Review: Treatment of *Helicobacter pylori* Infection 2019

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Abstract
This review summarizes important studies regarding *Helicobacter pylori* therapy published from May 2018 to May 2019. The main themes that emerge involve studies assessing the efficacy of bismuth-based regimens. While in recent years the efficacy of bismuth-based quadruple therapy as a second-line therapy has been clearly established, there is now substantial evidence that it is the best performing first-line therapy. Antibiotic resistance was again intensely studied this year, and a clear and dramatic increase in resistance is noted for clarithromycin and levofloxacin; most notably, it may not be possible to support these therapies in most regions of the world much longer without testing. The utility of vonoprazan as an alternative to proton-pump inhibitor therapy, especially in resistant and difficult to treat groups, has also been considered in greater detail this year, as well as means of supporting and enhancing adherence to therapy. Several studies showed that the diversity of gut microbiota was significantly altered shortly after *H pylori* eradication. However, the diversity was restored to pre-treatment state after 2 months in patients treated with triple therapy. More studies are warranted to assess the long-term changes of gut microbiota after *H pylori* eradication.

KEYWORDS
clarithromycin, dual therapy, proton-pump inhibitor, quadruple therapy, triple therapy, vonoprazan

1 | INTRODUCTION

The last year has been another busy period for research publications on the treatment of *Helicobacter pylori*, driven by a series of articles suggesting that eradication rates with conventional therapies have fallen to unacceptable levels. Data regarding specific regimens are explored in greater detail below but a number of other studies examined new treatments and novel paradigms for *H pylori* eradication therapy in order to address declining eradication rates.

Two systematic reviews were carried out this year on the principles of second-line therapy rather than the specific agents used. One concluded that more complex quadruple and 14-day regimens were generally more successful than shorter triple ones.¹ A second review found quinolone-based therapies of more than 10 days duration to be the most effective second-line therapy.²

In terms of new therapies, in an in vitro study, key lime (*Citrus aurantifolia*) was noted to inhibit growth of a triple drug-resistant form of *H pylori*.³ In a separate in vitro study, the anticancer compound 3-bromopyruvate was also observed to have some activity against *H pylori*.⁴ A Japanese series of three cases reported successful eradication of a resistant strain with the herbal medicine, goshuyuto.⁵ A Cochrane systematic review of N-acetylcysteine used as an adjuvant in *H pylori* eradication therapy failed to identify a benefit.⁶ The particular literature pertaining to the major treatment regimes is reviewed hereunder.

2 | DUAL THERAPY

It has been proposed that giving longer courses of less complex dual therapy with PPI and amoxicillin can also improve compliance...
and eradication rates. One study from Taiwan this year found an eradication rate of 92% for 14 days of such a regimen as opposed to 87% for 7-day non-bismuth quadruple therapy. A systematic review and meta-analysis found equivocal eradication rates for high-dose dual therapy (85%) compared to 87% for bismuth quadruple therapy.

3 | TRIPLE THERAPY

Triple therapy remains the standard of care in the published international guidelines of the European Helicobacter and Microbiota Study Group in areas of low clarithromycin resistance. A number of interesting studies looked this year at the role of triple therapy in contemporary H. pylori eradication treatment. A randomized controlled trial in Japan where clarithromycin resistance is a growing problem found metronidazole to be superior to clarithromycin as a 7-day first-line regimen in adolescents and young adults, achieving eradication in 98% for metronidazole-based triple therapy compared to just 60% for the clarithromycin-based regimen. By contrast, in Rwanda, in a separate randomized controlled trial, metronidazole-based triple therapy performed poorly with 36% treatment failure compared to 13% for a clarithromycin-based regimen and 18% for a ciprofloxacin-based regimen. A meta-analysis of studies of triple therapy regimens carried out in Turkey of varying durations and combinations also discouraged both low with eradication rates for 7 days of treatment (57%) and for 14 days of treatment (60%). Two other studies looked at how the efficacy of triple therapy might be optimized. A study in China compared a standard 7-day triple therapy with an extended 10-day regimen and a 7-day regimen with bismuth added. This revealed cure rates of 79% for 7-day standard triple therapy, 82% for 7-day standard triple therapy with bismuth, but 89% for 14-day standard triple therapy. The effect of complicated treatment regimens with multiple-daily dosing affecting compliance has long been proposed as an explanation for declining eradication rates for triple therapy. To counteract this, a randomized controlled trial in India investigated a daily single-dose triple therapy and found it to improve compliance and to increase eradication rates from 86% to 90% compared with conventional dosing.

4 | QUADRUPLE, CONCOMITANT, SEQUENTIAL, AND HYBRID THERAPIES

Original research on quadruple, concomitant, sequential, and hybrid therapies has been sparse this year. A systematic review and meta-analysis on concomitant therapy vs triple therapy for first-line treatment looked at 23 randomized controlled trials and 6632 patients and found that concomitant therapy given for 5 or 10 days was superior to 5- or 7-, or 10-day triple therapy with PPI, amoxicillin, and clarithromycin, but not to 14-day therapy. Hybrid therapy has been proposed as a means of combining the benefits of the sequential and concomitant regimes but has been criticized as over-complicated and hence compromising on adherence to therapy. The reverse hybrid therapy (PPI plus amoxicillin for 14 days, and clarithromycin plus metronidazole for the initial 7 days) has been proposed as a means of simplifying it. A randomized controlled trial of 352 patients in Taiwan found 96% eradication rates for both reverse hybrid and bismuth-based quadruple therapy. A prospective cross-sectional study conducted in Spain found very impressive eradication rates of 98% for concomitant quadruple therapy compared to 94% for bismuth-based quadruple therapy.

5 | ANTIBIOTIC RESISTANCE

A number of studies reported on the important topic of antimicrobial resistance of H. pylori strains. A very large meta-analysis including 178 studies, comprising 66 142 isolates from 65 countries, showed that primary and secondary resistance rates to clarithromycin, metronidazole, and levofloxacin were ≥15% in all WHO regions, except primary clarithromycin resistance in the Americas (10%) and South-East Asia region (10%), and primary levofloxacin resistance in the European region (11%). This is highly significant as it means that, in most parts of the world, resistance to the most commonly used antibiotics is greater than the threshold at which they ought not to be used for primary treatment. The individual studies detailing resistance are summarized in Table 1.

6 | SUSCEPTIBILITY-GUIDED THERAPY

Given the amount of data available on the burgeoning problem of antibiotic resistance, susceptibility-guided treatments have been proposed as a means of improving falling eradication rates. A German study looked at real-time genotypic clarithromycin and/or levofloxacin susceptibility as tested by PCR analysis of 144 H pylori-positive strains from patients with prior treatment failure. Cure, however, was only achieved in 68% of patients. More encouraging results were obtained in a large, multicenter open-label trial of 450 patients who had failed two previous treatment regimes where genotypic resistance tailored treatment led to 78% eradication, but in this case empirical quadruple sequential therapy with a cure rate of 71% was an acceptable alternative after consideration of accessibility, cost,
and patient preference. A systematic review of 36 eligible studies on this topic, including 2890 patients, indicated a cure rate of 72% in the patients harboring clarithromycin-susceptible strains after previous clarithromycin treatment, 93% in the metronidazole-susceptible strains, and 84% in the levofloxacin-susceptible strains. From a first-line perspective in an area of high antibiotic resistance in South Korea, eradication rates of 93% were obtained for culture-based therapy. Separately, a study from China compared eradication rates for first-line susceptibility-guided treatment with bismuth-based quadruple therapy and found excellent eradication rates for both regimes, 92% and 85%, respectively. Four articles from diverse parts of the world examined the role of levofloxacin-based therapies in \textit{H pylori} treatment this year. A randomized controlled trial from China looked at different dosages of levofloxacin as part of a bismuth quadruple regimen and found that 200 mg dosing, which achieved eradication in 79% of cases, was non-inferior to 500 mg dosages where 77% were cured, which has obvious cost and potential side effect implications. In Iran, a 10-day sequential regimen using levofloxacin was found to have a 78% success rate compared to an 83% cure rate for 14-day quadruple therapy. Finally, two studies compared levofloxacin-based therapy to standard triple therapy. In Mexico, 10-day triple regimens were compared, both with returning poor cure rates, the levofloxacin-based arm being 63% and the standard arm being 58%. A very similar study from Pakistan on 300 patients which looked at 14-day triple regimens showed better results, with 92% of patients receiving levofloxacin being cured vs 87% of those receiving standard clarithromycin-based triple therapy. The adjunctive antimicrobial properties of bovine lactoferrin from the whey protein of fermented milk have been analyzed in vitro against six \textit{H pylori} strains and found to inhibit the growth of 50% of strains when administered at a dose of 10 mg/mL and to kill 50% of bacteria at 40 mg/mL. When examined in vivo as an adjuvant to levofloxacin-based triple therapy, 96% of the patients receiving the lactoferrin were cured, as opposed to 75% in the group without.

### TABLE 1  \textit{Helicobacter pylori} resistance to antibiotics in the studies published during the last year worldwide

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Region</th>
<th>AMO, %</th>
<th>CLA, %</th>
<th>MET, %</th>
<th>Quinolone, %</th>
<th>TET, %</th>
<th>RIF, %</th>
<th>FUR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu21</td>
<td>1117</td>
<td>China</td>
<td>3.4</td>
<td>22.1</td>
<td>78.2</td>
<td>(LVX) 19.2</td>
<td>1.9</td>
<td>1.5</td>
<td>–</td>
</tr>
<tr>
<td>Fiorini22</td>
<td>1424</td>
<td>Italy</td>
<td>0.06</td>
<td>35.9</td>
<td>40.2</td>
<td>(LVX) 29.3</td>
<td>–</td>
<td>–</td>
<td>0.06</td>
</tr>
<tr>
<td>Bashir23</td>
<td>270</td>
<td>Algeria</td>
<td>5.2</td>
<td>29.7</td>
<td>46.7</td>
<td>(CIP) 17.9</td>
<td>17.2</td>
<td>2.6</td>
<td>–</td>
</tr>
<tr>
<td>Lopo24*</td>
<td>2194</td>
<td>Portugal</td>
<td>0.1</td>
<td>42</td>
<td>25</td>
<td>(LVX) 18</td>
<td>(CIP) 9</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Gonzalez-Hormazabal25</td>
<td>191</td>
<td>Chile</td>
<td>–</td>
<td>31.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mosites26</td>
<td>800</td>
<td>USA</td>
<td>–</td>
<td>29.8</td>
<td>42.8</td>
<td>(LVX) 14.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Saniee27</td>
<td>218</td>
<td>Iran</td>
<td>27.1</td>
<td>34.4</td>
<td>79.4</td>
<td>(OFX) 58.7</td>
<td>(CIP) 46.8</td>
<td>(LVX) 45</td>
<td>38.5</td>
</tr>
<tr>
<td>Khien28*</td>
<td>2318</td>
<td>Vietnam</td>
<td>15</td>
<td>34.1</td>
<td>69.4</td>
<td>(LEV) 27.9</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kageyama29</td>
<td>208</td>
<td>Japan</td>
<td>13</td>
<td>48</td>
<td>49</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>Zhang30</td>
<td>144</td>
<td>China</td>
<td>–</td>
<td>70</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pinkowska31</td>
<td>170</td>
<td>Poland</td>
<td>–</td>
<td>46</td>
<td>56</td>
<td>(LEV) 6</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lee32</td>
<td>74</td>
<td>South Korea</td>
<td>6.7</td>
<td>31</td>
<td>41.8</td>
<td>(MOX) 39.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: AMO, amoxicillin; CIP, ciprofloxacin; CLA, clarithromycin; FUR, furazolidone; LVX, levofloxacin; MET, metronidazole; MOX, moxifloxacin; OFX, ofloxacin; RIF, rifabutin; TET, tetracycline.

*Meta-analysis.

### 8 | BISMUTH-BASED THERAPY

Bismuth-based therapies were looked at in great detail this year both as primary- and second-line therapy. A very large study from the European Registry on the Management of \textit{H pylori} infection (Hp-EuReg) found that 1141 patients treated with first-line triple therapy plus bismuth achieved an 88% cure. A study of 101 treatment naïve patients in China receiving also a quadruple regimen with bismuth resulted in a cure 88% of the time. Two studies looked at the “single triple” capsule regimen where bismuth and two antibiotics are given in the same capsule (Pylera®), along with a PPI. In the first of these from China, 192 patients received therapy with bismuth, metronidazole, and tetracycline and were compared to another group of 192 patients who received bismuth, amoxicillin, and clarithromycin given separately. PPI was given separately in both arms. No significant difference between the eradication rates was achieved by both regimens (86% vs 87%). In Italy, where sequential therapy and...
bismuth-based quadruple therapy are the recommended first-line treatments, a study of almost 500 patients compared the Pylera® single triple capsule with sequential therapy and again found similar efficacy with eradication achieved in 91% and 92%, respectively.47 Again, with resistance in mind, two other interesting studies emerged from China. The first looked at a quadruple regimen with bismuth and furazolidone and found a cure rate of 87%.48 The second, from a region of high resistance, compared a number of regimens consisting of varying doses of rabeprazole with bismuth, amoxicillin, and either clarithromycin or tetracycline and found all to obtain eradication rates in the region of 86% to 88%.49 In Iran, another study of first-line patients with duodenal ulcer showed equivalent eradication rates for bismuth quadruple therapy whether amoxicillin or tetracycline was used.50 In the case of penicillin-allergic patients, a study from China reported an eradication rate of 85% for patients receiving bismuth, esomeprazole, clarithromycin, and metronidazole compared to 64% for those receiving antibiotics without bismuth.51

Two pragmatic real-world studies were carried out in Italy and Spain looking at the use of bismuth-based quadruple therapy in day-to-day clinical practice. These are summarized in Table 2.52,53

Two separate meta-analyses published in the last year examined the role of bismuth-based therapy. One found that a 10-day treatment with Pylera® achieved an effective eradication rate of 90% both in first- and second-line therapy, regardless of the type and dose of the PPI, in patients with clarithromycin- or metronidazole-resistant strains, and in those previously treated with clarithromycin.54 Another meta-analysis which had more non-English language publications reported a pooled eradication rate of 86%.55 Although bismuth-based regimens have usually been 10 days in length, one study on a 7-day bismuth-based treatment as second-line showed very high eradication rates of 94% compared to 74% for 14 days of moxifloxacin-based therapy.56

Even though bismuth is a very successful treatment for H pylori, failures and adverse events do occur. A multivariate analysis performed in Korea looking at compliance, treatment duration, age >60 years, minimum inhibitory concentrations for metronidazole and tetracycline, adverse events, and any other parameters associated with treatment failure, found metronidazole resistance to be the only independent risk factor for eradication failure.57

### TABLE 2 Real-world studies of bismuth-based quadruple regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Number</th>
<th>1st line (%)</th>
<th>2nd line (%)</th>
<th>3rd line (%)</th>
<th>Adverse events (%)</th>
<th>Abandoned (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zagari51</td>
<td>Italy</td>
<td>376</td>
<td>91.4</td>
<td>87.5</td>
<td>91.7</td>
<td>32.4</td>
<td>6.1</td>
</tr>
<tr>
<td>Agudo-Fernández52</td>
<td>Spain</td>
<td>185</td>
<td>78.2</td>
<td>85.3</td>
<td>61.3</td>
<td>3.8</td>
<td>4.9</td>
</tr>
</tbody>
</table>

9 | RIFABUTIN, FURAZOLIDONE, AND SITAFLOXACIN

Given falling eradication rates for all conventional therapies, there is a clear need for antibiotics, or combinations of antibiotics that are of particular interest in refractory and resistant cases of H pylori infection and for this reason resistance to these is examined separately for the purposes of this review. Three of the more prominent of these rescue antibiotics examined this year have been rifabutin, furazolidone, and sitafloxacin. In a study of 100 strains from Nepal and Bangladesh where resistance rates to clarithromycin, metronidazole, and levofloxacin are high, no resistance was seen to furazolidone or rifabutin and a high susceptibility of sitafloxacin (95% in Nepal and 98% in Bangladesh) was observed.58 A study of 63 strains from the Dominican Republic, conducted by the same investigators to the same standard, revealed no resistance to rifabutin, furazolidone, or sitafloxacin.59 A study from Italy looked at a 14-day triple therapy regime based on rifabutin for patients who had failed at least two prior eradication regimens and achieved a cure in 71% of the patients.60

10 | RECRUDESCENCE OF H PYLORI INFECTION

Two published works, both coming from Korea, looked at the phenomenon of recrudescence and reinfection with H pylori. One prevalence study from a screening cohort found a 3.2% rate of H pylori recurrence over a 5-year period with an annual recurrence rate of 0.91%.61 This study found older patients and males to be at the greatest risk of recurrence. The other study looked at 420 patients who had been successfully eradicated with standard triple therapy and found an eradication rate of 78% with repeated triple therapy, which was not significantly different from that of the index triple therapy.62 In that group, quadruple therapy for reinfection had a better eradication rate (87%) but without statistical significance.

11 | PROBIOTICS

Few studies have used probiotics this year. The proposed utility of probiotics has been that they decrease side effects, improve compliance, and thereby increase eradication rates. A study examining this was conducted in Spain where 209 consecutive patients were prescribed eradication therapy (10-day triple or non-bismuth quadruple concomitant therapy) and randomly received probiotics (Lactobacillus plantarum and Pedicioccus acidilactici) or matching placebo.63 Eradication rates were observed to be similar between groups (placebo 95% vs probiotic 97%), and no difference in compliance with therapy nor side effects was observed. One from China looking at the use of two probiotic compounds alongside bismuth-based therapy reported that Lactobacillus tablets and Saccharomyces...
boulardii" sachets reduced the overall side effect rates, with the former reducing the incidence of diarrhea, and the latter reducing the incidence of diarrhea, and also of abdominal distension and constipation. When used solely alongside PPI with no antibiotics or bismuth, a Lactobacillus reuteri preparation yielded a cure rate of 12% which, although poor, does offer some hope that for treatment regimens with 75%-80% efficacy, its addition could make those regimens acceptably efficacious. A network meta-analysis was done by a Chinese group on 40 studies and 8924 patients and found that probiotics improved the eradication rate and decreased the incidence of total side effects when added to the treatments designed to eradicate H pylori, with the best effect noted when probiotics were used before and throughout treatment. This study found that probiotics combined with the bismuth quadruple regimen was the best combination, and Lactobacillus and multiple strains to be the best choices for probiotic preparations. When probiotics were used alongside "three-in-one" bismuth quadruple therapy, they failed to improve compliance.

12 | VONOPRAZAN

Vonoprazan, a first-in-class orally bioavailable potassium-competitive acid blocker (P-CAB), inhibits the H+, K+-ATPase-mediated gastric acid secretion in a reversible and potassium-competitive manner and is thought to possess more potent inhibitory effects than PPIs offering a potential benefit for H pylori eradication. It is mainly used in Japan and in that country a study on a total of 1355 first-line patients found eradication rates of 97% for the vonoprazan-based triple therapy group compared to 86% for a PPI-based triple therapy. Elsewhere in Japan, another study found vonoprazan triple therapy to be significantly more effective than standard therapy as first line (91% vs 85%) but not second line (87% vs 88%). Two trials looked at the introduction of vonoprazan-based therapy as third line for patients who had failed two courses of PPI-based therapies. The first, a randomized controlled trial showed 76.8% eradication for vonoprazan, amoxicillin, and sitafloxacin, compared to 53% when PPI was used with those antibiotics. A second, retrospective study found the overall success rates of first- and third-line H pylori eradication to be significantly higher for vonoprazan-based triple therapy (88% and 93%, respectively, per protocol) than for PPI-based triple therapy (69% and 56%, respectively). A meta-analysis of five Japanese studies including 1599 patients reported that among those infected with clarithromycin-susceptible H pylori, eradication rates for vonoprazan-based and conventional PPI-based therapies did not significantly differ (95% vs 93%) in controlled trials, but with clarithromycin-resistant strains vonoprazan-based therapies were significantly more effective than PPI-based regimens (82% vs 40%). Vonoprazan may not remain for long the only agent in its class and a novel P-CAB, DWPI4012, was shown to be well tolerated, and have a rapid and long-lasting gastric acid suppression effect in healthy, non-H pylori infected subjects this year.

13 | ADHERENCE

One study from Taiwan looked at the effect of a Continuing Medical Education (CME) course in improving physician adherence to guidelines. After CME, the guidelines had a >90% adoption or improvement but, although commitment was good or fair after CME, there was a >20% gap between "commitment" and "no barrier" to adoption for 11 of 21 statements taught in the CME module, with practitioners reporting financial incentives as the main barrier to adoption. In Japan, a study looked at an enhanced compliance program by getting pharmacists to provide instruction for patients being prescribed eradication therapy but found modest, if any, benefit with 91% achievement in the intervention group compared to 88% in the group getting vonoprazan without special pharmacist instruction with a slight benefit in cost-effectiveness ratio (223 vs 224).

A study in Israel looked at educational interventions for primary care physicians and found that a program including distribution of printed materials, educational outreach visits, and education over a social media platform improved adherence to guidelines significantly. In China, it was shown that sending patients short phone text messages could increase compliance and improve adherence to therapy.

14 | IMPACT OF H PYLORI ERADICATION ON GUT MICROBIOTA

Six studies assessed the impact of H pylori eradication on the gut microbiota, two of them being published in 2018. Five of them reported the short-term changes (less than 3 months) and only three of them reported the long-term changes (48 weeks or more). Triple therapy (PPI-amoxicillin-clarithromycin) for 7 days was used in four studies. Bismuth-based quadruple therapy was used in two studies. The case numbers are relatively small, ranging from 6 to 70, with a total of 147 cases. Shortly after H pylori eradication therapy, the bacterial diversity was significantly reduced at the end of eradication therapy. In patients treated with triple therapy, the relative abundance of Firmicutes was reduced, whereas that of Proteobacteria was increased. In patients treated with bismuth quadruple therapy, the relative abundance of Proteobacteria was increased, whereas those of Bacteroidetes and Actinobacteria were reduced. Of the three studies that assessed the long-term changes of gut microbiota (N = 34 totally), the α-diversity and β-diversity of the microbiota and the relative abundance of all phyla were restored to pre-treatment states at 1 year. However, there were some notable changes at the genus level. More recently, a large-scale randomized trial from Taiwan compared the long-term changes of gut microbiota after 14-day triple therapy, 10-day concomitant therapy, and 10-day bismuth quadruple therapy. The α-diversity and β-diversity were altered to a greater extent with slower recovery in patients treated with concomitant therapy and bismuth quadruple therapy, compared to those treated with triple therapy. The α-diversity and β-diversity were restored to their pre-treatment state.
after week 8 in patients treated with triple therapy, but were not yet fully recovered at 1 year in patients treated with bismuth quadruple therapy and concomitant therapy. Nevertheless, some beneficial effects, including the reduction of insulin resistance and triglyceride levels and an increase in high-density lipoprotein, were observed at week 8 and 1 year. More studies are warranted on this issue.

15 | CONCLUSION

Many studies pertaining to H pylori eradication treatment have been published over the last 12 months, often with diverse results, although several broad themes did emerge. Clarithromycin resistance rates in almost all regions have now passed the point where clarithromycin-based triple therapy cannot be considered valid and it is time to reflect it for global clinical practice. Appraisal of the literature this year offers no conclusion other than that the various bismuth-based therapies show a clear advantage for first-line therapy. Again although availability and supply issues around bismuth and tetracycline limit their adoption in clinical practice in some countries, there is a need to address this. For example, the recently published Brazilian consensus guidelines still recommend clarithromycin-based therapy even though resistance exceeds 15% on the basis that bismuth cannot be sourced in that country. The same could also be said of vonoprazan, which shows considerable promise and may even help partially overcome clarithromycin resistance but this will need to be robustly examined in regions outside Japan.

Levofloxacin, sitafloxacin, furazolidone, and rifabutin remain useful alternatives, especially in rescue therapy settings. Interest in the sequential, concomitant, and hybrid therapies does not appear as strong as it was some years ago. Adherence to therapy remains the biggest issue in treatment failures alongside resistance and it is welcome that some trials have looked at methods of addressing this problem. The story around gastric cancer development in patients on long-term PPI after eradication therapy also needs to be further elucidated. The transient perturbation of gut microbiota was restored to pre-treatment states 2 months after triple therapy, but the recovery was slower in patients treated with concomitant therapy and quadruple therapy. More studies are warranted on this issue.

DISCLOSURES OF INTERESTS

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REFERENCES


