Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.14992

SOLICITED REVIEW

Treatment of *Helicobacter pylori* infection and its long-term impacts on gut microbiota

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Key words
Antibiotic resistance, Eradication, Gut microbiota, *H. pylori*, Long-term.

Accepted for publication 20 January 2020.

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Declaration of conflict of interest: All authors have nothing to disclose.
Author contribution: The study was conceived by J. M. Liou. J. M. Liou drafted the article, which was critically revised by Y. C. Lee and M. S. Wu. All authors commented on drafts and approved the final version. All authors participated in the decision to it submit for publication.
Ethical approval: Not applicable.
Financial support: The authors received grants from the Ministry of Science and Technology of Taiwan (grant numbers TCTC 108-2321-B-002-040, MOST 108-2314-B-002-187, and MOST 108-2314-B-002-209), the Ministry of Health and Welfare, Taiwan (grant number MOHW107-TDU-B-211-123002), "Center of Precision Medicine" from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education, Taiwan (grant number NTU-107L9014-1), National Taiwan University Hospital (grant numbers NTUH 106-P06 and NTUH 107-P05), and the Liver Disease Prevention & Treatment Research Foundation, Taiwan. The funding source had no role in study design, data collection, analysis or interpretation, report writing, or the decision to submit this paper for publication.
Consent for publication: Not applicable.
Availability of data materials: Not applicable.
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Abstract

The rising prevalence of antibiotic resistance and the long-term safety following eradication therapy are important issues in the management of *Helicobacter pylori* infection. The prevalence of clarithromycin, levofloxacin, and metronidazole resistance of *H. pylori* has increased to 21%, 27%, and 45%, respectively, in the Asia-Pacific region. Personalized treatment guided by susceptibility testing may provide a reliably excellent eradication rate in the first-line treatment but is costly and not widely available. Population-specific empirical therapy according to the local prevalence of antibiotic resistance may be an alternative strategy. Levofloxacin-based therapy and bismuth quadruple therapy are the recommended second-line rescue therapy. Susceptibility testing or genotypic resistance-guided therapy is the preferred treatment for refractory *H. pylori* infection, but empirical therapy may be an acceptable alternative. Eradication of *H. pylori* leads to short-term perturbation of gut microbiota. The diversity of gut microbiota can be restored months after eradication therapy, but the speed of recovery varies with regimens. The short-term increases of antibiotic resistance of *Escherichia coli* and *Klebsiella pneumoniae* may be restored to basal states months after *H. pylori* eradication. Future studies that apply in-depth sequencing, such as shotgun metagenomics sequencing, are needed to clarify whether the compositions of gut microbiota at the species level are fully restored.

Introduction

Eradication of *Helicobacter pylori* reduces the recurrence of peptic ulcer disease, cures two-third of patients with gastric mucosa-associated lymphoid tissue lymphoma, and may even reduce the risk of gastric cancer.[1–5] However, the efficacy of standard triple therapy is decreasing owing to the rising prevalence of clarithromycin resistance.[6] Our recent systematic review and meta-analysis showed that the resistant rate of clarithromycin, levofloxacin, and metronidazole was 21%, 27%, and 45% during 2011–2015 in Asia-Pacific regions, respectively.[6] Therefore, we conducted several trials to assess the efficacies of bismuth quadruple therapy and non-bismuth quadruple therapy in the first-line treatment of *H. pylori* infection in Taiwan.[7–11] We showed that levofloxacin triple therapy was inferior to clarithromycin triple therapy in the first-line treatment of *H. pylori* infection.[7] Fourteen-day sequential therapy, but not 10-day sequential therapy, was superior to 14-day triple therapy in the first-line treatment of *H. pylori* infection.[8,9] Ten-day bismuth quadruple therapy, but not 10-day concomitant therapy, was superior to 14-day triple therapy.[10] Fourteen-day sequential therapy was non-inferior to 10-day bismuth quadruple therapy, and both can be used in the

first-line treatment of *H. pylori* in Taiwan.[11] We also showed that levofloxacin sequential therapy was superior to levofloxacin triple therapy in the second-line treatment of *H. pylori* infection.[12,13] Genotypic resistance-guided therapy may achieve nearly an 80% eradication rate for those who failed after two or more eradication therapies.[14] However, properly designed empirical therapy may be an acceptable alternative option considering cost, accessibility, and the preference of patients.[15] Although emerging evidence showed that eradication of *H. pylori* infection reduces the risk of gastric cancer, there are some potential concerns regarding the mass eradication of *H. pylori* infection for gastric cancer prevention in the community, such as the emergence of antibiotic resistance, the perturbation of gut microbiota, and potential adverse impacts on metabolic disorders.[16–18] We reviewed current evidence and proposed some future research directions on these issues in this article.

Strategies to improve the efficacy of first-line eradication regimens

Key factors that lead to treatment failure following *H. pylori* eradication include the presence of antibiotic resistance, poor compliance to eradication regimens, inadequate treatment length, and inadequate gastric acid suppression.[19–21] The latter two can be improved by extending the treatment length to 14 days and the use of higher dosage of proton pump inhibitor (PPI) or more potent gastric acid suppressant, such as vonoprazan.[22,23] The uses of bismuth and non-bismuth quadruple therapy (concomitant, sequential, or hybrid therapies) or tailored therapy according to antibiotic resistance have also been tested widely in the first-line treatment of *H. pylori* infection.

Extending the treatment length to 14 days. A Cochrane meta-analysis of 59 randomized trials showed that extending the treatment length of standard triple therapy containing a PPI, amoxicillin, and clarithromycin to 14 days increased the eradication, compared with 7-day (81.9% *vs* 72.9%) and 10-day (84.4% *vs* 78.5%) regimens.[24] Our randomized trial and subsequent systematic review and meta-analysis showed that 14-day sequential therapy, but not 10-day sequential therapy, was superior to 14-day triple therapy in the first-line treatment.[8,9,25] Recent randomized trials and meta-analyses also showed that 14-day concomitant therapy, but not 10-day concomitant therapy, was superior to 14-day triple therapy.[10,26,27]

Interpretation of current evidence. The optimal treatment length varies with the local prevalence of clarithromycin resistance and ethnics. In regions with low prevalence of clarithromycin resistance (< 5–10%), a shorter treatment length might be sufficient. In regions with higher prevalence of clarithromycin resistance (10–15%), 14-day treatment length is suggested for clarithromycin-containing regimens. In regions with high prevalence of clarithromycin resistance (> 15–20%), bismuth quadruple therapy is the preferred regimen. Nevertheless, caution should be taken in the interpretation of results of meta-analyses in the treatment of *H. pylori* infection. First, it is not reasonable to analyze the trials conducted in regions with high prevalence and low prevalence of clarithromycin resistance because the results might be contradictory in the two regions.[19] This will lead to bias toward null. Unfortunately, susceptibility testing was not done in most of the published trials. Second, even if we extend the treatment length of triple therapy to 14 days, the overall eradication rate was only about 80–85%, which is still far from excellent. However, trials with homogenous study design and results may still be analyzed in a meta-analysis if the nonsignificant differences in the original trials are attributed to small sample size.

The use of potent gastric acid suppressant. Antibiotics, especially penicillin derivatives, macrolides, and fluoroquinolones, are degraded more rapidly in acidic environment. Therefore, the minimum inhibitory concentrations of these antibiotics are higher in acidic environment.[28] Graham et al. defined 20-mg omeprazole equivalents, b.i.d., as low dose for *H. pylori* eradication and 40-mg omeprazole equivalents, b.i.d., as high or double.[29] Earlier randomized trials and subsequent meta-analyses of six randomized trials (n = 1703) showed that the use of higher dosage of PPI may increase the efficacy of triple therapy.[22] More recently, vonoprazan, a potassium-competitive acid blocker, is shown to be more potent than PPI, especially in those with CYP2C19 extensive metabolizer. Three randomized trials and subsequent meta-analyses showed that vonoprazan-based triple therapy for 7 days was superior to lansoprazole-based triple therapy for 7 days in Japanese, especially in patients infected with clarithromycin-resistant strains.[23,30,31] Several retrospective or prospective nonrandomized studies also showed a higher eradication rate of vonoprazan-based triple therapy than PPI-based triple therapy in clarithromycin-resistant strains in Japanese.[32]

Interpretation of current evidence. The use of more potent gastric acid suppressant may increase the eradication rate of triple therapy. However, only two trials compared the same PPI of different dosages, and most of these trials did not provide information regarding the efficacies in antibiotic-susceptible and antibiotic-resistant strains. The efficacy of vonoprazan-based triple therapy should be validated in other ethnic populations.

Use of four-drug regimen (quadruple therapy). The efficacies of several four-drug regimens, including bismuth quadruple therapy and non-bismuth quadruple therapies (concomitant therapy, sequential therapy, and hybrid therapy) have been assessed in many randomized trials.[8–11,25–27,33] Recent randomized trials showed that bismuth quadruple therapy given for 10 to 14 days was superior to triple therapy, especially in regions with high clarithromycin resistance.[10,34] A meta-analysis of randomized trials showed that concomitant therapy for 5–10 days was superior to triple therapy for 7–10 days but was not superior to 14-day triple therapy.[27] However, a nonrandomized trial from Spain showed that 14-day concomitant therapy was superior to 14-day triple therapy.[26] Sequential therapy was more effective than triple therapy when both are given for the same duration.[8,9,25] Our recent randomized trial also showed that 14-day sequential therapy was not inferior to 10-day bismuth quadruple therapy in Taiwan where the prevalence of clarithromycin resistance was about 15%.[11]

Interpretation of current evidence. The efficacy of bismuth quadruple therapy is superior to that of clarithromycin-based therapy in regions with clarithromycin resistance higher than 10–15%. Non-bismuth quadruple therapy is usually more effective than clarithromycin triple therapy when both are given for the same treatment length. However, there are concerns regarding the emergence of antibiotic resistance with the use of non-bismuth quadruple regimens that contain three antibiotics.

Susceptibility testing guided therapy. The efficacy of susceptibility testing guided therapy *versus* empirical therapy in the first-line therapy has been assessed in 12 randomized trials.[35–37] Although a meta-analysis of these trials showed that susceptibility testing guided therapy was more effective than empirical triple therapy for 7 or 10 days in the first-line treatment,[36] there are some limitations of these trials that limit the wide application of tailored therapy in the first-line treatment (Fig. 1a). First, patients were randomized after endoscopy and/or culture in most of these trials, which is not similar to the clinical practice in real world because a significant proportion of patients might decline endoscopy. Besides, the successful rate of culture is only 70–90%, and the accuracy of susceptibility testing is not 100%. Second, triple therapy was given only for 7 to 10 days in most of these trials that was not optimized in terms of treatment length and was not an ideal regimen in regions with high clarithromycin resistance. Recently, two randomized trials showed that empirical bismuth quadruple therapy and empirical non-bismuth quadruple therapy were not inferior to tailored therapy in China and Korea where the clarithromycin resistance rate was higher than 15–20%.[35,37] The predicted efficacies of tailored therapy and empirical therapy are shown in Figure 1b.

Interpretation of current evidence. Susceptibility testing guided therapy is superior to empirical triple therapy for 7 or 10 days in those who undergo endoscopy and susceptibility testing. Properly chosen empirical therapy according to the local prevalence of antibiotic resistance with adequate treatment length may be an as effective alternative to tailored therapy considering accessibility to susceptibility testing, patient preference, and cost.

Choosing optimal empirical therapy according to the local prevalence of antibiotic resistance. The efficacy of *H. pylori* eradication regimen can be predicted if the regimen's efficacies against antibiotic-susceptible and antibiotic-resistant strains are known.[38] The efficacies of commonly used regimens in the first-line therapy are shown in Figure 2.[38] The predicted efficacies of these regimens in regions with different prevalence of clarithromycin resistance are shown in Figure 3.[38] Because the prevalence of antibiotic resistance varies greatly in different regions and may change over time in the same region, the predicted efficacies according to published trials may be a guide to decide an optimal empirical therapy (Fig. 4).[38] Periodic surveillance of the local prevalence of antibiotic resistance and monitoring of the national antibiotic consumption are needed.[39,40]

Development of effective rescue therapies

Second-line therapy. A recent meta-analysis of four randomized trials showed that susceptibility testing guided therapy was not superior to empirical therapy in the second-line treatment, probably attributed to the small sample size and the heterogeneity among these trials.[36] Therefore, the majority of patients were treated empirically in clinical practice. Because clarithromycin-resistant and levofloxacin-resistant strains are selected in the majority of patients after failure of regimens containing clarithromycin and levofloxacin, respectively, we should avoid reuse of these antibiotics empirically.[7] The most commonly used second-line rescue regimens are bismuth quadruple therapy and levofloxacin-containing regimens.[1,20,21] Our recent systematic review and meta-analysis showed that the efficacy of levofloxacin triple therapy was lower than 80% in the second-line treatment.[41] We showed that levofloxacin sequential therapy was superior to levofloxacin triple therapy in a large multicenter randomized trial.[12,13] Recently, we further showed that levofloxacin sequential therapy was non-inferior to bismuth quadruple therapy in the second-line treatment.

Interpretation of current evidence. For patients who fail after clarithromycin-containing regimens in the first-line therapy, bismuth quadruple therapy or levofloxacin-containing therapy are the treatment of choices, but bismuth quadruple therapy is preferred in regions with high levofloxacin resistance. For patients who fail after bismuth quadruple therapy in the first-line therapy, levofloxacin-containing therapy is the treatment of choice, although non-bismuth quadruple therapy may be an alternative.

Refractory H. pylori infection. Susceptibility testing is recommended by international consensus reports for patients with refractory *H. pylori* infection, although the evidence level is low for such recommendation.[1] However, susceptibility testing for *H. pylori* is time-consuming (2–4 weeks) and expensive, and the successful culture rate varies from 70% to 90%. More importantly, the efficacy of susceptibility testing guided therapy ranges from 36% to 91% in retrospective or prospective case series.[42] Therefore, the majority of patients are treated empirically because of low availability to susceptibility tests. Bismuth quadruple therapy and levofloxacin-based therapy are the most commonly used empirical third-line rescue regimens, whereas rifabutin-based therapy is usually reserved for fourth-line rescue therapy.[1,20,21] Alternatively, clarithromycin and levofloxacin resistance can be determined by detecting mutations at 23S rRNA and gyrase A, respectively.[43] A pilot trial showed that the eradication rate of genotypic resistance-guided therapy was 80% in the third-line treatment.[14] Subsequent multicenter randomized trials showed that the eradication rate was 78% (160/205) in patients receiving genotypic resistance-guided therapy and was 72.2% (148/205) in patients receiving empirical therapy.[15]

Interpretation of current evidence. Susceptibility testing or genotypic resistance-guided therapy is recommended for patients with refractory *H. pylori* infection. However, properly designed

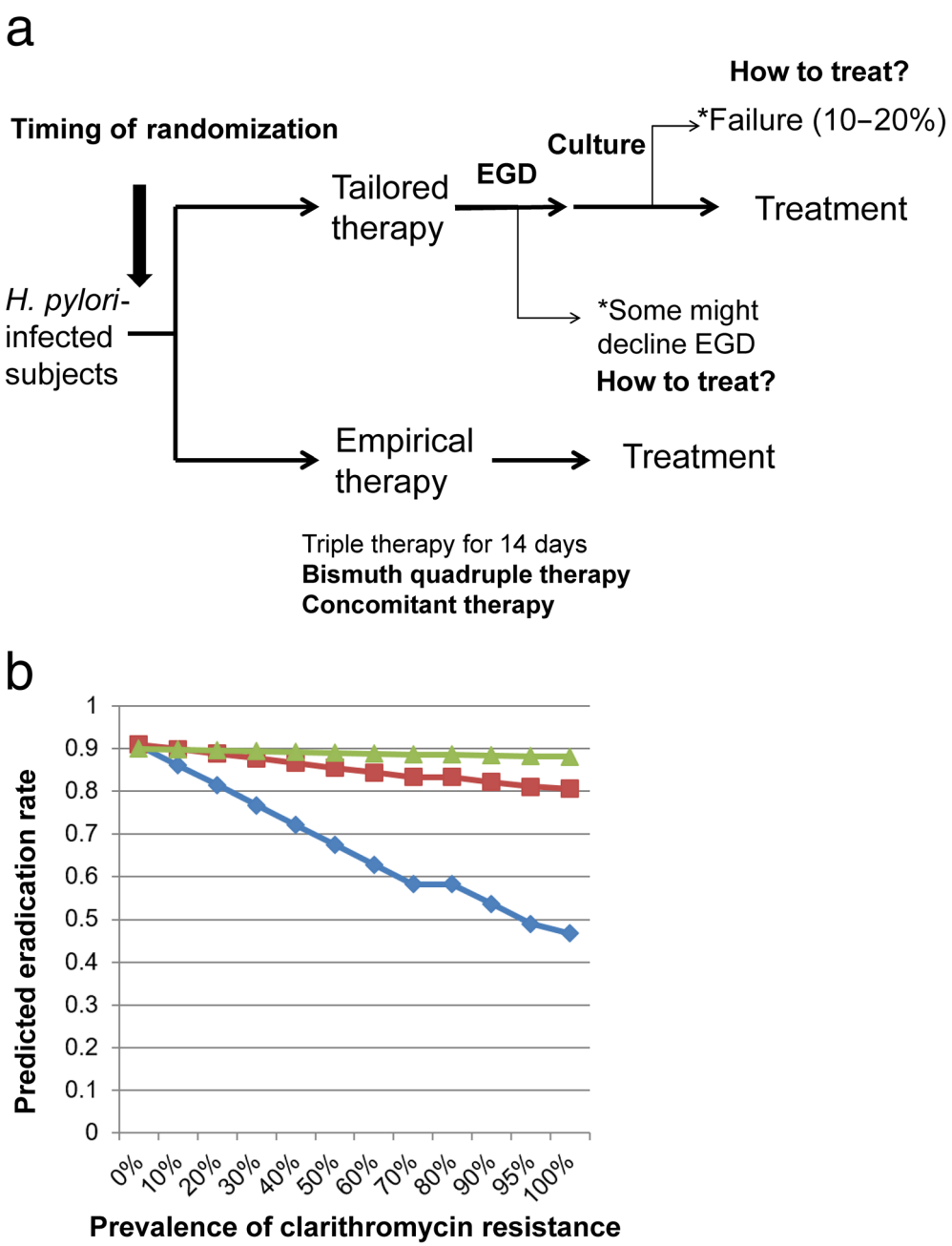

Figure 1 Tailored therapy versus empirical therapy in the first-line treatment of *H. pylori* infection. (a) Study design and potential limitations of published clinical trials. (b) Predicted efficacy of tailored therapy, empirical bismuth quadruple therapy, and empirical triple therapy in regions with different prevalence of clarithromycin resistance. EGD, esophagogastroduodenoscopy; *H. pylori, Helicobacter pylori.* , Empirical 7-day triple; , tailored; , empirical quadruple. [Color figure can be viewed at wileyonlinelibrary.com]

empirical therapy can be an acceptable alternative after consideration of cost, patient preference, and accessibility.

Long-term impacts of *H. pylori* eradication on gut microbiota

It is well-known that the use of antibiotics leads to short-term perturbation of gut microbiota. However, relatively little is known about the long-term impact of antibiotics on gut microbiota.[44] The extent and degree of perturbation of gut microbiota caused by antibiotics vary according to the class, pharmacokinetics, pharmacodynamics, dosage, duration, and administration route of the antibiotics.[44] Macrolides are excreted to biliary tract, whereas penicillin derivatives are excreted mainly through urinary tracts and also through biliary tract partially.[44] Antibiotic secreted through biliary tract may exert greater impact on gut microbiota. A cohort study in Finland preschool children showed that early life

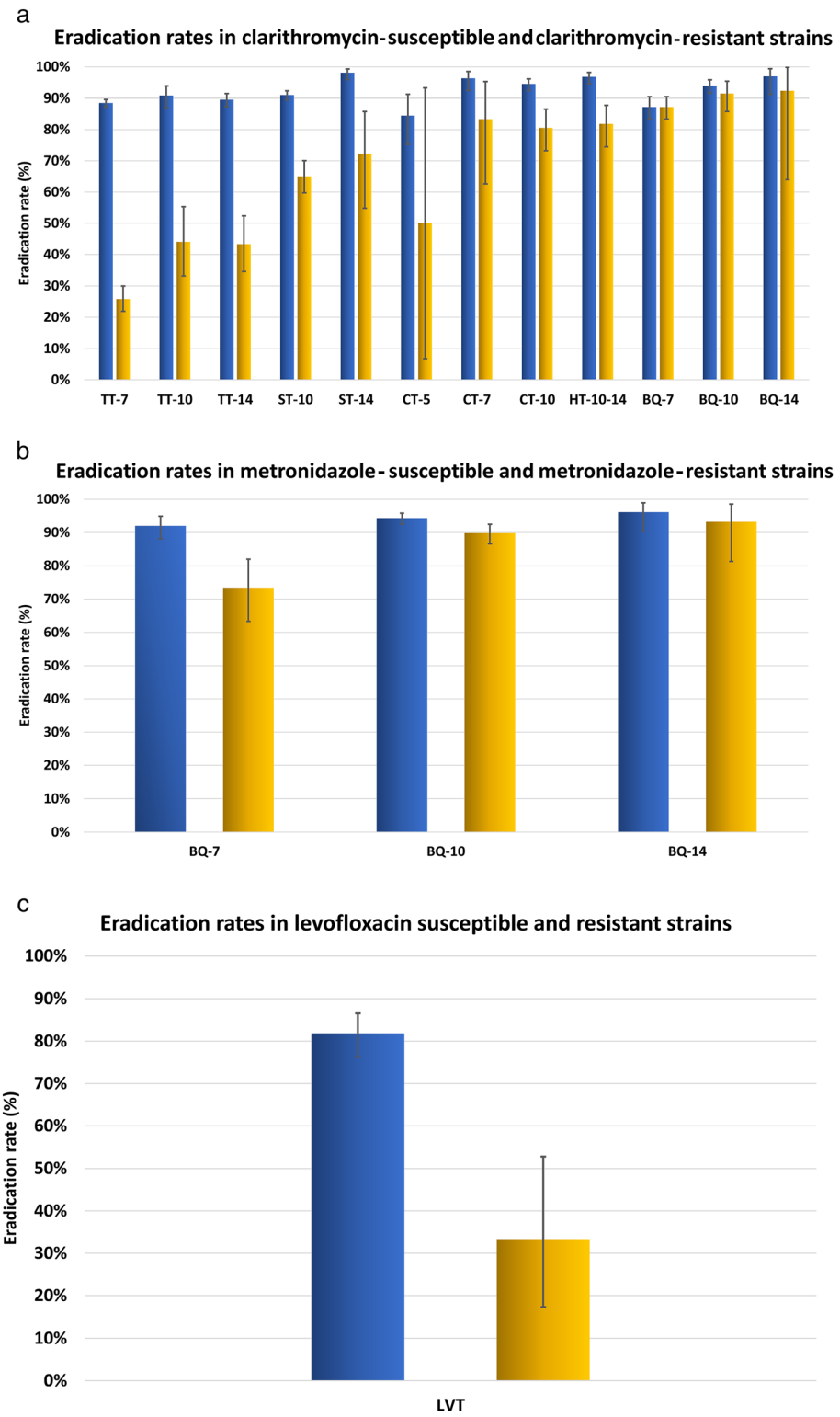

Figure 2 Eradication rate of each regimen according to the prevalence of (a) clarithromycin resistance, (b) metronidazole resistance, and (c) levofloxacin resistance.[38] T7, triple therapy for 7 days; T10, triple therapy for 10 days; T14, triple therapy for 14 days; S10, sequential therapy for 10 days; S14, sequential therapy for 14 days; C5, concomitant therapy for 5 days; C7, concomitant therapy for 7 days; C10, concomitant therapy for 10 days; H14, hybrid therapy for 14 days; BQ10, bismuth quadruple therapy for 10 days; BQ14, bismuth quadruple therapy for 14 days; LVT, levofloxacin triple therapy. (a) ■, Clarithromycin susceptible; ■, clarithromycin resistant. (b) ■, Metronidazole susceptible; ■, metronidazole resistant. (c) ■, Levofloxacin susceptible; ■, levofloxacin resistant. [Color figure can be viewed at wileyonlinelibrary.com]

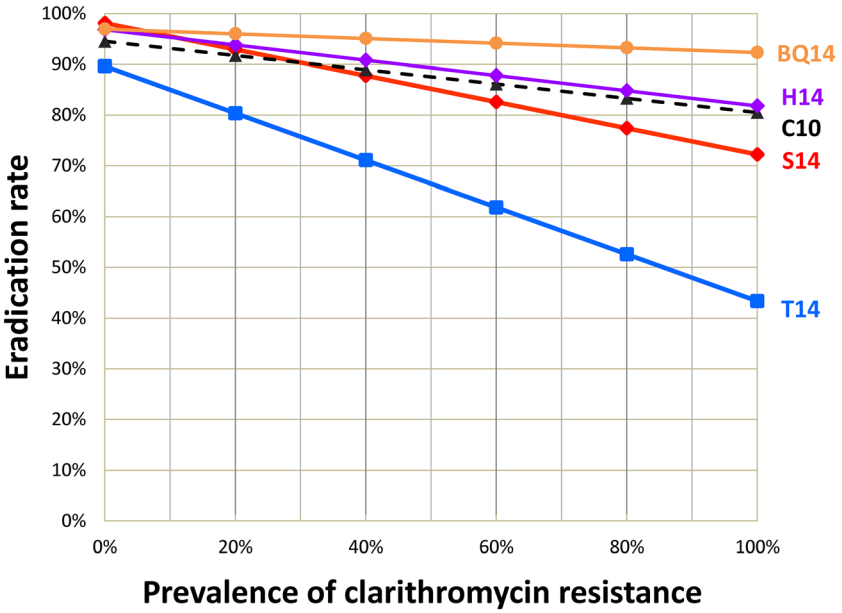

Figure 3 Predicted efficacy of each regimen according to prevalence of clarithromycin resistance.[38] T14, triple therapy for 14 days; S14, sequential therapy for 14 days; C10, concomitant therapy for 10 days; H14, hybrid therapy for 14 days; BQ14, bismuth quadruple therapy for 14 days. —■—, T14; —◆—, S14; —▲—, C10; —◆—, H14; —●—, BQ14. [Color figure can be viewed at wileyonlinelibrary.com]

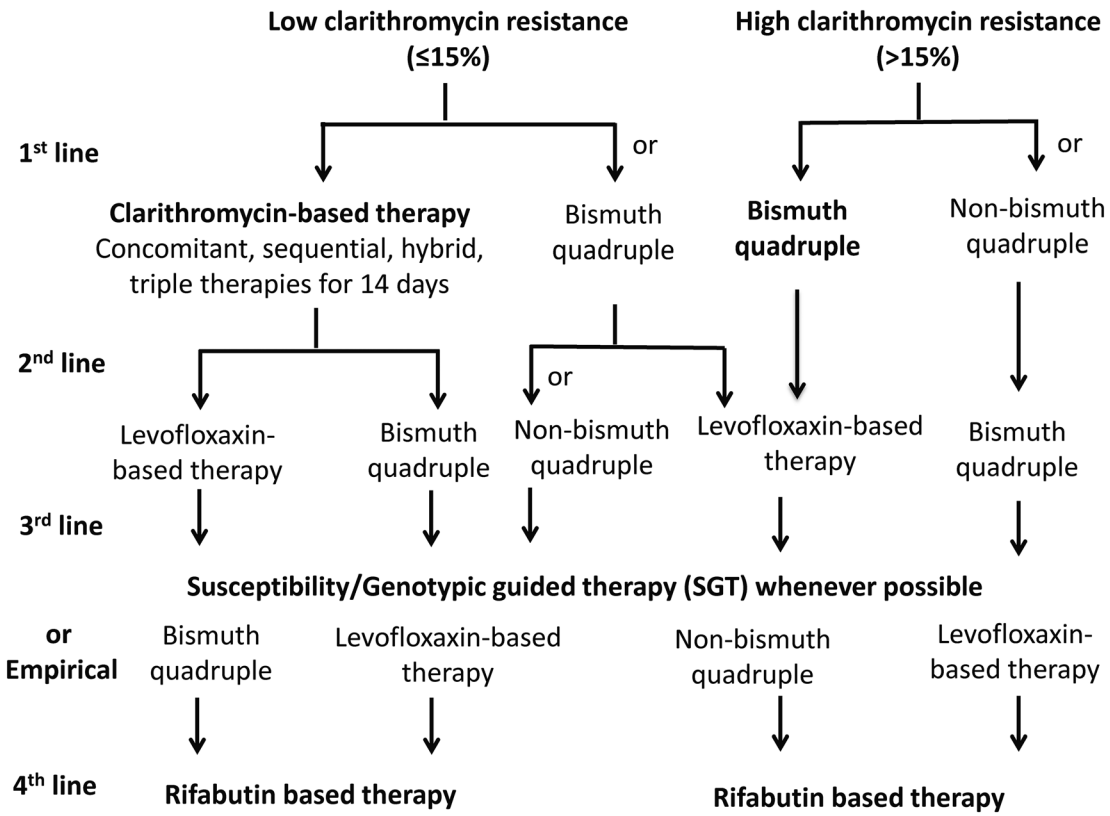

Figure 4 Recommended algorithm for population-specific treatment. Both clarithromycin-based therapy for 14 days and bismuth quadruple therapy can be used in regions with low clarithromycin resistance (≤ 15%). Bismuth quadruple therapy is the treatment of choice in regions with high clarithromycin resistance (> 15%). Levofloxacin-based therapy or bismuth quadruple therapy may be used as second-line rescue therapy. Susceptibility testing or genotypic resistance-guided therapy is the preferred treatment for refractory *Helicobacter pylori* infection. However, empirical therapy by avoiding reuse of levofloxacin and clarithromycin empirically may be an acceptable alternative. Rifabutin-based therapy for 14 days may serve as the fourth-line therapy.

Table 1 The impact of *Helicobacter pylori* eradication therapy on the gut microbiota (sequencing of 16S rRNA)

Authors, year	Case number	Regimen used for HP eradication	Time of sampling	Immediate changes (end of treatment)	Short-term changes (1–3 months)	Long-term changes* (at least 1 year)
Jakobsson et al. 2010[49]	6	PPI, amoxicillin, clarithromycin for 7 days	Day 0, days 8–13, 1 year, and 4 years	Bacterial diversity ↓1 week after antibiotic treatment	N/A	Diversity of the microbiota recovered to resemble the pre-treatment states, but some notable changes at the genus levels
Yap et al. 2015[50]	17	PPI, amoxicillin, clarithromycin for 7 days	Day 0, month 6, month 12, and month 18	N/A	N/A	No significant differences in richness and evenness of bacterial species; some notable changes at phylum and the genus levels
Oh et al. 2016[51]	23	PPI, amoxicillin, clarithromycin, +/− probiotics for 7 days	Day 0, week 2	Relative abundances of Firmicutes ↓, Proteobacteria ↑; higher changed proportions in triple alone than triple plus probiotics	N/A	N/A
Yanagi et al. 2017[52]	20	PPI, amoxicillin, clarithromycin for 7 days	Day 0, day 8, month 3	Increased anaerobes by culture method	No significant difference in α-diversity; Bacteroidetes: Firmicutes (B:F) ratio significantly greater than baseline	N/A
Chen et al. 2018[53]	70	Pantoprazole, amoxicillin, furazolidone, bismuth pectin +/−probiotics for 14 days	Day 0, day 14, and day 56	α-Diversity decreased; decrease in the B:F ratio from 0.98 to 0.34	α-Diversity was not completely recovered, but no significant difference compared with baseline; B:F ratio increased to 0.83 on day 56	N/A
Gotoda et al. 2018[54]	8	Vonoprazan, amoxicillin, clarithromycin for 7 days	Day 0, month 2	N/A	Nonsignificant difference of β-diversity at 2 months. Some changes at relative abundance at phylum, class, and order levels	
Hsu et al. 2018[55]	11	PPI, bismuth, metronidazole, tetracycline for 10 days	Day 0, week 2, week 8, week 48	α-Diversity ↓; altered β-diversity	Bacterial diversity ↓ at week 8; relative abundances of all genera restored to baseline levels at week 8	α-Diversities and β-diversities and relative abundances of all genera restored to baseline levels
Hsu et al. 2019[56]	12	PPI, amoxicillin, clarithromycin, metronidazole for 14 days	Day 0, week 2, week 8, week 48	α-Diversity ↓; altered β-diversity	α-Diversity and β-diversity restored to basal state at week 8	α-Diversities and β-diversities and relative abundances of all genera restored to baseline levels
He et al. 2019[57]	10	PPI, bismuth, amoxicillin, furazolidone for 14 days	Week 0, week 6, and week 26	N/A	Diversity of gut microbiota decreased after eradication	*Blautia* and *Lachnoclostridium* were enriched at week 26 compared with week 0, while *Alistipes* were depleted to a level close to that of the healthy controls
Martín-Núñez et al. 2019[58]	40 HP + 20 control	PPI, clarithromycin, amoxicillin for 10 days	Day 0 and month 2	N/A	Decreased bacterial richness and diversity	N/A
Olekhnovich et al. 2019[59]	40	PPI, bismuth, amoxicillin, clarithromycin for 14 days	Day 0 and day 14	α-Diversity ↓; altered β-diversity	N/A	N/A
Liou et al. 2019[48]	84	PPI, amoxicillin, clarithromycin for 14 days	Day 0, week 2,	α-Diversity ↓; altered β-diversity; significant changes at the genus level	α-Diversity and β-diversity restored to basal state at week 8	Diversity of the microbiota recovered to resemble the pre-treatment states at 1 year, but

(Continues)

Table 1. (Continued)

Authors, year	Case number	Regimen used for HP eradication	Time of sampling	Immediate changes (end of treatment)	Short-term changes (1–3 months)	Long-term changes* (at least 1 year)
			week 8, 1 year			some notable changes at the genus levels
	73	PPI, amoxicillin, clarithromycin, metronidazole for 10 days	Day 0, week 2, week 8, 1 year	α-Diversity ↓; altered β-diversity; significant changes at the genus level	α-Diversity ↓; altered β-diversity; but observed a trend of gradual recovery	Diversity of the microbiota has not yet fully recovered at 1 year, and there were some notable changes at the genus levels
	77	PPI, bismuth, metronidazole, tetracycline for 10 days	Day 0, week 2, week 8, 1 year	α-Diversity ↓; altered β-diversity; significant changes at the genus level	α-Diversity ↓; altered β-diversity; but observed a trend of gradual recovery	Diversity of the microbiota has not yet fully recovered at 1 year and there were some notable changes at the genus levels

HP, *Helicobacter pylori*; N/A: not available; PPI, proton pump inhibitor.

exposure to macrolides, but not penicillin, may induce long-term alteration of microbiota, particularly the reduction of bacterial diversity.[45] Several studies showed an inverse association between *H. pylori* and the diversity of gastric microbiota in the stomach.[46] Eradication of *H. pylori* may increase the bacterial diversity of stomach and restore the relative abundance of other bacteria to levels similar to those without *H. pylori* infection.[47]

Several studies have reported the short-term impacts of *H. pylori* eradication on fecal microbiota, but relatively few studies addressed on the long-term impacts. Recently, we conducted a multicenter randomized trial to compare the long-term impacts of 14-day triple therapy, 10-day concomitant therapy, and 10-day bismuth quadruple therapy on gut microbiota, antibiotic resistance, and metabolic parameters.[10,48] A total of 1620 treatment-naïve *H. pylori*-infected subjects were randomized. The eradication rate was 83.7% for triple therapy, 85.9% for concomitant therapy, and 90.4% for quadruple therapy.[10] We assessed the long-term outcomes, including reinfection rate, changes in the gut microbiota, antibiotic resistance, and metabolic parameters 1 year after completion of eradication therapy in patients with available data.[48] The V3 and V4 hypervariable regions of the 16S rRNA were amplified and sequenced in 84, 73, and 77 patients treated with triple therapy, concomitant therapy, and bismuth quadruple therapy, respectively.[48] We showed that compared with baseline, α-diversity was significantly reduced and β-diversity was significantly altered at the end of triple therapy, concomitant therapy, and bismuth quadruple therapy.[48] The degree of perturbation was greater in patients treated with concomitant therapy and bismuth quadruple therapy. α-Diversity and β-diversity were restored at week 8 and 1 year after triple therapy.[48] We also observed a trend of recovery in diversity at week 8 and 1 year in patients treated with concomitant therapy and bismuth quadruple therapy, but it was not fully recovered 1 year after treatment.[48]

Studies that reported the short-term and long-term changes of gut microbiota after *H. pylori* eradication were reviewed and summarized in Table 1.[48–59] Triple therapy and bismuth quadruple therapy were used in most of these studies. The long-term changes were reported in six studies, and the case number was small in most of these studies. All of these studies showed significant perturbation of the diversity and composition of gut microbiota immediately after *H. pylori* eradication. Of the six studies that assessed the long-term changes of gut microbiota 1 year after *H. pylori* eradication, full recovery of bacterial diversity was reported in most of these studies. However, although the diversities of gut microbiota were restored, some studies observed some notable changes of the abundance at the genus level 1 year after *H. pylori* eradication.

Interpretation of current evidence. There was significant short-term perturbation of gut microbiota after *H. pylori* eradication. The extent and severity of perturbation vary with regimens. The diversity of gut microbiota may be fully restored as short as 2 months after triple therapy but is not yet full 1 year after bismuth quadruple therapy and concomitant therapy. More studies with larger sample size and that assess the long-term changes of gut microbiota by shotgun metagenomics sequencing are warranted.

Impacts of *H. pylori* eradication on antibiotic resistance

Emergence of antibiotic resistance after widespread use of antibiotics is an important concern of mass screening and eradication of *H. pylori* for asymptomatic subjects in the community.[16] It is well-known that antibiotics cause a significant increase in antibiotic resistance immediately after antibiotic treatment.[44] However, relatively few studies reported the long-term changes of antibiotic resistance after *H. pylori* eradication. An earlier study showed an increase of clarithromycin resistance of *Enterococcus* shortly after triple therapy in all the five patients, compared with 0% (0/5) in the control group.[19] They reported persistent clarithromycin-resistant *Enterococcus* spp. in 50% (2/4) patients 1 year after triple therapy, compared with 0% (0/5) in the control group.[19] In another study, Jakobson et al. showed that the clarithromycin resistance rates of *Enterococcus* spp., *Streptococcus* spp., *Staphylococcus* spp., and *Bacteroides* spp. were significantly increased after triple therapy.[60] The clarithromycin resistance rates were still high 1 year later, but the differences were not statistically significant.[60] In our recent study, susceptibility testing of *Escherichia coli* and *Klebsiella pneumoniae* was done in 193, 190, and 170 patients after triple therapy, concomitant therapy, and bismuth quadruple therapy, respectively.[48] We showed that the antibiotic resistance rates to penicillin derivatives, cephalosporin, and fluoroquinolones of *E. coli*

and *K. pneumoniae* were significantly increased immediately after triple therapy and concomitant therapy but were not significantly changed after bismuth quadruple therapy.[48] However, the transient increases of antibiotic resistance were restored to baseline levels 2 months after eradication therapy.[48]

Interpretation of current evidence. The transient increase of antibiotic resistance of certain bacteria may be restored to basal state after *H. pylori* eradication. Bismuth quadruple therapy has minimum impact on the resistance of antibiotics commonly used for life-threatening infections. However, more studies are warranted on this issue.

Conclusion

Personalized treatment guided by susceptibility testing may provide a reliably excellent eradication rate in the first-line treatment but is costly and not widely available. Population-specific empirical therapy according to the local prevalence of antibiotic resistance may be an acceptable alternative. The short-term perturbation of the diversity of gut microbiota can be restored months after eradication therapy, but the speed of recovery varies with regimens and is faster with triple therapy. The short-term increases of antibiotic resistance of certain bacteria may be restored to basal states months after *H. pylori* eradication. More studies on the long-term safety issues of *H. pylori* eradication therapy are warranted.

Acknowledgments

The authors would like to express their special thanks to the staff of the Eighth Core Lab, Department of Medical Research, National Taiwan University Hospital, for their technological support. This article is funded by Liver Disease Prevention & Treatment Research Foundation, Taiwan and Ministry of Health and Welfare, Taiwan, Ministry of Education, Taiwan.

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