

EMERGING *HELICOBACTER PYLORI* RESISTANCE AND ITS ERADICATION

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Abstract- *Helicobacter pylori* is a gram-negative bacterium that infects roughly 4.4 billion people globally. Its prevalence varies geographically and is affected by a variety of factors. Various national and international guidelines for the management of *H. pylori* have been regularly updated for eradication. Recent worldwide guidelines for treating *H. Pylori* infections recommend bismuth or non-bismuth triple therapy for 14 days as a first-line treatment for *H. Pylori* in areas of high clarithromycin and/or metronidazole resistance. Antibiotic resistance in *H. pylori* has drastically increased on a global scale, which has an impact on the effectiveness of treatment. Although effective antibiotic therapy must be based on susceptibility testing, increasing antimicrobial resistance and widespread lack of antimicrobial susceptibility have led physicians to mostly depend on empiric regimens. Triple therapy with clarithromycin is no longer the recommended treatment for *H. Pylori* owing to the rising prevalence of antibiotic resistance, especially in some areas where local resistance to this treatment is over 20%. Alternative methods of eradicating *H. Pylori* infection have been proposed. Some of the novel therapeutic agents include vonoprazon, Levofloxacin and probiotic supplements. Although these new therapeutic interventions offer respectable *H. Pylori* eradication rates, they should not make *H. Pylori* more resistant to antimicrobials in the future.

Key words: H. Pylori; Resistance; Eradication; Treatment

INTRODUCTION:

More than half of the world's population has the gram-negative bacteria *Helicobacter pylori* (*H. Pylori*) in their gastrointestinal environment.[1] Studies show that the number of people who have *H. Pylori* depends on a number of factors, such as age, geography, place of residence, and socioeconomic status.[2] The primary method of *H. Pylori* transmission appears to be oral-to-oral transfer. Infection by *H. Pylori* is a leading cause of gastritis, gastric and duodenal ulcers, mucosal associated lymphoid tissue, and gastric cancer.[3] Therapy to get rid of *H. Pylori* has been shown to lower the risk of stomach cancer, ease stomach inflammation, and speed up ulcer healing.

The treatment of *H. Pylori* is becoming more difficult owing to rising antibiotic resistance. A proton pump inhibitor (PPI), amoxicillin (AMO), and clarithromycin (CAM) were previously suggested as elements of a 7-day conventional triple therapy for the treatment of *H. Pylori*. [4] Due to the rise in *H. Pylori* antibiotic resistance, the eradication rate that could be accomplished with this regimen has significantly decreased. Also, resistance to fluoroquinolones and metronidazole (MNZ), which are often used as "rescue" treatments,[5] has grown to more than 15% in some parts of the world in recent years. In regions with clarithromycin resistance rates exceeding 15% to 20%, the Maastricht IV/Florence Consensus Report advised discontinuing PPI-clarithromycin-containing triple treatment.[6] Also, bismuth-containing quadruple therapy (BQT) is recommended as a first-line treatment for getting rid of *H. Pylori* in places with high or low clarithromycin resistance because it works well, is safe, and is well tolerated. The World Health Organisation (WHO) has issued its first list of antimicrobial-resistant "priority pathogens," with *H. Pylori* listed as a high priority pathogen. This review summarises the current *H. Pylori* resistance and its various alternative treatment approaches.

Standard *H. Pylori* therapy:

Treatment should be prescribed to all patients who have a positive test for active infection, and the chosen treatment regimen should offer an eradication rate of at least 90%. Triple therapy, sequential therapy, quadruple therapy, and triple therapy based on levofloxacin are various treatment options for eradicating *H. Pylori*. [7] When choosing the best empirical treatment plan for *H. Pylori*, it's important to think about how the patient has been exposed to antibiotics in the past, how antibiotic resistance varies by region, and the rate of eradication. These factors may affect how well the treatment works.

Traditional triple regimen therapy:

The traditional triple therapy for managing *H. Pylori* infections was the gold standard therapy. The proton pump inhibitor, clarithromycin, and amoxicillin or metronidazole are the three key components of the traditional triple treatments. According to a systematic review and meta-analysis of 7722 participants, the optimal triple regimen treatment duration was 14 days. After 14 days, the eradication rate was greater than it was after 7 days (81.9 % versus 72.9 %). [8] A meta-analysis of 3715 individuals in Turkey revealed that the eradication rate was very low (60%), which may be attributed to the high levels of clarithromycin resistance in the region, regardless of whether the medication continued for 7 days or 14 days. [9] Most countries are currently trying to get rid of *H. Pylori* with a triple treatment based on clarithromycin, but this regimen no longer meets the standards for successful eradication. PAC(PPI/Amoxicillin/Clarithromycin) can only be used as a first-line treatment for *H. Pylori* in areas with low clarithromycin resistance (15%), according to international guidelines. [10] According to certain research, the PPI/Amoxicillin/Metronidazole

(PAM) regimen has a comparable global eradication rate to the PAC regimen. PAM has shown improved effectiveness in recent years, particularly in patients over the age of 60. In places where metronidazole resistance is low and clarithromycin resistance is high, the PAM regimen can achieve eradication rates as high as 92.5%. [11]

Bismuth quadruple therapy:

This treatment includes bismuth and PPI for 14 days, along with two antibiotics, tetracycline and metronidazole. This drug is used as a first-line treatment in places where there is a lot of resistance to clarithromycin. It is also used as a second-line treatment when the usual triple therapy for *H. Pylori* doesn't work. [12] In a meta-analysis of nine randomised controlled trials comparing bismuth quadruple therapy and clarithromycin triple therapy, Luther et al. [13] discovered that bismuth quadruple therapy eradicated the infection in 78.3% of patients while clarithromycin triple therapy eradicated the infection in 77% of patients. The researchers concluded that quadruple and triple regimens have comparable eradication rates as primary treatments for *H. Pylori* infection. On the other hand, the effectiveness of this therapy as a second-line treatment has been validated in a meta-analysis based on 30 trials, showing 77.6% eradication after the failure of conventional triple therapy. [14] The major hurdle to this therapy is the possible toxicity of bismuth as well as the lack of tetracycline or bismuth salts in some areas.

Non-bismuth quadruple therapy:

In nations where the prevalence of clarithromycin resistance is significant, it is yet another effective treatment. For 10 days, this treatment consists of PPI (without bismuth), clarithromycin, amoxicillin, and metronidazole. Non-bismuth quadruple treatment is available in three main types: Sequential Therapy (ST), Concomitant therapy (CT) and Hybrid therapy (HT). [15] The rate of eradication of ST was impacted by metronidazole or clarithromycin resistance, whereas the rate of eradication of CT was reduced by dual drug resistance. As a result, CT is used less frequently while ST is gradually being abandoned. Quadruple treatment also generally has several downsides, including complicated administration, various side effects, high cost, and low patient adherence. As a result, enhanced regimens have been researched. The concept of HT was developed with the objective of ensuring the regimen's effectiveness while reducing the number of pills patients needed to take every day. The advantages of ST and CT are combined in HT. The first 7 days involved the use of PPI and amoxicillin, while the next 7 days involved the addition of metronidazole and clarithromycin. A recent randomised controlled trial (Intention to Treat, 95.2% vs. 93.5%; $p = 0.582$) found that the number of bad side effects went down from 38.7% to 20.2% ($p = 0.001$). [16] HT has some disadvantages compared to other treatments, such as a complicated process and the use of two medications in the last week, which could be confusing for patients.

Sequential therapy:

Sequential treatment utilises the same antibiotics as conventional triple therapy, but they are administered sequentially: 5 days of PPI plus amoxicillin, followed by 5 days of PPI plus amoxicillin and clarithromycin. As amoxicillin disrupts bacterial cell walls, it prevents the development of efflux channels, which transfer the residual antibiotics out of bacteria. [17] There were several trials that were published in Italy where the outcome of sequential therapy was superior to conventional triple therapy. However, findings from more recent studies conducted in South America and Asia indicate that eradication rates are lower than 80%. [18] On the other hand, resistance to metronidazole and clarithromycin has made this plan less effective over time. [19] In Korea, where antibiotic resistance is high, ITT and PP analysis showed that 10-day sequential therapy worked 76.3% of the time and 85.0% of the time, respectively. This was not a good result, even though it was better than 7-day triple therapy with clarithromycin. [20]

Hybrid therapy:

This treatment consists of 7 days of PPI and amoxicillin therapy, followed by 7 days of PPI, clarithromycin, amoxicillin and metronidazole quadruple therapy. In recent years, hybrid treatment has attracted a huge amount of attention. According to a comprehensive review and meta-analysis of eight studies with a total of 2516 subjects, [21] the mean treatment outcomes of hybrid treatments were 88.5 percent (1207 patients) and 93.3 percent (1109 patients), respectively. There was no variation in the eradication rate between hybrid and concurrent treatment. Francesco et al. [22] recently did a prospective, open-label pilot study and found that a new hybrid therapy consisting of a 5-day dual therapy followed by a 5-day BMT therapy was effective as the first-line treatment for *H. Pylori* infection (ITT: 97.5%, PP: 100%). Also, reverse hybrid treatment (PPI plus amoxicillin for 14 days and clarithromycin plus metronidazole for the first 7 days) had the same eradication rate as 14-day BQT for strains that were resistant to either metronidazole or clarithromycin, or to both. Reverse hybrid treatment (18.7%) has seen fewer adverse events than BQT did (47.7%). [23] Even though concurrent therapy, hybrid therapy, and BQT all had similar results in some studies, [23,24] the fact that concurrent and hybrid therapy are hard to follow may affect how well patients take their medications.

Levofloxacin-based therapies:

Due to the increase in clarithromycin resistance, levofloxacin is indicated for the eradication of *H. Pylori* in substitution for clarithromycin in triple or sequential regimens. Levofloxacin-based treatments may have an eradication rate of more than 90%, especially in areas with lower (less than 10%) local levofloxacin resistance. Since quinolones are often used to treat urinary tract infections, clarithromycin and metronidazole are becoming more and more resistant to levofloxacin. Around 20% of patients in Europe, 15% of patients in America, and 10% of patients in Asia have quinolone resistance. [25] Due to how quickly secondary quinolone resistance develops, levofloxacin is often only used as a second-line treatment after clarithromycin and/or metronidazole-based plans have failed.

Table 1: *Helicobacter pylori* therapies and its successful eradication rates

Regimens	Antibiotics	PPI	Treatment duration	Eradication rates
Bismuth quadruple therapy	TC 125 mg <i>qid</i> ; MTZ 125 mg <i>qid</i>	Esomeprazole 20-40 mg <i>bid</i> ; Omeprazole 20-40 mg <i>bid</i>	10 d	90%[26]
Concomitant quadruple therapy	AMPC 750 mg-1 g <i>bid</i> ; CAM 200-500 mg <i>bid</i> ; MNZ or TNZ 250-500 mg <i>bid</i>	Esomeprazole 20-40 mg <i>bid</i> ; Lansoprazole 30 mg <i>bid</i> ; Omeprazole 20-40 mg <i>bid</i> ; Pantoprazole 40 mg <i>bid</i> ; Rabeprazole 10-20 mg <i>bid</i>	5-14 d	83%[27]
Standard triple therapy	AMPC 500 mg-1 g <i>bid</i> ; CAM 200-500 mg <i>bid</i>	Esomeprazole 40 mg <i>bid</i> ; Lansoprazole 30 mg <i>bid</i> ; Pantoprazole 40 mg <i>bid</i> ; Rabeprazole 10-20 mg <i>bid</i>	7 d; 14 d	73%[28]; 81%[29]
High dose dual therapy	AMPC 750 mg <i>qid</i>	Esomeprazole 20 mg <i>qid</i> ; Omeprazole 40 mg <i>qid</i> ; Rabeprazole 10-20 mg <i>qid</i>	14 d	86%[30]
Vonoprazan based triple therapy	AMPC 750 mg <i>bid</i> ; CAM 200- 400 mg <i>bid</i>	Vonoprazan 20 mg <i>bid</i>	7 d	88%[28]
Vonoprazan based dual therapy	AMPC 500 mg <i>tid</i>	Vonoprazan 20 mg <i>bid</i>	7 d	94%[31]

PPI: Proton pump inhibitor; TC: Tetracycline; MTZ: Metronidazole; AMPC: Amoxicillin potassium clavulanate; CAM: Clarithromycin; TNZ: Tinidazole.

ANTIMICROBIAL RESISTANCE:

H. Pylori eradication rates have been declining due to increased resistance to one or more antibiotics.[32] The World Health Organization categorises data on antimicrobial resistance by geography, and east Asian nations have a higher prevalence of Clarithromycin (CLR) resistance. Only Japan has a low level of metronidazole (MTZ) resistance. Along with China, Vietnam, Italy, and Mexico have also been found to have a significant prevalence of both CLR and MTZ resistance. Because CLR isn't used very often, there isn't much resistance to it in northern Europe. Given the growing concern about antibiotic resistance, these recommendations have been updated; Cefotetan (CTT) should now be used as first-line treatment only in areas with a known resistance prevalence rate of 15% and for patients who are macrolide sensitive. [33,36] This change was made because research showed that CTT is less likely to get acceptable eradication rates of > 90% in places where antibiotic resistance is higher.

Due to the fact that resistance to levofloxacin and CLR has spread around the world, there are now only a few places where levofloxacin or CLR-based regimens can still be used as a first-line treatment. Treatment plans must be changed country-by-country or region-by-region to match resistance patterns. Given that this regimen is a single-antibiotic therapy and that it is generally known that *H. Pylori* rarely develops resistance to Amoxicillin, dual therapy with AMPC and PPI may be an option. *H. Pylori* resistance to AMPC is currently very low (0%–5%). [33] Dual therapy with regular doses of PPI and AMPC was later used as a rescue therapy because it didn't work as well as other therapies [22,23].

A high-dose dual therapy consisting of AMPC and rabeprazole recently obtained an eradication rate of 95.3% in first-line therapy and 89.3% in rescue therapy, according to Yang et al. [24]. To achieve a satisfactory eradication rate of > 90%, this technique required a high frequency and high dose of AMPC and PPI for a longer period of time (e.g., rabeprazole 20 mg and amoxicillin 750 mg 4 times/d for 14 days), which resulted in a high cost, unfavourable side effects, and poor patient compliance.

Table 2: Antibiotic resistance rates in different continental areas [37]

Region(n)	Cla (%)	Amox (%)	Met (%)	Tet (%)	Lev (%)	Rif (%)
Asia (23748)	27.46	23.61	46.57	7.38	25.28	12.45

Europe (26024)	22.11	0.35	31.19	1.15	14.19	1
Africa (831)	5.46	40.87	75.02	50	15	NR
South America (587)	12.88	6.56	52.85	0	21.23	NR
North America (818)	30.8	2	30.5	0	19	NR
Total (52008)	19.74	14.67	47.22	11.70	18.94	6.75

Amax: Amoxicillin; Cla: Clarithromycin; Met: Metronidazole; Tet: Tetracycline; Lev: Levofloxacin; Rif: Rifabutin; n: Number of sample; NR: Not reported.

NOVEL THERAPEUTIC OPTIONS:

Vonoprazan based therapy:

Vonoprazan fumarate is a Potassium-Competitive Acid Blocker (P-CAB), that are agents that block K⁺, H⁺-adenosine triphosphatase (ATPase) via reversible K⁺-competitive ionic binding, resulting in gastric acid secretion suppression. Vonoprazan inhibits stomach acid secretion more effectively and for a longer period of time than PPIs. Additionally, it has a longer half-life and does not require pharmacological activation.[38] It is less negatively impacted by the CYP2C19 system than PPIs and is acid stable. The VAC combination includes vonoprazan 20 mg in combination with amoxicillin 750 mg and clarithromycin 200 mg or 400 mg, twice day for 7 days. In May 2022, the US Food and Drug Administration (FDA) has approved two vonoprazan-based therapies for *H. pylori* infection. The medications, marketed by Phathom Pharmaceuticals as Voquezna Triple Pak (vonoprazan, amoxicillin, clarithromycin) and Voquezna Dual Pak (vonoprazan, amoxicillin), were approved following the phase 3 PHALCON-HP trial's positive safety and effectiveness results.

According to a recent systematic review, the higher efficacy of VPZ-based triple therapy over PPI-based triple therapy was due to the higher eradication rate among clarithromycin-resistant *H. Pylori* strains.[39] Even though several Japanese studies have shown that it is safer and more effective than conventional PPIs, it is now exclusively sold in the Japanese market. In a meta-analysis comparing the effectiveness and safety of vonoprazan triple therapy versus PPI triple therapy for the treatment of *H. Pylori*, vonoprazan-based therapies were found to be more effective than PPI-based triple therapy in both intention-to-treat and per-protocol analyses (91.4% vs. 74.8%; 95% CI 1.87-7.26; p 0.05).[40]

LEVOFLOXACIN-BASED THERAPIES

Levofloxacin, a fluoroquinolone antibiotic, acts by interfering with DNA gyrase (encoded by the genes *gyrA* and *gyrB*). The recommended dosage of levofloxacin was 500 mg once daily or 250 mg twice daily with a PPI. According to the American College of Gastroenterology guidelines, 10 to 14 days are optimum therapy duration.[41] Due to the increase in clarithromycin resistance, levofloxacin is recommended for the eradication of *H. Pylori* in order to replace clarithromycin in triple or sequential regimens. Levofloxacin-based treatments may have an eradication rate of more than 90%, particularly in regions with low (less than 10%) local resistance to the drug. When compared to clarithromycin-based treatment, levofloxacin-based treatment had a higher eradication rate (62% vs. 74.5%, respectively; P = 0.04). Given that quinolones are frequently used to treat urinary infections, there is an increase in levofloxacin resistance for clarithromycin and metronidazole. In America, quinolone resistance is at 15%, while it is at 10% in Asia and 20% in Europe. [42]

PROBIOTICS:

Probiotics can be bacteria or yeast-related microbes. However, the majority of probiotics are bacteria, namely lactic acid bacteria, which are often found in the human gastrointestinal system. They contain Gram (+) cocci and rods *Lactobacillus* and *Bifidobacterium*, the two most popular species utilized as probiotics and the focus of significant research for their beneficial impacts on the host, including promotion of gut maturation and integrity, resistance to infections, regulation of the immune system, and inhibition of chemicals that promote tumour growth. The American Journal of Gastroenterology, suggests the use of probiotics as an adjuvant therapy in the eradication of *H. Pylori*. [43] Non-pathogenic microbes in the stomach may stop *H. Pylori* from growing

in this acidic environment by making antimicrobial substances (like organic fatty acids, ammonia, and H₂O₂), directly competing with *H. Pylori* for nutrients and space, taking up mucosal epithelial adherence sites, changing toxins or toxin receptors, and immunomodulating the immune system.[44]

Probiotic strains like *Saccharomyces boulardii*, *Lactobacillus reuteri*, and *L. rhamnosus* reduce gastrointestinal side effects of antibiotics, particularly diarrhoea. Even though there were no statistically significant differences in the rates of eradication, a Turkish study that looked at the possible benefits of the probiotic *S. boulardii* with CTT found that patients had fewer side effects (like diarrhoea and stomach pain) than those who took a placebo.[45] In contrast, a meta-analysis of numerous clinical studies, mostly conducted in China, found that the probiotic group's intention-to-treat eradication odds ratio (OR) was 2.07 (95% CI 1.40–3.06) compared to the control group [46]. In accordance with the Turkish study, the probiotic group's pooled OR of adverse effects was reduced (OR 0.31; 95% CI 0.12-0.79). Therefore, by minimising side effects, probiotics may aid in improving medication adherence. Unfortunately, further research is needed to see how they can increase eradication rates.

CONCLUSION:

Over the past few decades, several studies have evaluated the global eradication of *H. pylori* and its resistance. High-yield testing must be used to properly screen at-risk groups so that treatment can start early and major side effects can be avoided or lessened. It is now necessary to research other treatment options in order to eradicate the pathogen because the frequency of macrolide resistance, particularly to clarithromycin, has increased and reduced the efficacy of these treatments to very low levels in a significant portion of the world. New *H. Pylori* eradication medicines must be developed in order to stop the spread of *H. Pylori* antibiotic resistance and provide an adequate eradication rate, improved safety and tolerability profile, and good patient compliance. After the infection has been treated, it needs to be checked to see if it has completely gone. In the future, there is a need for the development of novel anti-*H. pylori* medications and the establishment of *H. pylori* databases in different locations.

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