

# Updates on Management of *Helicobacter pylori* Infection and Antibiotic Resistant *Helicobacter pylori* Infection Management

Saskia Aziza Nursyirwan, Marcellus Simadibrata

Division of Gastroenterology, Pancreatobiliary, and Digestive Endoscopy  
Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia/  
Dr. Cipto Mangunkusumo General National Hospital, Jakarta

## Corresponding author:

Marcellus Simadibrata. Division of Gastroenterology, Pancreatobiliary, and Digestive Endoscopy, Department of Internal Medicine, Dr. Cipto Mangunkusumo General National Hospital. Jl. Diponegoro No. 71 Jakarta Indonesia. Phone: +62-21-3153957; facsimile: +62-21-3142454. E-mail: [prof.marcellus.s@gmail.com](mailto:prof.marcellus.s@gmail.com)

## ABSTRACT

*H. pylori* is a common human pathogen and it is estimated that approximately 50% of the world's population are infected. Furthermore its prevalence infection in Indonesia is 20% but much higher among several ethnic groups (Papuan 42.9%, Batak 40.0%, and Bugis 36.7%). *H. pylori*'s growth and survival has been shown to be sensitive to a variety of antimicrobial agents. The success of the treatment depends on susceptibility, dosage, formulation, dose frequency, the use of adjuvants such as anti-secretory drugs, antacids or probiotics, and duration of treatment. Rational antimicrobial therapy is always based on susceptibility to germs, and governments should be emboldened to offer *H. pylori* resistance surveillance programs to provide physicians with up-to-date regional and local resistance prevalence reports and treatment guidelines. Therefore, *H. pylori* resistant management should be adapted to the results of the the culture of resistance and the guidelines of existing resistance patterns.

**Keywords:** *Helicobacter pylori*, antibiotic resistant, treatment

## ABSTRAK

*H. pylori* adalah patogen manusia yang umum dan diperkirakan sekitar 50% dari populasi dunia terinfeksi. Data prevalensi infeksi *H. pylori* di Indonesia secara umum adalah 20% tetapi jauh lebih tinggi di antara beberapa kelompok etnis (Papua 42,9%, Batak 40,0%, dan Bugis 36,7%). Pertumbuhan dan kelangsungan hidup *H. pylori* telah terbukti sensitif terhadap berbagai agen antimikroba. Keberhasilan pengobatan tergantung pada kerentanan, dosis, formulasi, frekuensi dosis, penggunaan adjuvant seperti obat anti-sekresi, antasida atau probiotik, dan durasi pengobatan. Terapi antimikroba rasional selalu didasarkan pada kerentanan terhadap kuman, dan program pengawasan resistensi *H. pylori* sebaiknya ada untuk menyediakan dokter dengan laporan prevalensi resistensi regional dan lokal terkini dan pedoman pengobatan. Oleh karena itu, pengelolaan resistensi *H. pylori* sebaiknya disesuaikan dengan hasil kultur resistensi dan pedoman pola resistensi yang ada.

**Kata kunci:** *Helicobacter pylori*, resistensi antibiotik, pengobatan

## INTRODUCTION

*H. pylori* is one of the most common human pathogens and it is estimated that about 50% of the world's population are infected. Furthermore its prevalence ranges from 11% in Sweden up to 60% in Spain, as high as 83% in China and about 30% in the United States.<sup>1-3</sup> Syam et al stated that the incidence of *H. pylori* infection in Indonesia is possible at 20% due to the influence of genetic polymorphisms on its infection, which is low.<sup>4</sup>

The resistance of *H. pylori* to antibiotics is increasing globally and factors influencing the failure of therapy are the widespread use of antibiotics in the community, inappropriate doses, poor quality of antibiotics, non-compliance with therapy protocols, consumption of alcohol and smoking, and genetic mutations.<sup>5</sup>

Rational antimicrobial therapy should always be based on susceptibility to germs, and *H. pylori* resistance surveillance programs should be updated to provide physicians with regional and local resistance prevalence reports and treatment guidelines.

## HELICOBACTER PYLORI AS A BACTERIAL INFECTION

*H. pylori* infection is a bacterial infection, and its growth and survival are vulnerable to a variety of antimicrobial agents. However, the in vitro susceptibility is sometimes incompatible with the in vivo susceptibility, and the antimicrobial treatment of the infection has proven to be more complicated than the treatment of other common infections because it resides in the human stomach. The stomach environment is acidic in nature, but most antibiotics require a neutral or almost neutral environment to be effective. Furthermore, *H. pylori* can also be found deep in the lining of the stomach and even in gastric epithelial cells.<sup>6</sup> These conditions make it difficult to provide active antimicrobials to ensure killing of all organisms. Another problem is the use of antibiotics, which are not well targeted and do not pay attention to local patterns of resistance.

With the application of all antimicrobial therapies, the success of treatment depends on the details of the therapy including: susceptibility, dosage, formulation, dose frequency, use of adjuvants such as anti-secretory drugs, antacids or probiotics, and duration of treatment. Some of these important factors have received detailed clinical assessment but the optimal regimen

is unknown. The effectiveness of some regimens can also vary in relation to host differences, for example, polymorphisms in drug-metabolizing enzymes such as cytochrome P450 2C9 (CYP2C19) can greatly influence effectiveness.<sup>7</sup>

## H. PYLORI THERAPY HISTORY

The first effective treatment with a cure rate of > 90%, is a triple acid-resistant antimicrobial therapy bismuth, metronidazole (MTZ), and tetracyclines. Over time, its effectiveness diminishes due to MTZ resistance. This problem was solved by increasing the dose of MTZ to 1.5 g or more and adding a proton pump inhibitor (PPI), and the regimen is called quadruple bismuth therapy. In MTZ sensitive infections, 5–7 days of administration have been shown to be highly effective, but 14 days of therapy are required in the presence of resistance.

The second widely used regimens, amoxicillin (AMX) and clarithromycin (CLR) and PPI, are all administered twice daily with an effective regimen using 200-500 mg of CLR twice daily therefore Quadruple bismuth therapy and CAM therapy can achieve a cure rate of 95% or more in drug-sensitive patients.<sup>8</sup>

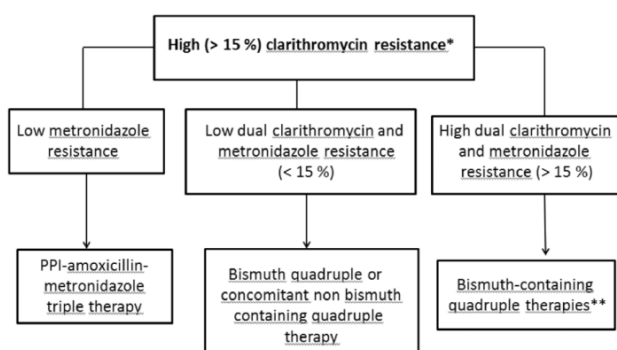
Due to its convenience, tolerability, and broad marketing support from the drug company, CLR triple therapy is becoming one of the most widely prescribed treatment regimens in the world. The best results are achieved with 14 days of therapy. Successfully, pharmaceutical companies have introduced triple therapy (7 or 10) of shorter duration, which is usually associated with a decrease in healing from > 95% to between 88% and 94%. This decrease was partly obscured by the increase in CLR resistance, which rapidly undermined the regimen's effectiveness. In contrast to the MTZ resistance, the CLR resistance reduced the effectiveness of all three treatment regimens only on AMX and PPI, which led to a significant reduction in the cure rate at the given dosage. The rapid increase in CLR resistance is associated with high use of macrolides worldwide for respiratory infections. In 2000, the cure rate for *H. pylori* with CLR was between 70 and 75%. The 2016 Maastricht V guidelines recommend not using CLR when the incidence of resistance is 15% or more. However, since doctors often do not have access to data on local resistance rates, the CLR regimen continues to be used.<sup>1</sup>

| Drug                                                                                                                                    | Dose          | Duration  |
|-----------------------------------------------------------------------------------------------------------------------------------------|---------------|-----------|
| <b>First line:</b>                                                                                                                      |               |           |
| PPI*                                                                                                                                    | 2x1           | 7-14 days |
| Amoxicillin                                                                                                                             | 1000 mg (2x1) |           |
| Clarithromycin                                                                                                                          | 500 mg (2x1)  |           |
| In an area where resistance to clarithromycin >20%                                                                                      |               |           |
| PPI*                                                                                                                                    | 2x1           | 7-14 days |
| Bismuth subsalicylate                                                                                                                   | 2x2 tablet    |           |
| Metronidazole                                                                                                                           | 500 mg (3x1)  |           |
| Tetracycline                                                                                                                            | 250 mg (4x1)  |           |
| When bismuth is not available:                                                                                                          |               |           |
| PPI*                                                                                                                                    | 2x1           | 7-14 days |
| Amoxicillin                                                                                                                             | 1000 mg (2x1) |           |
| Clarithromycin                                                                                                                          | 500 mg (2x1)  |           |
| Second line: this class of drugs is used when there is a failure with clarithromycin-based regimen                                      |               |           |
| PPI*                                                                                                                                    | 2x1           | 7-14 days |
| Bismuth subsalicylate                                                                                                                   | 2x2 tablets   |           |
| Metronidazole                                                                                                                           | 500 mg (3x1)  |           |
| PPI*                                                                                                                                    | 2x1           | 7-14 days |
| Amoxicillin                                                                                                                             | 1000 mg (2x1) |           |
| Levofloxacin                                                                                                                            | 500 mg (2x1)  |           |
| Third line: when the second line regimen fails.<br>Whenever possible, the selection is based on resistance test and/or clinical changes |               |           |
| PPI*                                                                                                                                    |               | 7-14 days |
| Amoxicillin                                                                                                                             | 2x1           |           |
| Levofloxacin                                                                                                                            | 1000 mg (2x1) |           |
| Rifabutin                                                                                                                               | 500 mg (2x1)  |           |

\*PPI agents that have been used are rabeprazole 20 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and esomeprazole 40 mg.

Notes: Sequential therapy (can be given as the first line when there is no data about resistance to clarithromycin): PPI + amoxicillin for 5 days followed by PPI + clarithromycin and nitroimidazole (tinidazole) for 5 days.

Figure 1. Therapy regimen for *H. pylori* eradication<sup>9</sup>



\* Regardless of their population expectations, individuals who have previously taken clarithromycin and/or metronidazole should be considered high risk patients for dual resistance.

\*\* If bismuth is not available, levofloxacin, rifabutin and high dose dual (PPI + amoxicillin) therapies might be considered. If tetracycline is not available, bismuth-containing quadruple therapy combining furazolidone-metronidazole or amoxicillin-metronidazole can be considered.

Figure 2. The Antibiotic Regimen Selection Approach Algorithm for *H. pylori* according to the Resistance Pattern<sup>1</sup>

## ANTIBIOTIC RESISTANCE

Since 2000, the eradication rate of *H. pylori* has decreased due to increased resistance to one or more antibiotics. The WHO grouped antimicrobial resistance data by region and among East Asian countries the prevalence of CLR resistance was quite high.

The MTZ resistance is low only in Japan. In addition, a high prevalence of resistance to CLR and MTZ was found in Italy, Vietnam, Mexico and China. In northern Europe, low resistance to CLR is generally found because of its limited use. The prevalence of bacterial resistance that occurs is related to the level of antibiotic consumption in the community. A retrospective review from 2017 in the Netherlands showed an increased resistance rate for CLR (from 9.8% to 18.1%), MTZ (20.7–23.23%) and AMX (6.3–10%) over 10 years. The first systemic review of primary antibiotic resistance in the Asia-Pacific region found an average resistance rate of 17% for CLR, 18% for levofloxacin, and 44% for MTZ. There is significant heterogeneity in resistance rates across countries.<sup>10</sup> The overall mean prevalence of resistance to MTZ is 44% ranging from 10% in Japan to 84% in Bangladesh and 88% in Nepal.

Resistance to AMX was generally less than 1% and overall there were no significant changes over time.<sup>11</sup> Kuo et al. 2007 reported a mean overall prevalence of resistance to levofloxacin of 18% (95% CI: 15-22), starting from 2% to 3% (Bhutan and Malaysia) to 66% in Bangladesh.<sup>10</sup> The analysis of the subgroups after the pooling period showed that the overall resistance to levofloxacin increased from 2% (95% CI: 0-13) before 2000 to 27% (95% CI: 21-34) between 2011 and 2015, with a significant heterogeneity between groups. Levofloxacin resistance increased over time in many countries. In addition, resistance to quinolones is in the range of 20% in Europe, 15% in America, and 10% in Asia, and is increasing rapidly.

As resistance to levofloxacin and CLR has increased worldwide, there are only a few areas where CLR or levofloxacin are still effective as empirical therapy and therefore treatment strategies need to be adapted to the resistance pattern in each country or region.<sup>10</sup>

## ANTIBIOTIC RESISTANCE TO *H. PYLORI* INFECTION IN INDONESIA

Although the overall prevalence of this infection in Indonesia is low (22.1%), several ethnic groups have a much higher prevalence of *H. pylori* infection (Papuan 42.9%, Batak 40.0%, and Bugis 36.7%).<sup>4</sup> The level of

resistance of MNZ is high in Indonesia. In addition, the two *H. pylori* groups, especially Batak and Papuas, show higher values than the preferred values according to the Masscht III Consensus Report (> 40%). The infection resistant to three or four therapies appears to be a serious challenge in the fight against infection and a barrier to the success of eradication regimens. Java and Sumatra Island can be two locations with a higher risk of treatment failure due to areas with high types of antibiotic resistance.<sup>12</sup>

In the study by Miftahussurur et al's, 15 of the 77 strains exhibited multiple drug resistance (11 strains for MNZ-LVX, two for CAM-LVX and one each for MNZAMX and LVX-AMX). Resistance to three antibiotics was observed in two lines isolated from Java (2.6%); one strain resistant to the combination of CAM, MNZ, and LVX. In addition, two strains (obtained from Sumatra and Java Island) were resistant to four drugs including LVX. Overall, Java (six strains) and Sumatra Island (seven strains) showed a higher prevalence of multi-drug resistance than other locations.<sup>12</sup>

**Table 1. Prevalence of *H. pylori* infection in Indonesia based on multiple tests<sup>12</sup>**

| Island (city)          | Year        | n   | Diagnostic method (%) |                            |                     |
|------------------------|-------------|-----|-----------------------|----------------------------|---------------------|
|                        |             |     | Culture               | Histology confirmed by IHC | At least one method |
| Bali (Bangli)          | 2015        | 61  | 6 (9.8)               | 7 (11.5)                   | 7 (11.5)            |
| Java                   |             | 424 | 14 (3.3)              | 15 (3.5)***                | 17 (4.0)            |
| Surabaya               | 2012 – 2015 | 296 | 12 (4.1)              | 14 (4.7)                   | 15 (5.1)            |
| Jakarta                | 2013        | 31  | 1 (0.1)               | 1 (0.1)                    | 1 (0.1)             |
| Malang                 | 2014        | 97  | 1 (1.0)               | **                         | 1 (1.0)             |
| Kalimantan (Pontianak) | 2014        | 90  | 5 (5.6)               | 4 (4.4)                    | 6 (6.7)             |
| Papua (Jayapura)       | 2013        | 21  | 9 (42.9)              | 9 (42.9)                   | 9 (42.9)            |
| Sumatera               |             | 131 | 19 (14.5)             | 20 (15.3)                  | 26 (19.8)           |
| Medan                  | 2014        | 93  | 19 (20.4)             | 20 (21.5)                  | 26 (27.9)           |
| Aceh                   | 2014        | 38  | 0 (0.0)               | 0 (0.0)                    | 0 (0.0)             |
| Sulawesi               |             | 87  | 13 (14.9)             | 13 (14.9)                  | 13 (14.9)           |
| Manado                 | 2015        | 57  | 7 (12.3)              | 7 (12.3)                   | 7 (12.3)            |
| Makassar               | 2014        | 30  | 6 (20.0)              | 6 (20.0)                   | 6 (20.0)            |
| Timor (Kupang)         | 2015        | 35  | 14 (40.0)             | 12 (34.3)                  | 14 (40.0)           |
| Total                  |             | 849 | 80 (9.4)              | 80 (9.4)***                | 88 (10.4)           |

IHC: immunohistochemistry

The most recent surveys that are not including in the previous publication (Syam et al, 2015)

\*\* sample obtain only from culture, there was no sample for histology examination

\*\*\* The total number does not include the Malang survey

**Table 2. Prevalence of antibiotic resistance of *H. pylori* isolates in Indonesia<sup>12</sup>**

| Characteristic   | n  | Antibiotics (%) |          |           |           |          |
|------------------|----|-----------------|----------|-----------|-----------|----------|
|                  |    | CAM             | AMX      | MNZ       | LVX       | TCN      |
| Total            | 77 | 7 (9.1)         | 4 (5.2)  | 36 (46.7) | 24 (31.2) | 2 (2.6)  |
| Gender           |    |                 |          |           |           |          |
| Male             | 38 | 3 (7.9)         | 2 (5.2)  | 21 (55.2) | 11 (28.9) | 1 (2.7)  |
| Female           | 39 | 4 (10.2)        | 2 (5.1)  | 15 (38.4) | 13 (33.3) | 1 (2.6)  |
| Age Groups       |    |                 |          |           |           |          |
| 17 – 30          | 9  | 0 (0.0)         | 0 (0.0)  | 6 (66.6)  | 3 (33.3)  | 0 (0.0)  |
| 31 – 40          | 10 | 2 (20.0)        | 0 (0.0)  | 6 (60.0)  | 3 (30.0)  | 1 (10.0) |
| 41-50            | 21 | 2 (9.1)         | 1 (4.7)  | 5 (22.7)  | 4 (18.1)  | 1 (4.5)  |
| 51-60            | 25 | 1 (4.1)         | 1 (4.0)  | 14 (58.3) | 10 (41.6) | 0 (0.0)  |
| > 61             | 12 | 2 (16.6)        | 2 (16.6) | 5 (41.6)  | 4 (33.3)  | 0 (0.0)  |
| Clinical outcome |    |                 |          |           |           |          |
| Gastritis        | 70 | 6 (8.9)         | 4 (5.9)  | 30 (44.7) | 21 (31.3) | 0 (0.0)  |
| PUD              | 7  | 0 (0.0)         | 0 (0.0)  | 3 (42.8)  | 0 (0.0)   | 0 (0.0)  |

AMX: amoxicillin, CAM: clarithromycin, MNZ: metronidazole, TCN: tetracycline, LVX: levofloxacin, PUD: peptic ulcer disease

## MANAGEMENT OF ANTIBIOTIC RESISTANT *H. PYLORI* INFECTION

Rational antimicrobial therapy is always based on susceptibility to germs, and governments should be emboldened to offer *H. pylori* resistance surveillance programs to provide physicians with up-to-date regional and local resistance prevalence reports and treatment guidelines.

However, treatment failure can occur, and one of the most common causes of treatment failure is when drugs are not taken as directed. This may be because the doctor is not giving adequate instructions (to the patient, or because of an intolerable side effect). With the selected treatment and patient constancy, treatment failure should be rare. Another cause of failure is the presence of unusual resistance such as AMX. If available, the best approach for choosing a second-choice therapy is to perform an antibiotic sensitivity test. If not available, the second option would be to use a different regimen. Two failures required antibiotic sensitivity testing.

### Triple Therapy (Other Than CLR)

Due to the increased CLR resistance, levofloxacin, a broad-spectrum quinolone, was used as a triple therapy. It was found that the 14-day therapy proved to be effective and achieved reliable eradication rates of over 90% in areas with low local resistance to levofloxacin. The use of quinolones around the world has increased so rapidly that no longer considered acceptable for empirical therapy except in some areas where resistance is low. Among the fourth generation quinolones (moxifloxacin, sitafloxacin,

and gemifloxacin) only sitafloxacin has been shown to be successful in eradication. Therefore, in areas where sitafloxacin is available, it is the quinolone recommended for empiric therapy.<sup>13</sup>

### Sequential, Hybrid, Concomitant Therapy

There are a number of empirically derived drug regimens using AMX, CLR, MTZ, and PPI. They are named in relation to how the medicine will be administered (e.g., sequentially, or all together). Sequential therapy achieved a higher cure rate against clarithromycin-resistant strains than 7 and 10 day triple therapy, but was not superior to 14 day therapy. In addition, sequential therapy achieved a lower cure rate compared to the concomitant clarithromycin therapy against clarithromycin resistant strains.<sup>13</sup>

Another important factor affecting the effectiveness of sequential therapy is resistance to metronidazole. In contrast to clarithromycin resistance, metronidazole resistance can be partially reduced by increasing the dose, frequency and duration of the antibiotics. Sequential therapy gives metronidazole for 5-7 days, hybrid therapy for 7 days, and concurrent therapy for 10-14 days. When comparing the effectiveness of sequential and concomitant therapy with metronidazole-resistant and clarithromycin-sensitive *H. pylori* strains, the cure rates of sequential therapy were lower than those of hybrid and concomitant therapies. If there is dual resistance to clarithromycin and metronidazole, the effectiveness of sequential, hybrid and concomitant therapy is reduced.<sup>1</sup> Sequential therapy is more complex and requires antibiotic replacement during the treatment phase, which can confuse the patient. Therefore, concomitant therapy is easier to adhere to by

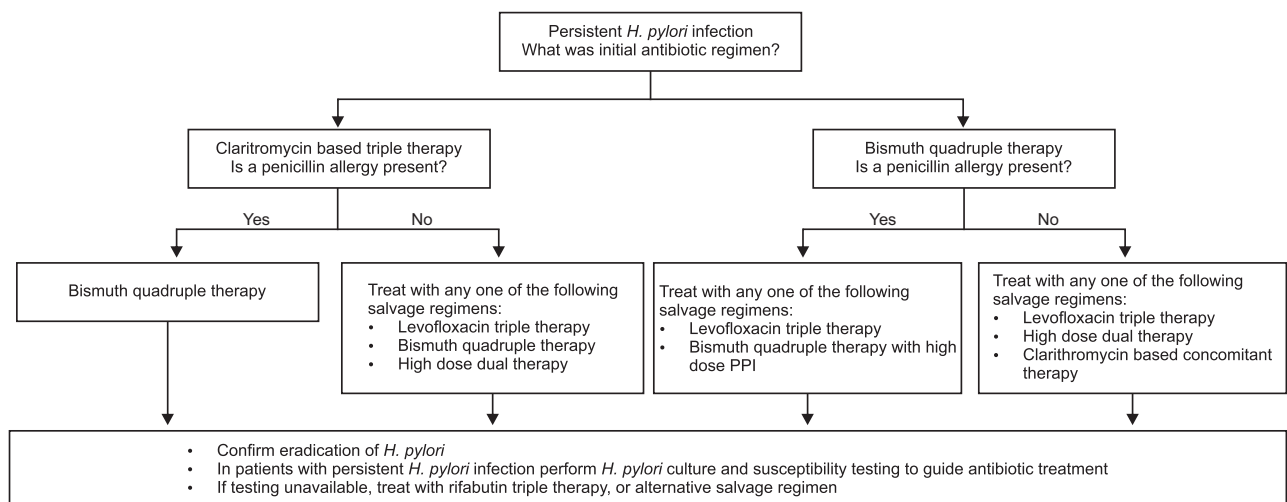


Figure 3. Approach to the selection of antibiotics for persistent *H. pylori* infection<sup>14</sup>

the patient than sequential therapy and its tolerability is similar to standard triple therapy. Hybrid therapy data are not generally available, possibly due to geographical differences in resistance patterns.<sup>1</sup>

### Bismuth Therapy

Although triple therapy and quadruple bismuth therapy were introduced early in the history of *H. pylori*, they were never popular. The problems with the therapy include intrinsic complexity, large number of tablets, four times a day, side effects, lack of support from pharmaceutical companies. The combination of high-dose MTZ and tetracyclines has been associated with multiple side effects, such as stomach upset, nausea, and vomiting that often result to poor adherence.

After the first failure, if endoscopy is performed, culture and standard antimicrobial susceptibility testing (AST) are recommended to adjust treatment, unless quadruple bismuth therapy is considered. When using quadruple bismuth therapy, AST is not recommended because the risk of such tetracycline resistance is very low and metronidazole resistance has shown no effect. In areas with high clarithromycin resistance (> 15%), a bismuth or non-bismuth quadruple (PPI, amoxicillin, clarithromycin and nitroimidazole) is recommended. In areas with high dual resistance to clarithromycin and metronidazole, bismuth quadruple therapy (BQT) is the recommended first-line treatment. If bismuth is not available in the dual resistance area of dual clarithromycin and metronidazole, then levofloxacin, rifabutin, and dual high-dose therapy (PPI + amoxicillin) can be considered. If tetracyclines are not available in areas of high dual resistance, quadruple therapy containing bismuth combining furazolidone plus metronidazole or amoxicillin plus metronidazole can be considered, as well as bismuth plus triple therapy (PPIs, amoxicillin, and clarithromycin or levofloxacin).<sup>13</sup>

### Vonoprazan

As described above, vonoprazan is a new P-CAB (Potassium-Competitive Acid Blockers). The inhibitory effect (pKa 9.4) is unaffected by the ambient pH and accumulates in the parietal cells under secretion and resting conditions. Furthermore, PPIs take 3 days or more to achieve full anti-secretory effectiveness, while vonoprazan is essentially at full efficiency on the first day. Vonoprazan is currently approved in Japan for first-line *H. pylori* eradication by triple

therapy containing CLR and for second-line therapy with MTZ and AMX. In one study, triple CLR therapy with lansoprazole and vonoprazan cured nearly 100% of *H. pylori* infections in infections prone to CLR. In contrast, with CLR-resistant strains, the resulting dual therapy (vonoprazan or lansoprazole plus AMX) was very different from that of lansoprazole-AMX, which cured 40% and vonoprazan-AMX that cured 80%.<sup>15</sup>

### Probiotics

The probiotic supplement is designed to change the microbiome and improve the results of *H. pylori* therapy and also reduce the side effects of antibiotic therapy such as diarrhea. The interest in probiotic therapy as an adjunct to eradication therapy has resulted in an increasing number of publications and meta-analyses. For example, a recent study reported that the addition of probiotics reduced the frequency of side effects from 28.2% to 12.2%.<sup>16</sup> A systematic review that analysed 30 RCTs involving 4,302 patients reported that addition of probiotics increased eradication rates by 12.2%.<sup>17</sup> A study mentions the combination of *Bacillus mesentericus*, *Clostridium butyricum*, and *Streptococcus faecalis* is reported as the optimal probiotic choice to reduce side effects and increased eradication rate when used to complement triple therapy for 14 days.<sup>18</sup> However, the effective strains that produce the benefits of increasing eradication rates and decreasing side effects have not been established. Generally, the role of probiotics is unclear and, consensus groups generally do not mention recommended probiotics.<sup>13</sup>

### Novel Therapy

Many studies were conducted over the past year to evaluate new treatment options for *H. pylori*. *H. pylori* urease has been the focus of attention for many years for the development of treatments or nutritional supplements with a narrower spectrum and for several potential inhibitors in vitro. However, many are less specific. The only bacterial urease inhibitor marketed, acetohydroxamic acid (Lithstat), is approved only as a drug for use in the treatment of struvite stones in the kidney due to urea-splitting pathogens.<sup>19</sup> Furthermore, it is not recommended to eradicate *H. pylori* because of its many and frequent side effects. Two mucolytic agents, erdosteine and N-acetylcysteine (NAC), were found to increase the eradication efficiency of *H. pylori* in clinical trials when administered in the supplement with triple therapy.<sup>20</sup> Studies in Iran show standard

triple therapy with curcumin (turmeric extract) increases *H. pylori* eradication rates and reduces endoscopic inflammation scores.<sup>21</sup> However, these drugs are not commonly used because of the need for high doses, and increased medical costs.

## CONCLUSION

The increasing number of cases of antibiotic resistance *H. pylori* infection around the world is a separate problem that needs to be adequately addressed. The management of resistant *H. pylori* should be adapted to the results of the resistance culture and the guidelines for the existing resistance patterns.

## REFERENCES

1. Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, et al. Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report. *Gut* 2017;66:6–30.
2. Chen Y, Blaser MJ. Association between gastric *Helicobacter pylori* colonization and glycated hemoglobin levels. *J Infect Dis* 2012;205:1195–202.
3. Kamada T, Haruma K, Ito M, Inoue K, Manabe N, Matsumoto H, et al. Time trends in *Helicobacter pylori* infection and atrophic gastritis over 40 years in Japan. *Helicobacter* 2015;20:192–8.
4. Syam AF. Current situation of *Helicobacter pylori* infection in Indonesia. *Medical Journal of Indonesia* 2016;25:263–6.
5. Khien VV, Thang DM, Hai TM, Duat NQ, Khanh PH, Ha DT, et al. Management of antibiotic-resistant *Helicobacter pylori* infection: perspectives from Vietnam. *Gut Liver* 2019;13:483–97.
6. Kwok T, Backert S, Schwarz H, Berger J, Meyer TF. Specific entry of *Helicobacter pylori* into cultured gastric epithelial cells via a zipper-like mechanism. *Infect Immun* 2002;70:2108–20.
7. Yang JC, Lin CJ, Wang HL, Chen JD, Kao JY, Shun CT, et al. High-dose dual therapy is superior to standard first-line or rescue therapy for *Helicobacter pylori* infection. *Clin Gastroenterol Hepatol* 2015;13:895–905.e5.
8. Hsu PI, Tsai FW, Kao SS, Hsu WH, Cheng JS, Peng NJ, et al. Ten-day quadruple therapy comprising proton pump inhibitor, bismuth, tetracycline, and levofloxacin is more effective than standard levofloxacin triple therapy in the second-line treatment of *Helicobacter pylori* infection: a randomized controlled trial. *Am J Gastroenterol* 2017;112:1374–81.
9. Syam AF, Simadibrata M, Makmun D, Abdullah M, Fauzi A, Renaldi K. National consensus on management of dyspepsia and *Helicobacter pylori* infection. *Acta Med Indones* 2017;49:279–87.
10. Kuo YT, Liou JM, Em E-O, El-Omar EM, Wu JY, Leow AH, et al. Primary antibiotic resistance in *Helicobacter pylori* in the Asia-Pacific region: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2017;2:707–15.
11. Kobayashi I, Murakami K, Kato M, Kato S, Azuma T, Takahashi S, et al. Changing antimicrobial susceptibility epidemiology of *Helicobacter pylori* strains in Japan between 2002 and 2005. *J Clin Microbiol* 2007;45:4006.
12. Miftahussurur M, Syam AF, Nusi IA, Makmun D, Waskito LA, Zein LH, et al. Surveillance of *Helicobacter pylori* antibiotic susceptibility in Indonesia: different resistance types among regions and with novel genetic mutations. *PLoS One* 2016;11:e0166199.
13. Matsumoto H, Shiotani A, Graham DY. Current and Future Treatment of *Helicobacter pylori* Infections. *Adv Exp Med Biol* 2019;1149:211–225.
14. Lamont JT. Treatment regimens for *Helicobacter pylori* in adults [serial online] [cited 8 Oct 2021]. Available from: <https://www.uptodate.com/contents/treatment-regimens-for-helicobacter-pylori-in-adults>
15. Murakami K, Sakurai Y, Shiino M, Funao N, Nishimura A, Asaka M. 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* 2016;65:1439–46.
16. Jung JH, Cho IK, Lee CH, Song GG, Lim JH. Clinical outcomes of standard triple therapy plus probiotics or concomitant therapy for *Helicobacter pylori* infection. *Gut Liver* 2018;12:165–72.
17. Lau CS, Ward A, Chamberlain RS. Probiotics improve the efficacy of standard triple therapy in the eradication of *Helicobacter pylori*: a meta-analysis. *Infect Drug Resist* 2016;9:275–89.
18. Wen J, Peng P, Chen P, Zeng L, Pan Q, Wei W, et al. Probiotics in 14-day triple therapy for Asian pediatric patients with *Helicobacter pylori* infection: a network meta-analysis. *Oncotarget* 2017;8:96409–18.
19. Debraekeleer A, Remaut H. Future perspective for potential *Helicobacter pylori* eradication therapies. *Future Microbiology* 2018;13:671–87.
20. Yoon H, Lee DH, Jang ES, Kim J, Shin CM, Park YS, et al. Effects of N-acetylcysteine on first-line sequential therapy for *Helicobacter pylori* infection: a randomized controlled pilot trial. *Gut Liver* 2016;10:520–5.
21. Judaki A, Rahmani A, Feizi J, Asadollahi K, Hafezi Ahmadi Mr. Curcumin in combination with triple therapy regimes ameliorates oxidative stress and histopathologic changes in chronic gastritis-associated *Helicobacter pylori* infection. *Arq Gastroenterol* 2017;54:177–82.