**Name of Journal: *World Journal of Gastrointestinal Pharmacology and Therapeutics***

**ESPS Manuscript NO: 18676**

**Manuscript Type: REVIEW**

**Antibiotic treatment for *Helicobacter pylori*: Is the end coming?**

Kim SY *et al*. Prospects for *Helicobacter pylori* treatment

**Su Young Kim, Duck Joo Choi, Jun-Won Chung**

**Su Young Kim, Duck Joo Choi, Jun-Won Chung,** Division of Gastroenterology, Department of Internal Medicine, Gachon University, Gil Medical Center, Incheon 405-760, South Korea

**Author contributions:** Kim SY and Chung JW contributed equally to this work that designed and wrote the manuscript; Choi DJ performed the collected the data.

**Conflict-of-interest** **statement:** No author has any personal or financial conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to: Jun-Won Chung, MD, PhD,** Division of Gastroenterology, Department of Internal Medicine, Gachon University, Gil Medical Center, 21, Namdong-daero 774 beon-gil, Namdong-gu, Incheon 405-760, South Korea. junwonchung@daum.net

**Telephone:** +82-32-4603778

**Fax:** +82-32-4603408

**Received:** April 26, 2015

**Peer-review started:** April 27, 2015

**First decision:** July 25, 2015

**Revised:** September 7, 2015

**Accepted:** September 25, 2015

**Article in press:**

**Published online:**

**Abstract**

Infection with the Gram-negative pathogen *Helicobacter pylori* (*H. pylori*) has been associated with gastro-duodenal disease and the importance of *H. pylori* eradication is underscored by its designation as a group I carcinogen. The standard triple therapy consists of a proton pump inhibitor, amoxicillin and clarithromycin, although many other regimens are used, including quadruple, sequential and concomitant therapy regimens supplemented with metronidazole, clarithromycin and levofloxacin. Despite these efforts, current therapeutic regimens lack efficacy in eradication due to antibiotic resistance, drug compliance and antibiotic degradation by the acidic stomach environment. Antibiotic resistance to clarithromycin and metronidazole is particularly problematic and several approaches have been proposed to overcome this issue, such as complementary probiotic therapy with *Lactobacillus*. Other studies have identified novel molecules with an anti-*H. pylori* effect, as well as tailored therapy and nanotechnology as viable alternative eradication strategies. This review discusses current antibiotic therapy for *H. pylori* infections, limitations of this type of therapy and predicts the availability of newly developed therapies for *H. pylori* eradication.

**Key words:** *Helicobacter pylori*; Treatment; Antibiotic resistance; Therapeutic regimens; Novel agents

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** This article reviews the recent literature describing antibiotic resistance and trends in *Helicobacter pylori* (*H. pylori*) treatment. As there is no effective conventional therapy, new treatments are being developed and bismuth quadruple, sequential, concomitant therapies are recommended as a first-line regimen in regions with high levels of clarithromycin resistance. Quinolones have also been used for *H. pylori* treatment, although the cure rate has gradually reduced with this approach. New therapeutic directions include probiotic supplementation, tailored therapy, novel agents, and nanotechnology.

Kim SY, Choi DJ, Chung JW. Antibiotic treatment for *Helicobacter pylori*: Is the end coming? *World J Gastrointest Pharmacol Ther* 2015; In press

**INTRODUCTION**

*Helicobacter pylori* (*H. pylori*) is a Gram-negative, flagellated, spiral shaped microaerophilic bacterium first identified by Marshall and Warren[[1-3](#_ENREF_1)]. These bacteria have morphological characteristics penetrate the mucosa and colonize the stomach and duodenum[[4](#_ENREF_4)]. *H. pylori* are responsible for the pathogenesis that leads to gastritis, peptic ulcer disease (PUD), gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[[3](#_ENREF_3),[5](#_ENREF_5),[6](#_ENREF_6)]. The World Health Organization has classified *H. pylori* as a group I carcinogen with a risk of stomach cancer[[7](#_ENREF_7),[8](#_ENREF_8)]. *H. pylori*-related stomach cancer represents 5.5% of all cancers worldwide and 25% of all infection-associated malignancies. Socioeconomically, *H. pylori* infection increases the risk of malignancy and the expense of *H. pylori*-associated morbidity[[9](#_ENREF_9)]. *H. pylori* infection has also been related to non-digestive conditions such as ischemic heart disease, stroke, Alzheimer’s disease, Parkinson’s disease, and iron deficient anemia[[4](#_ENREF_4),[10](#_ENREF_10)]. In other report, some patients with gastritis resolved *H. pylori* infection without using antibiotic treatment[[11](#_ENREF_11)]. Although the prevalence of *H. pylori* infection has been reduced in developed countries, it has remained prevalent in developing countries[[12](#_ENREF_12),[13](#_ENREF_13)] with rates of infection varying according to nation, patient age, and socioeconomic states[[14](#_ENREF_14)]. Eradication of *H. pylori* is an effective treatment for PUD, gastric MALT lymphoma, and preventing the recurrence of stomach cancer after endoscopic treatment[[15-17](#_ENREF_15)].

A standard triple therapy (STT), consisting of a proton pump inhibitor (PPI), clarithromycin and amoxicillin, was established in clinical practice for the eradication of *H. pylori* infection[[18](#_ENREF_18),[19](#_ENREF_19)]. However, in recent years, the efficacy of STT has been critically altered in many regions of the world as eradication rates have diminished to inadequately low levels[[18](#_ENREF_18),[20](#_ENREF_20)]. The causes for this decline may involve patient compliance, bacterial factors, obesity, smoking, reinfection, and genetic polymorphisms in CYP2C19. However, antibiotic resistance may be the primary reason for reduced eradication of *H. pylori* infection worldwide[[20-22](#_ENREF_20)]. In addition, the eradication rates differ by region, even in the same country. In South Korea, one study reported that the eradication rates of first-line therapy decreased from 81.3% to 77.5% from 2001-2007[[23](#_ENREF_23)], while another showed that no definite evidence of a significant change in the eradication rate during 2000-2010[[24](#_ENREF_24)]. This may be due to geographical differences in antibiotic resistance and the methods used to confirm eradication. In a region with high rates of clarithromycin resistance, sequential or concomitant therapy is recommended as the first-line *H. pylori* eradication treatment[[25](#_ENREF_25)]. The primary reason for the growth in antibiotic resistance is the emergence of point mutations in the *H. pylori* genome[[26](#_ENREF_26)]. Thus, the development of novel treatment methods to increase eradication rates and reduce antibiotic resistance is needed. The focus of this review will be on current *H. pylori* therapies and limitations, as well as alternative anti-*H. pylori* regimens.

**CURRENT ANTIBIOTIC RESISTANCE IN WORLDWIDE**

The most important antibiotics in *H. pylori* treatment are clarithromycin, metronidazole, and amoxicillin. Figure 1 illustrates recently reported clarithromycin and metronidazole resistance rates worldwide. Resistance to these antibiotics is thought to be the main cause of eradication failure[[27-29](#_ENREF_27)]. Antibiotic resistance is discovered by bacterial culture-based techniques (*E*-test, modified disk diffusion, agar dilution method, and breakpoint susceptibility test) and molecular methods [polymerase chain reaction (PCR), real-time PCR, allele-specific PCR, sequencing, and fluorescent *in situ* hybridization][[30](#_ENREF_30)]. Although these methods are useful for examining antibiotic resistance, their implementation at the early stages of *H. pylori* remains impractical due to the time required to obtain results and the high cost of the tests.

Clarithromycin is a macrolide antibiotic that inhibits protein synthesis by binding to and slowing the actions of the bacterial ribosome[[30](#_ENREF_30)]. Clarithromycin resistance is due to three point mutations at A2142C, A2142G, and A2143G in the *23s rRNA* gene[[31](#_ENREF_31)]. In particular, the A2143G mutation has been related to a very low eradication rate[[32](#_ENREF_32)]. In contrast, the A2143G mutation occurs in only 23% of resistant strains in Eastern countries[[31](#_ENREF_31)]. This suggests that clarithromycin point mutations may be geographically distinct between Eastern and Western countries and new point mutations have appeared in South America[[33](#_ENREF_33)]. Clarithromycin resistance is also different depending on the area. In Brazil, stomach biopsy specimens positive for *H. pylori* were analyzed by PCR to detect the point mutation associated with clarithromycin resistance[[34](#_ENREF_34)]. The results uncovered primary clarithromycin resistance in 16.5% patients. Recently, the clarithromycin resistance rate in South Korea was reported to range from 17.2% to 23.7%[[35](#_ENREF_35)]. In a study published in Japan, the clarithromycin resistance rate in 2002 was 18.9%; however, the clarithromycin resistance rate in 2006 increased to 27.2%[[36](#_ENREF_36)]. Even with third-line eradication therapy, clarithromycin resistance rates in Japan were reported as 86.4%[[37](#_ENREF_37)]. Several studies in China have reported increased resistance rates Shanghai[[38](#_ENREF_38)], 21.5% resistance in the southeast coastal region[[39](#_ENREF_39)], and a relatively high rate of 33% in Vietnam, which is near Southeast China[[40](#_ENREF_40)]. In Western Asia, resistance to clarithromycin has been reported to be > 10% in Iran and > 20% in Turkey[[13](#_ENREF_13)]. In one study, clarithromycin resistance was reported in 47.5% of patients with dyspepsia in Turkey[[41](#_ENREF_41)]. In sharp contrast to other Asian countries, no resistance to clarithromycin has been reported in Malaysia[[42](#_ENREF_42)] and the prevalence of resistance to clarithromycin in Gambia and Senegal also remains very low[[43](#_ENREF_43),[44](#_ENREF_44)]. Resistance to clarithromycin has also risen by > 20% in southern Europe, although in Northern Europe the resistance rate is less than 10%[[45](#_ENREF_45)] compared to 1.5% in a random adult Swedish population[[46](#_ENREF_46)] and 7.5% in central Germany[[47](#_ENREF_47)]. During the last 15 years, a twofold increase in clarithromycin resistance was reported in Italy[[48](#_ENREF_48)] and in Spain, where the mean clarithromycin resistance rate was 18.3% in 1709 patients[[49](#_ENREF_49)], and 34.7% in Portuguese children[[50](#_ENREF_50)]. In contrast to the general trend, the rate of *H. pylori* strains resistant to clarithromycin decreased from 34% to 22% during 6 years in Southern Poland[[51](#_ENREF_51)]. Despite these variations, the overall frequency of clarithromycin resistance has risen from 10.2% to 21.3% worldwide, and A2143G is the most frequently reported point mutation. Present European guidelines recommend 7 d of STT in regions in which the rate of clarithromycin resistance is < 20%, and 14 d in regions with clarithromycin resistance rates of > 20%[[25](#_ENREF_25),[45](#_ENREF_45)].

The mechanism mediating resistance to metronidazole is complex. Modifications in the *rdxA* gene, assumed to be point mutations, are considered a primary cause[[30](#_ENREF_30)]. Metronidazole resistance may also influence the treatment outcome, although it is generally considered less clinically important than clarithromycin resistance[[52](#_ENREF_52),[53](#_ENREF_53)]. Overall, the Eastern Asian region has higher metronidazole resistance rates with 95.4% in the southeast coastal region of China[[39](#_ENREF_39)] and 71.3% in Japan[[37](#_ENREF_37)]. In Vietnam, the resistance rate was 69.9% among 103 strains[[40](#_ENREF_40)]. Unlike the clarithromycin resistance rate, there was a high prevalence of resistance to metronidazole (75.5%) in Malaysia[[42](#_ENREF_42)], a 76.8% rate in Iran[[54](#_ENREF_54)] and a high resistance rate in Africa[[43](#_ENREF_43),[44](#_ENREF_44)]. Another study showed that 80% of strains in Mexico were resistant to metronidazole[[55](#_ENREF_55)]. Overall, metronidazole resistance is > 50% in much of the world but there are reports that metronidazole resistance has declined in Northern Europe[[9](#_ENREF_9),[30](#_ENREF_30)], while in the United States and Europe, the metronidazole resistance rate was reported to be < 40%[[30](#_ENREF_30),[56](#_ENREF_56)], and 22.5% in 102 isolates from Norway[[57](#_ENREF_57)]. However, in Central and Southern Europe, resistance rates remain markedly higher-34.9% in France and 32.7% in Germany[[47](#_ENREF_47),[58](#_ENREF_58)].

Amoxicillin is a beta-lactam antibiotic that was first used for *H. pylori* therapy[[25](#_ENREF_25)]. Unlike clarithromycin and metronidazole, amoxicillin resistance rates are low worldwide[[30](#_ENREF_30)]: 0% or < 1% in Europe[[30](#_ENREF_30)]. However, other studies revealed high amoxicillin resistance rates in Iran, Japan, and Cameroon[[37](#_ENREF_37),[45](#_ENREF_45),[54](#_ENREF_54)].

Fluoroquinolones are the sole class of antibiotics for treatment of *H. pylori* that directly inhibit bacterial DNA synthesis. Resistance to fluoroquinolones occurs primarily by mutation in the genes for topoisomerase IV and gyrase[[59](#_ENREF_59)]. Levofloxacin is currently recommended as a second-line *H. pylori* treatment when first-line therapy containing clarithromycin has failed, although levofloxacin resistance has been predicted to increase in the near future[[25](#_ENREF_25)]. Levofloxacin resistance rates in Asia differ from region to region with rates of 20.6% in the southeast coastal region of China and 18.4% in Vietnam[[39](#_ENREF_39),[40](#_ENREF_40)]. Fluoroquinolone resistance was noted as 62.3% in Pakistan[[60](#_ENREF_60)], while Japan and Malaysia had low resistance rates of 8.2% and 0%, respectively[[37](#_ENREF_37),[42](#_ENREF_42)]. Primary *H. pylori* resistance to ciprofloxacin occurred at a high frequency (15.7%) in South Korea[[61](#_ENREF_61)]. A study by Megraud *et al*[[62](#_ENREF_62)] of more than 2000 patients with *H. pylori* infection showed resistance rates of 14.1% for levofloxacin, with significantly higher fluoroquinolone resistance in Western/Southern Europe than in Northern Europe[[62](#_ENREF_62)]. O’Connor *et al*[[63](#_ENREF_63)]reported that 11.7% of patients had strains resistant to levofloxacin in Ireland and there was a 29.1% resistance rate in 2011 in Germany[[64](#_ENREF_64)], 15% in Senegal[[44](#_ENREF_44)] and 23% in Brazil[[65](#_ENREF_65)].

**THE EFFICACY OF STT AND BISMUTH QUADRUPLE THERAPY ARE DECREASING**

The first-line regimen for the eradication of *H. pylori* infection consists of STT using a PPI, amoxicillin and clarithromycin and was first introduced by Dr. Bazzoli. In studies conducted during the 1990s, STT yielded > 80% treatment success with reports of > 90% possible[[66](#_ENREF_66),[67](#_ENREF_67)]. However, the increased prevalence of clarithromycin resistance has accounted for the diminished efficacy of STT. Table 1 shows eradication rates from recent studies using STT. Generally, STT is not recommended as a first-line regimen when the clarithromycin resistance rate is > 15%-20%, and other therapies such as quadruple therapy or sequential therapy are suggested[[25](#_ENREF_25)]. Thus, a steady increase in *H. pylori* resistance to amoxicillin and metronidazole has also resulted in reduced treatment success of STT[[27](#_ENREF_27),[68](#_ENREF_68),[69](#_ENREF_69)]. The ideal outcome of *H. pylori* eradication is > 80% by intention to treat (ITT) analysis and > 90% by per protocol (PP) analysis. According to a recent study, the eradication rate was unacceptably low for treatment success, with only 18% exceeding 85% and approximately 60% failing to attain 80% eradication by ITT analysis[[20](#_ENREF_20)]. Over the past 20 years, the efficacy of STT has decreased, with eradication rates < 80% by ITT analysis[[41](#_ENREF_41)]. According to the present formula by Dr. Graham, if clarithromycin resistance rate of 20%, the outcome of clarithromycin containing triple therapy is reduced to 77.2% by PP analysis[[70](#_ENREF_70)]. Already in some countries the eradication rates have been reported to be < 50% and if this trend continues for another 20 years, the efficacy of STT will be negligible.

Various methods have been considered to circumvent the STT eradication rate decrease. The first method suggested that increasing the STT duration would improve treatment efficacy. In an early meta-analysis, a 14-d STT regimen raised the eradication rate compared to a 7-d regimen[[71](#_ENREF_71)]. Another meta-analysis supported this result by showing that extending STT over 7 d improved the eradication rate[[72](#_ENREF_72)]. However, other reports determined that extending STT was not cost-effective and increased adverse events and decreased compliance, resulting in no significant difference between the eradication rate and extended treatment duration[[73](#_ENREF_73)]. Another means of addressing the decrease in STT eradication rate is to increase the dose of PPI, which has a positive effect on treatment success. PPIs delay gastric emptying and increase gastric pH, which improves the effect of antibiotics by preventing acid-related degradation[[74](#_ENREF_74)]. A meta-analysis reported increased eradication rates from STT involving PPI administration twice per day compared with once per day[[75](#_ENREF_75)]. Another systematic review reported that utilizing a high dose of PPI increased the *H. pylori* treatment rate[[76](#_ENREF_76)] and the use of high-dose PPI increased the effectiveness of STT compared with a single does PPI[[77](#_ENREF_77)]. In spite of these positive outcomes, STT is now regarded as an outdated therapy.

Bismuth quadruple therapy (bismuth subcitrate potassium, metronidazole, tetracycline, PPI) has been suggested as a first-line treatment option for regions with a high (> 20%) incidence of clarithromycin resistance[[53](#_ENREF_53)]. In a meta-analysis of nine randomized controlled trials (RCTs), bismuth quadruple therapy and STT resulted in similar compliance rates, side effects, and eradication rates as a primary therapy for *H. pylori* infection[[78](#_ENREF_78)]. For example, the ITT eradication rate with modified bismuth quadruple therapy was 92.7% in a recent randomized study in Chinese patients[[79](#_ENREF_79)]. A pilot study in United States Hispanics showed that 14-d bismuth quadruple anti-*H. pylori* therapy achieved a > 95% eradication rate[[80](#_ENREF_80)]. However, in some studies the eradication rate of bismuth quadruple therapy was < 80%[[81-83](#_ENREF_81)]. A decrease in the bismuth quadruple therapy eradication rate was highly associated with metronidazole resistance[[20](#_ENREF_20)].

**ARE THERE SUITABLE SEQUENTIAL AND CONCOMITANT THERAPY ALTERNATIVES?**

Sequential therapy was introduced by Zullo *et al*[[84](#_ENREF_84)] in Italy in 2000. This regimen includes a PPI and amoxicillin for 5 d, followed by a PPI, clarithromycin, and tinidazole triple therapy for another 5 d. Several studies have indicated that the eradication rate of sequential therapy was significantly higher than that of STT[[85-87](#_ENREF_85)]. The reason that sequential therapy has a higher eradication rate than STT is that amoxicillin and PPI administered during the first 5 d decreases *H. pylori* density in the stomach, which increases clarithromycin and metronidazole efficacy[[32](#_ENREF_32),[88-90](#_ENREF_88)]. In addition, amoxicillin damages the bacterial cell wall and limits production of an efflux channel underlying drug resistance. However, it is uncertain whether improvement in the eradication rate is due to sequential therapy or additional use of antibiotics such as tinidazole. Recent data from South Korea, showed a lower *H. pylori* eradication rate with sequential therapy with eradication rates by ITT analysis of 79.0% and by PP analysis of 84.9%[[91](#_ENREF_91)]. Another study showed that the eradication rates by ITT were 72.1% and 80.2% in 10-d and 15-d sequential groups, respectively[[92](#_ENREF_92)]. Although the 15-d sequential therapy group cure rate was higher than that of the 10-d sequential therapy group, the eradication rate remains low. In the study by Zhou *et al*[[93](#_ENREF_93)], there was no significant difference between the eradication rates achieved with STT (66.4%) and sequential therapy (72.1%) by ITT analysis. Moreover, the sequential therapy group with dual clarithromycin resistance and metronidazole resistance had a lower eradication rate (43.9%) compared to the rate seen with only clarithromycin resistance (88.9%)[[93](#_ENREF_93)]. In a 2015 study from India that compared sequential therapy to ciprofloxacin-containing sequential therapy, the ITT cure rate in the sequential therapy group was 66% and only 73.5% in the ciprofloxacin group[[94](#_ENREF_94)]. Thus, the sequential therapy efficacy in Asia was lower than reported by earlier European studies. Another meta-analysis showed that the overall eradication rate of sequential therapy was 84.3% [95% confidence interval (CI): 82.1%–86.4%], although this was not superior to 14-d STT[[86](#_ENREF_86)]. However, sequential therapy was able to eradicate 72.8% of the *H. pylori* resistant to clarithromycin[[86](#_ENREF_86)]. In addition to the problem of sequential therapy eradication rate reduction, treatment compliance can be reduced due to medication changes during treatment. Furthermore, if eradication fails, no second-line treatment regimen has been established[[95](#_ENREF_95)].

Concomitant therapy, also known as non-bismuth quadruple therapy, consists of PPI and all three antibiotics (clarithromycin, amoxicillin, metronidazole) administered concomitantly to provide a simpler treatment regimen compared to sequential therapy[[96](#_ENREF_96)]. Recently, several studies have compared concomitant therapy to STT and sequential therapy. In one study, 10-d concomitant therapy resulted in a better eradication rate in settings with antibiotic-resistant *H. pylori* strains[[97](#_ENREF_97)]. Eradication rates for concomitant and sequential therapies were 100% *vs* 75% for clarithromycin-resistant strains and 75% *vs* 60% for clarithromycin-resistant/metronidazole-resistant strains[[97](#_ENREF_97)]. A meta-analysis of 15 studies showed a mean *H. pylori* eradication rate of 90% by ITT analysis for concomitant therapy and reported that longer treatment improved the outcomes compared to STT[[98](#_ENREF_98)]. Another meta-analysis showed that concomitant therapy was superior to STT[[99](#_ENREF_99)]. In studies published in South Korea, the eradication rate for concomitant therapy was considerably higher than that for sequential therapy[[100](#_ENREF_100),[101](#_ENREF_101)]. However, several other studies have reported no difference in eradication rates between sequential and the concomitant therapy[[102-104](#_ENREF_102)]. In a randomized open-label study, ITT eradication rates were 75.6% (95%CI: 66.3-84.9%) in the sequential therapy group and 80.8% (95%CI: 71.8%-88.5%) in the concomitant therapy group[[104](#_ENREF_104)]. In both groups, there was no difference in eradication rates and the treatment rate was lower than expected[[104](#_ENREF_104)]. Furthermore, in some studies, concomitant therapy had a lower eradication rate than other regimens[[83](#_ENREF_83),[105](#_ENREF_105),[106](#_ENREF_106)]. A total of 200 patients were randomized and the ITT eradication rates were 79% (95%CI: 71.0%-87.0%) in the bismuth group and 74% (95%CI: 68%-81%) in the concomitant group, although this was not statistically significant[[83](#_ENREF_83)]. Another study compared the eradication rate between 10-d sequential therapy, 5-d concomitant therapy, 14-d concomitant therapy and 14-d hybrid therapy[[105](#_ENREF_105)]. In ITT analysis, sequential therapy showed the highest eradication rate, which was higher than even 5-d concomitant therapy[[105](#_ENREF_105)]. This is supported by an RCT of 1463 patients in seven Latin American sites (Chile, Colombia, Costa Rica, Honduras, Nicaragua, Mexico) that reported the eradication rate with 14-d standard therapy was 82.2%, compared to 73.6% with 5-d concomitant therapy and 76.5% with 10-d sequential therapy[[106](#_ENREF_106)]. Currently, concomitant therapy has several limitations. First, side effects were reported to occur more frequently than with sequential therapy[[107](#_ENREF_107)]. Second, there are few data describing the effect of metronidazole resistance in concomitant therapy. Moreover if dual-resistance to clarithromycin and metronidazole was > 15%, the eradication rate decreased[[108](#_ENREF_108),[109](#_ENREF_109)]. Finally, as with sequential therapy, when first-line treatment fails no second-line treatment for concomitant therapy has been established. Tables 2 and 3 indicate that current trends of *H. pylori* eradication for sequential and concomitant therapy.

**ADDING LEVOFLOXACIN AND OTHER QUINOLONES TO EXISTING TREATMENT**

Levofloxacin has a large spectrum of activity against diverse Gram-positive and -negative bacteria[[110](#_ENREF_110)] though inhibition of bacterial topoisomerase II[[111](#_ENREF_111)]. There have been several studies of levofloxacin use as a first-line treatment[[112](#_ENREF_112)]. To overcome increasing clarithromycin resistance, levofloxacin has been used as a alternative to clarithromycin in either STT or sequential therapy[[53](#_ENREF_53)]. Table 4 shows *H. pylori* eradication rates following levofloxacin-containing therapy. According to a meta-analysis, 10-d of levofloxacin triple therapy is more efficacious than 7-d bismuth-based quadruple therapy (RR = 1.41, 95%CI: 1.25–1.59) in the eradication of *H. pylori* infection[[113](#_ENREF_113)]. In another study, levofloxacin-based triple therapy (ITT, 80.8%; 95%CI: 73%-88%) was more effective than STT (ITT: 64%, 95%CI: 55%-73%) and there were no differences in compliance or side effects[[114](#_ENREF_114)]. However, other studies reported that levofloxacin-containing regimens did not have superior eradication rates compared to other treatments. Meta-analyses and a recent study in 2014 have shown that the outcome of levofloxacin-based first-line therapy was similar to STT[[115](#_ENREF_115),[116](#_ENREF_116)] with an overall crude eradication rate of 79.1% in the levofloxacin group compared to 81.4% in the STT group[[116](#_ENREF_116)]. A recent RCT in Taiwan with over 153 patients determined there was an advantage to levofloxacin-amoxicillin/clavulanate-PPI therapy over STT, although there was a low eradication rate (ITT analysis: 78.1% *vs* 57.5%)[[117](#_ENREF_117)]. Unsatisfactory results were reported in an Asian meta-analysis, which showed that 7-d STT was more effective than 7-d levofloxacin-based therapy[[118](#_ENREF_118)]. However, in European countries, levofloxacin-based therapy was more effective than STT[[118](#_ENREF_118)]. Regional differences in *H. pylori* resistance to antibiotics might account for these results. Although levofloxacin has been suggested as a replacement for clarithromycin in *H. pylori* treatment, increasing quinolone resistance is a larger problem. According to Graham *et al*[[119](#_ENREF_119)], in the presence of fluoroquinolone resistance treatment success with quinolone-containing therapy decreases and these results can be predicted using a formula. A report published in United States in 2015 determined that the prevalence of levofloxacin resistance was 31.3% (95%CI: 23.1%-39.4%)[[120](#_ENREF_120)] and another study showed a high rate of quinolone resistance (50%) in Congo[[121](#_ENREF_121)]. We calculated the effect of quinolone resistance on treatment success using the proposed formula, which indicated success rates of 87.6% and 73.5%, respectively[[119](#_ENREF_119),[122](#_ENREF_122)]. The levofloxacin resistance rate is also relatively high in East Asia, where there is also a higher prevalence of stomach cancer compared to other regions[[122](#_ENREF_122),[123](#_ENREF_123)]. Sitafloxacin, which has lower minimum inhibitory concentration for *H. pylori*, and levofloxacin triple therapy combined with bismuth quadruple therapy have been suggested as solutions to this problem, although further evidence is required to establish this approach[[122](#_ENREF_122),[124](#_ENREF_124)].

**PROBIOTICS AS ANOTHER APPROACH TO IMPROVE ERADICATION RATES**

Many studies have demonstrated that probiotics have an inhibitory effect on *H. pylori*. Although some studies have reported that probiotics alone have limited efficacy[[125](#_ENREF_125),[126](#_ENREF_126)], they can be useful when used as a supplemental drug. In a study by Zhifa *et a*[[127](#_ENREF_127)], the cure rates in the probiotic supplementation group were superior to those in the group that did not receive probiotics (RR, 1.12; 95%CI: 1.06-1.19), and probiotics reduced the risk of *H. pylori* therapy related side effects (RR, 0.60; 95%CI: 0.40-0.91). In another meta-analysis, the pooled odd ratios (ORs) for the eradication rate were higher in the probiotic group than the control group (OR = 1.67; 95%CI: 1.38-2.02) by ITT, and adverse effects were lower in the probiotic group (OR = 0.49, 95%CI: 0.26-0.94)[[128](#_ENREF_128)]. This study also showed racial differences in the sensitivity to probiotics, with greater differences in Asian populations compared to Caucasians. Adults, as well as children, have reported that probiotics positively affect eradication rates[[129](#_ENREF_129)]. *Saccharomyces boulardii* is a type of probiotic gaining attention as a supplement for *H. pylori*. Recent reports have suggested that STT combined with *S. boulardii* could be effective for enhancing *H. pylori* eradication rates[[130](#_ENREF_130)]. Compared with no intervention, *S. boulardii-*including regimens significantly increased treatment success (RR, 1.13; 95%CI: 1.05-1.21) and reduced *H. pylori* therapy-related adverse effects (RR, 0.46; 95%CI: 0.3-0.7)[[131](#_ENREF_131)]. Furthermore, *Lactobacillus* and *Bifidobacterium* species also have an anti-*H. pylori* effect. A meta-analysis of 10 studies on *Lactobacillus-*containing and *Bifidobacterium-*containing probiotics use as a supplementation to *H. pylori* eradication therapy found that the pooled ORs by ITT analysis and PP analysis were 2.066 (95%CI: 1.398-3.055) and 2.321 (95%CI: 1.715-3.142), respectively[[132](#_ENREF_132)]. In addition to the above references, *Lactobacillus acidophilus* and *Bifidobacterium bifidum* supplementation to STT is effective for *H. pylori* eradication and dynamic changes in intestinal flora[[133](#_ENREF_133)]. In recent RCT study, *Lactobacillus reuteri* was identified as a new probiotic proposed for the treatment of *H. pylori* infection. A combination that includes *L. reuteri* was able to reduce antibiotic-associated adverse events and to increase the *H. pylori* eradication rate[[134](#_ENREF_134)]. Although more research into these probiotics is needed, it is important to note that there are reduced drug complications and treatment is comparatively free from resistance. Therefore, probiotics will be considered important future therapeutics for *H. pylori* eradication.

**IS TAILORED THERAPY ON THE HORIZON FOR *H. PYLORI* TREATMENT?**

It is well known that clarithromycin sensitivity of the *H. pylori* infection contributes to the success of the STT eradication rate[[52](#_ENREF_52),[135](#_ENREF_135)]. Generally in infectious disease treatment, bacterial culture is carried out prior to determine the antibiotic selection of the organism. However, *H. pylori* bacterial culture is difficult and time-consuming, with various protocols for evaluating resistance. Thus, *H. pylori* treatment has depended on empirical antibiotic treatment[[109](#_ENREF_109)]. In their study, Gerrits *et al*[[136](#_ENREF_136)] determined that the A2142G, A2143G mutations were highly related to resistance using PCR, which was partially used to identify resistance to clarithromycin in *H. pylori*[[137](#_ENREF_137)]. There are several advantages to this method because it is relatively simple and efficient with a cost similar to a rapid urease test[[135](#_ENREF_135)]. In a recent study of 1232 patients, the eradication rate by selective treatment in the tailored group was 91.2%, which was significantly higher than control groups (amoxicillin, rabeprazole, clarithromycin; 75.9% and amoxicillin, rabeprazole, metronidazole; 79.1%)[[138](#_ENREF_138)].

Appropriate stomach acid suppression, as well as resistant strains of *H. pylori*, remains a problem for successful eradication. PPI plays an important role in *H. pylori* eradication and the main enzyme involved in PPI metabolism is CYP2C19[[139](#_ENREF_139)] and CYP2C19 genotypes can influence PPI efficacy[[140](#_ENREF_140)]. Homozygous extensive metabolizer (HomEM) results in the highest rates of PPI metabolism, heterozygous extensive metabolizer (HetEM) results in moderate rates of PPI metabolism, while poor metabolizers (PM) exhibit the lowest rates of PPI metabolism[[139](#_ENREF_139)]. The frequency of CYP2C19 polymorphism differs depending on ethnicity. Asians have a higher proportion of PM compared with Western populations, particularly Caucasians and African-Americans[[139](#_ENREF_139),[141](#_ENREF_141)]. In contrast, Caucasians have a higher prevalence rate of HomEM compared with Asians[[142](#_ENREF_142)]. Accordingly, geographic differences should be considered in selecting doses or types of PPIs for *H. pylori* treatment since there is a significant difference between HetEM and HomEM (OR = 1.90; 95%CI: 1.38-2.60) in *H. pylori* eradication rate[[143](#_ENREF_143)]. In additional subanalysis of individual PPIs revealed that omeprazole was influenced by the CYP2C19 genotype[[143](#_ENREF_143)]. In another meta-analysis, successful eradication rates differed considerably between PM and HetEM (OR = 1.73, *P* = 0.002) and between PM and HomEM (OR = 2.79, *P* < 0.0001) and even between HetEM and HomEM (OR = 2.00, *P* < 0.0001)[[144](#_ENREF_144)]. This study showed that a regimen including rabeprazole was not affected by CYP2C19 genotype status[[144](#_ENREF_144)]. According to a meta-analysis of a RCT in 2013, regardless of the PPI being taken, the eradication rates of PM were higher than HetEM and HomEM[[145](#_ENREF_145)]. In addition, results of the sub-analysis of the PPI type, omeprazole and lansoprazole were affected by CYP2C19 genotype. Unlike above, esomeprazole and rabeprazole were not affected by CYP2C19 genotype[[145](#_ENREF_145)]. In studies published in Japan, esomeprazole and rabeprazole are less influenced by CYP2C19 genotype compared with another PPIs[[146](#_ENREF_146),[147](#_ENREF_147)]. The efficacy of tailored *H. pylori* eradication treatment was demonstrated by Sugimoto *et al*[[148](#_ENREF_148)]. In a tailored regimen, *H. pylori* patients with clarithromycin-sensitivity were treated with clarithromycin, amoxicillin, rabeprazole, while clarithromycin-resistant patients were treated with metronidazole, amoxicillin, rabeprazole for 1 wk. As a result, the overall eradication rate was 96.7% (95%CI: 92.5%-98.9%) by ITT analysis and 97.4% (95%CI: 93.4%-99.3%) by PP analysis[[148](#_ENREF_148)]. The method achieved high eradication rates of 94.3% in CYP2C19 rapid metabolizers[[148](#_ENREF_148)]. Although CYP2C19 genotyping remains difficult clinically, tailored therapy may be useful in overcoming decreased eradication rates.

**NEWER AGENTS AND NONTRADITIONAL THERAPIES FOR *H. PYLORI* ERADICATION: HOPE IS COMING?**

In the last decade, many researchers have argued that new classes of antimicrobials with novel mechanisms of action are necessary to overcome increasing drug resistance. Some agents have shown an antibacterial effect against *H. pylori* *in vitro* regardless of drug resistance and are effective even at low pH. Among them, pyloricidin A, B, and C have a strong and selective anti-*H. pylori* effect which an MIC90 value of 0.013 mg/L[[149](#_ENREF_149)]. Benzimidazole derivatives (MIC90 = 0.025), polycyclic compound (MIC90 = 0.2-0.39), arylthiazole derivative 44 (MIC90 = 0.0065) also were highly effective against *H. pylori*[[149](#_ENREF_149)].

Cathelicidins and defensins are examples of human antimicrobial peptides (AMPs) native to the innate immune system of many eukaryotes that have activity against *H. pylori*[[150](#_ENREF_150)]. LL-37 is a cathelicidin with an anti-*H. pylori* effect[[151](#_ENREF_151)], and a recent study demonstrated that cathelicidin limited *H. pylori* colonization and related gastritis in mouse models[[152](#_ENREF_152)]. Defensin peptides have also been indicated to impede *H. pylori*[[153](#_ENREF_153)]. Human beta defensin 2 and 3 are differentially expressed in gastric mucosa during *H. pylori* infection[[154](#_ENREF_154)]. Oligo-acyl-lysyl (OAK) peptides, which have a structure and function similar to those of natural AMPs, have broad-spectrum antibacterial activity and anti-*H. pylori* effect *in vivo*[[155](#_ENREF_155)]. Unlike the natural AMPs, OAK peptides are without known proteolytic cleavage sites and thus, resistant to enzymatic cleavage.

SQ109 was developed as a tuberculosis treatment and known to be safe and tolerated in human trials[[150](#_ENREF_150)]. In an *in vitro* study, SQ109 had anti-*H. pylori* activity and a low *H. pylori* resistance rate[[156](#_ENREF_156)]. Pyridodiazepines are potent and selective molecules that target the *H. pylori* MurI inhibitor not effective against other bacteria[[157](#_ENREF_157)]. Sulfonamides and sulfamates were potent anti-beta-carbonic anhydrase molecules[[150](#_ENREF_150)]. *H. pylori* beta-carbonic anhydrase catalyzes the hydration of carbon dioxide to proton and bicarbonate to facilitate *H. pylori* metabolism of urea and bicarbonate and survive in low pH. Sulfonamides and sulfamates, inhibit the enzyme and are effective against *H. pylori*[[158](#_ENREF_158)].

Phytotherapy is expected to be another promising therapy for *H. pylori* eradication. Ginger rhizome extract has been demonstrated to have defensive activity in the stomach, increase stomach mucin regeneration, reinforce antioxidant enzymes, and suppress *H. pylori* growth[[159](#_ENREF_159)]. Capsaicin has an anti-inflammatory effect and inhibited *H. pylori*-induced interleukin (IL)-8 production by gastric epithelial cells[[160](#_ENREF_160)]. Sulphoraphane has also been indicated to suppress colonization and inhibit gastritis in *H. pylori*-infected mice and humans[[161](#_ENREF_161)]. Red ginseng extract has inhibitory 5-LOX enzyme activity and LOX-inhibiting action that suppresses inflammation of *H. pylori*-infected gastric epithelial cells[[162](#_ENREF_162)]. Epigallocatechin gallate (EGCG), one of the green tea catechins, showed significant cytoprotective effects against *H. pylori* associated gastric cytotoxicity[[163](#_ENREF_163)]. Red wine and resveratrol have also been shown to inhibit the growth of *H. pylori cagA*+ strains *in vitro*[[164](#_ENREF_164)]. In an open-label RCT, adding vitamin C and E to antibiotic regimens showed excellent *H. pylori* eradication rates. Compared to the group that did not contain vitamin, the group that combined vitamin C and E to lansoprazole, amoxicillin, clarithromycin, and bismuth citrate treatment had significantly higher eradication rates of 91.3% by ITT analysis and 93.5% by PP analysis[[165](#_ENREF_165)]. Thus, vitamin supplementation may be a future treatment option for *H. pylori*-related disease.

**MICRO- AND NANO-TECHNOLOGY: IS THE ROAD TO *H. PYLORI* ERADICATION IN THE FUTURE?**

Recently, several studies have determined the antibacterial activity of micro- and nano-technology against *H. pylori*. Liposomes are spherical vesicles that contain amphiphilic lipids in a bi- or multi-layer with an aqueous core used to encapsulate several compounds[[4](#_ENREF_4)]. This material contains biocompatible and biodegradable constituents without significant toxicity[[4](#_ENREF_4)]. According to Obonyo *et al*[[166](#_ENREF_166)], a liposomal nanoformulation of linolenic acid is a favorable nanotherapeutic with bactericidal activity against resistant strains of *H. pylori*. Another study suggested that an epitope-based therapeutic *H. pylori* vaccine may be beneficial in eradicating *H. pylori*[[167](#_ENREF_167)] and a double liposome-based dual drug system may be helpful for treatment of *H. pylori* infection[[168](#_ENREF_168)].

Polymeric particles have a number of advantages for use as an antibiotic delivery factor with an anti-*H. pylori* effect. It is possible to manipulate their shape to affect biodistribution to increase interactions with the target cell. They also have mucoadhesive properties and protects drugs from proteolytic enzyme. Importantly polymeric particles possess several mechanisms to overpower microbes[[4](#_ENREF_4)]. Encapsulation of clarithromycin and omeprazole using gliadin nanoparticles as a mucoadhesive component has been reported for the treatment of *H. pylori*[[169](#_ENREF_169)]. Another study also showed that positively charged gelatin microspheres could be a feasible applicant delivery system for eradication of *H. pylori*[[170](#_ENREF_170)]. The amoxicillin-loaded chitosan mucoadhesive microspheres could increase gastrointestinal residence time and enhance amoxicillin stability to contribute to *H. pylor*i treatment[[171](#_ENREF_171)]. In addition, chitosan nanoparticles improved the anti-*H. pylori* effect of chitosan[[172](#_ENREF_172)]. Genipin-cross-linked fucose-chitosan/heparin nanoparticles diminished drug release in stomach acid and then released amoxicillin in an *H. pylori* survival situation to inhibit *H. pylori* proliferation. In addition, amoxicillin-loaded nanoparticles increased *H. pylori* eradication and decreased *H. pylori*-associated gastric inflammation in an animal model[[173](#_ENREF_173)]. The metronidazole-loaded porous microparticles that exhibit sustained release of metronidazole could assist *H. pylori* eradication and healing from mucosal damage[[174](#_ENREF_174)]. Silver nanoparticles may also be safer bactericidal agents for the treatment of *H. pylori*-induced gastritis[[175](#_ENREF_175)]. Berberine-loaded targeted nanoparticles stimulated *H. pylori* clearance and suppressed stomach inflammation in *H. pylori* infection[[176](#_ENREF_176)].

**CONCLUSION**

Many studies have determined that novel agents and treatment regimens can improve eradication of *H. pylori.* With STT, high doses of PPI and prolonged therapy duration can increase eradication rates; indeed, in Europe and some regions of Asia these results are improved further with concomitant therapy. Concomitant therapy is less affected by antibiotic resistance, which adds value as an alternative treatment. Nevertheless, the eradication rates following concomitant therapy will gradually decrease due to the rapidly emerging antibiotic resistance of *H. pylori* worldwide.

In this review, we highlighted new and promising directions in *H. pylori* eradication. Although there are some practical limitations in applying probiotics and tailored therapy, they could of assistance in fighting *H. pylori*. Newer agents, nontraditional therapy, and microtechnology are also expected to play a major role in *H. pylori* eradication. However, several issues need to be solved to apply these treatments to the clinic. First, novel agents must be devoid of known proteolytic cleavage sites and thus, resistant to human digestive enzymatic cleavage. Second, these agents must be effective in an acidic environment. Third, these novel agents should be free from antibiotic resistance such as OAK. OAK have multiple nonspecific actions, so it would be hard to occur antibiotic resistance of *H. pylori*. Fourth, further studies are necessary to assess micro- and nano-toxicity, *in vitro* as well as *in vivo*. The safety and pharmacokinetic properties of novel treatments for *H. pylori* in humans also need to be evaluated. Finally, although novel treatments have many advantages, clinical studies are required to determine whether these findings can be applied to humans. In order to improve the eradication rate for *H. pylori* infection, further studies must be required.

**REFERENCES**

1 **Marshall BJ**, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **1**: 1311-1315 [PMID: 6145023]

2 **Kandulski A**, Selgrad M, Malfertheiner P. Helicobacter pylori infection: a clinical overview. *Dig Liver Dis* 2008; **40**: 619-626 [PMID: 18396114 DOI: 10.1016/j.dld.2008.02.026]

3 **McColl KE**. Clinical practice. Helicobacter pylori infection. *N Engl J Med* 2010; **362**: 1597-1604 [PMID: 20427808 DOI: 10.1056/NEJMcp1001110]

4 **Lopes D**, Nunes C, Martins MC, Sarmento B, Reis S. Eradication of Helicobacter pylori: Past, present and future. *J Control Release* 2014; **189**: 169-186 [PMID: 24969353 DOI: 10.1016/j.jconrel.2014.06.020]

5 **Wang Y**, Wang B, Lv ZF, Yang Y, Wang F, Wang H, Chen S, Xie Y, Zhou X. Efficacy and safety of ecabet sodium as an adjuvant therapy for Helicobacter pylori eradication: a systematic review and meta-analysis. *Helicobacter* 2014; **19**: 372-381 [PMID: 24826809 DOI: 10.1111/hel.12136]

6 **NIH Consensus Conference**. Helicobacter pylori in peptic ulcer disease. NIH Consensus Development Panel on Helicobacter pylori in Peptic Ulcer Disease. *JAMA* 1994; **272**: 65-69 [PMID: 8007082]

7 **Bytzer P**, Dahlerup JF, Eriksen JR, Jarbøl DE, Rosenstock S, Wildt S. Diagnosis and treatment of Helicobacter pylori infection. *Dan Med Bull* 2011; **58**: C4271 [PMID: 21466771]

8 **Tytgat GN**. Etiopathogenetic principles and peptic ulcer disease classification. *Dig Dis* 2011; **29**: 454-458 [PMID: 22095009 DOI: 10.1159/000331520]

9 **Testerman TL**, Morris J. Beyond the stomach: an updated view of Helicobacter pylori pathogenesis, diagnosis, and treatment. *World J Gastroenterol* 2014; **20**: 12781-12808 [PMID: 25278678 DOI: 10.3748/wjg.v20.i36.12781]

10 **Georgopoulos SD**, Papastergiou V, Karatapanis S. Current options for the treatment of Helicobacter pylori. *Expert Opin Pharmacother* 2013; **14**: 211-223 [PMID: 23331077 DOI: 10.1517/14656566.2013.763926]

11 **Freeman HJ**. Disappearance of Helicobacter without antibiotics in 12 patients with gastritis. *Canadian journal of gastroenterology* 1997; 11(2): 167-172 [PMID: 9113817]

12 **Go MF**. Review article: natural history and epidemiology of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2002; **16** Suppl 1: 3-15 [PMID: 11849122]

13 **Fakheri H**, Bari Z, Aarabi M, Malekzadeh R. Helicobacter pylori eradication in West Asia: a review. *World J Gastroenterol* 2014; **20**: 10355-10367 [PMID: 25132752 DOI: 10.3748/wjg.v20.i30.10355]

14 **Bouvard V**, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V. A review of human carcinogens--Part B: biological agents. *Lancet Oncol* 2009; **10**: 321-322 [PMID: 19350698]

15 **Fukase K**, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, Terao S, Amagai K, Hayashi S, Asaka M. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008; **372**: 392-397 [PMID: 18675689 DOI: 10.1016/S0140-6736(08)61159-9]

16 **Suzuki H**, Nishizawa T, Hibi T. Helicobacter pylori eradication therapy. *Future Microbiol* 2010; **5**: 639-648 [PMID: 20353303 DOI: 10.2217/fmb.10.25]

17 **Nishizawa T**, Nishizawa Y, Yahagi N, Kanai T, Takahashi M, Suzuki H. Effect of supplementation with rebamipide for Helicobacter pylori eradication therapy: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2014; **29** Suppl 4: 20-24 [PMID: 25521728 DOI: 10.1111/jgh.12769]

18 **Molina-Infante J**, Gisbert JP. Optimizing clarithromycin-containing therapy for Helicobacter pylori in the era of antibiotic resistance. *World J Gastroenterol* 2014; **20**: 10338-10347 [PMID: 25132750 DOI: 10.3748/wjg.v20.i30.10338]

19 **Gisbert JP**, González L, Calvet X, García N, López T, Roqué M, Gabriel R, Pajares JM. Proton pump inhibitor, clarithromycin and either amoxycillin or nitroimidazole: a meta-analysis of eradication of Helicobacter pylori. *Aliment Pharmacol Ther* 2000; **14**: 1319-1328 [PMID: 11012477]

20 **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]

21 **Gasparetto M**, Pescarin M, Guariso G. Helicobacter pylori Eradication Therapy: Current Availabilities. *ISRN Gastroenterol* 2012; **2012**: 186734 [PMID: 22900197 DOI: 10.5402/2012/186734]

22 **Xie C**, Lu NH. Review: clinical management of Helicobacter pylori infection in China. *Helicobacter* 2015; **20**: 1-10 [PMID: 25382801 DOI: 10.1111/hel.12178]

23 **Chung JW**, Lee GH, Han JH, Jeong JY, Choi KS, Kim do H, Jung KW, Choi KD, Song HJ, Jung HY, Kim JH. The trends of one-week first-line and second-line eradication therapy for Helicobacter pylori infection in Korea. *Hepatogastroenterology* 2011; **58**: 246-250 [PMID: 21510323]

24 **Yoon JH**, Baik GH, Sohn KM, Kim DY, Kim YS, Suk KT, Kim JB, Kim DJ, Kim JB, Shin WG, Kim HY, Baik IH, Jang HJ. Trends in the eradication rates of Helicobacter pylori infection for eleven years. *World J Gastroenterol* 2012; **18**: 6628-6634 [PMID: 23236238 DOI: 10.3748/wjg.v18.i45.6628]

25 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]

26 **Boyanova L**. Prevalence of multidrug-resistant Helicobacter pylori in Bulgaria. *J Med Microbiol* 2009; **58**: 930-935 [PMID: 19502370 DOI: 10.1099/jmm.0.009993-0]

27 **Nishizawa T**, Suzuki H, Suzuki M, Takahashi M, Hibi T. Proton pump inhibitor-amoxicillin-clarithromycin versus proton pump inhibitor-amoxicillin-metronidazole as first-line Helicobacter pylori eradication therapy. *J Clin Biochem Nutr* 2012; **51**: 114-116 [PMID: 22962528 DOI: 10.3164/jcbn.D-11-00029R1]

28 **Oh HS**, Lee DH, Seo JY, Cho YR, Kim N, Jeoung SH, Kim JW, Hwang JH, Park YS, Lee SH, Shin CM, Cho HJ, Jung HC, Song IS. Ten-day sequential therapy is more effective than proton pump inhibitor-based therapy in Korea: a prospective, randomized study. *J Gastroenterol Hepatol* 2012; **27**: 504-509 [PMID: 21916989 DOI: 10.1111/j.1440-1746.2011.06922.x]

29 **Perri F**, Villani MR, Festa V, Quitadamo M, Andriulli A. Predictors of failure of Helicobacter pylori eradication with the standard 'Maastricht triple therapy'. *Aliment Pharmacol Ther* 2001; **15**: 1023-1029 [PMID: 11421878]

30 **Ierardi E**, Giorgio F, Losurdo G, Di Leo A, Principi M. How antibiotic resistances could change Helicobacter pylori treatment: A matter of geography? *World J Gastroenterol* 2013; **19**: 8168-8180 [PMID: 24363506 DOI: 10.3748/wjg.v19.i45.8168]

31 **Oleastro M**, Ménard A, Santos A, Lamouliatte H, Monteiro L, Barthélémy P, Mégraud F. Real-time PCR assay for rapid and accurate detection of point mutations conferring resistance to clarithromycin in Helicobacter pylori. *J Clin Microbiol* 2003; **41**: 397-402 [PMID: 12517879]

32 **De Francesco V**, Margiotta M, Zullo A, Hassan C, Troiani L, Burattini O, Stella F, Di Leo A, Russo F, Marangi S, Monno R, Stoppino V, Morini S, Panella C, Ierardi E. Clarithromycin-resistant genotypes and eradication of Helicobacter pylori. *Ann Intern Med* 2006; **144**: 94-100 [PMID: 16418408]

33 **Barile KA**, Silva AL, Xavier JN, Assumpção MB, Corvelo TC. Characterization of 23S rRNA domain V mutations in gastric biopsy patients from the eastern Amazon. *Mem Inst Oswaldo Cruz* 2010; **105**: 314-317 [PMID: 20512246]

34 **Lins AK**, Lima RA, Magalhães M. Clarithromycin-resistant Helicobacter pylori in Recife, Brazil, directly identified from gastric biopsies by polymerase chain reaction. *Arq Gastroenterol* 2010; **47**: 379-382 [PMID: 21225149]

35 **Lee JW**, Kim N, Kim JM, Nam RH, Chang H, Kim JY, Shin CM, Park YS, Lee DH, Jung HC. Prevalence of primary and secondary antimicrobial resistance of Helicobacter pylori in Korea from 2003 through 2012. *Helicobacter* 2013; **18**: 206-214 [PMID: 23241101 DOI: 10.1111/hel.12031]

36 **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]

37 **Murakami K**, Furuta T, Ando T, Nakajima T, Inui Y, Oshima T, Tomita T, Mabe K, Sasaki M, Suganuma T, Nomura H, Satoh K, Hori S, Inoue S, Tomokane T, Kudo M, Inaba T, Take S, Ohkusa T, Yamamoto S, Mizuno S, Kamoshida T, Amagai K, Iwamoto J, Miwa J, Kodama M, Okimoto T, Kato M, Asaka M. Multi-center randomized controlled study to establish the standard third-line regimen for Helicobacter pylori eradication in Japan. *J Gastroenterol* 2013; **48**: 1128-1135 [PMID: 23307042 DOI: 10.1007/s00535-012-0731-8]

38 **Sun QJ**, Liang X, Zheng Q, Gu WQ, Liu WZ, Xiao SD, Lu H. Resistance of Helicobacter pylori to antibiotics from 2000 to 2009 in Shanghai. *World J Gastroenterol* 2010; **16**: 5118-5121 [PMID: 20976850]

39 **Su P**, Li Y, Li H, Zhang J, Lin L, Wang Q, Guo F, Ji Z, Mao J, Tang W, Shi Z, Shao W, Mao J, Zhu X, Zhang X, Tong Y, Tu H, Jiang M, Wang Z, Jin F, Yang N, Zhang J. Antibiotic resistance of Helicobacter pylori isolated in the Southeast Coastal Region of China. *Helicobacter* 2013; **18**: 274-279 [PMID: 23418857 DOI: 10.1111/hel.12046]

40 **Binh TT**, Shiota S, Nguyen LT, Ho DD, Hoang HH, Ta L, Trinh DT, Fujioka T, Yamaoka Y. The incidence of primary antibiotic resistance of Helicobacter pylori in Vietnam. *J Clin Gastroenterol* 2013; **47**: 233-238 [PMID: 23090037 DOI: 10.1097/MCG.0b013e3182676e2b]

41 **Dos Santos AA**, Carvalho AA. Pharmacological therapy used in the elimination of Helicobacter pylori infection: a review. *World J Gastroenterol* 2015; **21**: 139-154 [PMID: 25574087 DOI: 10.3748/wjg.v21.i1.139]

42 **Goh KL**, Navaratnam P. High Helicobacter pylori resistance to metronidazole but zero or low resistance to clarithromycin, levofloxacin, and other antibiotics in Malaysia. *Helicobacter* 2011; **16**: 241-245 [PMID: 21585611 DOI: 10.1111/j.1523-5378.2011.00841.x]

43 **Secka O**, Berg DE, Antonio M, Corrah T, Tapgun M, Walton R, Thomas V, Galano JJ, Sancho J, Adegbola RA, Thomas JE. Antimicrobial susceptibility and resistance patterns among Helicobacter pylori strains from The Gambia, West Africa. *Antimicrob Agents Chemother* 2013; **57**: 1231-1237 [PMID: 23263004 DOI: 10.1128/AAC.00517-12]

44 **Seck A**, Burucoa C, Dia D, Mbengue M, Onambele M, Raymond J, Breurec S. Primary antibiotic resistance and associated mechanisms in Helicobacter pylori isolates from Senegalese patients. *Ann Clin Microbiol Antimicrob* 2013; **12**: 3 [PMID: 23298145 DOI: 10.1186/1476-0711-12-3]

45 **De Francesco V**, Giorgio F, Hassan C, Manes G, Vannella L, Panella C, Ierardi E, Zullo A. Worldwide H. pylori antibiotic resistance: a systematic review. *J Gastrointestin Liver Dis* 2010; **19**: 409-414 [PMID: 21188333]

46 **Storskrubb T**, Aro P, Ronkainen J, Wreiber K, Nyhlin H, Bolling-Sternevald E, Talley NJ, Engstrand L, Agréus L. Antimicrobial susceptibility of Helicobacter pylori strains in a random adult Swedish population. *Helicobacter* 2006; **11**: 224-230 [PMID: 16882324 DOI: 10.1111/j.1523-5378.2006.00414.x]

47 **Selgrad M**, Meissle J, Bornschein J, Kandulski A, Langner C, Varbanova M, Wex T, Tammer I, Schlüter D, Malfertheiner P. Antibiotic susceptibility of Helicobacter pylori in central Germany and its relationship with the number of eradication therapies. *Eur J Gastroenterol Hepatol* 2013; **25**: 1257-1260 [PMID: 23863261 DOI: 10.1097/MEG.0b013e3283643491]

48 **De Francesco V**, Margiotta M, Zullo A, Hassan C, Giorgio F, Burattini O, Stoppino G, Cea U, Pace A, Zotti M, Morini S, Panella C, Ierardi E. Prevalence of primary clarithromycin resistance in Helicobacter pylori strains over a 15 year period in Italy. *J Antimicrob Chemother* 2007; **59**: 783-785 [PMID: 17329269 DOI: 10.1093/jac/dkm005]

49 **Molina-Infante J**, Gisbert JP. [Update on the efficacy of triple therapy for Helicobacter pylori infection and clarithromycin resistance rates in Spain (2007-2012)]. *Gastroenterol Hepatol* 2013; **36**: 375-381 [PMID: 23623461 DOI: 10.1016/j.gastrohep.2013.02.006]

50 **Oleastro M**, Cabral J, Ramalho PM, Lemos PS, Paixão E, Benoliel J, Santos A, Lopes AI. Primary antibiotic resistance of Helicobacter pylori strains isolated from Portuguese children: a prospective multicentre study over a 10 year period. *J Antimicrob Chemother* 2011; **66**: 2308-2311 [PMID: 21764826 DOI: 10.1093/jac/dkr293]

51 **Karczewska E**, Klesiewicz K, Skiba I, Wojtas-Bonior I, Sito E, Czajecki K, Zwolińska-Wcisło M, Budak A. Variability in Prevalence of Helicobacter pylori Strains Resistant to Clarithromycin and Levofloxacin in Southern Poland. *Gastroenterol Res Pract* 2012; **2012**: 418010 [PMID: 22693490 DOI: 10.1155/2012/418010]

52 **Houben MH**, van de Beek D, Hensen EF, de Craen AJ, Rauws EA, Tytgat GN. A systematic review of Helicobacter pylori eradication therapy--the impact of antimicrobial resistance on eradication rates. *Aliment Pharmacol Ther* 1999; **13**: 1047-1055 [PMID: 10468680]

53 **Papastergiou V**, Georgopoulos SD, Karatapanis S. Treatment of Helicobacter pylori infection: Past, present and future. *World J Gastrointest Pathophysiol* 2014; **5**: 392-399 [PMID: 25400982 DOI: 10.4291/wjgp.v5.i4.392]

54 **Milani M**, Ghotaslou R, Akhi MT, Nahaei MR, Hasani A, Somi MH, Rafeey M, Sharifi Y. The status of antimicrobial resistance of Helicobacter pylori in Eastern Azerbaijan, Iran: comparative study according to demographics. *J Infect Chemother* 2012; **18**: 848-852 [PMID: 22581031 DOI: 10.1007/s10156-012-0425-4]

55 **Torres J**, Camorlinga-Ponce M, Pérez-Pérez G, Madrazo-De la Garza A, Dehesa M, González-Valencia G, Muñoz O. Increasing multidrug resistance in Helicobacter pylori strains isolated from children and adults in Mexico. *J Clin Microbiol* 2001; **39**: 2677-2680 [PMID: 11427594 DOI: 10.1128/JCM.39.7.2677-2680.2001]

56 **Duck WM**, Sobel J, Pruckler JM, Song Q, Swerdlow D, Friedman C, Sulka A, Swaminathan B, Taylor T, Hoekstra M, Griffin P, Smoot D, Peek R, Metz DC, Bloom PB, Goldschmidt S, Parsonnet J, Triadafilopoulos G, Perez-Perez GI, Vakil N, Ernst P, Czinn S, Dunne D, Gold BD. Antimicrobial resistance incidence and risk factors among Helicobacter pylori-infected persons, United States. *Emerg Infect Dis* 2004; **10**: 1088-1094 [PMID: 15207062 DOI: 10.3201/eid1006.030744]

57 **Larsen AL**, Ragnhildstveit E, Moayeri B, Eliassen L, Melby KK. Resistance rates of metronidazole and other antibacterials in Helicobacter pylori from previously untreated patients in Norway. *APMIS* 2013; **121**: 353-358 [PMID: 23083455 DOI: 10.1111/apm.12009]

58 **Mégraud F**. Current recommendations for Helicobacter pylori therapies in a world of evolving resistance. *Gut Microbes* 2013; **4**: 541-548 [PMID: 23929066 DOI: 10.4161/gmic.25930]

59 **Rispo A**, Capone P, Castiglione F, Pasquale L, Rea M, Caporaso N. Fluoroquinolone-based protocols for eradication of Helicobacter pylori. *World J Gastroenterol* 2014; **20**: 8947-8956 [PMID: 25083067 DOI: 10.3748/wjg.v20.i27.8947]

60 **Rajper S**, Khan E, Ahmad Z, Alam SM, Akbar A, Hasan R. Macrolide and fluoroquinolone resistance in Helicobacter pylori isolates: an experience at a tertiary care centre in Pakistan. *J Pak Med Assoc* 2012; **62**: 1140-1144 [PMID: 23866399]

61 **Chung JW**, Lee GH, Jeong JY, Lee SM, Jung JH, Choi KD, Song HJ, Jung HY, Kim JH. Resistance of Helicobacter pylori strains to antibiotics in Korea with a focus on fluoroquinolone resistance. *J Gastroenterol Hepatol* 2012; **27**: 493-497 [PMID: 21793912 DOI: 10.1111/j.1440-1746.2011.06874.x]

62 **Mégraud F**. H pylori antibiotic resistance: prevalence, importance, and advances in testing. *Gut* 2004; **53**: 1374-1384 [PMID: 15306603 DOI: 10.1136/gut.2003.022111]

63 **O'Connor A**, Taneike I, Nami A, Fitzgerald N, Ryan B, Breslin N, O'Connor H, McNamara D, Murphy P, O'Morain C. Helicobacter pylori resistance rates for levofloxacin, tetracycline and rifabutin among Irish isolates at a reference centre. *Ir J Med Sci* 2013; **182**: 693-695 [PMID: 23625165 DOI: 10.1007/s11845-013-0957-3]

64 **Wueppenhorst N**, Stueger HP, Kist M, Glocker EO. High secondary resistance to quinolones in German Helicobacter pylori clinical isolates. *J Antimicrob Chemother* 2013; **68**: 1562-1566 [PMID: 23463210 DOI: 10.1093/jac/dkt061]

65 **Eisig JN**, Silva FM, Barbuti RC, Navarro-Rodriguez T, Moraes-Filho JP, Pedrazzoli Jr J. Helicobacter pylori antibiotic resistance in Brazil: clarithromycin is still a good option. *Arq Gastroenterol* 2011; **48**: 261-264 [PMID: 22147131]

66 Current European concepts in the management of Helicobacter pylori infection. The Maastricht Consensus Report. European Helicobacter Pylori Study Group. *Gut* 1997; **41**: 8-13 [PMID: 9274464]

67 **Lind T**, Veldhuyzen van Zanten S, Unge P, Spiller R, Bayerdörffer E, O'Morain C, Bardhan KD, Bradette M, Chiba N, Wrangstadh M, Cederberg C, Idström JP. Eradication of Helicobacter pylori using one-week triple therapies combining omeprazole with two antimicrobials: the MACH I Study. *Helicobacter* 1996; **1**: 138-144 [PMID: 9398894]

68 **Romano M**, Cuomo A. Eradication of Helicobacter pylori: a clinical update. *MedGenMed* 2004; **6**: 19 [PMID: 15208531]

69 **Nishizawa T**, Suzuki H, Takahashi M, Suzuki M, Hibi T. Delay of second-line eradication therapy for Helicobacter pylori can increase eradication failure. *J Gastroenterol Hepatol* 2013; **28**: 1608-1610 [PMID: 23701705 DOI: 10.1111/jgh.12281]

70 **Graham DY**. Helicobacter pylori update: gastric cancer, reliable therapy, and possible benefits. *Gastroenterology* 2015; **148**: 719-731.e3 [PMID: 25655557 DOI: 10.1053/j.gastro.2015.01.040]

71 **Calvet X**, García N, López T, Gisbert JP, Gené E, Roque M. A meta-analysis of short versus long therapy with a proton pump inhibitor, clarithromycin and either metronidazole or amoxycillin for treating Helicobacter pylori infection. *Aliment Pharmacol Ther* 2000; **14**: 603-609 [PMID: 10792124]

72 **Yuan Y**, Ford AC, Khan KJ, Gisbert JP, Forman D, Leontiadis GI, Tse F, Calvet X, Fallone C, Fischbach L, Oderda G, Bazzoli F, Moayyedi P. Optimum duration of regimens for Helicobacter pylori eradication. *Cochrane Database Syst Rev* 2013; **12**: CD008337 [PMID: 24338763 DOI: 10.1002/14651858.CD008337.pub2]

73 **Fuccio L**, Minardi ME, Zagari RM, Grilli D, Magrini N, Bazzoli F. Meta-analysis: duration of first-line proton-pump inhibitor based triple therapy for Helicobacter pylori eradication. *Ann Intern Med* 2007; **147**: 553-562 [PMID: 17938394]

74 **Smith SM**, Haider RB, O'Connor H, McNamara D, O'Morain C. Practical treatment of Helicobacter pylori: a balanced view in changing times. *Eur J Gastroenterol Hepatol* 2014; **26**: 819-825 [PMID: 24892516 DOI: 10.1097/MEG.0000000000000130]

75 **Vallve M**, Vergara M, Gisbert JP, Calvet X. Single vs. double dose of a proton pump inhibitor in triple therapy for Helicobacter pylori eradication: a meta-analysis. *Aliment Pharmacol Ther* 2002; **16**: 1149-1156 [PMID: 12030958]

76 **Villoria A**, Garcia P, Calvet X, Gisbert JP, Vergara M. Meta-analysis: high-dose proton pump inhibitors vs. standard dose in triple therapy for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2008; **28**: 868-877 [PMID: 18644011 DOI: 10.1111/j.1365-2036.2008.03807.x]

77 **Nagaraja V**, Eslick GD. Evidence-based assessment of proton-pump inhibitors in Helicobacter pylori eradication: a systematic review. *World J Gastroenterol* 2014; **20**: 14527-14536 [PMID: 25356018 DOI: 10.3748/wjg.v20.i40.14527]

78 **Luther J**, Higgins PD, Schoenfeld PS, Moayyedi P, Vakil N, Chey WD. Empiric quadruple vs. triple therapy for primary treatment of Helicobacter pylori infection: Systematic review and meta-analysis of efficacy and tolerability. *Am J Gastroenterol* 2010; **105**: 65-73 [PMID: 19755966 DOI: 10.1038/ajg.2009.508]

79 **Liu KS**, Hung IF, Seto WK, Tong T, Hsu AS, Lam FY, But DY, Wong SY, Leung WK. Ten day sequential versus 10 day modified bismuth quadruple therapy as empirical firstline and secondline treatment for Helicobacter pylori in Chinese patients: an open label, randomised, crossover trial. *Gut* 2014; **63**: 1410-1415 [PMID: 24295850 DOI: 10.1136/gutjnl-2013-306120]

80 **Salazar CO**, Cardenas VM, Reddy RK, Dominguez DC, Snyder LK, Graham DY. Greater than 95% success with 14-day bismuth quadruple anti- Helicobacter pylori therapy: a pilot study in US Hispanics. *Helicobacter* 2012; **17**: 382-390 [PMID: 22967122 DOI: 10.1111/j.1523-5378.2012.00962.x]

81 **Sapmaz F**, Kalkan IH, Güliter S, Atasoy P. Comparison of Helicobacter pylori eradication rates of standard 14-day quadruple treatment and novel modified 10-day, 12-day and 14-day sequential treatments. *Eur J Intern Med* 2014; **25**: 224-229 [PMID: 24268371 DOI: 10.1016/j.ejim.2013.11.006]

82 **Uygun A**, Kadayifci A, Safali M, Ilgan S, Bagci S. The efficacy of bismuth containing quadruple therapy as a first-line treatment option for Helicobacter pylori. *J Dig Dis* 2007; **8**: 211-215 [PMID: 17970879 DOI: 10.1111/j.1751-2980.2007.00308.x]

83 **Kadayifci A**, Uygun A, Polat Z, Kantarcioğlu M, Kılcıler G, Başer O, Ozcan A, Emer O. Comparison of bismuth-containing quadruple and concomitant therapies as a first-line treatment option for Helicobacter pylori. *Turk J Gastroenterol* 2012; **23**: 8-13 [PMID: 22505373]

84 **Zullo A**, Rinaldi V, Winn S, Meddi P, Lionetti R, Hassan C, Ripani C, Tomaselli G, Attili AF. A new highly effective short-term therapy schedule for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2000; **14**: 715-718 [PMID: 10848654]

85 **Nasa M**, Choksey A, Phadke A, Sawant P. Sequential therapy versus standard triple-drug therapy for Helicobacter pylori eradication: a randomized study. *Indian J Gastroenterol* 2013; **32**: 392-396 [PMID: 24158898 DOI: 10.1007/s12664-013-0357-7]

86 **Gatta L**, Vakil N, Vaira D, Scarpignato C. Global eradication rates for Helicobacter pylori infection: systematic review and meta-analysis of sequential therapy. *BMJ* 2013; **347**: f4587 [PMID: 23926315 DOI: 10.1136/bmj.f4587]

87 **Chung JW**, Ha M, Yun SC, Kim JH, Lee JJ, Kim YJ, Kim KO, Kwon KA, Park DK, Lee DH. Meta-analysis: Sequential therapy is superior to conventional therapy for Helicobacter pylori infection in Korea. *Korean J Gastroenterol* 2013; **62**: 267-271 [PMID: 24262591]

88 **Murakami K**, Fujioka T, Okimoto T, Sato R, Kodama M, Nasu M. Drug combinations with amoxycillin reduce selection of clarithromycin resistance during Helicobacter pylori eradication therapy. *Int J Antimicrob Agents* 2002; **19**: 67-70 [PMID: 11814770]

89 **Webber MA**, Piddock LJ. The importance of efflux pumps in bacterial antibiotic resistance. *J Antimicrob Chemother* 2003; **51**: 9-11 [PMID: 12493781]

90 **Maconi G**, Parente F, Russo A, Vago L, Imbesi V, Bianchi Porro G. Do some patients with Helicobacter pylori infection benefit from an extension to 2 weeks of a proton pump inhibitor-based triple eradication therapy? *Am J Gastroenterol* 2001; **96**: 359-366 [PMID: 11232676 DOI: 10.1111/j.1572-0241.2001.03519.x]

91 **Lee H**, Hong SN, Min BH, Lee JH, Rhee PL, Lee YC, Kim JJ. Comparison of efficacy and safety of levofloxacin-containing versus standard sequential therapy in eradication of Helicobacter pylori infection in Korea. *Dig Liver Dis* 2015; **47**: 114-118 [PMID: 25467826 DOI: 10.1016/j.dld.2014.10.014]

92 **Lee JW**, Kim N, Kim JM, Nam RH, Kim JY, Lee JY, Lee DH, Jung HC. A comparison between 15-day sequential, 10-day sequential and proton pump inhibitor-based triple therapy for Helicobacter pylori infection in Korea. *Scand J Gastroenterol* 2014; **49**: 917-924 [PMID: 24988873 DOI: 10.3109/00365521.2014.896409]

93 **Zhou L**, Zhang J, Chen M, Hou X, Li Z, Song Z, He L, Lin S. A comparative study of sequential therapy and standard triple therapy for Helicobacter pylori infection: a randomized multicenter trial. *Am J Gastroenterol* 2014; **109**: 535-541 [PMID: 24642580 DOI: 10.1038/ajg.2014.26]

94 **Ben Chaabane N**, Al-Adhba HS. Ciprofloxacin-containing versus clarithromycin-containing sequential therapy for Helicobacter pylori eradication: A randomized trial. *Indian J Gastroenterol* 2015; **34**: 68-72 [PMID: 25721770 DOI: 10.1007/s12664-015-0535-x]

95 **Kang BK**, Park SM, Kim BW. [New therapeutic strategies against Helicobacter pylori]. *Korean J Gastroenterol* 2014; **63**: 146-150 [PMID: 24651587]

96 **Gisbert JP**, Calvet X. Update on non-bismuth quadruple (concomitant) therapy for eradication of Helicobacter pylori. *Clin Exp Gastroenterol* 2012; **5**: 23-34 [PMID: 22457599 DOI: 10.2147/CEG.S25419]

97 **Molina-Infante J**, Pazos-Pacheco C, Vinagre-Rodriguez G, Perez-Gallardo B, Dueñas-Sadornil C, Hernandez-Alonso M, Gonzalez-Garcia G, Mateos-Rodriguez JM, Fernandez-Bermejo M, Gisbert JP. Nonbismuth quadruple (concomitant) therapy: empirical and tailored efficacy versus standard triple therapy for clarithromycin-susceptible Helicobacter pylori and versus sequential therapy for clarithromycin-resistant strains. *Helicobacter* 2012; **17**: 269-276 [PMID: 22759326 DOI: 10.1111/j.1523-5378.2012.00947.x]

98 **Gisbert JP**, Calvet X. Review article: non-bismuth quadruple (concomitant) therapy for eradication of Helicobater pylori. *Aliment Pharmacol Ther* 2011; **34**: 604-617 [PMID: 21745241 DOI: 10.1111/j.1365-2036.2011.04770.x]

99 **Essa AS**, Kramer JR, Graham DY, Treiber G. Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing "concomitant therapy" versus triple therapy for Helicobacter pylori eradication. *Helicobacter* 2009; **14**: 109-118 [PMID: 19298338 DOI: 10.1111/j.1523-5378.2009.00671.x]

100 **Lee HJ**, Kim JI, Lee JS, Jun EJ, Oh JH, Cheung DY, Chung WC, Kim BW, Kim SS. Concomitant therapy achieved the best eradication rate for Helicobacter pylori among various treatment strategies. *World J Gastroenterol* 2015; **21**: 351-359 [PMID: 25574111 DOI: 10.3748/wjg.v21.i1.351]

101 **Kim SY**, Park DK, Kwon KA, Kim KO, Kim YJ, Chung J. [Ten day concomitant therapy is superior to ten day sequential therapy for Helicobacter pylori eradication]. *Korean J Gastroenterol* 2014; **64**: 260-267 [PMID: 25420735]

102 **Ang TL**, Fock KM, Song M, Ang D, Kwek AB, Ong J, Tan J, Teo EK, Dhamodaran S. Ten-day triple therapy versus sequential therapy versus concomitant therapy as first-line treatment for Helicobacter pylori infection. *J Gastroenterol Hepatol* 2015; **30**: 1134-1139 [PMID: 25639278 DOI: 10.1111/jgh.12892]

103 **McNicholl AG**, Marin AC, Molina-Infante J, Castro M, Barrio J, Ducons J, Calvet X, de la Coba C, Montoro M, Bory F, Perez-Aisa A, Forné M, Gisbert JP. Randomised clinical trial comparing sequential and concomitant therapies for Helicobacter pylori eradication in routine clinical practice. *Gut* 2014; **63**: 244-249 [PMID: 23665990 DOI: 10.1136/gutjnl-2013-304820]

104 **Lim JH**, Lee DH, Choi C, Lee ST, Kim N, Jeong SH, Kim JW, Hwang JH, Park YS, Lee SH, Shin CM, Jo HJ, Jang ES, Song Is, Jung HC. Clinical outcomes of two-week sequential and concomitant therapies for Helicobacter pylori eradication: a randomized pilot study. *Helicobacter* 2013; **18**: 180-186 [PMID: 23305083 DOI: 10.1111/hel.12034]

105 **De Francesco V**, Hassan C, Ridola L, Giorgio F, Ierardi E, Zullo A. Sequential, concomitant and hybrid first-line therapies for Helicobacter pylori eradication: a prospective randomized study. *J Med Microbiol* 2014; **63**: 748-752 [PMID: 24586031 DOI: 10.1099/jmm.0.072322-0]

106 **Greenberg ER**, Anderson GL, Morgan DR, Torres J, Chey WD, Bravo LE, Dominguez RL, Ferreccio C, Herrero R, Lazcano-Ponce EC, Meza-Montenegro MM, Peña R, Peña EM, Salazar-Martínez E, Correa P, Martínez ME, Valdivieso M, Goodman GE, Crowley JJ, Baker LH. 14-day triple, 5-day concomitant, and 10-day sequential therapies for Helicobacter pylori infection in seven Latin American sites: a randomised trial. *Lancet* 2011; **378**: 507-514 [PMID: 21777974 DOI: 10.1016/S0140-6736(11)60825-8]

107 **Zullo A**, Scaccianoce G, De Francesco V, Ruggiero V, D'Ambrosio P, Castorani L, Bonfrate L, Vannella L, Hassan C, Portincasa P. Concomitant, sequential, and hybrid therapy for H. pylori eradication: a pilot study. *Clin Res Hepatol Gastroenterol* 2013; **37**: 647-650 [PMID: 23747131 DOI: 10.1016/j.clinre.2013.04.003]

108 **Graham DY**, Lee YC, Wu MS. Rational Helicobacter pylori therapy: evidence-based medicine rather than medicine-based evidence. *Clin Gastroenterol Hepatol* 2014; **12**: 177-186.e3; Discussion e12-13 [PMID: 23751282 DOI: 10.1016/j.cgh.2013.05.028]

109 **Lee JY**, Kim N. [Future trends of Helicobacter pylori eradication therapy in Korea]. *Korean J Gastroenterol* 2014; **63**: 158-170 [PMID: 24651589]

110 **Schito AM**, Schito GC. Levofloxacin, a broad spectrum anti-infective: from Streptococcus pneumoniae to Pseudomonas aeruginosa. *J Chemother* 2004; **16** Suppl 2: 3-7 [PMID: 15255554]

111 **Just PM**. Overview of the fluoroquinolone antibiotics. *Pharmacotherapy* 1993; **13**: 4S-17S [PMID: 8386356]

112 **O'Connor A**, Gisbert JP, McNamara D, O'Morain C. Treatment of Helicobacter pylori infection 2011. *Helicobacter* 2011; **16** Suppl 1: 53-58 [PMID: 21896086 DOI: 10.1111/j.1523-5378.2011.00881.x]

113 **Saad RJ**, Schoenfeld P, Kim HM, Chey WD. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent Helicobacter pylori infection: a meta-analysis. *Am J Gastroenterol* 2006; **101**: 488-496 [PMID: 16542284 DOI: 10.1111/j.1572-0241.1998.455\_t.x]

114 **Molina-Infante J**, Perez-Gallardo B, Fernandez-Bermejo M, Hernandez-Alonso M, Vinagre G, Dueñas C, Mateos-Rodriguez JM, Gonzalez-Garcia G, Abadia EG, Gisbert JP. Clinical trial: clarithromycin vs. levofloxacin in first-line triple and sequential regimens for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2010; **31**: 1077-1084 [PMID: 20180787 DOI: 10.1111/j.1365-2036.2010.04274.x]

115 **Ye CL**, Liao GP, He S, Pan YN, Kang YB, Zhang ZY. Levofloxacin and proton pump inhibitor-based triple therapy versus standard triple first-line therapy for Helicobacter pylori eradication. *Pharmacoepidemiol Drug Saf* 2014; **23**: 443-455 [PMID: 24677603 DOI: 10.1002/pds.3581]

116 **Peedikayil MC**, Alsohaibani FI, Alkhenizan AH. Levofloxacin-based first-line therapy versus standard first-line therapy for Helicobacter pylori eradication: meta-analysis of randomized controlled trials. *PLoS One* 2014; **9**: e85620 [PMID: 24465624 DOI: 10.1371/journal.pone.0085620]

117 **Chen MC**, Lei WY, Lin JS, Yi CH, Wu DC, Hu CT. Levofloxacin-amoxicillin/clavulanate-rabeprazole versus a standard seven-day triple therapy for eradication of Helicobacter pylori infection. *Biomed Res Int* 2014; **2014**: 158520 [PMID: 24995271 DOI: 10.1155/2014/158520]

118 **Xiao SP**, Gu M, Zhang GX. Is levofloxacin-based triple therapy an alternative for first-line eradication of Helicobacter pylori? A systematic review and meta-analysis. *Scand J Gastroenterol* 2014; **49**: 528-538 [PMID: 24611790 DOI: 10.3109/00365521.2014.887765]

119 **Graham DY**, Shiotani A. Which Therapy for Helicobacter pylori Infection? *Gastroenterology* 2012; **143**: 10-12 [PMID: 22613622 DOI: 10.1053/j.gastro.2012.05.012]

120 **Shiota S**, Reddy R, Alsarraj A, El-Serag HB, Graham DY. Antibiotic Resistance of Helicobacter pylori Among Male United States Veterans. *Clin Gastroenterol Hepatol* 2015; **13**: 1616-1624 [PMID: 25681693 DOI: 10.1016/j.cgh.2015.02.005]

121 **Ontsira Ngoyi EN**, Atipo Ibara BI, Moyen R, Ahoui Apendi PC, Ibara JR, Obengui O, Ossibi Ibara RB, Nguimbi E, Niama RF, Ouamba JM, Yala F, Abena AA, Vadivelu J, Goh KL, Menard A, Benejat L, Sifre E, Lehours P, Megraud F. Molecular Detection of Helicobacter pylori and its Antimicrobial Resistance in Brazzaville, Congo. *Helicobacter* 2015; **20**: 316-320 [PMID: 25585658 DOI: 10.1111/hel.12204]

122 **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]

123 **Kim JY**, Kim NY, Kim SJ, Baik GH, Kim GH, Kim JM, Nam RH, Kim HB, Lee DH, Jung HC, Song IS. [Regional difference of antibiotic resistance of helicobacter pylori strains in Korea]. *Korean J Gastroenterol* 2011; **57**: 221-229 [PMID: 21519175 DOI: 10.4166/2011.57.4.221]

124 **Furuta T**, Sugimoto M, Kodaira C, Nishino M, Yamade M, Uotani T, Sahara S, Ichikawa H, Yamada T, Osawa S, Sugimoto K, Watanabe H, Umemura K. Sitafloxacin-based third-line rescue regimens for Helicobacter pylori infection in Japan. *J Gastroenterol Hepatol* 2014; **29**: 487-493 [PMID: 24224808 DOI: 10.1111/jgh.12442]

125 **Akcam M**, Koca T, Salman H, Karahan N. The effects of probiotics on treatment of Helicobacter pylori eradication in children. *Saudi Med J* 2015; **36**: 286-290 [PMID: 25737169 DOI: 10.15537/smj.2015.3.10124]

126 **Navarro-Rodriguez T**, Silva FM, Barbuti RC, Mattar R, Moraes-Filho JP, de Oliveira MN, Bogsan CS, Chinzon D, Eisig JN. Association of a probiotic to a Helicobacter pylori eradication regimen does not increase efficacy or decreases the adverse effects of the treatment: a prospective, randomized, double-blind, placebo-controlled study. *BMC Gastroenterol* 2013; **13**: 56 [PMID: 23530767 DOI: 10.1186/1471-230X-13-56]

127 **Lv Z**, Wang B, Zhou X, Wang F, Xie Y, Zheng H, Lv N. Efficacy and safety of probiotics as adjuvant agents for Helicobacter pylori infection: A meta-analysis. *Exp Ther Med* 2015; **9**: 707-716 [PMID: 25667617 DOI: 10.3892/etm.2015.2174]

128 **Zhu R**, Chen K, Zheng YY, Zhang HW, Wang JS, Xia YJ, Dai WQ, Wang F, Shen M, Cheng P, Zhang Y, Wang CF, Yang J, Li JJ, Lu J, Zhou YQ, Guo CY. Meta-analysis of the efficacy of probiotics in Helicobacter pylori eradication therapy. *World J Gastroenterol* 2014; **20**: 18013-18021 [PMID: 25548501 DOI: 10.3748/wjg.v20.i47.18013]

129 **Li S**, Huang XL, Sui JZ, Chen SY, Xie YT, Deng Y, Wang J, Xie L, Li TJ, He Y, Peng QL, Qin X, Zeng ZY. Meta-analysis of randomized controlled trials on the efficacy of probiotics in Helicobacter pylori eradication therapy in children. *Eur J Pediatr* 2014; **173**: 153-161 [PMID: 24323343 DOI: 10.1007/s00431-013-2220-3]

130 **Song MJ**, Park DI, Park JH, Kim HJ, Cho YK, Sohn CI, Jeon WK, Kim BI. The effect of probiotics and mucoprotective agents on PPI-based triple therapy for eradication of Helicobacter pylori. *Helicobacter* 2010; **15**: 206-213 [PMID: 20557362 DOI: 10.1111/j.1523-5378.2010.00751.x]

131 **Szajewska H**, Horvath A, Piwowarczyk A. Meta-analysis: the effects of Saccharomyces boulardii supplementation on Helicobacter pylori eradication rates and side effects during treatment. *Aliment Pharmacol Ther* 2010; **32**: 1069-1079 [PMID: 21039671 DOI: 10.1111/j.1365-2036.2010.04457.x]

132 **Wang ZH**, Gao QY, Fang JY. Meta-analysis of the efficacy and safety of Lactobacillus-containing and Bifidobacterium-containing probiotic compound preparation in Helicobacter pylori eradication therapy. *J Clin Gastroenterol* 2013; **47**: 25-32 [PMID: 23090045 DOI: 10.1097/MCG.0b013e318266f6cf]

133 **Wang YH**, Huang Y. Effect of Lactobacillus acidophilus and Bifidobacterium bifidum supplementation to standard triple therapy on Helicobacter pylori eradication and dynamic changes in intestinal flora. *World J Microbiol Biotechnol* 2014; **30**: 847-853 [PMID: 24233772 DOI: 10.1007/s11274-013-1490-2]

134 **Francavilla R**, Polimeno L, Demichina A, Maurogiovanni G, Principi B, Scaccianoce G, Ierardi E, Russo F, Riezzo G, Di Leo A, Cavallo L, Francavilla A, Versalovic J. Lactobacillus reuteri strain combination in Helicobacter pylori infection: a randomized, double-blind, placebo-controlled study. *J Clin Gastroenterol* 2014; **48**: 407-413 [PMID: 24296423 DOI: 10.1097/MCG.0000000000000007]

135 **Hwang TJ**, Kim N, Kim HB, Lee BH, Nam RH, Park JH, Lee MK, Park YS, Lee DH, Jung HC, Song IS. Change in antibiotic resistance of Helicobacter pylori strains and the effect of A2143G point mutation of 23S rRNA on the eradication of H. pylori in a single center of Korea. *J Clin Gastroenterol* 2010; **44**: 536-543 [PMID: 20179610 DOI: 10.1097/MCG.0b013e3181d04592]

136 **Gerrits MM**, van Vliet AH, Kuipers EJ, Kusters JG. Helicobacter pylori and antimicrobial resistance: molecular mechanisms and clinical implications. *Lancet Infect Dis* 2006; **6**: 699-709 [PMID: 17067919 DOI: 10.1016/S1473-3099(06)70627-2]

137 **Woo HY**, Park DI, Park H, Kim MK, Kim DH, Kim IS, Kim YJ. Dual-priming oligonucleotide-based multiplex PCR for the detection of Helicobacter pylori and determination of clarithromycin resistance with gastric biopsy specimens. *Helicobacter* 2009; **14**: 22-28 [PMID: 19191892 DOI: 10.1111/j.1523-5378.2009.00654.x]

138 **Lee HJ**, Kim JI, Cheung DY, Kim TH, Jun EJ, Oh JH, Chung WC, Kim BW, Kim SS, Park SH, Kim JK. Eradication of Helicobacter pylori according to 23S ribosomal RNA point mutations associated with clarithromycin resistance. *J Infect Dis* 2013; **208**: 1123-1130 [PMID: 23801607 DOI: 10.1093/infdis/jit287]

139 **Kuo CH**, Lu CY, Shih HY, Liu CJ, Wu MC, Hu HM, Hsu WH, Yu FJ, Wu DC, Kuo FC. CYP2C19 polymorphism influences Helicobacter pylori eradication. *World J Gastroenterol* 2014; **20**: 16029-16036 [PMID: 25473155 DOI: 10.3748/wjg.v20.i43.16029]

140 **Ishizaki T**, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors--emphasis on rabeprazole. *Aliment Pharmacol Ther* 1999; **13 Suppl 3**: 27-36 [PMID: 10491726]

141 **Chong E**, Ensom MH. Pharmacogenetics of the proton pump inhibitors: a systematic review. *Pharmacotherapy* 2003; **23**: 460-471 [PMID: 12680476]

142 **Ishizaki T**, Sohn DR, Kobayashi K, Chiba K, Lee KH, Shin SG, Andersson T, Regårdh CG, Lou YC, Zhang Y. Interethnic differences in omeprazole metabolism in the two S-mephenytoin hydroxylation phenotypes studied in Caucasians and Orientals. *Ther Drug Monit* 1994; **16**: 214-215 [PMID: 8009572]

143 **Padol S**, Yuan Y, Thabane M, Padol IT, Hunt RH. The effect of CYP2C19 polymorphisms on H. pylori eradication rate in dual and triple first-line PPI therapies: a meta-analysis. *Am J Gastroenterol* 2006; **101**: 1467-1475 [PMID: 16863547 DOI: 10.1111/j.1572-0241.2006.00717.x]

144 **Zhao F**, Wang J, Yang Y, Wang X, Shi R, Xu Z, Huang Z, Zhang G. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for Helicobacter pylori eradication: a meta-analysis. *Helicobacter* 2008; **13**: 532-541 [PMID: 19166419 DOI: 10.1111/j.1523-5378.2008.00643.x]

145 **Tang HL**, Li Y, Hu YF, Xie HG, Zhai SD. Effects of CYP2C19 loss-of-function variants on the eradication of H. pylori infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. *PLoS One* 2013; **8**: e62162 [PMID: 23646118 DOI: 10.1371/journal.pone.0062162]

146 **Sugimoto M**, Shirai N, Nishino M, Kodaira C, Uotani T, Sahara S, Ichikawa H, Kagami T, Sugimoto K, Furuta T. Comparison of acid inhibition with standard dosages of proton pump inhibitors in relation to CYP2C19 genotype in Japanese. *Eur J Clin Pharmacol* 2014; **70**: 1073-1078 [PMID: 24996380 DOI: 10.1007/s00228-014-1713-y]

147 **Sahara S**, Sugimoto M, Uotani T, Ichikawa H, Yamade M, Iwaizumi M, Yamada T, Osawa S, Sugimoto K, Umemura K, Miyajima H, Furuta T. Twice-daily dosing of esomeprazole effectively inhibits acid secretion in CYP2C19 rapid metabolisers compared with twice-daily omeprazole, rabeprazole or lansoprazole. *Aliment Pharmacol Ther* 2013; **38**: 1129-1137 [PMID: 24099474 DOI: 10.1111/apt.12492]

148 **Sugimoto M**, Uotani T, Sahara S, Ichikawa H, Yamade M, Sugimoto K, Furuta T. Efficacy of tailored Helicobacter pylori eradication treatment based on clarithromycin susceptibility and maintenance of acid secretion. *Helicobacter* 2014; **19**: 312-318 [PMID: 24690010 DOI: 10.1111/hel.12128]

149 **Fiorini G**, Zullo A, Gatta L, Castelli V, Ricci C, Cassol F, Vaira D. Newer agents for Helicobacter pylori eradication. *Clin Exp Gastroenterol* 2012; **5**: 109-112 [PMID: 22767998 DOI: 10.2147/CEG.S25422]

150 **Makobongo MO**, Gilbreath JJ, Merrell DS. Nontraditional therapies to treat Helicobacter pylori infection. *J Microbiol* 2014; **52**: 259-272 [PMID: 24682990 DOI: 10.1007/s12275-014-3603-5]

151 **Leszczyńska K**, Namiot A, Fein DE, Wen Q, Namiot Z, Savage PB, Diamond S, Janmey PA, Bucki R. Bactericidal activities of the cationic steroid CSA-13 and the cathelicidin peptide LL-37 against Helicobacter pylori in simulated gastric juice. *BMC Microbiol* 2009; **9**: 187 [PMID: 19728885 DOI: 10.1186/1471-2180-9-187]

152 **Zhang L**, Yu J, Wong CC, Ling TK, Li ZJ, Chan KM, Ren SX, Shen J, Chan RL, Lee CC, Li MS, Cheng AS, To KF, Gallo RL, Sung JJ, Wu WK, Cho CH. Cathelicidin protects against Helicobacter pylori colonization and the associated gastritis in mice. *Gene Ther* 2013; **20**: 751-760 [PMID: 23254369 DOI: 10.1038/gt.2012.92]

153 **Uehara N**, Yagihashi A, Kondoh K, Tsuji N, Fujita T, Hamada H, Watanabe N. Human beta-defensin-2 induction in Helicobacter pylori-infected gastric mucosal tissues: antimicrobial effect of overexpression. *J Med Microbiol* 2003; **52**: 41-45 [PMID: 12488564]

154 **Bauer B**, Wex T, Kuester D, Meyer T, Malfertheiner P. Differential expression of human beta defensin 2 and 3 in gastric mucosa of Helicobacter pylori-infected individuals. *Helicobacter* 2013; **18**: 6-12 [PMID: 23067102 DOI: 10.1111/hel.12000]

155 **Makobongo MO**, Gancz H, Carpenter BM, McDaniel DP, Merrell DS. The oligo-acyl lysyl antimicrobial peptide C₁₂K-2β₁₂ exhibits a dual mechanism of action and demonstrates strong in vivo efficacy against Helicobacter pylori. *Antimicrob Agents Chemother* 2012; **56**: 378-390 [PMID: 22064541 DOI: 10.1128/AAC.00689-11]

156 **Makobongo MO**, Einck L, Peek RM, Merrell DS. In vitro characterization of the anti-bacterial activity of SQ109 against Helicobacter pylori. *PLoS One* 2013; **8**: e68917 [PMID: 23935905 DOI: 10.1371/journal.pone.0068917]

157 **Geng B**, Basarab G, Comita-Prevoir J, Gowravaram M, Hill P, Kiely A, Loch J, MacPherson L, Morningstar M, Mullen G, Osimboni E, Satz A, Eyermann C, Lundqvist T. Potent and selective inhibitors of Helicobacter pylori glutamate racemase (MurI): pyridodiazepine amines. *Bioorg Med Chem Lett* 2009; **19**: 930-936 [PMID: 19097892 DOI: 10.1016/j.bmcl.2008.11.113]

158 **Nishimori I**, Minakuchi T, Kohsaki T, Onishi S, Takeuchi H, Vullo D, Scozzafava A, Supuran CT. Carbonic anhydrase inhibitors: the beta-carbonic anhydrase from Helicobacter pylori is a new target for sulfonamide and sulfamate inhibitors. *Bioorg Med Chem Lett* 2007; **17**: 3585-3594 [PMID: 17482815 DOI: 10.1016/j.bmcl.2007.04.063]

159 **Haniadka R**, Saldanha E, Sunita V, Palatty PL, Fayad R, Baliga MS. A review of the gastroprotective effects of ginger (Zingiber officinale Roscoe). *Food Funct* 2013; **4**: 845-855 [PMID: 23612703 DOI: 10.1039/c3fo30337c]

160 **Lee IO**, Lee KH, Pyo JH, Kim JH, Choi YJ, Lee YC. Anti-inflammatory effect of capsaicin in Helicobacter pylori-infected gastric epithelial cells. *Helicobacter* 2007; **12**: 510-517 [PMID: 17760719 DOI: 10.1111/j.1523-5378.2007.00521.x]

161 **Yanaka A**, Fahey JW, Fukumoto A, Nakayama M, Inoue S, Zhang S, Tauchi M, Suzuki H, Hyodo I, Yamamoto M. Dietary sulforaphane-rich broccoli sprouts reduce colonization and attenuate gastritis in Helicobacter pylori-infected mice and humans. *Cancer Prev Res* (Phila) 2009; **2**: 353-360 [PMID: 19349290 DOI: 10.1158/1940-6207.CAPR-08-0192]

162 **Park S**, Yeo M, Jin JH, Lee KM, Kim SS, Choi SY, Hahm KB. Inhibitory activities and attenuated expressions of 5-LOX with red ginseng in Helicobacter pylori-infected gastric epithelial cells. *Dig Dis Sci* 2007; **52**: 973-982 [PMID: 17333352 DOI: 10.1007/s10620-006-9440-6]

163 **Lee KM**, Yeo M, Choue JS, Jin JH, Park SJ, Cheong JY, Lee KJ, Kim JH, Hahm KB. Protective mechanism of epigallocatechin-3-gallate against Helicobacter pylori-induced gastric epithelial cytotoxicity via the blockage of TLR-4 signaling. *Helicobacter* 2004; **9**: 632-642 [PMID: 15610077 DOI: 10.1111/j.1083-4389.2004.00281.x]

164 **Mahady GB**, Pendland SL, Chadwick LR. Resveratrol and red wine extracts inhibit the growth of CagA+ strains of Helicobacter pylori in vitro. *Am J Gastroenterol* 2003; **98**: 1440-1441 [PMID: 12818294 DOI: 10.1111/j.1572-0241.2003.07513.x]

165 **Sezikli M**, Cetinkaya ZA, Sezikli H, Güzelbulut F, Tiftikçi A, Ince AT, Gökden Y, Yaşar B, Atalay S, Kurdaş OO. Oxidative stress in Helicobacter pylori infection: does supplementation with vitamins C and E increase the eradication rate? *Helicobacter* 2009; **14**: 280-285 [PMID: 19674132 DOI: 10.1111/j.1523-5378.2009.00686.x]

166 **Obonyo M**, Zhang L, Thamphiwatana S, Pornpattananangkul D, Fu V, Zhang L. Antibacterial activities of liposomal linolenic acids against antibiotic-resistant Helicobacter pylori. *Mol Pharm* 2012; **9**: 2677-2685 [PMID: 22827534 DOI: 10.1021/mp300243w]

167 **Moss SF**, Moise L, Lee DS, Kim W, Zhang S, Lee J, Rogers AB, Martin W, De Groot AS. HelicoVax: epitope-based therapeutic Helicobacter pylori vaccination in a mouse model. *Vaccine* 2011; **29**: 2085-2091 [PMID: 21236233 DOI: 10.1016/j.vaccine.2010.12.130]

168 **Singh DY**, Prasad NK. Double liposomes mediated dual drug targeting for treatment of Helicobacter pylori infections. *Pharmazie* 2011; **66**: 368-373 [PMID: 21699071]

169 **Ramteke S**, Jain NK. Clarithromycin- and omeprazole-containing gliadin nanoparticles for the treatment of Helicobacter pylori. *J Drug Target* 2008; **16**: 65-72 [PMID: 18172822 DOI: 10.1080/10611860701733278]

170 **Wang J**, Tauchi Y, Deguchi Y, Morimoto K, Tabata Y, Ikada Y. Positively charged gelatin microspheres as gastric mucoadhesive drug delivery system for eradication of H. pylori. *Drug Deliv* 2000; **7**: 237-243 [PMID: 11195431 DOI: 10.1080/107175400455173]

171 **Patel JK**, Patel MM. Stomach specific anti-helicobacter pylori therapy: preparation and evaluation of amoxicillin-loaded chitosan mucoadhesive microspheres. *Curr Drug Deliv* 2007; **4**: 41-50 [PMID: 17269916]

172 **Luo D**, Guo J, Wang F, Sun J, Li G, Cheng X, Chang M, Yan X. Preparation and evaluation of anti-Helicobacter pylori efficacy of chitosan nanoparticles in vitro and in vivo. *J Biomater Sci Polym Ed* 2009; **20**: 1587-1596 [PMID: 19619399 DOI: 10.1163/092050609X12464345137685]

173 **Lin YH**, Tsai SC, Lai CH, Lee CH, He ZS, Tseng GC. Genipin-cross-linked fucose-chitosan/heparin nanoparticles for the eradication of Helicobacter pylori. *Biomaterials* 2013; **34**: 4466-4479 [PMID: 23499480 DOI: 10.1016/j.biomaterials.2013.02.028]

174 **Hao S**, Wang Y, Wang B, Zou Q, Zeng H, Chen X, Liu X, Liu J, Yu S. A novel gastroretentive porous microparticle for anti-Helicobacter pylori therapy: preparation, in vitro and in vivo evaluation. *Int J Pharm* 2014; **463**: 10-21 [PMID: 24406672 DOI: 10.1016/j.ijpharm.2013.12.052]

175 **Amin M**, Hameed S, Ali A, Anwar F, Shahid SA, Shakir I, Yaqoob A, Hasan S, Khan SA. Green Synthesis of Silver Nanoparticles: Structural Features and In Vivo and In Vitro Therapeutic Effects against Helicobacter pylori Induced Gastritis. *Bioinorg Chem Appl* 2014; **2014**: 135824 [PMID: 25214825 DOI: 10.1155/2014/135824]

176 **Lin YH**, Lin JH, Chou SC, Chang SJ, Chung CC, Chen YS, Chang CH. Berberine-loaded targeted nanoparticles as specific Helicobacter pylori eradication therapy: in vitro and in vivo study. *Nanomedicine* (Lond) 2015; **10**: 57-71 [PMID: 25177920 DOI: 10.2217/nnm.14.76]

177 **Na HS**, Hong SJ, Yoon HJ, Maeng JH, Ko BM, Jung IS, Ryu CB, Kim JO, Cho JY, Lee JS, Lee MS, Shim CS, Kim BS. [Eradication rate of first-line and second-line therapy for Helicobacter pylori infection, and reinfection rate after successful eradication]. *Korean J Gastroenterol* 2007; **50**: 170-175 [PMID: 17885282]

178 **Chung JW**, Jung YK, Kim YJ, Kwon KA, Kim JH, Lee JJ, Lee SM, Hahm KB, Lee SM, Jeong JY, Yun SC. Ten-day sequential versus triple therapy for Helicobacter pylori eradication: a prospective, open-label, randomized trial. *J Gastroenterol Hepatol* 2012; **27**: 1675-1680 [PMID: 22849546 DOI: 10.1111/j.1440-1746.2012.07249.x]

179 **Asaka M**, Sugiyama T, Kato M, Satoh K, Kuwayama H, Fukuda Y, Fujioka T, Takemoto T, Kimura K, Shimoyama T, Shimizu K, Kobayashi S. A multicenter, double-blind study on triple therapy with lansoprazole, amoxicillin and clarithromycin for eradication of Helicobacter pylori in Japanese peptic ulcer patients. *Helicobacter* 2001; **6**: 254-261 [PMID: 11683930]

180 **Fujioka T**, Aoyama N, Sakai K, Miwa Y, Kudo M, Kawashima J, Matsubara Y, Miwa J, Yakabi K. A large-scale nationwide multicenter prospective observational study of triple therapy using rabeprazole, amoxicillin, and clarithromycin for Helicobacter pylori eradication in Japan. *J Gastroenterol* 2012; **47**: 276-283 [PMID: 22065160 DOI: 10.1007/s00535-011-0487-6]

181 **Nishida T**, Tsujii M, Tanimura H, Tsutsui S, Tsuji S, Takeda A, Inoue A, Fukui H, Yoshio T, Kishida O, Ogawa H, Oshita M, Kobayashi I, Zushi S, Ichiba M, Uenoyama N, Yasunaga Y, Ishihara R, Yura M, Komori M, Egawa S, Iijima H, Takehara T. Comparative study of esomeprazole and lansoprazole in triple therapy for eradication of Helicobacter pylori in Japan. *World J Gastroenterol* 2014; **20**: 4362-4369 [PMID: 24764674 DOI: 10.3748/wjg.v20.i15.4362]

182 **Sheu BS**, Lee SC, Yang HB, Kuo AW, Wang YL, Shiesh SC, Wu JJ, Lin XZ. Selection of lower cutoff point of [13C]urea breath test is helpful to monitor H. pylori eradication after proton pump inhibitor-based triple therapy. *Dig Dis Sci* 2000; **45**: 1330-1336 [PMID: 10961711]

183 **Ozçay F**, Koçak N, Temizel IN, Demir H, Ozen H, Yüce A, Gürakan F. Helicobacter pylori infection in Turkish children: comparison of diagnostic tests, evaluation of eradication rate, and changes in symptoms after eradication. *Helicobacter* 2004; **9**: 242-248 [PMID: 15165260 DOI: 10.1111/j.1083-4389.2004.00230.x]

184 **Kutluk G**, Tutar E, Bayrak A, Volkan B, Akyon Y, Celikel C, Ertem D. Sequential therapy versus standard triple therapy for Helicobacter pylori eradication in children: any advantage in clarithromycin-resistant strains? *Eur J Gastroenterol Hepatol* 2014; **26**: 1202-1208 [PMID: 25171023 DOI: 10.1097/MEG.0000000000000190]

185 **Catalano F**, Branciforte G, Catanzaro R, Bentivegna C, Cipolla R, Nuciforo G, Brogna A. Comparative treatment of Helicobacter pylori-positive duodenal ulcer using pantoprazole at low and high doses versus omeprazole in triple therapy. *Helicobacter* 1999; **4**: 178-184 [PMID: 10469192]

186 **Paoluzi OA**, Visconti E, Andrei F, Tosti C, Lionetti R, Grasso E, Ranaldi R, Stroppa I, Pallone F. Ten and eight-day sequential therapy in comparison to standard triple therapy for eradicating Helicobacter pylori infection: a randomized controlled study on efficacy and tolerability. *J Clin Gastroenterol* 2010; **44**: 261-266 [PMID: 20195162 DOI: 10.1097/MCG.0b013e3181acebef]

187 **Pontone S**, Standoli M, Angelini R, Pontone P. Efficacy of H. pylori eradication with a sequential regimen followed by rescue therapy in clinical practice. *Dig Liver Dis* 2010; **42**: 541-543 [PMID: 20061196 DOI: 10.1016/j.dld.2009.12.007]

188 **Kongchayanun C**, Vilaichone RK, Pornthisarn B, Amornsawadwattana S, Mahachai V. Pilot studies to identify the optimum duration of concomitant Helicobacter pylori eradication therapy in Thailand. *Helicobacter* 2012; **17**: 282-285 [PMID: 22759328 DOI: 10.1111/j.1523-5378.2012.00953.x]

189 **Choi KH**, Chung WC, Lee KM, Paik CN, Kim EJ, Kang BK, Oak JH, Jung SH. Efficacy of levofloxacin and rifaximin based quadruple therapy in Helicobacter pylori associated gastroduodenal disease: a double-blind, randomized controlled trial. *J Korean Med Sci* 2011; **26**: 785-790 [PMID: 21655065 DOI: 10.3346/jkms.2011.26.6.785]

190 **Liou JM**, Lin JT, Chang CY, Chen MJ, Cheng TY, Lee YC, Chen CC, Sheng WH, Wang HP, Wu MS. 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* 2010; **59**: 572-578 [PMID: 20427390 DOI: 10.1136/gut.2009.198309]

**P-Reviewer:** Castillo A, Sharara A **S-Editor:** Ji FF **L-Editor: E-Editor:**



**Figure 1 Worldwide rates of resistance to clarithromycin and metronidazole.**

**Table 1 Decline in rates of *Helicobacter pylori* eradication following first-line standard triple therapy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Country | Ref. | Publication | Treatment duration | Patients | Therapy regimen | Eradication rate(ITT) | Eradication rate(PP) |
| South Korea | Na *et al*[[177](#_ENREF_177)] | 2007 | 7 d | 3267 | Standard PPICla 500 mg bidAmo 1 g bid | NA | 84.3% |
|  | Chung *et al*[[178](#_ENREF_178)] | 2012 | 10 d | 80 | Lan 30 mg bidCla 500 mg bidAmo 1 g bid | 58.7% | 67.6% |
| Japan | Asaka *et al*[[179](#_ENREF_179)] | 2001 | 7 d | 96 | Lan 30 mg bidCla 200 mg bidAmo 750 mg bid | NA | 90.7% |
|  | Fujioka*et al*[[180](#_ENREF_180)] | 2012 | 7 d | 3162 | Rab 10 mg bidAmo 750 mg bidCla 200 mg bid | 80.7% | NA |
|  | Nishizawa *et al*[[27](#_ENREF_27)] | 2012 | 7 d | 55 | Lan 30 mg bidCla 400 mg bidAmo 750 mg bid | 74.5% | 80.4% |
|  | Nishida *et al*[[181](#_ENREF_181)] | 2014 | 7 d | 134/134 | Eso 20 mg bidCla 400 mg bidAmo 750 mg bid**/**Lan 30 mg bidCla 400 mg bidAmo 750 mg bid | 69.4%**/** 73.9% | 76.9%**/**79.8% |
| Taiwan | Sheu *et al*[[182](#_ENREF_182)] | 2000 | 7 d or 2 wk | 286 | Ome 20 mg bidAmo 1 g bidCla or Met bid | NA | 87.8% |
|  | Chen *et al*[[117](#_ENREF_117)] | 2014 | 7 d | 73 | Rab 20 mg bidCla 500 mg bidAmo 1 g bid | 57.5% | 61.8% |
| Turkey | Ozcay *et al*[[183](#_ENREF_183)] | 2004 | 4 wk: PPI2 wk:Cla, Amo | 102 | Ome or LanCla 7.5 mg/kg bidAmo 20 mg/kg bid | NA | 75.7% |
|  | Kutluk *et al*[[184](#_ENREF_184)] | 2014 | 10 d | 74 | Lan 1 mg/kg per dayCla 20 mg/kg per dayAmo 50 mg/kg per day | 52.7% | 55.7% |
| Italy | Catalano *et al*[[185](#_ENREF_185)] | 1999 | 10 d | 84 | Ome 20 mg bidCla 500 mg bidAmo 1 g bid | NA | 94.0% |
|  | Paoluzi *et al*[[186](#_ENREF_186)] | 2010 | 7 d | 90 | Eso 20 mg bidCla 500 mg bidAmo 1 g bid | 66.0% | 75.0% |
| Latin America | Greenberg *et al*[[106](#_ENREF_106)] | 2011 | 14 d | 488 | Lan 30 mg bidCla 500 mg bidAmo 1 g bid | 82.2% | 87.1% |

ITT: Intention to treat; PP: Per protocol; PPI: Proton pump inhibitor; NA: Not available; Cla: Clarithromycin; Amo: Amoxicillin; Lan: Lansoprazole; Rab: Rabeprazole; Eso: Esomeprazole; Ome: Omeprazole; Met: Metronidazole.

**Table 2 *Helicobacter pylori* eradication rates following first-line sequential therapy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Country | REF. | Publication | Treatment duration | Patients | Therapy regimen | Eradication rate(ITT) | Eradication rate(PP) |
| South Korea | Lee *et al*[[92](#_ENREF_92)] | 2014 | 10 d | 111 | 1st 5 d: Eso + Amo 2nd 5 d: Eso + Cla + Met | 72.1% | 78.4% |
|  | Lee *et al*[[91](#_ENREF_91)] | 2015 | 10 d | 100 | 1st 5 d: Rab + Amo 2nd 5 d: Rab + Cla + Met | 79.0% | 84.9% |
| China | Zhou *et al*[[93](#_ENREF_93)] | 2014 | 10 d | 140 | 1st 5 d: Eso + Amo 2nd 5 d: Eso + Cla + Tin | 72.1% | 76.5% |
| Qatar | Chaabane *et al*[[94](#_ENREF_94)] | 2015 | 14 d | 106 | 1st 7 d: Rab + Amo 2nd 7 d: Rab + Cla + Met | 66.0% | 76.0% |
| Italy | Pontone *et al*[[187](#_ENREF_187)] | 2010 | 10 d | 84 | 1st 5 d: Lan + Amo 2nd 5 d: Lan + Cla + Met | 83.3% | 90.9% |
| Spain | Molina-Infante *et al*[[114](#_ENREF_114)] | 2010 | 10 d | 115 | 1st 5 d: Ome + Amo 2nd 5 d: Ome + Cla + Met | 76.5% | 80.8% |

ITT: Intention to treat; PP: Per protocol; Lan: Lansoprazole; Amo: Amoxicillin; Cla: Clarithromycin; Met: Metronidazole; Ome: Omeprazole; Eso: Esomeprazole; Tin: Tinidazole; Rab: Rabeprazole.

**Table 3 *Helicobacter pylori* eradication rates following first-line concomitant therapy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Country | Ref. | Publication | Treatment duration | Patients | Therapy regimen | Eradication rate(ITT) | Eradication rate(PP) |
| South Korea | Lim *et al*[[104](#_ENREF_104)] | 2013 | 14 d | 78 | Rab 20 mg bidAmo 1 g bidCla 500 mg bidMet 500 mg bid | 80.8% | 81.3% |
|  | Lee *et al*[[100](#_ENREF_100)] | 2015 | 7 d | 170 | Rab 20 mg bidAmo 1 g bidCla 500 mg bidMet 500 mg tid | 79.4% | 94.4% |
| Thailand | Kongchaya-nun *et al*[[188](#_ENREF_188)] | 2012 | 5 d/10 d | 55/55 | Rab 20 mg bidAmo 1 g bidMet 400 mg tidCla 1 g qd | 89.1%/96.4% | NA |
| Singapore | Ang *et al*[[102](#_ENREF_102)] | 2015 | 10 d | 153 | PPI standard doesAmo 1 g bidCla 500 mg bidMet 400 mg bid | 81.7% | 95.4% |
| Spain | Molina-Infante *et al*[[97](#_ENREF_97)] | 2012 | 10 d | 209 | PPI standard doesAmo 1 g bidCla 500 mg bidMet 500 mg bid | 87.0% | 89.0% |
|  | McNicholl *et al*[[103](#_ENREF_103)] | 2014 | 10 d | 168 | Ome 20 mg bidAmo 1 g bidCla 500 mg bidMet 500 mg bid | 87.0% | 91.0% |
| Latin America | Greenberg *et al*[[106](#_ENREF_106)] | 2011 | 5 d | 489 | Lan 30 mg bidAmo 1 g bidCla 500 mg bidMet 500 mg bid | 73.6% | NA |

ITT: Intention to treat; PP: Per protocol; NA: Not available; Lan: Lansoprazole; Amo: Amoxicillin; Cla: Clarithromycin; Met: Metronidazole; PPI: Proton pump inhibitor; Rab: Rabeprazole; Ome: Omeprazole.

**Table 4 *Helicobacter pylori* eradication rates following first-line levofloxacin-containing therapy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Country | Ref. | Publication | Treatment duration | Patients | Therapy regimen | Eradication rate(ITT) | Eradication rate(PP) |
| South Korea | Choi *et al*[[189](#_ENREF_189)] | 2011 | 7 d | 98 | Ome 20 mg bidLev 200 mg bidAmo 1 g bid | 65.3% | 73.6% |
| China | Liao *et al*[[122](#_ENREF_122)] | 2013 | 14 d | 81 | Lan 30 mg bidLev 500 mg qdAmo 1 g bid | 82.7% | 85.9% |
| Taiwan | Liou *et al*[[190](#_ENREF_190)] | 2010 | 7 d | 217 | Lan 30 mg bidLev 750 mg qdAmo 1 g bid | 74.2% | 80.1% |
|  | Chen *et al*[[117](#_ENREF_117)] | 2014 | 7 d | 73 | Rab 20 mg bidLev 500 mg bidAmo 1 g bid | 78.1% | 80.9% |
| Spain | Molina-Infante *et al*[[114](#_ENREF_114)] | 2010 | 10 d | 115 | Ome 20 mg bidLev 500 mg bidAmo 1 g bid | 80.8% | 82.6% |

ITT: Intention to treat; PP: Per protocol; Lan: Lansoprazole; Lev: Levofloxacin; Amo: Amoxicillin; Rab: Rabeprazole; Eso: Esomeprazole; Cla: Clarithromycin; Ome: Omeparzole.