Review Article

Optimal First-Line Treatment for *Helicobacter pylori* Infection: Recent Strategies

Ju Yup Lee and Kyung Sik Park

*Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Republic of Korea*

Correspondence should be addressed to Kyung Sik Park; seenae99@dsmc.or.kr

Received 11 August 2016; Revised 15 October 2016; Accepted 3 November 2016

Academic Editor: Vikram Kate

Copyright © 2016 J. Y. Lee and K. S. Park. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

A new treatment strategy is needed, as the efficacy of triple therapy containing clarithromycin—the current standard treatment for *Helicobacter pylori* infection—is declining. Increasing antibiotic resistance of *H. pylori* is the most significant factor contributing to eradication failure. Thus, selecting the most appropriate regimen depending on resistance is optimal, but identifying resistance to specific antibiotics is clinically challenging. In a region suspected to have high clarithromycin resistance, bismuth quadruple therapy and so-called nonbismuth quadruple therapies (sequential, concomitant, and sequential-concomitant hybrid) are some first-line regimen options. However, more research is needed regarding appropriate second-line treatments after first-line treatment failure. Tailored therapy, which is based on antibiotic sensitivity testing, would be optimal but has several limitations for clinical use, and an alternative technique is required. A novel potassium-competitive acid blocker-based eradication regimen could be a valuable eradication option in the near future.

1. Introduction

Although triple therapy containing proton pump inhibitors (PPIs), amoxicillin, and clarithromycin has been recommended worldwide as the standard treatment for *Helicobacter pylori* infection, the need for a new treatment strategy has developed, since the efficacy of triple therapy is declining in most countries [1]. Several factors play a role in the failure of *H. pylori* eradication, but resistance to antibiotics is considered the major cause [2]. Hence, the present study examines the recommended first-line treatments in different countries and analyzes the problems associated with such regimens in association with antibiotic resistance, in an attempt to identify appropriate treatment strategies.

2. First-Line Treatment Recommendations and the Problem of Antibiotic Resistance

The 2013 revision of the Korea Guideline for *H. pylori* recommends triple therapy containing clarithromycin as the first-line treatment and bismuth quadruple therapy in regions with suspected clarithromycin resistance [3]. However, according to a recent meta-analysis conducted in Korea, the eradication rate with triple therapy containing clarithromycin has been in significant decline for the last 10 years [4] as a result of antibiotic resistance of *H. pylori*. In fact, worldwide reports and a Korean report of primary antibiotic resistance in *H. pylori* suggest that the resistance rate is >20% for clarithromycin, >40% for metronidazole, and >10% for quinolones [5].

Similar to Korea, China recommends a 7–14 day regimen of the standard triple therapy containing clarithromycin and amoxicillin as first-line treatment [6], but the eradication rate is known to be <80% [7]. Hence, bismuth quadruple therapy is recommended as first-line treatment in regions where *H. pylori* resistance to clarithromycin exceeds 15–20% [6]. Because there are considerable regional differences in *H. pylori* antibiotic resistance in China, regional characteristics should be considered when determining treatment [8, 9]; most regions have high metronidazole and clarithromycin resistance rates. For example, the *H. pylori* rate of resistance to metronidazole in Shanghai is approximately 60–70%, while the rate of resistance to clarithromycin is approximately 20–38% [10].
On the other hand, Japan uses lower doses of antibiotics for eradication than Korea or China [11]. The recommended primary treatment comprises twice-a-day administration of a standard dose of PPI, amoxicillin 750 mg, and clarithromycin 200 or 400 mg for 7 days, while the secondary treatment comprises twice-a-day administrations of PPI, amoxicillin 750 mg, and metronidazole 250 mg for 7 days. Fourteen-day treatment or bismuth quadruple treatment is not recommended as first- or second-line therapy in Japan [7]. The eradication rate associated with first-line treatment in Japan is 70%, while that for second-line treatment is 90%, maintaining an eradication rate >95% with these two regimens [12, 13]. One notable phenomenon in Japan is that it has relatively low antibiotic resistance rates of H. pylori compared to those of other countries; thus, the high eradication rates in Japan are a testament to the fact that triple therapy containing clarithromycin or metronidazole remains efficacious in regions with low antibiotic resistance rates. However, the prevalence of H. pylori antibiotic resistance is growing in Japan as well. According to a multi-institutional survey in Japan, the clarithromycin resistance rate of H. pylori was 18.9% in 2002, which escalated to 27.2% in 2006 [14]. Although there are some regional differences, metronidazole resistance largely remains low at 2.1–24.0% [14].

The 2012 revision of the European guideline for Helicobacter introduces a treatment strategy for clarithromycin-resistant H. pylori [15]. Whereas triple therapy containing clarithromycin is recommended as first-line treatment in regions with a clarithromycin resistance rate <20%, bismuth quadruple therapy, sequential therapy, or concomitant therapy is recommended as first-line treatment in regions with clarithromycin resistance >20% [15]. According to prior reports, despite the fact that sequential or concomitant therapies contain clarithromycin, they overcome clarithromycin resistance to a certain extent, with approximately 75–95% therapeutic success rates.

### 3. First-Line Treatment Options for Cases with High Antibiotic Resistance

Alternatives to primary treatment with clarithromycin triple therapy include bismuth quadruple therapy and so-called nonbismuth quadruple therapies: sequential, concomitant, and sequential-concomitant hybrid. The treatment strategy and administration method for each regimen are shown in Figure 1 [15, 16].

#### 3.1. Bismuth Quadruple Therapy

Traditional bismuth quadruple therapy involves 7- or 14-day administration of a standard dose of PPI (twice daily), bismuth 120 mg (4 times/day), tetracycline 500 mg (4 times/day), and metronidazole 500 mg (3 times/day). Theoretically, bismuth easily reaches H. pylori since it is released into the gastric mucosa and is associated with low resistance; thus, there have been arguments that quadruple therapy containing bismuth should preferentially be employed as the first-line treatment for H. pylori infection instead of triple therapy containing a PPI [17]. Discussions on whether bismuth quadruple therapy can replace PPI triple therapy as first-line treatment are ongoing, but for now, this is considered the most appropriate alternative, especially in regions with high clarithromycin resistance. In a meta-analysis conducted in 2003, there was no statistically significant difference between PPI triple therapy and bismuth quadruple therapy [18], and a meta-analysis conducted in 2013 of 12 randomized controlled trials (RCTs) reported that the eradication rate associated with bismuth quadruple therapy was 77.6%, while that associated with PPI triple therapy was 68.9% (relative risk [RR], 1.13; 95% confidence interval [CI], 1.04–1.22).
The eradication rate with sequential therapy in the presence of clarithromycin resistance was 70.3% and 33.8%, indicating higher eradication rates for sequential and standard therapy in the expected rate. For instance, one meta-analysis reported antibiotic resistance would reduce such results to below higher eradication rate than that of standard triple therapy [42–45]. However, sequential therapy is associated with a rate associated with sequential therapy slightly decreases success rates outside Italy, where metronidazole has generally remains markedly higher than that of standard triple therapy [31, 33, 55, 56] but is associated with more frequent side effects [31]. The compliance with concomitant therapy was similar to that for sequential therapy [45, 56, 57]. However, higher compliance was achieved with concomitant therapy than with sequential therapy in a meta-analysis of RCTs in Chinese regions [58]. Concomitant therapy is known to demonstrate better eradication rates in patients with clarithromycin- or metronidazole-resistant strains [59, 60], and the selection of secondary antibiotics after first-line concomitant therapy failure remains challenging.

3.3. Concomitant Therapy. Concomitant therapy involves the simultaneous administration of PPI, amoxicillin, clarithromycin, and metronidazole. ITT analyses in two meta-analyses on studies published up until the early 2000s revealed that the eradication rate with concomitant therapy was approximately 90%, exceeding that of standard triple therapy [51, 52]. It was about 5% higher than the eradication rate with 14-day hybrid therapy and 14-day sequential therapy performed by the same institution [62]. However, there were no differences in the side effects with concomitant therapy versus triple therapy, and none of the prior studies reported severe side effects associated with concomitant therapies [51]. Several studies reported that concomitant therapy has therapeutic effects similar to that of sequential therapy [31, 33, 55, 56] but is associated with more frequent side effects [31]. The compliance with concomitant therapy was similar to that for sequential therapy [45, 56, 57]. However, higher compliance was achieved with concomitant therapy than with sequential therapy in a meta-analysis of RCTs in Chinese regions [58]. Concomitant therapy is known to demonstrate better eradication rates in patients with clarithromycin- or metronidazole-resistant strains [59, 60], and the selection of secondary antibiotics after first-line concomitant therapy failure remains challenging.
difference in eradication rates between hybrid and sequential (RR 1.01, 95% CI: 0.92–1.11) or concomitant therapy (RR 0.98, 95% CI: 0.93–1.02) [16]. However, it is difficult to generalize a conclusion regarding hybrid therapy because the number of studies remains small, while studies that compared hybrid therapy with sequential and concomitant therapies involved different administration durations [57]. Nevertheless, eradication rates associated with hybrid therapy have been determined to exceed those of standard triple therapy. Recently, Hsu et al. [65] showed a high eradication rate with reverse hybrid therapy. Reverse hybrid therapy consists of a PPI and amoxicillin for 14 days, with addition of clarithromycin and metronidazole for the first 7 days. The ITT eradication rate of reverse hybrid therapy was 93.6%, which was superior to that of standard triple therapy [65]. The drug compliance rates for hybrid and reverse hybrid therapy were 96.2% [16] and 96.8% [65], respectively, and were comparable to those for standard triple therapy. Hybrid therapy displayed a slightly higher compliance rate than concomitant therapy (95.8% versus 93.2%) in a recent meta-analysis including 12 RCTs of hybrid therapy [57].

3.5. Tailored Therapy. Since antibiotic resistance is the main cause of eradication failure, a tailored therapy that selects the most appropriate regimen to overcome antibiotic resistance would be the optimal treatment. However, tailored therapies are complex and costly. Therefore, a new method to detect antibiotic resistance is needed. One such solution is the polymerase chain reaction (PCR) kit, which uses the dual-priming oligonucleotide-based multiplex PCR test [66]. This kit identifies the presence of point mutations of clarithromycin 23S rRNA that are known to be associated with resistance, namely, A2142G and A2143G, using a PCR [67]. The test can be performed with a sample of gastric mucosa and takes only a few hours, making it relatively simple to use; its sensitivity and specificity are approximately 80–85% [68].

3.6. Potassium-Competitive Acid Blocker. The potassium-competitive acid blocker (P-CAB), vonoprazan, could improve eradication rates by increasing the intragastric pH and thus increasing bacterial antibiotic susceptibility. Vonoprazan 20 mg demonstrated a more rapid and sustained acid-inhibitory effect than esomeprazole 20 mg or rabeprazole 10 mg [69]. Recent studies revealed that P-CAB based triple therapy was more effective than PPI-based triple therapy as a first-line H. pylori eradication method [70–73]. Furthermore, even in the presence of clarithromycin-resistant strains, P-CAB-based triple therapy showed good eradication rates that were superior to those for PPI-based triple therapy (76.1% versus 40.2%) [74].

4. Conclusion

Triple therapy containing clarithromycin is now largely considered a "legacy therapy" because its therapeutic efficacy decreases even with a clarithromycin resistance of 7–10% [75]; thus, it has become ineffective in regions with high clarithromycin resistance. Hence, sequential or concomitant regimens are recommended as first-line treatment in regions with high clarithromycin resistance rates. However, the therapeutic effects of these two regimens in the presence of dual resistance to clarithromycin and metronidazole have yet to be determined [60]. In such cases, the hybrid regimen could be an alternative [64]. The bismuth quadruple regimen could be a good first-line alternative regardless of clarithromycin resistance rates, but its efficacy parallels that of triple therapy and it requires a 14-day administration, which would undermine medication compliance. When first-line therapy of the bismuth quadruple or nonbismuth quadruple regimen fails, an appropriate second-line regimen should contain a quinolone; however, there is little research to support this, and it should be noted that many regions have high quinolone resistance rates. Tailored therapy based on antibiotic sensitivity testing would be the optimal approach but has several limitations for clinical use, calling for the development of a new alternative technique. A novel P-CAB-based regimen would be a valuable H. pylori eradication option.

Competing Interests

The authors declare no competing interests.

Acknowledgments

This work was supported by the National Research Foundation of Korea (NRF) Grant funded by the Korean Government (MSIP) (no. 2014R1A5A2010008).

References

[1] D. Y. Graham and L. Fischbach, “Helicobacter pylori treatment in the era of increasing antibiotic resistance,” Gut, vol. 59, no. 8, pp. 1143–1153, 2010.

[2] F. Mégraud, “H pylori antibiotic resistance: prevalence, importance, and advances in testing,” Gut, vol. 53, no. 9, pp. 1374–1384, 2004.

[3] S. G. Kim, H.-K. Jung, H. L. Lee et al., “Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition,” Journal of Gastroenterology and Hepatology, vol. 29, no. 7, pp. 1371–1386, 2014.

[4] E. J. Gong, S.-C. Yun, H.-Y. Jung et al., “Meta-analysis of first-line triple therapy for Helicobacter pylori eradication in Korea: is it time to change?” Journal of Korean Medical Science, vol. 29, no. 5, pp. 704–713, 2014.

[5] L. Boyanova and I. Mitov, “Geographic map and evolution of primary Helicobacter pylori resistance to antibacterial agents,” Expert Review of Anti-Infective Therapy, vol. 8, no. 1, pp. 59–70, 2010.

[6] W. Z. Liu, Y. Xie, H. Cheng et al., “Fourth Chinese National Consensus Report on the management of Helicobacter pylori infection,” Journal of Digestive Diseases, vol. 14, no. 5, pp. 211–221, 2013.

[7] S.-Y. Lee, “Current progress toward eradicating helicobacter pylori in East Asian countries: differences in the 2013 revised guidelines between China, Japan, and South Korea,” World Journal of Gastroenterology, vol. 20, no. 6, pp. 1493–1502, 2014.
[8] P. Su, Y. Li, H. Li et al., "Antibiotic resistance of Helicobacter pylori isolated in the Southeast Coastal Region of China," *Helicobacter*, vol. 18, no. 4, pp. 274–279, 2013.

[9] W. Cai, L. Zhou, W. Ren, L. Deng, and M. Yu, "Variables influencing outcome of Helicobacter pylori eradication therapy in South China," *Helicobacter*, vol. 14, no. 5, pp. 91–96, 2009.

[10] Q.-J. Sun, X. Liang, Q. Zheng et al., "Resistance of *Helicobacter pylori* to antibiotics from 2000 to 2009 in Shanghai," *World Journal of Gastroenterology*, vol. 16, no. 40, pp. 5188–5211, 2010.

[11] M. Asaka, "A new approach for elimination of gastric cancer deaths in Japan," *International Journal of Cancer*, vol. 132, no. 6, pp. 1272–1276, 2013.

[12] N. Horiki, F. Omata, M. Uemura et al., "Annual change of primary resistance to clarithromycin among helicobacter pylori isolates from 1996 through 2008 in Japan," *Helicobacter*, vol. 14, no. 5, pp. 86–90, 2009.

[13] T. Shimoyama, S. Fukuda, T. Mikami, M. Fukushi, and A. Munakata, "Efficacy of metronidazole for the treatment of clarithromycin-resistant *Helicobacter pylori* infection in a Japanese population," *Journal of Gastroenterology*, vol. 39, no. 10, pp. 927–930, 2004.

[14] I. Kobayashi, K. Murakami, M. Kato et al., "Changing antimicrobial susceptibility epidemiology of *Helicobacter pylori* strains in Japan between 2002 and 2005," *Journal of Clinical Microbiology*, vol. 45, no. 12, pp. 4006–4010, 2007.

[15] P. Malfertheiner, F. Megraud, C. A. O’Morain et al., "Management of *Helicobacter pylori* infection—the Maastricht IV/Florence Consensus Report," *Gut*, vol. 61, no. 5, pp. 646–664, 2012.

[16] P.-I. Hsu, P.-C. Lin, and D. Y. Graham, "Hybrid therapy for *Helicobacter pylori* infection: a systemic review and meta-analysis," *World Journal of Gastroenterology*, vol. 21, no. 45, pp. 12954–12962, 2015.

[17] H. J. Jo, D. H. Lee, S. J. Kang et al., "Comparison of the efficacy of Bismuth containing PPI-based quadruple therapy with PPI-based triple therapy only as first-line Treatment for *Helicobacter pylori* Infection," *Korean Journal of Gastroenterology*, vol. 37, no. 4, pp. 259–264, 2008.

[18] E. Gené, X. Calvet, R. Azagra, and J. P. Gisbert, "Triple vs. quadruple therapy for treating Helicobacter pylori infection: a meta-analysis," *Alimentary Pharmacology and Therapeutics*, vol. 17, no. 9, pp. 1137–1143, 2003.

[19] M. Venerito, T. Krieger, T. Ecker, G. Leandro, and P. Malfertheiner, "Meta-analysis of bismuth quadruple therapy versus clarithromycin triple therapy for empiric primary treatment of *Helicobacter pylori* infection," *Digestion*, vol. 88, no. 1, pp. 33–45, 2013.

[20] P. Malfertheiner, F. Bazzoli, J.-C. Delchier et al., "Helicobacter pylori eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracyclines given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial," *The Lancet*, vol. 377, no. 9769, pp. 905–913, 2011.

[21] L. Laine, R. Hunt, H. El-Zimaity, B. Nguyen, M. Osato, and J. Spenard, "Bismuth-based quadruple therapy using a single capsule of bismuth biskalcitrate, metronidazole, and tetracycline given with omeprazole versus omeprazole, amoxicillin, and clarithromycin for eradication of Helicobacter pylori in duodenal ulcer patients: a prospective, randomised, multicenter, North American trial," *American Journal of Gastroenterology*, vol. 98, no. 3, pp. 562–567, 2003.

[22] V. de Francesco, F. Giorgio, C. Hassan et al., "Worldwide *H. pylori* antibiotic resistance: a systematic review," *Journal of Gastrointestinal and Liver Diseases*, vol. 19, no. 4, pp. 409–414, 2010.

[23] F. Megraud, S. Coenen, A. Versporten et al., "Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption," *Gut*, vol. 62, no. 1, pp. 34–42, 2013.

[24] A. Zullo, V. Rinaldi, S. Winn et al., "A new highly effective short-term therapy schedule for *Helicobacter pylori* eradication," *Alimentary Pharmacology and Therapeutics*, vol. 14, no. 6, pp. 715–718, 2000.

[25] N. S. Jafri, C. A. Hornung, and C. W. Howden, "Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment," *Annals of Internal Medicine*, vol. 148, no. 12, pp. 923–931, 2008.

[26] L. Gatta, N. Vakil, G. Leandro, F. Di Mario, and D. Vaira, "Sequential therapy or triple therapy for *Helicobacter pylori* infection: Systematic review and meta-analysis of randomized controlled trials in adults and children," *American Journal of Gastroenterology*, vol. 104, no. 12, pp. 3069–3079, 2009.

[27] J. L. Tong, Z. H. Ran, J. Shen, and S. D. Xiao, "Sequential therapy vs. standard triple therapies for *Helicobacter pylori* infection: a meta-analysis," *Journal of Clinical Pharmacology and Therapeutics*, vol. 34, no. 1, pp. 41–53, 2009.

[28] R. Urgesi, G. Pelecca, R. Cianci et al., "*Helicobacter pylori* infection: is sequential therapy superior to standard triple therapy? A single-centre Italian study in treatment-naive and non-treatment-naive patients," *Canadian Journal of Gastroenterology*, vol. 25, no. 6, pp. 315–318, 2011.

[29] O. A. Paoluzi, E. Visconti, F. Andrei et al., "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," *Journal of Clinical Gastroenterology*, vol. 44, no. 4, pp. 261–266, 2010.

[30] M. Romano, A. Cuomo, A. G. Gravina et al., "Empirical levofloxacin-containing versus clarithromycin-containing sequential therapy for *Helicobacter pylori* eradication: a randomised trial," *Gut*, vol. 59, no. II, pp. 1465–1470, 2010.

[31] A. Zullo, G. Scaccianoce, V. De Francesco et al., "Concomitant, sequential, and hybrid therapy for *H. pylori* eradication: A Pilot Study," *Clinics and Research in Hepatology and Gastroenterology*, vol. 37, no. 6, pp. 647–650, 2013.

[32] J. Molina-Infante, B. Perez-Gallardo, M. Fernandez-Bermejo et al., "Clinical trial: clarithromycin vs. levofloxacin in first-line triple and sequential regimens for *Helicobacter pylori* eradication," *Alimentary Pharmacology and Therapeutics*, vol. 31, no. 10, pp. 1077–1084, 2010.

[33] A. G. McNicholl, A. C. Marin, J. Molina-Infante et al., "Randomised clinical trial comparing sequential and concomitant therapies for *Helicobacter pylori* eradication in routine clinical practice," *Gut*, vol. 63, no. 2, pp. 244–249, 2014.

[34] L. Gatta, N. Vakil, D. Vaira, and C. Scaccianoce, "Global eradication rates for *Helicobacter pylori* infection: systematic review and meta-analysis of sequential therapy," *The British Medical Journal*, vol. 347, no. 7920, Article ID F4587, 2013.

[35] H. Yoon, D. H. Lee, N. Kim et al., "Meta-analysis: is sequential therapy superior to standard triple therapy for *Helicobacter pylori* infection in Asian adults?" *Journal of Gastroenterology and Hepatology*, vol. 28, no. 12, pp. 1801–1809, 2013.

[36] J. S. Kim, B. W. Kim, S. J. Hong et al., "Sequential therapy versus triple therapy for the first line treatment of *Helicobacter pylori* in Korea," *Gastroenterology Research and Practice*, vol. 2013, Article ID 586269, 2013.
in Korea: a nationwide randomized trial,” Gut Liver, vol. 10, no. 4, pp. 556–561, 2016.

[37] D. Vaira, A. Zullo, N. Vakil et al., “Sequential therapy versus standard triple-drug therapy for Helicobacter pylori eradication: a randomized trial,” Annals of Internal Medicine, vol. 146, no. 8, pp. 556–563, 2007.

[38] A. Zullo, F. Perna, C. Hassan et al., “Primary antibiotic resistance in Helicobacter pylori strains isolated in northern and central Italy,” Alimentary Pharmacology and Therapeutics, vol. 25, no. 12, pp. 1429–1434, 2007.

[39] S. P. Thyagarajan, P. Ray, B. K. Das et al., “Geographical difference in antimicrobial resistance pattern of Helicobacter pylori clinical isolates from Indian patients: multicentric study,” Journal of Gastroenterology and Hepatology, vol. 18, no. 12, pp. 1373–1378, 2003.

[40] J.-W. Chung, Y. K. Jung, Y. J. Kim et al., “Ten-day sequential versus triple therapy for Helicobacter pylori eradication: a prospective, open-label, randomized trial,” Journal of Gastroenterology and Hepatology, vol. 27, no. 11, pp. 1675–1680, 2012.

[41] D. Vaira, A. Zullo, C. Hassan, G. Fiorini, and N. Vakil, “Sequential therapy for Helicobacter pylori eradication: the time is now!,” Therapeutic Advances in Gastroenterology, vol. 2, no. 6, pp. 317–322, 2009.

[42] V. De Francesco, M. Margiotta, A. Zullo et al., “Clarithromycin-resistant genotypes and eradication of Helicobacter pylori,” Annals of Internal Medicine, vol. 144, no. 2, pp. 94–100, 2006.

[43] V. Mahachai, N. Sirimontaporn, S. Tumwasorn, D. Thong-Ngam, and R.-K. Vilaichone, “Sequential therapy in clarithromycin-sensitive and -resistant Helicobacter pylori based on polymerase chain reaction molecular test,” Journal of Gastroenterology and Hepatology, vol. 26, no. 5, pp. 825–828, 2011.

[44] N. Sirimontaporn, D. Thong-Ngam, S. Tumwasorn, and V. Mahachai, “Ten-day sequential therapy of Helicobacter pylori infection in Thailand,” The American Journal of Gastroenterology, vol. 105, no. 5, pp. 1071–1075, 2010.

[45] J. W. Chung, J. P. Han, K. O. Kim et al., “Ten-day empirical sequential or concomitant therapy is more effective than triple therapy for Helicobacter pylori eradication: a multicenter, prospective study,” Digestive and Liver Disease, vol. 48, no. 8, pp. 888–892, 2016.

[46] R. Francavilla, E. Lionetti, S. P. Castellaneta et al., “Improved efficacy of 10-day sequential treatment for Helicobacter pylori eradication in children: a randomized trial,” Gastroenterology, vol. 129, no. 5, pp. 1414–1419, 2005.

[47] A. Zullo, L. Gatta, V. De Francesco et al., “High rate of Helicobacter pylori eradication with sequential therapy in elderly patients with peptic ulcer: A Prospective Controlled Study,” Alimentary Pharmacology and Therapeutics, vol. 21, no. 12, pp. 1419–1424, 2005.

[48] A. Tursi, W. Elisei, G. Giorgetti, M. Picchio, and G. Brandimarte, “Efficacy, tolerability, and factors affecting the efficacy of the sequential therapy in curing Helicobacter pylori infection in clinical setting,” Journal of Investigative Medicine, vol. 59, no. 6, pp. 917–920, 2011.

[49] M. Manfredi, B. Bizzarri, and G. L. deAngelis, “Helicobacter pylori infection: sequential therapy followed by levofloxacin-containing triple therapy provides a good cumulative eradication rate,” Helicobacter, vol. 17, no. 4, pp. 246–253, 2012.

[50] S. Pontone, M. Standoli, R. Angelini, and P. Pontone, “Efficacy of H. pylori eradication with a sequential regimen followed by rescue therapy in clinical practice,” Digestive and Liver Disease, vol. 42, no. 8, pp. 541–543, 2010.

[51] A. S. Essa, J. R. Kramer, D. Y. Graham, and G. Treiber, “Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing ‘concomitant therapy’ versus triple therapy for helicobacter pylori eradication,” Helicobacter, vol. 14, no. 2, pp. 109–118, 2009.

[52] L. A. Fischbach, S. V. Van Zanten, and J. Dickason, “Meta-analysis: the efficacy, adverse events, and adherence related to first-line anti-Helicobacter pylori quadruple therapies,” Alimentary Pharmacology and Therapeutics, vol. 20, no. 10, pp. 1071–1082, 2004.

[53] J. P. Gisbert and X. Calvet, “Review article: non-bismuth quadruple (concomitant) therapy for eradication of Helicobacter pylori,” Alimentary Pharmacology and Therapeutics, vol. 34, no. 6, pp. 604–617, 2011.

[54] J. P. Gisbert and X. Calvet, “Update on non-bismuth quadruple (concomitant) therapy for eradication of Helicobacter pylori,” Clinical and Experimental Gastroenterology, vol. 5, no. 1, pp. 23–34, 2012.

[55] S. M. Park, J. S. Kim, B. W. Kim, J. S. Ji, and H. Seong, “Comparing the efficacy of concomitant therapy with sequential therapy as the first-line therapy of Helicobacter pylori eradication,” Gastroenterology Research and Practice, vol. 2016, Article ID 1293649, 2016.

[56] S. M. Park, J. S. Kim, B. W. Kim, J. S. Ji, and H. Choi, “A randomised clinical trial comparing 10- or 14-day sequential therapy and 10- or 14-day concomitant therapy for the first line empirical treatment of Helicobacter pylori infection,” Journal of Gastroenterology and Hepatology, 2016.

[57] Z. Q. Song and L. Y. Zhou, “Hybrid, sequential and concomitant therapies for Helicobacter pylori eradication: a systematic review and meta-analysis,” World Journal of Gastroenterology, vol. 22, no. 19, pp. 4766–4775, 2016.

[58] L. C. Lin, T. H. Hsu, K. W. Huang, and K. W. Tam, “Nonbismuth concomitant quadruple therapy for Helicobacter pylori eradication in Chinese regions: a meta-analysis of randomized controlled trials,” World Journal of Gastroenterology, vol. 22, no. 23, pp. 5445–5453, 2016.

[59] B. Tepes, M. Vujasinovic, M. Seruga, M. Stefanovic, A. Forte, and S. Jeverica, “Randomized clinical trial comparing 10-day sequential, 7-day concomitant and 7-day standard triple therapies for Helicobacter pylori eradication,” European Journal of Gastroenterology and Hepatology, vol. 28, no. 6, pp. 676–683, 2016.

[60] D. Y. Graham, Y.-C. Lee, and M.-S. Wu, “Rational Helicobacter pylori therapy: evidence-based medicine rather than medicine-based evidence,” Clinical Gastroenterology and Hepatology, vol. 12, no. 2, pp. 177.e3–186.e3, 2014.

[61] P.-I. Hsu, D.-C. Wu, J.-Y. Wu, and D. Y. Graham, “Modified sequential Helicobacter pylori therapy: proton pump inhibitor and amoxicillin for 14 days with clarithromycin and metronidazole added as a quadruple (hybrid) therapy for the final 7 days,” Helicobacter, vol. 16, no. 2, pp. 139–145, 2011.

[62] P. I. Hsu, D.-C. Wu, J.-Y. Wu, and D. Y. Graham, “Is there a benefit to extending the duration of Helicobacter pylori sequential therapy to 14 days?” Helicobacter, vol. 16, no. 2, pp. 146–152, 2011.

[63] D. H. Oh, D. H. Lee, K. K. Kang et al., “The efficacy of hybrid therapy as first-line regimen for Helicobacter pylori infection compared with sequential therapy,” Journal of Gastroenterology and Hepatology, vol. 29, no. 6, pp. 1171–1176, 2014.
[64] J. Molina-Infante, M. Romano, M. Fernandez-Bermejo et al., “Optimized nonbismuth quadruple therapies cure most patients with Helicobacter pylori infection in populations with high rates of antibiotic resistance,” Gastroenterology, vol. 145, no. 1, pp. 121.e1–128.e1, 2013.

[65] P.-I. Hsu, S.-S. Kao, D.-C. Wu et al., “A randomized controlled study comparing reverse hybrid therapy and standard triple therapy for helicobacter pylori infection,” Medicine, vol. 94, no. 48, Article ID e2104, 2015.

[66] H.-Y. Woo, D. I. Park, H. Park et al., “Dual-priming oligonucleotide-based multiplex PCR for the detection of Helicobacter pylori and determination of clarithromycin resistance with gastric biopsy specimens,” Helicobacter, vol. 14, no. 1, pp. 22–28, 2009.

[67] M. M. Gerrits, A. H. van Vliet, E. J. Kuipers, and J. G. Kusters, “Helicobacter pylori and antimicrobial resistance: molecular mechanisms and clinical implications,” Lancet Infectious Diseases, vol. 6, no. 11, pp. 699–709, 2006.

[68] T. J. Hwang, N. Kim, H. B. Kim et al., “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,” Journal of Clinical Gastroenterology, vol. 44, no. 8, pp. 536–543, 2010.

[69] Y. Sakurai, Y. Mori, H. Okamoto et al., “Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects—A Randomised Open-Label Cross-Over Study,” Alimentary Pharmacology and Therapeutics, vol. 42, no. 6, pp. 719–730, 2015.

[70] S. Shichijo, Y. Hirata, R. Niikura et al., “Vonoprazan versus conventional proton pump inhibitor-based triple therapy as first-line treatment against Helicobacter pylori: a multicenter retrospective study in clinical practice,” Journal of Digestive Diseases, 2016.

[71] K. Murakami, Y. Sakurai, M. Shiino, N. Funao, A. Nishimura, and M. Asaka, “Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for Helicobacter pylori eradication: a phase III, randomised, double-blind study,” Gut, vol. 65, no. 9, pp. 1439–1446, 2016.

[72] S. Suzuki, T. Gotoda, C. Kusano, K. Iwatsuka, and M. Moriyama, “The efficacy and tolerability of a triple therapy containing a potassium-competitive acid blocker compared with a 7-day, PPI-based low-dose clarithromycin triple therapy,” The American Journal of Gastroenterology, vol. 111, no. 7, pp. 949–956, 2016.

[73] H. Noda, S. Noguchi, T. Yoshimine et al., “A novel potassium-competitive acid blocker improves the efficacy of Clarithromycin-containing 7-day triple therapy against Helicobacter pylori,” Journal of Gastrointestinal and Liver Diseases, vol. 25, no. 3, pp. 283–288, 2016.

[74] H. Matsumoto, A. Shiotani, R. Katsumata et al., “Helicobacter pylori eradication with proton pump inhibitors or potassium-competitive acid blockers: the effect of clarithromycin resistance,” Digestive Diseases and Sciences, vol. 61, no. 11, pp. 3215–3220, 2016.

[75] A. Federico, A. G. Gravina, A. Miranda, C. Loguerco, and M. Romano, “Eradication of Helicobacter pylori infection: which regimen first?” World Journal of Gastroenterology, vol. 20, no. 3, pp. 665–672, 2014.