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Treatment of refractory *Helicobacter pylori* infection: A new challenge for clinicians

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Patients who have failed two or more attempts to eradicate *Helicobacter pylori* are commonly referred to as refractory. Although the incidence of refractory *Helicobacter pylori* infection is only 10–20%, with the increasing rate of antibiotic resistance in various regions, the treatment of refractory *Helicobacter pylori* infection has gradually become a difficult problem faced by clinicians. When choosing a rescue therapy, the physician must consider numerous factors. A longer treatment duration, higher doses of proton pump inhibitors (PPIs), or the use of potassium-competitive acid blocker (P-CAB) may increase the efficacy of triple therapy or bismuth quadruple therapy. Rescue treatment based on bismuth quadruple therapy usually achieves better results. At the same time, treatment based on drug susceptibility tests or genotypic resistance is recommended where available. Of course, appropriate empiric treatment can also be selected according to local drug resistance, a patient's previous medication history and compliance. It is the best choice if it can improve the success rate of the first treatment and reduce the occurrence of refractory *Helicobacter pylori* infection. This review aims to summarize the articles related to refractory *Helicobacter pylori* in recent years and to explore a better remedial treatment plan for clinicians.

KEYWORDS

refractory *Helicobacter pylori* infection, rescue therapy, antibiotic resistance, antibiotic susceptibility testing, empirical treatments

Introduction

Eradication with *Helicobacter pylori* can reduce the recurrence rate of peptic ulcers, reduce the incidence of *Helicobacter pylori*-associated gastritis, cure patients with mucosa-associated lymphoid tissue lymphoma (MALT), and reduce the risk of gastric cancer (Lee et al., 2016; Malfertheiner et al., 2017; Liou et al., 2019). Currently, the eradication rate of clarithromycin triple therapy, a commonly used first-line treatment regimen, is less than 80% (Malfertheiner et al., 2017; Liou et al., 2020), and quadruple

therapy with levofloxacin and bismuth agents is often selected as the second-line treatment (Liou et al., 2010; Fallone et al., 2016). However, approximately 10–20% of patients still fail treatment (Liou et al., 2011, 2016). Patients who fail two or more treatments are often referred to as patients with refractory *Helicobacter pylori* infection, and treating these patients is still a difficult problem in the clinic (Losurdo et al., 2022a). Therefore, we reviewed the evidence from previous studies to identify more appropriate treatment options.

Status of refractory *Helicobacter pylori* infection

Helicobacter pylori is a major carcinogen that can cause gastric cancer, with 1–3% of *Helicobacter pylori* patients eventually developing stomach cancer (Blaser, 2016). Therefore, the eradication of *Helicobacter pylori* plays a very important role in the prevention and control of gastric cancer. Current first-line treatment regimens have good eradication rates. However, antibiotic resistance rates have risen around the world. The success rate of initial eradication is challenged by multiple resistant bacteria (Savoldi et al., 2018; Lin et al., 2021). Accordingly, the occurrence of refractory *Helicobacter pylori* infection is increasing, becoming a concern that cannot be ignored (Liou et al., 2011, 2016). Therefore, it is necessary to perform in-depth research on refractory *Helicobacter pylori* infection to explore its causes and potential treatment modalities.

The causes of treatment failure

Antibiotic resistance

Antibiotic resistance is currently the main cause of refractory *Helicobacter pylori* infection, and antibiotic resistance is mainly a concern for clarithromycin, metronidazole and levofloxacin (Sugano et al., 2015; Malfetheriner et al., 2017). A report published in 2018 looked at antibiotic resistance in 65 countries and territories around the world. The primary and secondary drug resistance rates of clarithromycin, metronidazole and levofloxacin in other regions of the world were $\geq 15\%$, except for the Americas, Southeast Asia and some parts of Europe. However, due to the large heterogeneity of studies in different regions, the results need to be discussed and analyzed separately by region (Kuo et al., 2017; Savoldi et al., 2018; Hulten et al., 2021; Megraud et al., 2021). In the Asia-Pacific region, the drug resistance of clarithromycin, metronidazole and levofloxacin is also serious, and the drug resistance rate of metronidazole is as high as 44% (Table 1). In China, studies have shown that secondary resistance to clarithromycin, metronidazole and levofloxacin is greater than 50% and even greater than 90% in some areas. Not only has

the prevalence of single-resistant strains increased, but that of double- and multiple-resistant strains has also increased. This has become an important reason for the annual increase in *Helicobacter pylori* eradication failure. In these highly resistant areas, eradication therapies containing clarithromycin, metronidazole and levofloxacin are clearly no longer suitable (Baylina et al., 2019; Li et al., 2020, 2021; Kuo et al., 2021; Resina and Gisbert, 2021). How to choose antibiotics to eradicate *Helicobacter pylori* is a new challenge for clinicians (Savoldi et al., 2018).

Helicobacter pylori-related factors

Helicobacter pylori can increase its resistance to antibiotics through mutation of drug resistance genes. Studies have shown that *Helicobacter pylori* can increase its resistance to metronidazole by upregulating the expression of *hefA*, a key gene of the drug efflux pump, and mutation of *rdxA* (Lee et al., 2018a). Mutations in the A2142G and A2143G loci may lead to increased clarithromycin resistance (Hamza et al., 2018). Other studies have also shown that *gyrA*, 23S rRNA and 16S rRNA mutations in *Helicobacter pylori* are also responsible for other increased resistance (Nezami et al., 2019). In addition, *Helicobacter pylori* can also escape the effects of antibiotics through internalization. Research by Apolinaria Garcia-Cancino revealed that *Helicobacter pylori* can hide in *Candida albicans* under clarithromycin and amoxicillin and avoid their effects (Sánchez-Alonzo et al., 2021). At the same time, another study revealed that *Helicobacter pylori* entered the gastric mucosal tissues of patients in whom *Helicobacter pylori* eradication had failed, mainly in the gastric body (95.2%). Standard clarithromycin-containing triple therapy failed even though the internalized *Helicobacter pylori* was mostly clarithromycin-sensitive, suggesting that cellular internalization of *Helicobacter pylori* may have contributed to the failure (Beer et al., 2021). In addition, *Helicobacter pylori* will activate the chromosomal type I toxin antitoxin system (*AapA1* *IsoA1*) under the oxidative stress, and further express *AapA1* toxin to induce the formation of coccoids, so as to avoid the influence of antibiotics. This process did not destroy the integrity of *Helicobacter pylori* biofilm and did not produce changes in membrane potential, which may be related to the interference of cell elongation/division interference. But the specific mechanism still needs more research and discussion (El Mortaji et al., 2020).

Host factors

Host factors are also important causes of refractory *Helicobacter pylori* infection. Most proton pump inhibitors (PPIs) need to be metabolized through the CYP2C19 pathway, and the metabolic type of CYP2C19 can affect the eradication effect of *Helicobacter pylori* by affecting the metabolism of PPIs. Patients with the fast metabolic type need to increase the

TABLE 1 Antibiotics resistance of *Helicobacter pylori*.

References	Region	Antibiotic resistance		
		Clarithromycin	Metronidazole	Levofloxacin
Megraud et al. (2021)	European	21.4%	38.9%	15.8%
Hulten et al. (2021)	The United States	17.4%	43.9%	57.8%
Kuo et al. (2017)	Asia	17%	44%	18%
Camargo et al. (2014)	Latin America	12%	53%	15%
Savoldi et al. (2018)	Africa	15%	91%	14%

dose of PPIs to maintain a high eradication rate (Fontes et al., 2019). Studies have shown that vitamin D can affect *Helicobacter pylori* colonization and eradication by affecting the autophagy pathway, and the eradication rate of *Helicobacter pylori* is low in patients with vitamin D deficiency (Hu et al., 2019; Shatla et al., 2021). The family environment is also one of the possible causes of eradication failure. *Helicobacter pylori* is easily transmitted among family members. Studies have shown that there is a significant correlation between a history of eradication failure in parents and eradication failure in offspring (Deguchi et al., 2019; Ding et al., 2022). Therefore, emphasis should be placed on the eradication of *Helicobacter pylori* in the home. Older age, prior eradication treatment, and a history of PPI use also increased the risk of eradication failure (Yan et al., 2020). Otherwise, studies have suggested that smoking, non-alcoholic fatty liver disease, and human immunodeficiency virus (HIV) infection may have contributed to the failure of eradication, but more research is needed to confirm these results (Itskoviz et al., 2017; Hanafy and Seleem, 2019; Takara et al., 2019; Nkuize et al., 2021).

Options for rescue treatment: Antibiotic-susceptibility testing or empirical treatment

Antibiotic-susceptibility testing

How should rescue treatment be chosen? We generally have two options: experiential treatment and drug sensitivity-guided regimens, both of which have their own advantages. With the increase in antibiotic resistance rates in various regions of the world, drug sensitivity-guided regimens are increasingly being chosen by more clinicians. The advantage of drug sensitivity guidance is to be able to know the individual's sensitivity to antibiotics and to use sensitive antibiotics specifically to increase the success rate of eradication. Not only is this approach recommended in the guidelines, but many regional studies provide strong evidence to support this view (Lee et al., 2016; Malferteiner et al., 2017; Liou et al., 2019). The study revealed that in patients with more than two eradication failures, the eradication rate of both the triple and quadruple regimens

guided by drug sensitivity reached more than 90%, especially in patients with penicillin allergy. The treatment guided by drug sensitivity achieved almost perfect results, with an eradication rate as high as 99% (Huang et al., 2018; Yu et al., 2019; Luo et al., 2020; Gingold-Belfer et al., 2021; Lee et al., 2021). However, not all hospitals meet the criteria necessary to carry out drug sensitivity testing because it requires great laboratories and professional testing personnel. This is the reason why drug-sensitive guided treatment is not widely available (Gisbert, 2020).

Empirical treatment

Empirical treatment is more acceptable because it does not require additional testing to evaluate drug sensitivities. However, clinicians need to predict the effectiveness of treatment options based on local epidemiology, population resistance, and whether patients have been previously exposed to antibiotics for any reason (Gisbert, 2020). Although empirical therapy cannot provide individualized precision treatment compared with drug sensitivity therapy, it is an alternative in areas lack of medical facilities for laboratory testing. Moreover, there are also more studies showing that empirical treatment of refractory *Helicobacter pylori* infection has a good effect, with an eradication rate of 75–90% (Gisbert, 2020; Ji et al., 2020; Nyssen et al., 2021). Since the main resistant antibiotics are clarithromycin, levofloxacin and metronidazole, more studies are needed to investigate the efficacy of other antibiotics as an empirical treatment option.

Dosage and selection of proton pump inhibitors

Due to polymorphism in the CYP2C19 gene among patients, the dose of PPIs will affect the efficacy of eradication therapy. In clinical trials, 20 mg (low dose) and 40 mg (high dose) are usually used for comparison (Graham et al., 2019). High doses of PPI significantly improved the outcome of standard triple therapy (Katelaris and Katelaris, 2017; Ierardi et al., 2019;

TABLE 2 Eradication rate of tetracycline-containing rescue therapy.

References	Dosing frequency	Duration of therapy	Eradication rate %
Nyssen et al. (2020)	Tetracycline 500 mg qid; metronidazole 500 mg tid; bismuth 240 bid; PPI 20 mg bid	10/14	Over all: 77%; PP:NA ITT:NA
Kim et al. (2022)	Tetracycline 1 g bid; metronidazole 500 mg tid; bismuth 600 mg bid; PPI 20 mg bid	14	Over all: 92.5% PP:NA ITT:NA
Hsu et al. (2021)	Tetracycline 500 mg qid; levofloxacin 500 mg qd; bismuth 300 mg qid; PPI 40 mg bid	10	Over all:NA ITT:89.3% PP:89.1%
Shin et al. (2021)	Tetracycline 500 mg qid; metronidazole 500 mg tid; bismuth 120 mg qid; PPI 20 mg bid	7/10/14	Over all:NA ITT:80.7% PP:93.3%
Losurdo et al. (2022b)	Pylera (Tetracycline/ metronidazole/bismuth) bid; PPI 20 mg bid	10	Over all:NA ITT:84.9% PP:86.1%
De Francesco et al. (2021)	Pylera (Tetracycline/ metronidazole/bismuth) bid; PPI 20 mg bid	–	Over all:NA ITT:90.6% PP:94%
Fiorini et al. (2017)	Pylera (Tetracycline/ metronidazole/bismuth) bid; PPI 20 mg bid	10	Over all:NA ITT:81% PP:87%

Losurdo et al., 2022b). Therefore, a double dose of PPIs is recommended for rescue therapy. In addition, the selection of new-generation PPIs to replace existing drugs is also an option to improve treatment effectiveness. Such as Rabeprazole, Esomperazole, they are less affected by CYP2C19 polymorphisms. A Japanese study showed that a 7-day triple therapy based on vonoprazan proved superior to lansoprazole-based triple therapy for 7 days. This is especially true in patients infected with clarithromycin-resistant strains (Murakami et al., 2016). Another Japanese study showed that the annual eradication rates of second-line therapy between 2013 and 2018 were 90, 82.6, 88.8, 87.5, 91.8, and 90.1%, respectively. The use of vanorazan was an independent factor in the success of second-line treatment (Mori et al., 2019).

New antibiotics

It is very important to optimize the treatment plan and choose more efficient antibiotics for rescue treatment. We need to find some antibiotics that are more effective as rescue treatment and in how they are administered. In past reports of rescue treatment, tetracycline and rifabutin were assessed in many studies, and both achieved good results. In recent years, many studies have reported the role of tetracycline in remedial therapy. Two studies from Taiwan, China, compared the efficacy of tetracycline regimens in rescue therapy. The first study compared the 10-day TL regimen (tetracycline plus levofloxacin bismuth quadruple regimen) with the AL triple regimen (amoxicillin plus levofloxacin triple regimen) in

remedial therapy. The eradication rate in the TL group was 98% higher than that in the AL group (69.2%) (Hsu et al., 2017). Another study compared the 10-day TL regimen with the AL regimen as a remedial treatment for *Helicobacter pylori*. The eradication rate of 89.3% in the TL group was only 69.6% in the AL group, and the eradication rate of levofloxacin-resistant strains in the TL group was also higher than that in the AL group (Hsu et al., 2021). The 10–14-day regimen was associated with a higher eradication rate than the 7-day regimen with tetracycline (Shin et al., 2021). Studies have shown that the minimum inhibitory concentration (MIC) of tetracycline can achieve a better effect as long as it reaches 0.094 mg/L (Hsieh et al., 2020). At the same time, the Korean study compared the eradication rate of the tetracycline regimen with different dosing methods, and the dosage of 2,000 mg tetracycline per day, whether 500 mg qid or 1,000 mg bid, had a good eradication effect (Kim et al., 2022). Otherwise, many studies have reported that the Pylera three-in-one capsule combined with PPI achieved a good curative effect in remedial treatment.

In addition to tetracycline, many studies have reported the role of other antibiotics in rescue treatment (Table 2). A meta-analysis showed that quinolones are the best second-line treatment option in Western countries (Yeo et al., 2019). Antofloxacin is a new quinolone drug. A Chinese study compared antofloxacin with a 14-day triple therapy with levofloxacin. The eradication rate of the levofloxacin group was higher than that of the antofloxacin group (87.6 vs. 68.5%) when the levofloxacin resistance rate was over 40%. Antofloxacin has both good efficacy and safety (Mori et al., 2020; He et al., 2022). Second, previous reports have

TABLE 3 Eradication rate of rifabutin-containing rescue therapy.

References	Dosing frequency	Duration of therapy	Eradication rate %
Kuo et al. (2020)	Rifabutin 150 mg bid; amoxicillin 1 g bid; PPI 40 mg bid	10	Over all:79.5% ITT:NA PP:NA
Fiorini et al. (2018)	Rifabutin 150 mg bid; amoxicillin 1 g bid; PPI 40 mg bid	12	Over all:NA ITT:82.9% PP:88.7%
Hirata et al. (2020)	Rifabutin 150 mg bid; amoxicillin 750 mg bid; PPI 20 mg bid	10	Over all:NA ITT:100% PP:100%
Saracino et al. (2020)	Rifabutin 150 mg bid; amoxicillin 1 g bid; PPI 40 mg bid	12	Over all:NA ITT:51.9% PP:61.9%
Ribaldone et al. (2019)	Rifabutin 150 mg bid; amoxicillin 1 g bid; PPI 20 mg bid	14	Over all:NA ITT:71.5% PP:72.7%

demonstrated that furazolidone has a good eradication effect in first-line treatment. It also had a significant effect on rescue therapy in patients who had failed previous clarithromycin or levofloxacin quadruple therapy. The 14-day quadruple furazolidone regimen achieved 90% eradication in patients with clarithromycin and levofloxacin resistance rates of more than 40% (Kong et al., 2020; Resina and Gisbert, 2021). However, some countries do not allow the use of furazolidone for safety reasons, so more studies are needed to explore the safety of furazolidone use. Otherwise, a large number of studies have reported the efficacy of rifabutin in rescue therapy (Ierardi et al., 2014; Nyssen et al., 2022; Table 3). Studies have shown that rifabutin triple therapy has an obvious antibacterial effect on multiple drug-resistant *Helicobacter pylori*, and the eradication rate can reach more than 80% (Fiorini et al., 2018; Siavoshi et al., 2018; Ribaldone et al., 2019; Kuo et al., 2020). At present, the main rescue therapy contains rifabutin, amoxicillin and PPIs. More studies are needed to compare the efficacy of other antibiotics combined with rifabutin in rescue therapy. In conclusion, in the absence of drug sensitivity guidance, clinicians should consider the use of the above antibiotics to address refractory *Helicobacter pylori* infection.

Duration of therapy

Insufficient time is also an important factor in eradication failure. A treatment duration extended by 14 days with triple therapy was superior to the same regimen of 7 or 10 days with first-line therapy (Yuan et al., 2013). Therefore, various guidelines recommend a duration of 14 days for first-line treatment, unless shorter durations are locally proven to be non-inferior and yield reliably high success rates (Fallone et al., 2016; Liou et al., 2018). Among second- or third-line treatments, the

cure rates of levofloxacin triple therapy at 7, 10, and 14 days were 58.3, 68.2, and 93.3%, respectively (Noh et al., 2016). However, the benefit of extending treatment to 14 days was minimal in susceptible strains (Liou et al., 2018). In strains resistant to clarithromycin, the eradication rate can be increased due to the effect of PPI-amoxicillin dual therapy. In summary, we recommend 14 days of treatment for refractory *Helicobacter pylori*.

Other treatments

Does the addition of adjunctive agents on a triple or quadruple basis increase the efficacy of remedial therapy? In recent years, many studies have combined probiotics, biological extracts, traditional Chinese medicine and other adjuvant drugs with traditional therapy to increase the eradication effect of rescue treatment. A study from China treated patients with refractory *Helicobacter pylori* with *Lactobacillus* for 2 weeks followed by 10-day quadruplex therapy with tetracycline and furazolidone as rescue treatment. The overall eradication rate was 92% in the intention-to-treat (ITT) analysis and 91.8% in the Per-Protocol (PP) analysis, with fewer adverse reactions and a good safety profile (Liu et al., 2020). The Iranian study also found that in patients in whom eradication had failed, quadruple therapy containing *Lactobacillus* was more effective as a rescue therapy than non-probiotic treatment (Karbalaee and Keikha, 2021). In addition, there are also studies on the role of traditional Chinese medicine as an adjuvant therapy in remedial therapy. A Chinese meta-analysis revealed that integrated traditional Chinese and Western medicine treatment had a higher eradication rate and fewer adverse reactions than Western medicine alone (OR 2.21, 95% CI: 1.74, 2.81) (Zhong et al., 2022). Other studies demonstrated that the combination of berberine or WUZHUYUTANG combined with the antibiotic

bismuth can improve the eradication effect of rescue treatment (Nagata et al., 2018; Zhang et al., 2020). However, these studies were only conducted in China, and more Western studies are needed to confirm whether this treatment is suitable for patients in other parts of the world. It was also found that the extracts of lime could inhibit the growth and urease activity of clarithromycin, metronidazole and levofloxacin triple-drug-resistant strains; therefore, these extracts could have therapeutic potential (Lee et al., 2018b).

Conclusion

In conclusion, in the remedial treatment of refractory *Helicobacter pylori* infection, it is recommended to use a higher dose of PPI quadruple therapy for 14 days, and vonoprazan is a better choice when necessary. When conditions permit, it is recommended to use drug sensitivity tests or genotype resistance guidance therapy. Of course, taking into account the economy, compliance and feasibility of patients, appropriate empiric treatment can be an acceptable alternative to drug sensitivity treatment based on previous drug use and prevailing drug resistance in the region. Tetracycline, furazolidone, rifabutin, or a new generation of quinolone-based therapy or bismuth quadruple therapy may be a good option. Further large randomized studies are needed to determine the best treatment for refractory *Helicobacter pylori* infection.

References

- Baylina, M., Muñoz, N., Sánchez-Delgado, J., López-Góngora, S., Calvet, X., and Puig, I. (2019). Systematic review: Would susceptibility-guided treatment achieve acceptable cure rates for second-line *Helicobacter pylori* therapy as currently practiced? *Helicobacter* 24:e12584. doi: 10.1111/hel.12584
- Beer, A., Hudler, H., Hader, M., Kundi, M., Hudler, S., Täuber, V., et al. (2021). Apparent intracellular *Helicobacter pylori* detected by immunohistochemistry: The missing link in eradication failure. *Clin. Infect. Dis.* 73, e1719–e1726. doi: 10.1093/cid/ciaa839
- Blaser, M. J. (2016). Antibiotic use and its consequences for the normal microbiome. *Science* 352, 544–545.
- Camargo, M. C., García, A., Riquelme, A., Otero, W., Camargo, C. A., Hernandez-García, T., et al. (2014). The problem of *Helicobacter pylori* resistance to antibiotics: A systematic review in Latin America. *Am. J. Gastroenterol.* 109, 485–495.
- De Francesco, V., Zullo, A., Gatta, L., Manta, R., Pavoni, M., Saracino, I. M., et al. (2021). Rescue therapies for *H. pylori* infection in Italy. *Antibiotics* 10:525.
- Deguchi, H., Yamazaki, H., Yamamoto, Y., and Fukuhara, S. (2019). Association between parental history of *Helicobacter pylori* treatment failure and treatment failure in the offspring. *J. Gastroenterol. Hepatol.* 34, 2112–2117.
- Ding, S. Z., Du, Y. Q., Lu, H., Wang, W. H., Cheng, H., Chen, S. Y., et al. (2022). Chinese consensus report on family-based *Helicobacter pylori* infection control and management (2021 Edition). *Gut* 71, 238–253. doi: 10.1136/gutjnl-2021-325630
- El Mortaji, L., Tejada-Arranz, A., Rifflet, A., Boneca, I. G., Pehau-Arnaudet, G., Radicella, J. P., et al. (2020). A peptide of a type I toxin-antitoxin system induces

Author contributions

CH: give the idea. XX: write the article. YZ: offer a suggestion. All authors contributed to the article and approved the submitted version.

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Helicobacter pylori morphological transformation from spiral shape to coccoids. *Proc. Natl. Acad. Sci. U.S.A.* 117, 31398–31409. doi: 10.1073/pnas.2016195117

Fallone, C. A., Chiba, N., van Zanten, S. V., Fischbach, L., Gisbert, J. P., Hunt, R. H., et al. (2016). The Toronto consensus for the treatment of *Helicobacter pylori* infection in adults. *Gastroenterology* 151, 51–69.e14.

Fiorini, G., Saracino, I. M., Zullo, A., Gatta, L., Pavoni, M., and Vaira, D. (2017). Rescue therapy with bismuth quadruple regimen in patients with *Helicobacter pylori* -resistant strains. *Helicobacter* 22, 113–130. doi: 10.1111/hel.12448

Fiorini, G., Zullo, A., Vakil, N., Saracino, I. M., Ricci, C., Castelli, V., et al. (2018). Rifabutin triple therapy is effective in patients with multidrug-resistant strains of *Helicobacter pylori*. *J. Clin. Gastroenterol.* 52, 137–140. doi: 10.1097/MCG.0000000000000540

Fontes, L. E. S., Martimbiano, A. L. C., Zanin, C., and Riera, R. (2019). N-acetylcysteine as an adjuvant therapy for *Helicobacter pylori* eradication. *Cochrane Database Syst. Rev.* 2:CD012357.

Gingold-Belfer, R., Niv, Y., Schmilovitz-Weiss, H., Levi, Z., and Boltin, D. (2021). Susceptibility-guided versus empirical treatment for *Helicobacter pylori* infection: A systematic review and meta-analysis. *J. Gastroenterol. Hepatol.* 36, 2649–2658.

Gisbert, J. P. (2020). Empirical or susceptibility-guided treatment for *Helicobacter pylori* infection? A comprehensive review. *Ther. Adv. Gastroenterol.* 13:1756284820968736.

Graham, D. Y., Lu, H., and Dore, M. P. (2019). Relative potency of proton-pump inhibitors, *Helicobacter pylori* therapy cure rates, and meaning of double-dose PPI. *Helicobacter* 24:e12554. doi: 10.1111/hel.12554

- Hamza, D., Elhelw, R., Elhariri, M., and Ragab, E. (2018). Genotyping and antimicrobial resistance patterns of *Helicobacter pylori* in human and dogs associated with A2142G and A2143G point mutations in clarithromycin resistance. *Microb. Pathog.* 123, 330–338. doi: 10.1016/j.micpath.2018.07.016
- Hanafy, A. S., and Selem, W. M. (2019). Refractory *Helicobacter pylori* gastritis: The hidden predictors of resistance. *J. Glob. Antimicrob. Resist.* 19, 194–200. doi: 10.1016/j.jgar.2019.05.015
- He, X. J., Zeng, X. P., Jiang, C. S., Liu, G., Li, D. Z., and Wang, W. (2022). Efficacy and safety of antofloxacin-based triple therapy for *Helicobacter pylori* eradication failure in China. *Dig. Dis. Sci.* 67, 208–215. doi: 10.1007/s10620-021-06856-z
- Hirata, Y., Yamada, A., Niikura, R., Shichijo, S., Hayakawa, Y., and Koike, K. (2020). Efficacy and safety of a new rifabutin-based triple therapy with vonoprazan for refractory *Helicobacter pylori* infection: A prospective single-arm study. *Helicobacter* 25:e12719. doi: 10.1111/hel.12719
- Hsieh, M. T., Chang, W. L., Wu, C. T., Yang, H. B., Kuo, H. Y., Lin, M. Y., et al. (2020). Optimizing the MIC breakpoints of amoxicillin and tetracycline for antibiotic selection in the rescue therapy of *H. pylori* with bismuth quadruple regimen. *Eur. J. Clin. Pharmacol.* 76, 1581–1589. doi: 10.1007/s00228-020-02938-5
- Hsu, P. I., Tsai, F. W., Kao, S. S., Hsu, W. H., Cheng, J. S., Peng, N. J., et al. (2017). Ten-day quadruple therapy comprising proton pump inhibitor, bismuth, tetracycline, and levofloxacin is more effective than standard levofloxacin triple therapy in the second-line treatment of *Helicobacter pylori* infection: A randomized controlled trial. *Am. J. Gastroenterol.* 112, 1374–1381. doi: 10.1038/ajg.2017.195
- Hsu, P. I., Tsay, F. W., Kao, J. Y., Peng, N. J., Chen, Y. H., Tang, S. Y., et al. (2021). Tetracycline-levofloxacin versus amoxicillin-levofloxacin quadruple therapies in the second-line treatment of *Helicobacter pylori* infection. *Helicobacter* 26:e12840. doi: 10.1111/hel.12840
- Hu, W., Zhang, L., Li, M. X., Shen, J., Liu, X. D., Xiao, Z. G., et al. (2019). Vitamin D3 activates the autolysosomal degradation function against *Helicobacter pylori* through the PDIA3 receptor in gastric epithelial cells. *Autophagy* 15, 707–725. doi: 10.1080/15548627.2018.1557835
- Huang, H. T., Wang, H. M., Yang, S. C., Tai, W. C., Liang, C. M., Wu, K. L., et al. (2018). Efficacy of a 14-day quadruple-therapy regimen for third-line *Helicobacter pylori* eradication. *Infect. Drug Resist.* 11, 2073–2080. doi: 10.2147/IDR.S185511
- Hulten, K. G., Lamberth, L. B., Kalfus, I. N., and Graham, D. Y. (2021). National and regional US antibiotic resistance to *Helicobacter pylori*: Lessons from a clinical trial. *Gastroenterology* 161, 342–344e341. doi: 10.1053/j.gastro.2021.03.045
- Ierardi, E., Giangaspero, A., Losurdo, G., Giorgio, F., Amoroso, A., De Francesco, V., et al. (2014). Quadruple rescue therapy after first and second line failure for *Helicobacter pylori* treatment: Comparison between two tetracycline-based regimens. *J. Gastrointest. Liver Dis.* 23, 367–370. doi: 10.15403/jgld.2014.1121.234.qrth
- Ierardi, E., Losurdo, G., Fortezza, R. F., Principi, M., Barone, M., and Leo, A. D. (2019). Optimizing proton pump inhibitors in *Helicobacter pylori* treatment: Old and new tricks to improve effectiveness. *World J. Gastroenterol.* 25, 5097–5104. doi: 10.3748/wjg.v25.i34.5097
- Itskoviz, D., Boltin, D., Leibovitz, H., Tsadok Perets, T., Comaneshter, D., Cohen, A., et al. (2017). Smoking increases the likelihood of *Helicobacter pylori* treatment failure. *Dig. Liver Dis.* 49, 764–768. doi: 10.1016/j.dld.2017.03.010
- Ji, C. R., Liu, J., Li, Y. Y., Qiao, C., Qu, J. Y., Hu, J. N., et al. (2020). Susceptibility-guided quadruple therapy is not superior to medication history-guided therapy for the rescue treatment of *Helicobacter pylori* infection: A randomized controlled trial. *J. Dig. Dis.* 21, 549–557.
- Karbalaei, M., and Keikha, M. (2021). Rescue effects of *Lactobacillus*-containing bismuth regimens after *Helicobacter pylori* treatment failure. *New Microbes New Infect.* 42:100904. doi: 10.1016/j.nmni.2021.100904
- Katellaris, P. H., and Katellaris, A. L. (2017). A prospective evaluation of levofloxacin-based triple therapy for refractory *Helicobacter pylori* infection in Australia. *Intern. Med. J.* 47, 761–766. doi: 10.1111/imj.13432
- Kim, J., Gong, E. J., Seo, M., Seo, H. I., Park, J. K., Lee, S. J., et al. (2022). Efficacy of twice a day bismuth quadruple therapy for second-line treatment of *Helicobacter pylori* infection. *J. Pers. Med.* 12:56.
- Kong, S., Huang, K., Wang, J., Wang, X., Yang, N., Dong, Y., et al. (2020). Efficacy of tailored second-line therapy of *Helicobacter pylori* eradication in patients with clarithromycin-based treatment failure: A multicenter prospective study. *Gut Pathog.* 12:39. doi: 10.1186/s13099-020-00378-1
- Kuo, C. J., Lee, C. H., Chang, M. L., Lin, C. Y., Lin, W. R., Su, M. Y., et al. (2021). Multidrug resistance: The clinical dilemma of refractory *Helicobacter pylori* infection. *J. Microbiol. Immunol. Infect.* 54, 1184–1187. doi: 10.1016/j.jmii.2021.03.006
- Kuo, C. J., Lin, C. Y., Le, P. H., Chang, P. Y., Lai, C. H., Lin, W. R., et al. (2020). Rescue therapy with rifabutin regimen for refractory *Helicobacter pylori* infection with dual drug-resistant strains. *BMC Gastroenterol.* 20:218. doi: 10.1186/s12876-020-01370-4
- Kuo, Y. T., Liou, J. M., El-Omar, E. M., Wu, J. Y., Leow, A. H. R., Goh, K. L., et al. (2017). Primary antibiotic resistance in *Helicobacter pylori* in the Asia-Pacific region: A systematic review and meta-analysis. *Lancet Gastroenterol. Hepatol.* 2, 707–715.
- Lee, J. W., Kim, N., Nam, R. H., Jang, J. Y., Choi, Y., and Lee, D. H. (2021). Favorable outcomes of rescue second- or third-line culture-based *Helicobacter pylori* eradication treatment in areas of high antimicrobial resistance. *Helicobacter* 26:e12844.
- Lee, S. M., Kim, N., Kwon, Y. H., Nam, R. H., Kim, J. M., Park, J. Y., et al. (2018a). rdxA, frxA, and efflux pump in metronidazole-resistant *Helicobacter pylori*: Their relation to clinical outcomes. *J. Gastroenterol. Hepatol.* 33, 681–688. doi: 10.1111/jgh.13906
- Lee, S. M., Park, S. Y., Kim, M. J., Cho, E. A., Jun, C. H., Park, C. H., et al. (2018b). Key lime (*Citrus aurantifolia*) inhibits the growth of triple drug resistant *Helicobacter pylori*. *Gut Pathog.* 10:16. doi: 10.1186/s13099-018-0244-y
- Lee, Y. C., Chiang, T. H., Chou, C. K., Tu, Y. K., Liao, W. C., Wu, M. S., et al. (2016). Association between *Helicobacter pylori* eradication and gastric cancer incidence: A systematic review and meta-analysis. *Gastroenterology* 150, 1113–1124.e5.
- Li, J., Deng, J., Wang, Z., Li, H., and Wan, C. (2020). Antibiotic resistance of *Helicobacter pylori* strains isolated from pediatric patients in Southwest China. *Front. Microbiol.* 11:621791. doi: 10.3389/fmicb.2020.621791
- Li, S. Y., Li, J., Dong, X. H., Teng, G. G., Zhang, W., Cheng, H., et al. (2021). The effect of previous eradication failure on antibiotic resistance of *Helicobacter pylori*: A retrospective study over 8 years in Beijing. *Helicobacter* 26:e12804. doi: 10.1111/hel.12804
- Lin, Y., Zheng, Y., Wang, H. L., and Wu, J. (2021). Global patterns and trends in gastric cancer incidence rates (1988–2012) and predictions to 2030. *Gastroenterology* 161, 116–127.e8. doi: 10.1053/j.gastro.2021.03.023
- Liou, J. M., Bair, M. J., Chen, C. C., Lee, Y. C., Chen, M. J., Chen, C. C., et al. (2016). Levofloxacin sequential therapy vs levofloxacin triple therapy in the second-line treatment of *Helicobacter pylori*: A randomized trial. *Am. J. Gastroenterol.* 111, 381–387. doi: 10.1038/ajg.2015.439
- Liou, J. M., Chen, C. C., Chen, M. J., Chang, C. Y., Fang, Y. J., Lee, J. Y., et al. (2011). Empirical modified sequential therapy containing levofloxacin and high-dose esomeprazole in second-line therapy for *Helicobacter pylori* infection: A multicentre clinical trial. *J. Antimicrob. Chemother.* 66, 1847–1852. doi: 10.1093/jac/dkr217
- Liou, J. M., Chen, P. Y., Kuo, Y. T., and Wu, M. S. (2018). Toward population specific and personalized treatment of *Helicobacter pylori* infection. *J. Biomed. Sci.* 25:70. doi: 10.1186/s12929-018-0471-z
- Liou, J. M., Lee, Y. C., El-Omar, E. M., and Wu, M. S. (2019). Efficacy and long-term safety of *H. pylori* eradication for gastric cancer prevention. *Cancers* 11:593.
- Liou, J. M., Lin, J. T., Chang, C. Y., Chen, M. J., Cheng, T. Y., Lee, Y. C., et al. (2010). Levofloxacin-based and clarithromycin-based triple therapies as first-line and second-line treatments for *Helicobacter pylori* infection: A randomised comparative trial with crossover design. *Gut* 59, 572–578. doi: 10.1136/gut.2009.198309
- Liou, J. M., Malfertheiner, P., Lee, Y. C., Sheu, B. S., Sugano, K., Cheng, H. C., et al. (2020). Screening and eradication of *Helicobacter pylori* for gastric cancer prevention: The Taipei global consensus. *Gut* 69, 2093–2112. doi: 10.1136/gutjnl-2020-322368
- Liu, A., Wang, Y., Song, Y., and Du, Y. (2020). Treatment with compound *Lactobacillus acidophilus* followed by a tetracycline- and furazolidone-containing quadruple regimen as a rescue therapy for *Helicobacter pylori* infection. *Saudi J. Gastroenterol.* 26, 78–83. doi: 10.4103/sjg.SJG_589_19
- Losurdo, G., D'Abramo, F. S., Piazzolla, M., Rima, R., Continisio, A., Pricci, M., et al. (2022a). Second line therapy for *Helicobacter pylori* eradication: State of art. *Mini Rev. Med. Chem.* 22, 2430–2437.
- Losurdo, G., Lacavalla, I., Russo, F., Riezzo, G., Brescia, I. V., Rendina, M., et al. (2022b). Empiric “Three-in-One” bismuth quadruple therapy for second-line *Helicobacter pylori* eradication: An intervention study in Southern Italy. *Antibiotics* 11:78. doi: 10.3390/antibiotics11010078
- Luo, L., Huang, Y., Liang, X., Ji, Y., Yu, L., and Lu, H. (2020). Susceptibility-guided therapy for *Helicobacter pylori*-infected penicillin-allergic patients: A prospective clinical trial of first-line and rescue therapies. *Helicobacter* 25:e12699. doi: 10.1111/hel.12699

- Malfertheiner, P., Megraud, F., O'Morain, C. A., Gisbert, J. P., Kuipers, E. J., Axon, A. T., et al. (2017). Management of *Helicobacter pylori* infection—the Maastricht V/Florence consensus report. *Gut* 66, 6–30. doi: 10.1136/gutjnl-2016-312288
- Megraud, F., Bruyndonckx, R., Coenen, S., Wittkop, L., Huang, T. D., Hoebeke, M., et al. (2021). *Helicobacter pylori* resistance to antibiotics in Europe in 2018 and its relationship to antibiotic consumption in the community. *Gut* 70, 1815–1822. doi: 10.1136/gutjnl-2021-324032
- Mori, H., Suzuki, H., Matsuzaki, J., Masaoka, T., and Kanai, T. (2020). 10-year trends in *Helicobacter pylori* eradication rates by sitafloxacin-based third-line rescue therapy. *Digestion* 101, 644–650. doi: 10.1159/000501610
- Mori, H., Suzuki, H., Omata, F., Masaoka, T., Asaoka, D., Kawakami, K., et al. (2019). Current status of first- and second-line *Helicobacter pylori* eradication therapy in the metropolitan area: A multicenter study with a large number of patients. *Ther. Adv. Gastroenterol.* 12:1756284819858511. doi: 10.1177/1756284819858511
- Murakami, K., Sakurai, Y., Shiino, M., Funao, N., Nishimura, A., and Asaka, M. (2016). 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* 65, 1439–1446. doi: 10.1136/gutjnl-2015-311304
- Nagata, Y., Nagasaka, K., Koyama, S., Murase, M., Saito, M., Yazaki, T., et al. (2018). Successful eradication of *Helicobacter pylori* with a herbal medicine, goshuyuto (Wu Zhu Yu Tang), plus rabeprazole after failure of triplet therapy with Vonoprazan: A report of three cases. *J. Dig. Dis.* 19, 439–442. doi: 10.1111/1751-2980.12537
- Nezami, B. G., Jani, M., Alouani, D., Rhoads, D. D., and Sadri, N. (2019). *Helicobacter pylori* mutations detected by next-generation sequencing in formalin-fixed, paraffin-embedded gastric biopsy specimens are associated with treatment failure. *J. Clin. Microbiol.* 57:e01834-18. doi: 10.1128/JCM.01834-18
- Nkuize, M., Vanderpas, J., Buset, M., Delforge, M., Cadière, G. B., and De Wit, S. (2021). Failure to eradicate *Helicobacter pylori* infection is more frequent among HIV-positive patients. *HIV Med.* 22, 547–556. doi: 10.1111/hiv.13083
- Noh, H. M., Hong, S. J., Han, J. P., Park, K. W., Lee, Y. N., Lee, T. H., et al. (2016). Eradication rate by duration of third-line rescue therapy with levofloxacin after *Helicobacter pylori* treatment failure in clinical practice. *Korean J. Gastroenterol.* 68, 260–264. doi: 10.4166/kjg.2016.68.5.260
- Nyssen, O. P., Perez-Aisa, A., Rodrigo, L., Castro, M., Mata Romero, P., Ortuño, J., et al. (2020). Bismuth quadruple regimen with tetracycline or doxycycline versus three-in-one single capsule as third-line rescue therapy for *Helicobacter pylori* infection: Spanish data of the European *Helicobacter pylori* registry (Hp-EuReg). *Helicobacter* 25:e12722.
- Nyssen, O. P., Vaira, D., Pérez Aísa, Á., Rodrigo, L., Castro-Fernandez, M., Jonaitis, L., et al. (2021). Empirical second-line therapy in 5000 patients of the European registry on *Helicobacter pylori* management (Hp-EuReg). *Clin. Gastroenterol. Hepatol.* 20, 2243–2257. doi: 10.1016/j.cgh.2021.12.025
- Nyssen, O. P., Vaira, D., Saracino, I. M., Fiorini, G., Caldas, M., Bujanda, L., et al. (2022). Experience with rifabutin-containing therapy in 500 patients from the European registry on *Helicobacter pylori* management (Hp-EuReg). *J. Clin. Med.* 11:1658. doi: 10.3390/jcm11061658
- Resina, E., and Gisbert, J. P. (2021). Rescue therapy with furazolidone in patients with at least five eradication treatment failures and multi-resistant *H. pylori* infection. *Antibiotics* 10:1028. doi: 10.3390/antibiotics10091028
- Ribaldone, D. G., Fagoonee, S., Astegiano, M., Durazzo, M., Morgando, A., Sprujevnik, T., et al. (2019). Rifabutin-based rescue therapy for *Helicobacter pylori* eradication: A long-term prospective study in a large cohort of difficult-to-treat patients. *J. Clin. Med.* 8:199. doi: 10.3390/jcm8020199
- Sánchez-Alonzo, K., Belmar, L., Parra-Sepúlveda, C., Bernasconi, H., Campos, V. L., Smith, C. T., et al. (2021). Antibiotics as a stressing factor triggering the harboring of *Helicobacter pylori* J99 within *Candida albicans* ATCC10231. *Pathogens* 10:382. doi: 10.3390/pathogens10030382
- Saracino, I. M., Pavoni, M., Zullo, A., Fiorini, G., Saccomanno, L., Lazzarotto, T., et al. (2020). Rifabutin-based triple therapy or bismuth-based quadruple regimen as rescue therapies for *Helicobacter pylori* infection. *Eur. J. Intern. Med.* 81, 50–53.
- Savoldi, A., Carrara, E., Graham, D. Y., Conti, M., and Tacconelli, E. (2018). Prevalence of antibiotic resistance in *Helicobacter pylori*: A systematic review and meta-analysis in World Health Organization regions. *Gastroenterology* 155, 1372–1382.e17. doi: 10.1053/j.gastro.2018.07.007
- Shatla, M. M., Faisal, A. S., and El-Readi, M. Z. (2021). Is vitamin D deficiency a risk factor for *Helicobacter pylori* eradication failure? *Clin. Lab.* 67. doi: 10.7754/Clin.Lab.2020.200118
- Shin, K., Cho, M. J., Oh, J. H., and Lim, C. H. (2021). Second-line bismuth-containing quadruple therapy for *Helicobacter pylori* infection: A 12-year study of annual eradication rates. *J. Clin. Med.* 10:3273. doi: 10.3390/jcm10153273
- Sivavoshi, F., Saniee, P., and Malekzadeh, R. (2018). Effective antimicrobial activity of rifabutin against multidrug-resistant *Helicobacter pylori*. *Helicobacter* 23:e12531. doi: 10.1111/hel.12531
- Sugano, K., Tack, J., Kuipers, E. J., Graham, D. Y., El-Omar, E. M., Miura, S., et al. (2015). Kyoto global consensus report on *Helicobacter pylori* gastritis. *Gut* 64, 1353–1367.
- Takara, Y., Endo, H., Nakano, R., Kawachi, K., Hidaka, H., Matsunaga, T., et al. (2019). Smoking and drinking did not increase the failure of therapeutic *Helicobacter pylori* eradication by vonoprazan, clarithromycin, and amoxicillin. *Digestion* 99, 172–178.
- Yan, T. L., Gao, J. G., Wang, J. H., Chen, D., Lu, C., and Xu, C. F. (2020). Current status of *Helicobacter pylori* eradication and risk factors for eradication failure. *World J. Gastroenterol.* 26, 4846–4856.
- Yeo, Y. H., Hsu, C. C., Lee, C. C., Ho, H. J., Lin, J. T., Wu, M. S., et al. (2019). Systematic review and network meta-analysis: Comparative effectiveness of therapies for second-line *Helicobacter pylori* eradication. *J. Gastroenterol. Hepatol.* 34, 59–67. doi: 10.1111/jgh.14462
- Yu, L., Luo, L., Long, X., Liang, X., Ji, Y., Chen, Q., et al. (2019). Susceptibility-guided therapy for *Helicobacter pylori* infection treatment failures. *Ther. Adv. Gastroenterol.* 12:1756284819874922. doi: 10.1177/1756284819874922
- Yuan, Y., Ford, A. C., Khan, K. J., Gisbert, J. P., Forman, D., Leontiadis, G. I., et al. (2013). Optimum duration of regimens for *Helicobacter pylori* eradication. *Cochrane Database Syst. Rev.* CD008337.
- Zhang, J., Han, C., Lu, W. Q., Wang, N., Wu, S. R., Wang, Y. X., et al. (2020). A randomized, multicenter and noninferiority study of amoxicillin plus berberine vs tetracycline plus furazolidone in quadruple therapy for *Helicobacter pylori* rescue treatment. *J. Dig. Dis.* 21, 256–263. doi: 10.1111/1751-2980.12870
- Zhong, M. F., Li, J., Liu, X. L., Gong, P., and Zhang, X. T. (2022). TCM-based therapy as a rescue therapy for re-eradication of *Helicobacter pylori* infection: A systematic review and meta-analysis. *Evid. Based Complement. Alternat. Med.* 2022:5626235. doi: 10.1155/2022/5626235