Microb Health Dis 2023; 5: e917

REVIEW – TREATMENT OF *HELICOBACTER PYLORI* INFECTION 2023

M. Nkuize[1,5], V.Y. Miendje Deyi[2,5], R. Ntounda[3,5], F. Mana[4,5]

[1]Department of Gastroenterology and Hepatology, CHU Saint Pierre de Bruxelles, Université libre de Bruxelles, Brussels, Belgium
[2]Department of Microbiology, Laboratoire Hospitalier Universitaire de Bruxelles – Universitair Laboratorium Brussel (LHUB-ULB), Université libre de Bruxelles, Brussels, Belgium
[3]Department of Gastroenterology and Hepatology, CHRSM site Sambre, Auvelais, Belgium
[4]Department of Gastroenterology and Hepatology, Clinique Saint Jean, H.UNI, Brussels, Belgium
[5]Belgian *Helicobacter pylori* and Microbiota Study Group

Corresponding Author: Nkuize M, MD; email: marcel.nkuize@stpierre-bru.be

Abstract – *Helicobacter pylori* infection is an infectious disease and should be managed accordingly. Factors that affect patient outcomes, particularly proton inhibitor metabolism, compliance, and antibiotic resistance, are topics of active research. Studies carried out this year aimed to address the above issues by means of comparative studies, meta-analyses, and guidelines. For this year's review, we have selected studies that are relevant to clinical practice, particularly in the areas of bismuth quadruple therapy (BQT), individualized treatment, high acid suppression therapy, probiotics, barriers to treatment, and factors affecting treatment success. It appears that the globally persistent increasing level of *H. pylori* antibiotic resistance has led to treatment strategy adaptations, such as prescribing first-line BQT or individualizing first-line treatment based on antimicrobial susceptibility testing. Novel regimens like high-dose dual therapy and vonoprazan-based therapy provide excellent efficacy, while large international studies are still awaited. Compliance should be improved through the awareness of the patient's concerns and the use of multimedia by the doctor/pharmacist. Future perspectives include making BQT regimens universally available and testing new molecules/regimens.

Keywords: Antibiotic resistance, Compliance, Bismuth-based therapy, High dose dual therapy, Vonoprazan, HIV.

INTRODUCTION

Helicobacter pylori infection is an infectious disease and should be managed accordingly[1]. Only treatment regimens that provide an eradication rate ≥ 90% should be used in clinical practice[2]. The best approach to treatment continues to be debated in consensus conferences and guidelines with regard to the factors that affect outcomes, particularly proton pump inhibitor (PPI) metabolism, compliance, and antibiotic resistance[3,4,5]. For this year's review on the treatment of *H. pylori* infection, studies relevant to clinical practice were selected.

Bismuth Quadruple Therapy

The 2022 Maastricht VI/Florence consensus recommends a 14-day course of bismuth quadruple therapy (BQT) as first-line empirical therapy, particularly if the results of the antimicrobial susceptibility test (AST) are unknown and/or the clarithromycin (CLA) resistance rate is >15%[3].

Several trials have compared BQT to other regimens as first- and second-line empirical therapies. The control arms were either standard regimens or novel regimens such as high-dose dual therapy (HDDT) with a potassium-competitive acid blocker (P-CAB) vonoprazan dual or triple therapy[3,6-11].

First-line therapy: A number of studies with different study designs confirmed the first-line efficacy of BQT. A single-center, open-label randomized controlled trial (RCT) included 800 patients on four regimens, depending on prior antibiotic use: empirical triple therapy plus bismuth (eTTB), containing CLA, levofloxacin (LEVO), or metronidazole (MET), versus tailored therapy (tTTB)[12]. The eradication rates in the tTTB arm were significantly higher than the empiric eTTB arms according to the intention-to-treat (ITT) (89.5% for tTTB *vs*. 80.0%, 81.5%, and 81.5% for eTTB-CLA, -LEVO, and -MET, respectively) and per-protocol (PP) analysis (95.1% for tTTB *vs*. 86.7%, 86.5%, and 87.8%, for eTTB-CLA, -LEVO, and -MET, respectively). The limitations of this study were its monocentric design and doubt concerning antibiotic history accuracy.

The effectiveness and safety of empirical first-line treatment were studied in 2,996 patients from Italian centers participating in the European Registry on H. pylori Management (Hp-EuReg)[13]. Sequential therapy and BQT-three-in-one single capsule (BQT-TSC) were prescribed in 57.5% and 20% of patients, respectively. The eradication rates in the ITT and PP populations were 81.9% and 91.8% for sequential therapy and 87.1% and 96.5% for BQT-TSC, respectively. However, the PPI omeprazole doses varied from 20 to 60 mg.

A RCT from China evaluated whether amoxicillin (AMO) could replace tetracycline (TET) in the BQT as first-line treatment in 404 *H. pylori*-infected individuals[14]. A similar eradication rate was observed in the ITT (81.7% *vs*. 83.2%) and PP analyses (89.0% *vs*. 91.6%), for AMO and TET, respectively. The rate of drug side effects was 29.5% *vs*. 39.7% in the AMO- *vs*. TET-containing BQT but compliance for both regimens was similar (92.0% *vs*. 89.9%).

The treatment of penicillin-allergic patients is challenging in the setting of antibiotic resistance and the lack of availability of TET in some regions has led to the search for alternative antibiotics such as cefuroxime**.** A first-line randomized trial on 450 patients with penicillin allergies compared 14 days of BQT containing either minocycline (100 mg twice daily) and MET (400 mg four times daily) with minocycline (100 mg twice daily) and cefuroxime (500 mg twice daily) or cefuroxime (500 mg twice daily) and MET (400 mg four times daily)[15]. The eradication rates were not significantly different ($p>0.5$) in the ITT (84%, 82.7%, and 82%) and PP (91.7%, 90.9%, and 88.2%) populations, and adverse events and compliance were also similar between groups.

Finally, in a review paper, BQT for at least 10 days has been suggested as first-line or rescue therapy for HIV-infected people[16] because primary (single and multiple) resistance to antibiotics is very frequent in *H. pylori* strains isolated from this group[17].

Second-line therapy: Several studies have demonstrated the effectiveness of BQT as rescue and salvage therapy. In Taiwan, a RCT in patients who failed first-line CLA-containing therapy compared LEVO-containing QT [Esomeprazole (40 mg), AMO (1 g), LEVO (500 mg), and MET (500 mg), all twice daily] for 14 days (L-QT14) (n=280) with BQT [Esomeprazole (40 mg twice daily), bismuth tripotassium dicitrate (300 mg four times daily), TET (500 mg four times daily), and MET (500 mg three times daily)] for 10 days (BQT10) (n=280)[18]. The eradication rates for the ITT population were 88% *vs*. 88%, and for the PP population 90% *vs*. 93%, for L-QT14, and BQT10, respectively. The difference was not statistically different. The frequency of adverse events was higher with BQ10 (77%) than with L-QT14 (48%).

Another multicentric study evaluated the efficacy and safety of BQT as second-line or salvage therapy in 151 patients previously treated with either triple CLA-based (33.5%), sequential (25%), concomitant (7.5%), other (5.2%), or unknown (28.8%) therapy[19]. The eradication rate was 90.1% while compliance was 93%. Sixty-three patients experienced side effects, of which 15 were severe. Side effects and price were the main limitations of the treatment. Previous use of rifabutin and the number of prior treatments negatively impacted the treatment outcome.

Italian centers participating in the Hp-EuReg assessed the effectiveness and the safety of the second-line treatments in 722 patients[13]. The BQT-three-in-one single capsule (BQT-TSC) for 10 days was the most prescribed in 159 patients (46%), followed by triple therapy containing LEV (32%), rifabutin (15%), and sequential (7%). Eradication was achieved in 83.6% of patients

in the ITT analysis and 92.5% in the PP analysis in the BQT group. Among all second-line therapies, BQT-TSC was the only one that provided an eradication rate of >90% in spite of more frequent side effects.

Finally, among new molecules, antofloxacin-based BQT has shown promising results[20-22]. Antofloxacin is a newly developed derivative of levofloxacin. It has demonstrated more potent antimicrobial activity than that of ciprofloxacin, ofloxacin, and sparfloxacin against strains that are quinolone-resistant.

Individualized Treatment

A meta-analysis, including 34 studies and 9,613 patients, evaluated the use of antimicrobial susceptibility testing (tailored therapy) *vs.* empirical locally preferred therapy (ELPT)[23]. The results showed that tailored therapy performed better than ELPT with an odds ratio (OR) of 2.7 and 95% confidence interval (95%CI) of 2.53-2.79. However, for tailored therapy, eradication rates of >90% and 95% were achieved in only 44% and 15% of studies, respectively. Hypotheses that might explain the less potent effectiveness of tailored therapy than expected included: a) host metabolism by cytochrome 2C19 polymorphism: only esomeprazole and rabeprazole are metabolized by another enzymatic route independent of this polymorphism[24]; b) drug pharmacokinetics: among PPIs, esomeprazole and rabeprazole are the most potent for *H. pylori* eradication, providing the best intragastric alkalinization which is important for the optimal efficacy of acid-sensitive antibiotics like CLA and AMO. Esomeprazole (40 mg) and rabeprazole (20 mg) provide a pH >4 for 58.4% and 50.3%, over a period of 24 hours, respectively. A network meta-analysis comparing the efficacy and safety of different dosages of esomeprazole and rabeprazole suggested that both at 40 mg twice daily may be the optimum dosage[25]. Further studies are necessary to confirm these findings.

High Acid Suppression and Dual Therapy

Vonoprazan (VONO) has been tested extensively as dual therapy with AMO, the most acid-sensitive antibiotic with very low resistance. Furthermore, AMO is a time-dependent antibiotic, an argument for increasing the frequency of administration to 3 to 4 times a day. VONO has a rapid onset of action, is capable of achieving therapeutic levels after the first dose and is more potent than PPIs[26].

This P-CAB was studied in various RCTs, including short triple therapy (7 days) versus classical triple therapy; VONO versus PPI; VONO (2 x 20 mg) dual therapy with high and low dose AMO, 7 or 10 days; and VONO with divided doses of AMO four times per day (q.i.d.)[10,27-29].

Nearly all showed the same positive results for eradication rates >85% or >90%, VONO was non-inferior or better than PPI, VONO was better than PPI in CLA-resistant (R), and VONO dual therapy was non-inferior to triple therapy with PPI.

A systemic review and a meta-analysis including 5 and 8 RCTs, respectively, concluded that VONO-based therapies are better than PPI-based therapies, that VONO/AMO dual therapy is non-inferior to VONO-based triple therapy and superior to omeprazole- or lansoprazole-based triple therapy, with fewer side effects[30,31]. Patients with CLA-R strains particularly benefited from VONO-based therapy (dual or triple).

The only European/US RCT first-line trials performed, compared VONO and high dose AMO (3 x 1 g) as dual therapy with two classical triple therapies, one with PPI and one with VONO. These studies confirmed the superiority of VONO therapy in CLA-R strains. However, no difference was observed in CLA-susceptible (S) strains and all eradication rate results were <85%. Resistance in this group was high with CLA-R rates between 20% and 23% and MET-R around 70%. It must be said that, in this study, all medication was taken before meals, including the antibiotics[32].

The comparison of study results provides limited information due to different study designs, different doses and schedules of PPI compared with VONO, and no information on whether the PPIs were started before eradication (VONO achieves full effectiveness within a single day of administration *vs.* PPI which requires 3-5 days), and timing of administration with respect to intake of food was not mentioned[33,34].

HDDT has also been compared with other eradication schemes. A meta-analysis, including 14 RCTs (2 rescue studies and 12 first line) and 5,121 patients, compared HDDT (PPI >2x/day, AMO >2 g for 14 days) with BQT for 10 (n=3) or 14 days. The results suggested that HDDT using PPI is as effective as BQT. HDDT had fewer adverse events, but compliance was similar[9]. However, the studies were very heterogeneous and compared different dosing regimens of dual therapy (PPI and/or AMO 2, 3 to 4 times daily) with different bismuth-based combination treatments.

HDDT for 14 days (esomeprazole (20 mg)/AMO (750 mg) q.i.d.) was also compared with culture-based therapy as rescue therapy. They also examined the results in the context of CYP2C19 polymorphisms in intermediate/poor metabolizers. Eradication rates of 85% were reached in both arms. In intermediate and poor metabolizers, 90% eradication was reached with dual therapy[35].

From these studies, we can conclude that VONO is more effective than PPI in first-line treatment, especially for CLA-R strains. Dual therapy is effective and can be used if high-dose acid suppression is combined with high-dose AMO and the treatment is given >2 times daily. The only study that came from non-Asian countries reported less impressive results.

Probiotics

Review articles from 2022 confirm that adding probiotics increases the eradication rates in many prospective trials. Monotherapy, however, decreases the bacterial load only by 14%[36-38].

In terms of the possible mechanisms of action of probiotics that have been explored in this setting, the following beneficial effects have been mentioned: a decrease in side effects, an increase in IgA levels, strengthening of the mucosal barrier, competitively interacting with *H. pylori* at the microbial adherence sites, enhancing immune responses, and control of antibiotic resistance by suppression of drug-resistant bacterial growth and drug-resistant gene transmission. Conflicting results exist, which could be partly due to the fact that not all mixtures are effective[36-38]. The most promising probiotics appears to be from the Lactobacillus group. In two prospective trials, BQT was compared with or without Lactobacilli (*Lactobacillus rhamnosus* or *Lactobacillus reuteri*). No significant differences were reported (ITT and PP)[39,40]. In another controlled trial, where bismuth therapy was used alone or combined with a mixture of *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* capsules, the combination was superior to BQT alone[41].

Microbiota

Two interesting studies were conducted recently in this area. One RCT in Taiwan compared the outcome of a second-line eradication therapy with either L-QT14 or BQT10[18]. The results showed that the recovery of the microbiota diversity was slower with BQT10 and that the recovery of species abundance was partial after both therapies. A fluctuation in resistome levels, particularly a significant transient increase at week two followed by a return to baseline by week eight after both regimens, was also observed. At the same time, the resistance rates of *Escherichia coli* and *Klebsiella pneumoniae* to LEVO, ampicillin, and various cephalosporins were significantly increased in the L-QT14 group compared with BQT10 at week 2. These resistance levels were restored to pretreatment levels and showed no significant differences at week 8 and 1 year[18]. Another study reported comparable results with a return to baseline composition of the microbiome after weeks or months[42,43].

Taken together, it appears that the alterations in gut microbiota (diversity, composition, and function) induced by *H. pylori* treatment may be transient.

Barriers to Treatment

Barriers to treatment have been assessed in a few articles concerning knowledge and experience of *H. pylori*, compliance, and the affordability of BQT. Among a sample of US individ-

uals who responded to an online questionnaire[44], knowledge of *H. pylori* infection was low, while recognition of difficulties with treatment compliance was high. In another study[45], patient experience with *H. pylori* management was often perceived negatively due to the context of decision-making, health beliefs, barriers experienced, cues to action, and the impact of new knowledge. At the same time, internal cues like symptoms and fear of cancer may modify the patient's perception and acceptance of the treatment. Thus, increasing patient awareness of *H. pylori* infection and increasing provider awareness about patient values, beliefs, anxieties, and expectations surrounding *H. pylori* diagnosis/treatment may improve provider-patient communication. A meta-analysis of nine studies suggested that using technology-enhanced communication initiatives can effectively improve compliance (OR 4.52, 95% CI 2.09-9.77, $p<0.01$) and eradication rate (OR 1.98, 95% CI 1.34-2.93, $p<0.01$) but not the rate of adverse events (OR 0.65, 95% CI 0.27-1.57, $p=0.34$)[46]. Even a simple telephone follow-up by a clinical pharmacist can improve eradication[16,47]. Furthermore, BQT can be limited by price or availability[3,22]. This was demonstrated in a study from Portugal[19].

Factors Affecting Treatment Success

The main factor affecting treatment success is antibiotic resistance[3]. Many studies have focused on the trends in resistance over decades or years showing that CLA is the most affected molecule. A systematic review and meta-analysis including 248 publications revealed that the overall prevalence of CLA resistance worldwide is 27.5% with a significant increase from 2010-2017 (24.3%) to 2018-2021 (32.1%), and the top three resistance areas being in Switzerland (67.2%), Portugal (48.1%), and Israel (46.1%)[48]. Boyanova et al. summarized trends in resistance over the last four years (2018-2022) and confirmed the high variability between countries. AMO resistance, generally rare (0 to <2%), showed a trend toward increasing in Bulgaria, China, Iran, and Vietnam. TET resistance remained very low (<1%), except in Iran (18% in 2017-2019). The good news is that trends are moving toward decreasing or stabilization for CLA, LEV, or MET in France, Russia, Spain, China, Chile, and Columbia[49]. The recent trend of systematic use of antimicrobial susceptibility testing (AST) in the US seems to be cost-effective and it could overcome the escalation in resistance if combined with patient education[50].

The simultaneous presence in a stomach of resistant and susceptible isolates to the same antibiotic, so-called heteroresistance, is one of the factors leading to eradication failure. A meta-analysis including 26 studies on heteroresistance from 2001 to 2022 revealed particularly high levels of heteroresistance to MET (61.1%), CLA (60.1%), and LEVO (46.1%) compared to a previous meta-analysis that reported rates of 14% to MET and 7% to CLA[51,52].

Interesting data from Germany pointed out the high prevalence of resistance and heteroresistance in atrophic regions of the stomach: 81.2% of patients with advanced gastritis (OLGA III-IV) compared to 45.5% of patients with mild gastritis (OLGA I-II)[53].

Owing to the increasing *H. pylori* resistance rate to antimicrobials, coupled with the declining eradication rates in most parts of the world, all the published data emphasize the need for systematic AST to tailor eradication therapy and educate patients.

See Table 1 for the summary of *H. pylori* primary resistance to antibiotics during the last year worldwide in adult patients.

CONCLUSIONS

During the past twelve months, studies on the treatment of *H. pylori* have attempted to address issues of antibiotic resistance and compliance. First, the increasing level of antibiotic resistance that persists globally has led to treatment strategy adaptations including prescribing the most potent first-line and salvage therapy, namely BQT, or individualizing first-line treatment based on using AST when available, which is cost-effective. Novel regimens (i.e., HDDT, VONO-based) have demonstrated great efficacy in Asian studies while in other regions large studies are awaited. Furthermore, their position in the current therapeutic strategy needs clarification. Second, compliance should be improved through good communication that relies on the doctor's awareness of the patient's beliefs and the use of multimedia by

TABLE 1. *HELICOBACTER PYLORI* PRIMARY RESISTANCE TO ANTIBIOTICS.

Author, year	Region	Period	N	AMO (%)	CLA (%)	LEVO (%)	MET (%)	TET (%)
Chey et al[32] 2022	US & Europe	Dec 2019 Jan 2021	907	1.2	22.1	-	69.2	-
Miendje Deyi et al[54] 2023	Belgium	2021	269	0	19	26.8	54	0
Jiang et al[55] 2022	China (Nanjing)	Jan 2018 May 2021	2109	0.76	36	24.2	67.2	0.3
Xu et al[56] 2022	China Northwest	Sep 2018 Dec 2020	150	13	42.7	40.7	84	6
Pei et al[57] 2022	Singapore	2019-2020	387	7.2	13.7	16.9	-	0
Buran et al[58] 2022	Turkey	Apr 2016 May 2018	140	-	43.1	27.6	-	-

Studies published during the last year worldwide and including adult patients. N = number, AMO = Amoxicillin, CLA = Clarithromycin; LEVO = Levofloxacin; MET = metronidazole; TET: tetracycline.

the doctor/pharmacist. Finally, the benefit of adding probiotics to the eradication strategy is not consistently observed and the impact of *H. pylori* treatment in terms of alterations to the microbiota appears to be transient. Future perspectives include finding ways to make BQT regimens universally available and testing of non-drug/natural products and new molecules/regimens.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

We thank S. Field for the editing assistance.

Informed Consent

Not applicable.

Funding

None.

REFERENCES

1. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, Haruma K, Asaka M, Uemura N, Malfertheiner P; faculty members of Kyoto Global Consensus Conference. Kyoto global consensus report on Helicobacter pylori gastritis. Gut 2015; 64: 1353-1367.
2. Graham DY, Lu H, Yamaoka Y. A report card to grade Helicobacter pylori therapy. Helicobacter 2007; 12: 275-278.
3. Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou JM, Schulz C, Gasbarrini A, Hunt RH, Leja M, O'Morain C, Rugge M, Suerbaum S, Tilg H, Sugano K, El-Omar EM; European Helicobacter and Microbiota Study group. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. Gut 2022; 71: 1724-1762.
4. Garcés-Duran R, Kindt S, Kotilea K, François S, Rasschaert G, Smet A, Hauser B, Driessen A, Nkuize M, Burette A, Lamy V, Bontems P, Louis H, Ntounda R, Miendje Deyi VY, Mana F. Belgian consensus for Helicobacter pylori management 2023. Acta Gastroenterol Belg 2023; 86: 74-91.
5. Cho JH, Jin SY. Current guidelines for Helicobacter pylori treatment in East Asia 2022: Differences among China, Japan, and South Korea. World J Clin Cases. 2022; 10: 6349-6359.
6. Aumpan N, Mahachai V, Vilaichone RK. Management of Helicobacter pylori infection. JGH Open 2022; 7: 3-15.

7. Yun JW, Wang C, Yu Y, Xu HM, Gou LZ, Li XL, Yi GR, Lin YM, Han TY, Zhang DK. High-dose amoxicillin-proton pump inhibitor dual therapy as first-line treatment for Helicobacter pylori infection in Northwest China: A prospective, randomised controlled trial. Br J Clin Pharmacol 2023; 89: 232-241.
8. Zhang C, Zhang J, Cheng YJ. High-dose dual therapy versus bismuth-containing quadruple therapy for the treatment of Helicobacter pylori infection: A meta-analysis of randomized controlled trials. Saudi J Gastroenterol 2023; 29: 88-94.
9. Zhou BG, Mei YZ, Zhang M, Jiang X, Li YY, Ding YB. High-dose dual therapy versus bismuth-containing quadruple therapy for Helicobacter pylori eradication: a systematic review and meta-analysis with trial sequential analysis. Therap Adv Gastroenterol 2023; 16: 17562848221147756.
10. Qian HS, Li WJ, Dang YN, Li LR, Xu XB, Yuan L, Zhang WF, Yang Z, Gao X, Zhang M, Li X, Zhang GX. Ten-day vonoprazan-amoxicillin dual therapy as a first-line treatment of Helicobacter pylori infection compared with bismuth-containing quadruple therapy. Am J Gastroenterol 2023; 118: 627-634.
11. Lu L, Wang Y, Ye J, Han Y, Lou G, Li Y, Yan H, Du Q. Quadruple therapy with vonoprazan 20 mg daily as a first-line treatment for Helicobacter pylori infection: A single-center, open-label, noninferiority, randomized controlled trial. Helicobacter 2023; 28: e12940.
12. Song Z, Suo B, Tian X, Ren X, Xue Y, Niu Z, Zhou L. Tailored triple plus bismuth therapy based on previous antibiotic medication history for first-line Helicobacter pylori eradication: A randomized trial. Dig Liver Dis 2023; 55: 601-607.
13. Gatta L, Nyssen OP, Fiorini G, Saracino IM, Pavoni M, Romano M, Gravina AG, Granata L, Pellicano R, Gasbarrini A, Di Leo A, Losurdo G, Franceschi F, Nardone G, Rocco A, Dore MP, Farinati F, Ghisa M, Bellini M, Holton J, Puig I, Vaira D, Borghi C, Mégraud F, O'Morain C, Gisbert JP. Effectiveness of first and second-line empirical treatment in Italy: Results of the European registry on Helicobacter pylori management. United European Gastroenterol J 2023; 11: 103-113.
14. Tian XL, Suo BJ, Zhang H, Lu HP, Li CL, Zhang YX, Ren XL, Yao XY, Zhou LY, Song ZQ. Bismuth, esomeprazole, metronidazole and amoxicillin or tetracycline as a first-line regimen for Helicobacter pylori eradication: A randomized controlled trial. Helicobacter 2023; 28: e12935.
15. Zhang Y, Suo B, Tian X, Zhang H, Lu H, Yao X, Li C, Ren X, Zhou L, Song Z. New regimens as first-line eradication therapy for Helicobacter pylori infection in patients allergic to penicillin: A randomized controlled trial. Helicobacter 2023; 28: e12956.
16. Nkuize M. The best strategy for Helicobacter pylori eradication in people living with HIV in the era of antibiotic resistance. Microb Health Dis 2022; 4: e673.
17. Nkuize M, Vanderpas J, Buset M, Gomez-Galdon M, Delforge M, Miendje-Deyi VY, Muls V, De Wit S. Primary antibiotic resistance of Helicobacter pylori isolates is twofold more frequent in HIV-positive than HIV-negative individuals: A descriptive observational study. Microbiologyopen 2021; 10: e1184.
18. Liou JM, Jiang XT, Chen CC, Luo JC, Bair MJ, Chen PY, Chou CK, Fang YJ, Chen MJ, Chen CC, Lee JY, Yang TH, Yu CC, Kuo CC, Chiu MC, Chen CY, Shun CT, Hu WH, Tsai MH, Hsu YC, Tseng CH, Chang CY, Lin JT, El-Omar EM, Wu MS; Taiwan Gastrointestinal Disease and Helicobacter Consortium. Second-line levofloxacin-based quadruple therapy versus bismuth-based quadruple therapy for Helicobacter pylori eradication and long-term changes to the gut microbiota and antibiotic resistome: a multicentre, open-label, randomised controlled trial. Lancet Gastroenterol Hepatol 2023; 8: 228-241
19. Correia C, Almeida N, Leal C, Branquinho D, Fernandes A, Gravito-Soares E, Calhau C, Bastos I, Vasconcelos H, Figueiredo P. Single-capsule bismuth-based quadruple therapy as a rescue therapy for Helicobacter pylori eradication. Scand J Gastroenterol 2023; 58: 227-231.
20. He XJ, Wang XL, Huang XY, Li DZ, Liu G, Wang W, Li DL. Comparison of 10 and 14 days of antofloxacin-based versus 14 days of clarithromycin-based bismuth quadruple therapy for Helicobacter pylori eradication: A randomized trial. Clin Res Hepatol Gastroenterol 2023; 47: 102052.
21. Ye H, Wu JM, Yang YS, Chen KX, Ji RY. Antibacterial activities of the derivatives-YH54 and YH57 of levofloxacin in vitro. Chin Pharmacol Bull 2002; 18: 112-113.
22. Shih CA, Shie CB, Hsu PI. Update on the first-line treatment of Helicobacter pylori infection in areas with high and low clarithromycin resistances. Therap Adv Gastroenterol 2022; 15: 17562848221138168.
23. Rokkas T, Ekmektzoglou K, Graham DY. Current role of tailored therapy in treating Helicobacter pylori infections. A systematic review, meta-analysis and critical analysis. Helicobacter 2023; 28: e12936.
24. Scott DR, Sachs G, Marcus EA. The role of acid inhibition in Helicobacter pylori eradication. F1000Res 2016; 5: F1000 Faculty Rev-1747.
25. Wang Y, Dai X, Gao C, Yang X. Network meta-analysis of different dosages of esomeprazole and rabeprazole for the treatment of Helicobacter pylori. Helicobacter 2023; 28: e12948.
26. Graham DY, Lu H, Dore MP. Relative potency of proton-pump inhibitors, Helicobacter pylori therapy cure rates, and meaning of double-dose PPI. Helicobacter 2019; 4: e12554.
27. Ang D, Koo SH, Chan YH, Tan TY, Soon GH, Tan CK, Lin KW, Krishnasamy-Balasubramanian JK, Wong YJ, Kumar R, Rajesh R, Tan Y, Ong PJ, Tan YJ, Li JW, Kwek AB, Ang TL. Clinical trial: seven-day vonoprazan- versus 14-day proton pump inhibitor-based triple therapy for first-line Helicobacter pylori eradication. Aliment Pharmacol Ther 2022; 56: 436-449.
28. Hu Y, Xu X, Liu XS, He C, Ouyang YB, Li NS, Xie C, Peng C, Zhu ZH, Xie Y, Shu X, Zhu Y, Graham DY, Lu NH. Fourteen-day vonoprazan and low- or high-dose amoxicillin dual therapy for eradicating Helicobacter pylori infection: A prospective, open-labeled, randomized non-inferiority clinical study. Front Immunol 2023; 13: 1049908.
29. Sue S, Kondo M, Sato T, Oka H, Sanga K, Ogashiwa T, Matsubayashi M, Kaneko H, Irie K, Maeda S. Vonoprazan and high-dose amoxicillin dual therapy for Helicobacter pylori first-line eradication: A single-arm, interventional study. JGH Open 2022; 7: 55-60.
30. Zhang WL, Lin BS, Li YY, Ding YM, Han ZX, Ji R. Efficacy and safety of vonoprazan and amoxicillin dual therapy for Helicobacter pylori eradication: A systematic review and meta-analysis. Digestion 2023; 4: 1-13.

31. Sun Y, Lei Yue L, Hu W. Effectiveness and safety of vonoprazan based regimens compared with those of proton pump inhibitor (PPI)–based regimens as first line agents for Helicobacter pylori: a meta analysis of randomized clinical trials. Eur J Clin Pharmacol 2023; 79: 279-288.
32. Chey WD, Mégraud F, Laine L, López LJ, Hunt BJ, Howden CW. Vonoprazan triple and dual therapy for Helicobacter pylori infection in the US and Europe: randomized clinical trial. Gastroenterology 2022; 163: 608-619.
33. Graham DY, Lu H, Dore MP. Relative potency of proton-pump inhibitors, Helicobacter pylori therapy cure rates, and meaning of double-dose PPI. Helicobacter 2019; 24: e12554.
34. Mulford DJ, Leifke E, Hibberd M, Howden CW. The effect of food on the pharmacokinetics of the potassium-competitive acid blocker vonoprazan. Clin Pharmacol Drug Develop 2022; 11: 278-284.
35. Zhao Z, Zou PY, Su NY, Guo Y, Wang XW, Zhao JT, Mei H, Qing Shi Q, Wang B, Chen DF, Lan CH. High-dose dual therapy versus culture-based susceptibility-guided therapy as a rescue regimen for Helicobacter pylori infection: a randomized controlled trial. Ther Adv Gastroenterol 2022; 15: 1-14.
36. Bai X, Zhu M, He Y, Wang T, Tian D, Shu J. The impacts of probiotics in eradication therapy of Helicobacter pylori. Arch Microbiol 2022; 204: 692.
37. Liang B, Yuan Y, Peng XJ, Liu XL, Hu XK, Xing DM. Current and future perspectives for Helicobacter pylori treatment and management: From antibiotics to probiotics. Front Cell Infect Microbiol 2022; 12: 1042070.
38. Luo Q, Liu N, Pu S, Zhuang Z, Gong H, Zhang D. A review on the research progress on non-pharmacological therapy of Helicobacter pylori. Front Microbiol 2023; 14: 1134254.
39. Marinelli P, Scalese G, Covelli A, Ruffa A, Bedetti G, Bruno G, Severi C. Lactobacillus rhamnosus GG supplementation on eradication rate and dyspepsia in Helicobacter pylori infection treated with three-in-one bismuth quadruple therapy. Front Microbiol 2022; 13: 932331.
40. Mohtasham M, Joukar F, Maroufizadeh S, Mojtahedi K, Asgharnezhad M, Mansour-Ghanaei F. Lactobacillus ruteri compared with placebo as an adjuvant in quadruple therapy for Helicobacter pylori-eradication: A randomized, double-blind, controlled trial. Arab J Gastroenterol 2023; 24: 40-44.
41. Zhou Y, Li T. Effects of quadruple therapy combined with probiotics on Helicobacter pylori-related peptic ulcer. Comput Math Methods Med 2022; 2022: 1221190.
42. Cui MY, Cui ZY, Zhao MQ, Zhang MJ, Jiang QL, Wang JJ, Lu LG, Lu YY. The impact of Helicobacter pylori infection and eradication therapy containing minocycline and metronidazole on intestinal microbiota. BMC Microbiol 2022; 22: 321.
43. Liou JM, Chen CC, Chang CM, Fang YJ, Bair MJ, Chen PY, Chang CY, Hsu YC, Chen MJ, Chen CC, Lee JY, Yang TH, Luo JC, Chen CY, Hsu WF, Chen YN, Wu JY, Lin JT, Lu TP, Chuang EY, El-Omar EM, Wu MS; Taiwan Gastrointestinal Disease and Helicobacter Consortium. 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; 19: 1109-1120.
44. Bailey KS, Brown HE, Lekic V, Pradeep K, Merchant JL, Harris RB. Helicobacter pylori treatment knowledge, access and barriers: A cross-sectional study. Helicobacter 2023; 28: e12954.
45. Shah SC, Bonnet K, Schulte R, Peek RM Jr, Schlundt D, Roumie CL. Helicobacter pylori Management Is Associated with Predominantly Negative Patient Experiences: Results from a Focused Qualitative Analysis. Dig Dis Sci 2022; 67: 4387-4394.
46. Chua BQY, Chong VWS, Teng TZJ, Chia CTW, Aung MO, Shelat VG. Does technology-enhanced communication improve Helicobacter pylori eradication outcomes? - A meta-analysis. Helicobacter 2022; 27: e12890.
47. Weng A, Su X, Yang C, Zheng B, Zheng L, Jian C, Fang J. Telephone follow-up by clinical pharmacists can improve treatment outcomes in patients with peptic ulcers: A prospective randomized study. Medicine (Baltimore) 2022; 101: e31150.
48. Sholeh M, Khoshnood S, Azimi T, Mohamadi J, Kaviar VH, Hashemian M, Karamollahi S, Sadeghifard N, Heidarizadeh H, Heidary M, Saki M. The prevalence of clarithromycin-resistant Helicobacter pylori isolates: a systematic review and meta-analysis. Peer J 2023; 11: e15121.
49. Boyanova L, Hadzhiyski P, Gergova R, Markovska R. Evolution of Helicobacter pylori Resistance to Antibiotics: A Topic of Increasing Concern. Antibiotics 2023; 12: 332.
50. Graham DY. Implications of the paradigm shift in management of Helicobacter pylori infections. Therap Adv Gastroenterol 2023; 16: 17562848231160858.
51. Keikha M, Karbalaei M. Prevalence of antibiotic heteroresistance associated with Helicobacter pylori infection: A systematic review and meta-analysis. Microb Pathog 2022; 170: 105720.
52. Kouhsari E, Sadeghifard N, Khadiv A, Sayadi H, Amiriani T, Ghafourian S, Valadbeigi H, Krutova M. Heteroresistance to clarithromycin and metronidazole in patients with a Helicobacter pylori infection: a systematic review and meta-analysis. Ann Clin Microbiol Antimicrob 2022; 21: 19.
53. Goni E, Tammer I, Schütte K, Thon C, Jechorek D, Mahajan UM, Vasapolli R, Macke L, Aulinger B, Selgrad M, Link A, Malfertheiner P, Schulz C. The influence of gastric atrophy on Helicobacter pylori antibiotics resistance in therapy-naïve patients. Front Microbiol 2022; 1938676.
54. Miendje Deyi VY, Ntounda R, Louis H, Kahegeshe NL, Nkuize M, Burette A, Kotilea K, Gossum MV, Delhaye M, Bontems P. Primary Helicobacter pylori resistance to antimicrobials in the Brussels area in 2021. Diagn Microbiol Infect Dis 2023; 105: 115855.
55. Jiang Z, Qian X, Wang Z, Dong Y, Pan Y, Zhang Z, Wang S. Antibiotic resistance of Helicobacter pylori isolated from patients in Nanjing, China: A cross-section study from 2018 to 2021. Front Cell Infect Microbiol 2022; 12: 970630.
56. Xu H, Yun J, Li R, Ma X, Gou L, Che T, Zhang D. Antibiotics Resistance Prevalence of Helicobacter pylori Strains in Northwest China. Infect Drug Resist 2022; 15: 5519-5528.
57. Pei Y, Ang D, Kwek ABE, Ang TL. The changing profile of Helicobacter pylori primary antibiotic resistance in Singapore over two decades. J Dig Dis. 2022. Epub ahead of print. PMID: 35849105
58. Buran T, Sürücüoğlu S, Kurutepe S, Gazi H. Recent trends in the antibiotic resistance of Helicobacter pylori in patient with dyspepsia. Medicine (Baltimore) 2022; 101: e29801.