clin Gastroenterol*. 2020 Oct;54(9):806–12.
- 23 Song Z, Zhou L, Xue Y, Suo B, Tian X, Niu Z. A comparative study of 14-day dual therapy (esomeprazole and amoxicillin four times daily) and triple plus bismuth therapy for first-line *Helicobacter pylori* infection eradication: a randomized trial. *Helicobacter*. 2020 Dec;25(6):e12762.
- 24 Suzuki S, Gotoda T, Kusano C, Ikehara H, Ichijima R, Ohyauchi M, et al. Seven-day vonoprazan and low-dose amoxicillin dual therapy as first-line *Helicobacter pylori* treatment: a multicentre randomised trial in Japan. *Gut*. 2020;69(6):1019–26.
- 25 Rokkas T, Gisbert JP, Malfertheiner P, Niv Y, Gasbarrini A, Leja M, et al. Comparative effectiveness of multiple different first-line treatment regimens for *Helicobacter pylori* infection: a network meta-analysis. *Gastroenterology*. 2021 Aug;161(2):495–507.e4.
- 26 Megraud F, Bruyndonckx R, Coenen S, Wittkop L, Huang TD, Hoebeke M, et al. *Helicobacter pylori* resistance to antibiotics in Europe in 2018 and its relationship to antibiotic consumption in the community. *Gut*. 2021 Apr 9.
- 27 Savoldi A, Carrara E, Graham DY, Conti M, Tacconelli E. Prevalence of antibiotic resistance in *Helicobacter pylori*: a systematic review and meta-analysis in World Health Organization regions. *Gastroenterology*. 2018 Nov;155(5):1372–82.e17.
- 28 World Health Organization (WHO). Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. 2017.
- 29 Horie R, Handa O, Ando T, Ose T, Murakami T, Suzuki N, et al. *Helicobacter pylori* eradication therapy outcome according to clarithromycin susceptibility testing in Japan. *Helicobacter*. 2020 Aug;25(4):e12698.
- 30 Fujimura KE, Slusher NA, Cabana MD, Lynch SV. Role of the gut microbiota in defining human health. *Expert Rev Anti Infect Ther*. 2010 Apr;8(4):435–54.
- 31 Roca-Rodriguez MM, Coin-Araguez L, Cornejo-Pareja I, Alcaide J, Clu-Fernandez C, Munoz-Garach A, et al. Carbohydrate metabolism improvement after *Helicobacter pylori* eradication. *Diabetes Metab*. 2016 Apr;42(2): 130–4.
- 32 Guo Y, Zhang Y, Gerhard M, Gao JJ, Mejias-Luque R, Zhang L, et al. Effect of *Helicobacter pylori* on gastrointestinal microbiota: a population-based study in Linqu, a high-risk area of gastric cancer. *Gut*. 2020 Sep;69(9):1598–607.
- 33 Liou JM, Chen CC, Chang CM, Fang YJ, Bair MJ, Chen PY, et al. Long-term changes of gut microbiota, antibiotic resistance, and metabolic parameters after *Helicobacter pylori* eradication: a multicentre, open-label, randomised trial. *Lancet Infect Dis*. 2019 Oct; 19(10):1109–20.
- 34 Horii T, Suzuki S, Takano C, Shibuya H, Ichijima R, Kusano C, et al. Lower impact of vonoprazan-amoxicillin dual therapy on gut microbiota for *Helicobacter pylori* eradication. *J Gastroenterol Hepatol*. 2021 Jun 9.
- 35 Gotoda T, Takano C, Kusano C, Suzuki S, Ikehara H, Hayakawa S, et al. Gut microbiome can be restored without adverse events after *Helicobacter pylori* eradication therapy in teenagers. *Helicobacter*. 2018 Dec;23(6): e12541.
- 36 Gotoda T, Kusano C, Suzuki S, Horii T, Ichijima R, Ikehara H. Clinical impact of vonoprazan-based dual therapy with amoxicillin for *H. pylori* infection in a treatment-naïve cohort of junior high school students in Japan. *J Gastroenterol*. 2020;55(10):969–76.
- 37 Furuta T, Yamade M, Kagami T, Uotani T, Suzuki T, Higuchi T, et al. Dual therapy with vonoprazan and amoxicillin is as effective as triple therapy with vonoprazan, amoxicillin and clarithromycin for eradication of *Helicobacter pylori*. *Digestion*. 2020;101(6):743–51.
- 38 Eto H, Suzuki S, Kusano C, Ikehara H, Ichijima R, Ito H, et al. Impact of body size on first-line *Helicobacter pylori* eradication success using vonoprazan and amoxicillin dual therapy. *Helicobacter*. 2021 Apr;26(2): e12788.