

Second-line rescue treatment of *Helicobacter pylori* infection: Where are we now?

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Abstract

At present, the best rescue therapy for *Helicobacter*

pylori (*H. pylori*) infection following failure of first-line eradication remains unclear. The Maastricht V /Florence Consensus Report recommends bismuth quadruple therapy, or fluoroquinolone-amoxicillin triple/quadruple therapy as the second-line therapy for *H. pylori* infection. Meta-analyses have shown that bismuth quadruple therapy and levofloxacin-amoxicillin triple therapy have comparable eradication rates, while the former has more adverse effects than the latter. There are no significant differences between the eradication rates of levofloxacin-amoxicillin triple and quadruple therapies. However, the eradication rates of both levofloxacin-containing treatments are suboptimal. An important caveat of levofloxacin-amoxicillin triple or quadruple therapy is poor eradication efficacy in the presence of fluoroquinolone resistance. High-dose dual therapy is an emerging second-line therapy and has an eradication efficacy comparable with levofloxacin-amoxicillin triple therapy. Recently, a 10-d tetracycline-levofloxacin (TL) quadruple therapy comprised of a proton pump inhibitor, bismuth, tetracycline and levofloxacin has been developed, which achieves a markedly higher eradication rate compared with levofloxacin-amoxicillin triple therapy (98% vs 69%) in patients with failure of standard triple, bismuth quadruple or non-bismuth quadruple therapy. The present article reviews current second-line anti-*H. pylori* regimens and treatment algorithms. In conclusion, bismuth quadruple therapy, levofloxacin-amoxicillin triple/quadruple therapy, high-dose dual therapy and TL quadruple therapy can be used as second-line treatment for *H. pylori* infection. Current evidence suggests that 10-d TL quadruple therapy is a simple and effective regimen, and has the potential to become a universal rescue treatment following eradication failure by all first-line eradication regimens for *H. pylori* infection.

Key words: *Helicobacter pylori*; Rescue treatment; Levofloxacin-amoxicillin triple therapy; Bismuth quadruple therapy; Tetracycline-levofloxacin quadruple therapy; High-dose dual therapy

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Core tip: The present article reviews current second-line anti-*Helicobacter pylori* (*H. pylori*) regimens. Bismuth quadruple therapy and levofloxacin-amoxicillin triple therapy have comparable eradication rates in the rescue treatment of *H. pylori* infection, while the former has more adverse effects than the latter. High-dose dual therapy has an eradication rate comparable with levofloxacin-amoxicillin triple therapy. Ten-day tetracycline-levofloxacin quadruple therapy achieves a markedly higher eradication rate compared with levofloxacin-amoxicillin triple therapy (98% vs 69%) in patients with failure of standard triple, bismuth quadruple or non-bismuth quadruple therapy. In conclusion, tetracycline-levofloxacin quadruple therapy has the potential to become a universal second-line treatment for *H. pylori* infection.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infects > 50% of humans globally. It is a major cause of chronic gastritis, peptic ulcer disease, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma^[1,2]. With the rising prevalence of global antibiotic resistance, the eradication rate of *H. pylori* with standard triple therapy has decreased to < 80% worldwide^[3]. Although there are other emerging 1st-line therapies, including bismuth quadruple therapy and non-bismuth quadruple (sequential, concomitant or hybrid) therapy, which can increase the eradication rate, *H. pylori* eradication still fails in 3%-24% of infected patients^[4-7]. At present, the optimal choice for second-line anti-*H. pylori* therapy has not been well established. The present article aims to review and update the current options for second-line therapy against *H. pylori* infections.

ANTIBIOTIC RESISTANCE IN ANTI-*H. PYLORI* THERAPY

Causes of treatment failure of anti-*H. pylori* therapies include antibiotic resistant bacteria, poor patient compliance, low gastric pH and a high bacterial load. Among these reasons, antibiotic resistance is the main factor which determines the efficacy of an eradication therapy^[8]. Primary resistance to amoxicillin is either null or < 1% in most countries^[9]. In contrast, the rate of primary clarithromycin-resistance ranges from 49% (Spain) to 1% (the Netherlands) worldwide^[10]. High

primary resistance to clarithromycin and low resistance to metronidazole have been observed in Japan; moderate resistance to clarithromycin and high resistance to metronidazole were reported in South Korea; and high primary resistance to both clarithromycin and metronidazole was observed in China^[11]. High primary resistance to both clarithromycin and metronidazole has also been reported in some other countries, such as Italy, Spain, Mexico and Vietnam. Low clarithromycin resistance is generally observed in northern Europe, including the Netherlands, Sweden and Ireland^[10,11].

In patients who experience eradication failure following standard triple therapy, the rates of drug resistance to clarithromycin, metronidazole, levofloxacin, amoxicillin and tetracycline are 65%-75%, 30%-56%, 26%-37%, 0%-6.1% and 0%-10%, respectively^[12-16]. Whereas for patients who experience failure of non-bismuth quadruple therapy, the rates of drug resistance to clarithromycin, metronidazole, levofloxacin, amoxicillin and tetracycline are 75%, 75%, 25%, 0%, and 0%, respectively^[17,18]. This data implies that amoxicillin, tetracycline and levofloxacin are good choices of antibiotics for rescue treatment of *H. pylori* infection.

Point mutations play a primary role in the antimicrobial resistance of *H. pylori*, and different mutations involving the *rdxA* gene have been identified in metronidazole resistant strains^[19]. Resistance to clarithromycin in *H. pylori* is commonly caused by point mutations in the *rfl* gene encoding two 23S rRNA nucleotides, namely 2142 and 2143^[20]. Another mechanism associated with the development of clarithromycin resistance is the efflux pump system^[21,22]. Fluoroquinolone acts on the site of the type A DNA gyrase enzyme, which is encoded by the *gyrA* gene, to inhibit DNA cleavage and rejoining^[23]. Gene mutations in *gyrA* are associated with fluoroquinolone resistance. In particular double mutations at both N87 and D91 in *gyrA* have been reported to increase fluoroquinolone resistance^[24].

UPDATED SECOND-LINE THERAPIES

Current updated second-line therapies include bismuth quadruple therapy, fluoroquinolone-amoxicillin triple therapy, fluoroquinolone-amoxicillin quadruple therapy, tetracycline-levofloxacin (TL) quadruple therapy and high-dose dual therapy.

Bismuth quadruple therapy

Bismuth quadruple therapy consists of a proton pump inhibitor (PPI), bismuth, metronidazole and tetracycline (Table 1). The standard regimen comprises PPI twice daily, colloidal bismuth subcitrate 120 mg four times daily, tetracycline 500 mg four times daily and metronidazole 500 mg three times daily for 10 to 14 d. A pool analysis demonstrated that bismuth quadruple therapy fails in 5%-63% of patients as a second-line therapy and achieves a mean 76% eradication rate^[25-27]. Its efficacy is related to metronidazole resistance in

Table 1 Regimens for second-line anti-*Helicobacter pylori* therapy

Regimen	Drug					Duration of therapy	
	PPI	Bismuth	Levo	Amox	Tetra		Metro
Bismuth-containing quadruple therapy	SD, <i>b.i.d.</i>	120 mg, <i>q.i.d.</i>				500 mg, <i>q.i.d.</i>	10-14 d
Levofloxacin-containing triple therapy	SD, <i>b.i.d.</i>		500 mg, <i>q.d.</i>	1 g, <i>b.i.d.</i>			10-14 d
Levofloxacin-amoxicillin quadruple therapy	SD, <i>b.i.d.</i>	120 mg, <i>q.i.d.</i>	500 mg, <i>q.d.</i>	1 g, <i>b.i.d.</i>			10-14 d
Tetracycline-levofloxacin quadruple therapy	SD, <i>b.i.d.</i>	120 mg, <i>q.i.d.</i>	500 mg, <i>q.d.</i>		500 mg, <i>q.i.d.</i>		10 d
High-dose dual therapy	SD, <i>q.i.d.</i>			750 mg, <i>b.i.d.</i>			14 d

PPI: Proton pump inhibitor; Levo: Levofloxacin; Amox: Amoxicillin; Tetra: Tetracycline; Metro: Metronidazole.

H. pylori strains and the duration of the regimens^[28]. Meta-analysis of randomized controlled trials of bismuth quadruple therapy as a rescue treatment after failure of clarithromycin triple therapy revealed a significantly higher eradication rate for the 14-d regimen compared with the 7-d regimen^[29]. Therefore, it is reasonable to encourage a 14-d regimen duration for bismuth quadruple therapy when used as a second-line treatment for *H. pylori* infection.

Fluoroquinolone-based triple/quadruple therapy

The most commonly used fluoroquinolone-based triple therapy is composed of levofloxacin 500 mg daily, amoxicillin 1 g twice daily and a PPI (standard dose) twice daily for 10 to 14 d (Table 1). Meta-analyses revealed that levofloxacin-amoxicillin triple therapy and bismuth quadruple therapy had comparable eradication rates, whereas the former had fewer adverse effects than the latter^[30]. A systemic review and meta-analysis revealed that levofloxacin-amoxicillin triple therapy achieved an overall eradication rate of 78% after failure of a non-bismuth quadruple therapy^[31]. It was similarly effective after failure of sequential and concomitant therapies (81% vs 78%, respectively), and the cure rate of levofloxacin-amoxicillin triple therapy following hybrid therapy was 50%.

An important drawback of levofloxacin-amoxicillin triple therapy is poor eradication efficacy in the presence of fluoroquinolone resistance. Bismuth salts have a synergistic effect on antibiotics and have been used to increase eradication rates^[32]. The Maastricht V/Florence Consensus Report also recommended the application of fluoroquinolone-amoxicillin quadruple therapy as a second-line therapy for *H. pylori* infection^[31]. Levofloxacin-amoxicillin quadruple therapy is composed of levofloxacin 500 mg daily, amoxicillin 1 g twice daily, PPI (standard dose) twice daily and bismuth 240 mg twice daily for 10 to 14 d (Table 1). A randomized controlled trial showed there were no significant differences between the eradication rates of second-line 14-d levofloxacin-amoxicillin quadruple therapy and 14-d levofloxacin-amoxicillin triple therapy (87% vs 83%, respectively)^[33]. However, the former had a higher eradication rate for levofloxacin-resistant strains than the latter (71% vs 37%)^[33].

TL quadruple therapy

Recently, Hsu *et al*^[17] developed a novel TL quadruple

therapy as a rescue treatment for *H. pylori* infection. It consists of esomeprazole 40 mg twice daily, tripotassium dicitrate bismuthate 120 mg four times daily, tetracycline 500 mg four times daily, and levofloxacin 500 mg once daily for 10 d (Table 1). The simple regimen maintains a high eradication rate for *H. pylori* strains with levofloxacin resistance^[17]. A randomized control study showed that as a second-line anti-*H. pylori* treatment, 10-d of TL quadruple therapy achieved a much higher eradication rate compared with 10-d levofloxacin triple therapy containing esomeprazole, amoxicillin and levofloxacin (98% vs 68%, respectively)^[34]. Subgroup analysis revealed that the former was superior to the latter in patients with failure of either standard triple therapy (100% vs 75%) or non-bismuth quadruple therapy (95% vs 53%). There were only 7 patients recruited into the study with eradication failure by bismuth quadruple therapy as a first-line treatment, and both TL quadruple and levofloxacin-amoxicillin triple therapies had a 100% eradication rate in this subgroup of patients. The data suggests that 10-d TL quadruple therapy is a good option for second-line treatment after failure of standard triple, concomitant and bismuth quadruple therapies.

High-dose dual therapy

High-dose dual therapy is another emerging second-line treatment for *H. pylori* infection^[35]. The new therapy consists of high-dose PPI and amoxicillin (Table 1), which keep the intragastric pH higher than 6.5 regardless of *CYP2C19* genotype^[36], and maintain a steady plasma concentration of amoxicillin above the minimal inhibitory concentration for *H. pylori*^[37]. A randomized control trial from Taiwan revealed that 14-d high-dose dual therapy achieved a higher eradication rate than 10-d sequential therapy as a second-line treatment for *H. pylori* infection (89% vs 52%), and had an eradication rate comparable with 7-d levofloxacin-amoxicillin triple therapy (79%)^[35]. Another randomized controlled trial from Germany demonstrated that 14-d high-dose dual therapy and 14-d bismuth quadruple therapy had comparable efficacies as a rescue treatment for *H. pylori* infection (76% vs 81%, respectively)^[38].

TREATMENT ALGORITHM

After a first failure of *H. pylori* treatment, if an endoscopy is arranged, the Maastricht V/Florence Consensus Report recommends antimicrobial susceptibility testing

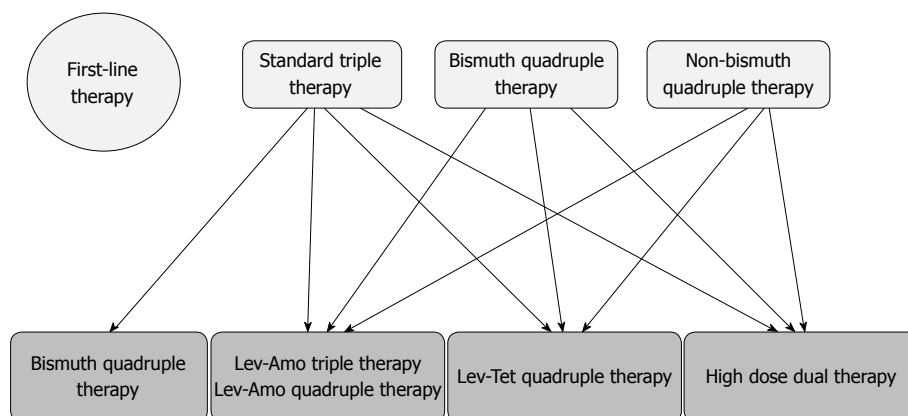


Figure 1 Algorithm for second-line therapy of *Helicobacter pylori* infection. Lev: Levofloxacin; Amo: Amoxicillin; Tet: Tetracycline.

(AST)^[31] to enable tailoring of the rescue eradication therapy. However, AST is not routinely performed in clinical practice due to the invasiveness of the endoscopy procedure, the availability of laboratory culture facilities and cost considerations. If AST data are not available, 10-d TL quadruple therapy can be used as a rescue treatment since it achieves an eradication rate of > 90% following failure of standard triple, concomitant and bismuth quadruple therapies. In addition, the novel 10-d TL quadruple regimen can maintain a high eradication rate (> 90%) for *H. pylori* strains with levofloxacin resistance^[34]. However, the choice of second line rescue regimen also depends on regional factors. In Japan, PPI-containing triple therapy with metronidazole and amoxicillin is the standard second line regimen and is covered under Japan's national health insurance. This second-line therapy can also achieve an eradication rate of around 90% because metronidazole resistance rate is relatively low in Japan.

After failure of a standard triple therapy

According to the Maastricht V/Florence Consensus Report^[31], bismuth-containing quadruple therapy, fluoroquinolone-containing triple therapy or fluoroquinolone-amoxicillin quadruple therapy are recommended following failure of standard triple therapy. As TL quadruple therapy achieves a higher eradication rate than levofloxacin triple therapy, and high-dose dual therapy has a comparable eradication rate with levofloxacin-amoxicillin triple therapy in patients with failure of standard triple therapy^[34,35], both TL quadruple and high-dose dual therapies can be recommended as a rescue regimen following failure of standard triple therapy (Figure 1).

After failure of a non-bismuth quadruple therapy

The Maastricht V/Florence Consensus Report recommends bismuth quadruple therapy, levofloxacin-amoxicillin triple therapy and levofloxacin-amoxicillin quadruple therapy as rescue treatments after failure of a non-bismuth quadruple therapy^[31]. As 10-d TL quadruple therapy is superior to 10-d levofloxacin-amoxicillin triple therapy, it is reasonable to recommend TL-quadruple therapy as the

rescue treatment for patients with eradication failure by non-bismuth quadruple therapy (Figure 1).

After failure of a bismuth quadruple therapy

According to the Maastricht V/Florence Consensus Report^[31], fluoroquinolone-containing triple or fluoroquinolone-amoxicillin quadruple therapy can be recommended for patients with eradication failure by bismuth quadruple therapy for *H. pylori* infection. As both TL quadruple and levofloxacin-amoxicillin triple therapies achieved a 100% cure rate in this setting, TL quadruple therapy may also be considered as an option for the rescue treatment of bismuth quadruple therapy (Figure 1).

CONCLUSION

The current updated second-line therapies include bismuth quadruple therapy, fluoroquinolone-amoxicillin triple therapy, fluoroquinolone-amoxicillin quadruple therapy, TL quadruple therapy and high-dose dual therapy. Ten-day TL quadruple therapy has great potential to become a universal rescue treatment following eradication failure by all first-line eradication regimens for *H. pylori* infection, and warrants further investigation.

REFERENCES

- 1 **Suerbaum S**, Michetti P. *Helicobacter pylori* infection. *N Engl J Med* 2002; **347**: 1175-1186 [PMID: 12374879 DOI: 10.1056/NEJMra020542]
- 2 **Zucca E**, Dreyling M; ESMO Guidelines Working Group. Gastric marginal zone lymphoma of MALT type: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009; **20** Suppl 4: 113-114 [PMID: 19454427 DOI: 10.1093/annonc/mdp146]
- 3 **Camargo MC**, García A, Riquelme A, Otero W, Camargo CA, Hernandez-García T, Candia R, Bruce MG, Rabkin CS. The problem of *Helicobacter pylori* resistance to antibiotics: a systematic review in Latin America. *Am J Gastroenterol* 2014; **109**: 485-495 [PMID: 24589670 DOI: 10.1038/ajg.2014.24]
- 4 **Gatta L**, Vakil N, Leandro G, Di Mario F, Vaira D. Sequential therapy or triple therapy for *Helicobacter pylori* infection: systematic review and meta-analysis of randomized controlled trials in adults and children. *Am J Gastroenterol* 2009; **104**: 3069-79; quiz

- 1080 [PMID: 19844205 DOI: 10.1038/ajg.2009.555]
- 5 **Hsu PI**, Wu DC, Wu JY, Graham DY. Is there a benefit to extending the duration of Helicobacter pylori sequential therapy to 14 days? *Helicobacter* 2011; **16**: 146-152 [PMID: 21435093 DOI: 10.1111/j.1523-5378.2011.00829.x]
 - 6 **Hsu PI**, Wu DC, Wu JY, Graham DY. Modified sequential Helicobacter pylori therapy: proton pump inhibitor and amoxicillin for 14 days with clarithromycin and metronidazole added as a quadruple (hybrid) therapy for the final 7 days. *Helicobacter* 2011; **16**: 139-145 [PMID: 21435092 DOI: 10.1111/j.1523-5378.2011.00828.x]
 - 7 **Kao SS**, Chen WC, Hsu PI, Lai KH, Yu HC, Cheng HH, Peng NJ, Lin CK, Chan HH, Tsai WL, Wang HM, Tsai TJ, Lin KH, Tsay FW. 7-Day Nonbismuth-Containing Concomitant Therapy Achieves a High Eradication Rate for Helicobacter pylori in Taiwan. *Gastroenterol Res Pract* 2012; **2012**: 463985 [PMID: 22888337 DOI: 10.1155/2012/463985]
 - 8 **Graham DY**, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. *Gut* 2010; **59**: 1143-1153 [PMID: 20525969 DOI: 10.1136/gut.2009.192757]
 - 9 **Kobayashi I**, Murakami K, Kato M, Kato S, Azuma T, Takahashi S, Uemura N, Katsuyama T, Fukuda Y, Haruma K, Nasu M, Fujioka T. Changing antimicrobial susceptibility epidemiology of Helicobacter pylori strains in Japan between 2002 and 2005. *J Clin Microbiol* 2007; **45**: 4006-4010 [PMID: 17942652 DOI: 10.1128/JCM.00740-07]
 - 10 **Chuah SK**, Tsay FW, Hsu PI, Wu DC. A new look at anti-Helicobacter pylori therapy. *World J Gastroenterol* 2011; **17**: 3971-3975 [PMID: 22046084 DOI: 10.3748/wjg.v17.i35.3971]
 - 11 **Suzuki H**, Mori H. World trends for H. pylori eradication therapy and gastric cancer prevention strategy by H. pylori test-and-treat. *J Gastroenterol* 2018; **53**: 354-361 [PMID: 29138921 DOI: 10.1007/s00535-017-1407-1]
 - 12 **Wu IT**, Chuah SK, Lee CH, Liang CM, Lu LS, Kuo YH, Yen YH, Hu ML, Chou YP, Yang SC, Kuo CM, Kuo CH, Chien CC, Chiang YS, Chiou SS, Hu TH, Tai WC. Five-year sequential changes in secondary antibiotic resistance of Helicobacter pylori in Taiwan. *World J Gastroenterol* 2015; **21**: 10669-10674 [PMID: 26457027 DOI: 10.3748/wjg.v21.i37.10669]
 - 13 **Kuo CH**, Hu HM, Kuo FC, Hsu PI, Chen A, Yu FJ, Tsai PY, Wu IC, Wang SW, Li CJ, Weng BC, Chang LL, Jan CM, Wang WM, Wu DC. Efficacy of levofloxacin-based rescue therapy for Helicobacter pylori infection after standard triple therapy: a randomized controlled trial. *J Antimicrob Chemother* 2009; **63**: 1017-1024 [PMID: 19246508 DOI: 10.1093/jac/dkp034]
 - 14 **Rendell-Baker L**. Nineteenth-century resuscitation apparatus. *Anaesthesia* 1981; **36**: 1058-1059 [PMID: 7032348 DOI: 10.1111/j.1365-2362.2006.01725.x]
 - 15 **Liou JM**, Bair MJ, Chen CC, Lee YC, Chen MJ, Chen CC, Tseng CH, Fang YJ, Lee JY, Yang TH, Luo JC, Wu JY, Chang WH, Chang CC, Chen CY, Chen PY, Shun CT, Hsu WF, Hung HW, Lin JT, Chang CY, Wu MS; Taiwan Gastrointestinal Disease and Helicobacter Consortium. Levofloxacin Sequential Therapy vs Levofloxacin Triple Therapy in the Second-Line Treatment of Helicobacter pylori: A Randomized Trial. *Am J Gastroenterol* 2016; **111**: 381-387 [PMID: 26832653 DOI: 10.1038/ajg.2015.439]
 - 16 **Cao Z**, Chen Q, Zhang W, Liang X, Liao J, Liu W, Xiao S, Lu H. Fourteen-day optimized levofloxacin-based therapy versus classical quadruple therapy for Helicobacter pylori treatment failures: a randomized clinical trial. *Scand J Gastroenterol* 2015; **50**: 1185-1190 [PMID: 25881966 DOI: 10.3109/00365521.2015.1037345]
 - 17 **Hsu PI**, Chen WC, Tsay FW, Shih CA, Kao SS, Wang HM, Yu HC, Lai KH, Tseng HH, Peng NJ, Chen A, Kuo CH, Wu DC; Taiwan Acid-Related Disease (TARD) Study Group. Ten-day Quadruple therapy comprising proton-pump inhibitor, bismuth, tetracycline, and levofloxacin achieves a high eradication rate for Helicobacter pylori infection after failure of sequential therapy. *Helicobacter* 2014; **19**: 74-79 [PMID: 24033865 DOI: 10.1111/hel.12085]
 - 18 **Gisbert JP**, Molina-Infante J, Marin AC, Vinagre G, Barrio J, McNicholl AG. Second-line rescue triple therapy with levofloxacin after failure of non-bismuth quadruple "sequential" or "concomitant" treatment to eradicate H. pylori infection. *Scand J Gastroenterol* 2013; **48**: 652-656 [PMID: 23556551 DOI: 10.3109/00365521.2013.786132]
 - 19 **Masaoka T**, Suzuki H, Kurabayashi K, Nomoto Y, Nishizawa T, Mori M, Hibi T. Could frameshift mutations in the frxA and rdxA genes of Helicobacter pylori be a marker for metronidazole resistance? *Aliment Pharmacol Ther* 2006; **24** Suppl 4: 81-87 [DOI: 10.1111/j.1746-6342.2006.00029.x]
 - 20 **Arslan N**, Yılmaz Ö, Demiray-Gürbüz E. Importance of antimicrobial susceptibility testing for the management of eradication in Helicobacter pylori infection. *World J Gastroenterol* 2017; **23**: 2854-2869 [PMID: 28522904 DOI: 10.3748/wjg.v23.i16.2854]
 - 21 **Bina JE**, Alm RA, Uria-Nickelsen M, Thomas SR, Trust TJ, Hancock RE. Helicobacter pylori uptake and efflux: basis for intrinsic susceptibility to antibiotics in vitro. *Antimicrob Agents Chemother* 2000; **44**: 248-254 [PMID: 10639345 DOI: 10.1128/AAC.44.2.248-254.2000]
 - 22 **Hirata K**, Suzuki H, Nishizawa T, Tsugawa H, Muraoka H, Saito Y, Matsuzaki J, Hibi T. Contribution of efflux pumps to clarithromycin resistance in Helicobacter pylori. *J Gastroenterol Hepatol* 2010; **25** Suppl 1: S75-S79 [PMID: 20586871 DOI: 10.1111/j.1440-1746.2009.06220.x]
 - 23 **Nishizawa T**, Suzuki H. Mechanisms of Helicobacter pylori antibiotic resistance and molecular testing. *Front Mol Biosci* 2014; **1**: 19 [PMID: 25988160 DOI: 10.3389/fmolb.2014.00019]
 - 24 **Mori H**, Suzuki H, Matsuzaki J, Masaoka T, Kanai T. Acquisition of double mutation in gyrA caused high resistance to sitafloxacin in Helicobacter pylori after unsuccessful eradication with sitafloxacin-containing regimens. *United European Gastroenterol J* 2018; **6**: 391-397 [PMID: 29774152 DOI: 10.1177/2050640617737215]
 - 25 **Wu DC**, Hsu PI, Tseng HH, Tsay FW, Lai KH, Kuo CH, Wang SW, Chen A. Helicobacter pylori infection: a randomized, controlled study comparing 2 rescue therapies after failure of standard triple therapies. *Medicine (Baltimore)* 2011; **90**: 180-185 [PMID: 21512411 DOI: 10.1097/MD.0b013e31821c9d1c]
 - 26 **Gisbert JP**. "Rescue" regimens after Helicobacter pylori treatment failure. *World J Gastroenterol* 2008; **14**: 5385-5402 [PMID: 18803350 DOI: 10.3748/wjg.14.5385]
 - 27 **Hojo M**, Miwa H, Nagahara A, Sato N. Pooled analysis on the efficacy of the second-line treatment regimens for Helicobacter pylori infection. *Scand J Gastroenterol* 2001; **36**: 690-700 [PMID: 11444467 DOI: 10.1080/00365520116825]
 - 28 **Lee BH**, Kim N, Hwang TJ, Lee SH, Park YS, Hwang JH, Kim JW, Jeong SH, Lee DH, Jung HC, Song IS. Bismuth-containing quadruple therapy as second-line treatment for Helicobacter pylori infection: effect of treatment duration and antibiotic resistance on the eradication rate in Korea. *Helicobacter* 2010; **15**: 38-45 [PMID: 20302588 DOI: 10.1111/j.1523-5378.2009.00735.x]
 - 29 **Chey WD**, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. *Am J Gastroenterol* 2017; **112**: 212-239 [PMID: 28071659 DOI: 10.1038/ajg.2016.563]
 - 30 **Di Caro S**, Fini L, Daoud Y, Grizzi F, Gasbarrini A, De Lorenzo A, Di Renzo L, McCartney S, Bloom S. Levofloxacin/amoxicillin-based schemes vs quadruple therapy for Helicobacter pylori eradication in second-line. *World J Gastroenterol* 2012; **18**: 5669-5678 [PMID: 23155306 DOI: 10.3748/wjg.v18.i40.5669]
 - 31 **Malfertheiner P**, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M, Selgrad M, Suerbaum S, Sugano K, El-Omar EM; European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. *Gut* 2017; **66**: 6-30 [PMID: 27707777 DOI: 10.1136/gutjnl-2016-312288]
 - 32 **Goodwin CS**, Marshall BJ, Blinow ED, Wilson DH, Blackburn S, Phillips M. Prevention of nitroimidazole resistance in Campylobacter pylori by coadministration of colloidal bismuth subcitrate: clinical and in vitro studies. *J Clin Pathol* 1988; **41**: 207-210 [PMID: 3280609 DOI: 10.1136/jcp.41.2.207]

- 33 **Liao J**, Zheng Q, Liang X, Zhang W, Sun Q, Liu W, Xiao S, Graham DY, Lu H. Effect of fluoroquinolone resistance on 14-day levofloxacin triple and triple plus bismuth quadruple therapy. *Helicobacter* 2013; **18**: 373-377 [PMID: 23581720 DOI: 10.1111/hel.12052]
- 34 **Hsu PI**, Tsai FW, Kao SS, Hsu WH, Cheng JS, Peng NJ, Tsai KW, Hu HM, Wang YK, Chuah SK, Chen A, Wu DC. 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* 2017; **112**: 1374-1381 [PMID: 28719592 DOI: 10.1038/ajg.2017.195]
- 35 **Yang JC**, Lin CJ, Wang HL, Chen JD, Kao JY, Shun CT, Lu CW, Lin BR, Shieh MJ, Chang MC, Chang YT, Wei SC, Lin LC, Yeh WC, Kuo JS, Tung CC, Leong YL, Wang TH, Wong JM. High-dose dual therapy is superior to standard first-line or rescue therapy for *Helicobacter pylori* infection. *Clin Gastroenterol Hepatol* 2015; **13**: 895-905.e5 [PMID: 25460556 DOI: 10.1016/j.cgh.2014.10.036]
- 36 **Sugimoto M**, Furuta T, Shirai N, Kajimura M, Hishida A, Sakurai M, Ohashi K, Ishizaki T. Different dosage regimens of rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotype status. *Clin Pharmacol Ther* 2004; **76**: 290-301 [PMID: 15470328 DOI: 10.1016/j.clpt.2004.06.008]
- 37 **Craig WA**. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998; **26**: 1-10; quiz 11-12 [PMID: 9455502 DOI: 10.1086/516284]
- 38 **Miehlke S**, Kirsch C, Schneider-Brachert W, Haferland C, Neumeyer M, Bästlein E, Papke J, Jacobs E, Vieth M, Stolte M, Lehn N, Bayerdörffer E. A prospective, randomized study of quadruple therapy and high-dose dual therapy for treatment of *Helicobacter pylori* resistant to both metronidazole and clarithromycin. *Helicobacter* 2003; **8**: 310-319 [PMID: 12950604 DOI: 10.1046/j.1523-5378.2003.00158.x]

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