

Antibiotic Resistance in the Treatment of Helicobacter Pylori: The Status and Future Directions

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Abstract. Helicobacter pylori (H. pylori) infection is one of the most common chronic bacterial infections in humans that affect a global prevalence of up to 50%. The extensive use of antibiotics has led to a sharp rise in resistance rates in recent years, accompanied by the emergence of multidrug resistance. Successful treatment for H. pylori eradication has become a real challenge and a critical issue. This essay introduces the status of antibiotic resistance in H. pylori in different regions and the resistant mechanisms to amoxicillin, clarithromycin, levofloxacin and metronidazole. Then multidrug resistance profiles, associated factors, underlying mechanisms and strategies to tackle the growing challenge of antibiotic resistance.

Keywords: Helicobacter pylori; antibiotic resistance; multidrug resistance.

1. Introduction

Helicobacter pylori (H pylori) is a gram-negative bacterium that can survive in strongly acidic gastric juice. The crude global prevalence of H. pylori was 43.9% in adults during 2015 through 2022[1]. Infection prevalence rates range widely among geographic regions, showing a close relationship with economic level, sanitary conditions, and education [2]. Take China as an example: between 2014 and 2023, the combined prevalence of H. pylori infection in mainland China was 42.8%, the highest prevalence was in north-west China with 51.3%, in Qinghai province the prevalence reached 60.2%, while in north-east China the prevalence was 29.6% [3]. The presence of H pylori infection is related to various gastrointestinal diseases, such as indigestion, gastritis, peptic ulcer, and gastric cancer. Among these, a previous study showed that the prevalence of gastric cancer (GC) due to H pylori infection was 19.46% [4]. According to data, the incidence rate of gastric cancer was 4.9% and the mortality rate was 6.8% across 185 countries and regions worldwide in 2022 [5]. Therefore, treatment and eradication of H pylori is important to decrease the incidence of GC.

Clinically, antibiotics are commonly used to treat and eradicate H. pylori infections. At present, bismuth preparations are inexpensive, safe, and effective, consequently making bismuth quadruple therapy a preferred choice for initial and rescue treatment, which can enhance the average eradication rate from 71.3% to 81.3% compared with triple therapy [6]. The bismuth quadruple therapy includes proton pump inhibitor (PPI), bismuth preparations and two antibiotics. The recommended antibiotics in bismuth quadruple therapy include metronidazole, levofloxacin, clarithromycin, amoxicillin, and tetracycline. However, in recent years, with wide application of antibiotics, the drug resistance rate has increased year by year, and the emergence of H pylori resistant strains has induced the decreased eradication rate of H pylori. Multiple factors are associated with the failure of H. pylori eradication, including poor patient compliance, high gastric acidity, and, most importantly, resistance to antibiotics. A meta-analysis evaluating primary drug resistance of H pylori in China suggested that the resistant level of metronidazole, levofloxacin, clarithromycin and amoxicillin in adults was as follows: 69.32%, 29.45%, 23.76% and 1.35% respectively [7]. There is no doubt that such a high rate of antibiotic resistance hinders the eradication of H. pylori and may create economic burden for patients.

With the development of molecular biology techniques, the potential mechanisms of antibiotic resistance have been reported and the type of resistant strains can be detected to realize precision medicine and reduce the costs of treatment and eradication of H pylori. This essay synthesizes the mechanisms of single-drug resistance and multidrug resistance in H. pylori against commonly used

antibiotics, while proposing actionable strategies to combat resistance, thereby offering a comprehensive perspective on addressing this global health challenge.

2. The mechanisms of antibiotic resistance

2.1. Metronidazole

Metronidazole (MTZ) is a synthetic nitroimidazole antibiotic whose chemical name is 1 - (2 - hydroxyethyl) - 2 - methyl - 5 - nitroimidazole. As a prodrug, MTZ is inactive until taken up and reduced. Reductive activation of the nitro group can activate MTZ resulting in imidazole fragmentation and cytotoxicity or DNA damage [8].

Among MTZ, levofloxacin, clarithromycin and amoxicillin, a meta-analysis showed that the prevalence of primary resistance of *H. pylori* to MTZ was 59.6%, the highest rate. The prevalence of primary resistance to MTZ was 66.1%, 29.9%, 48.1% in Asia, Europe, and the Americas versus 84.2% in Africa [9]. Overall, the resistance rate to MTZ remains alarmingly high in most countries, posing a significant challenge to the effective eradication of *H. pylori*.

Resistance to MTZ is mainly due to the inactivation of RdxA, an oxygen-insensitive NADPH nitro reductase, which is encoded by *rdxA* gene and can catalyze the reduction of MTZ to form hydroxylamine. Gong et al separated 511 *H. pylori* clinical strains, extracted genomic DNA, sequenced *rdxA* and found amino acid mutations, such as R16H/C, Y47C, A67V/T, and V204I substitutions were associated with MTZ resistance. These mutations were potentially helpful for identifying resistant strains. Also, V204I substitutions may potentially be used to identify MTZ resistance in *H. pylori* [10]. Besides, the resistance nodulation cell division (RND) family efflux pump system is also associated with MTZ resistance in *H. pylori*. Lee et al indicated the direct involvement of *hefA* in MTZ-resistant strains through knockout and genetic complementation test for *hefA* [11]. In addition, mutations in other genes such as *frxA* (encoding the NADPH flavin oxidoreductase) and *fdxB* (encoding the ferredoxin-like protein) might also induce *H. pylori* resistance to MTZ [12].

2.2. Levofloxacin

The prevalence of primary resistance of *H. pylori* to levofloxacin (LEV) is 26.2% in recent 10 years. Globally, the primary resistance rate to LEV varies significantly across different geographical regions. Specifically, the rate is 31.4% in Asia, 13.1% in Europe, 14.2% in Africa, and 25.0% in the Americas [9].

LEV represents a fluoroquinolone drug that can bind to bacterial DNA gyrase encoded by two genes named *gyrA* and *gyrB* to exert a bactericidal effect through interfering with chromosome replication. Therefore, point mutations in the quinolone resistance determination region (QRDR) of *gyrA* might restrict this effect, leading to fluoroquinolone resistance of *H. pylori*. Gene mutations in *gyrA* mainly change amino acids 87 and 91, listed as follows: N87I, N87K, D91Y, D91N and D91G. The mutations detected in *gyrB* are D481E and R484K which are also related to drug resistance [13].

2.3. Clarithromycin

Clarithromycin (CLR) is widely used around the world. However, its resistance rate is continuously increasing in some regions and countries. Yu et al. assessed the CLR - resistance rate of *H. pylori*. all over the world. The results showed that primary antibiotic resistance to CLR was 26.7% globally, and 28.9% in Asia, 21.3% in Europe, 24.6% in Africa and 16.0% in Americas [9].

CLR is a macrolide antibiotic whose action is based on the interaction with the peptidyl transferase loop of the V domain of the 23S ribosomal RNA molecule inhibiting bacterial protein synthesis, which means mutations in the 23S rRNA gene may induce CLR resistance [12]. Serra Örstén et al. reckon the most common mutations associated with CLR resistance in *H. pylori* are A2143G, A2142G, and A2142C by detecting point mutations in 46 of the isolates and note other mutations detected such as T2188C, G1949A, G1940A, and C1944T are not associated with CLR resistance in

H. pylori [14]. The efflux pump system is another potential mechanism in CLR resistance of *H. Pylori* and data suggest that the existence of efflux pumps could induce antibiotic resistance in parallel with 23S rRNA mutations [12]. It has been discovered that at least five conserved families of efflux pump systems are associated with bacterial antibiotic resistance. These include the ATP-binding cassette (ABC) family, the Major Facilitator Superfamily (MFS), the Multidrug and Toxic Compound Extrusion (MATE) family, the Metabolite Transporter (DMT) superfamily, and the RND family. Among them, the RND family is the primary efflux pump system responsible for CLR resistance in *H. pylori* [15]. In addition, outer membrane proteins (OMPs) may associate with CLR resistance. Smiley et al. reported that iron-regulated membrane protein, urease B, elongation factor thermo unstable, and putative OMP were downregulated, whereas HopT (BabB) transmembrane protein, HofC, and OMP31 were upregulated in clarithromycin-resistant *H. pylori* [16].

2.4. Amoxicillin

As a semisynthetic penicillin broad - spectrum β - lactam antibiotic, Amoxicillin (AMX) interacts with penicillin-binding proteins (PBPs) and hinders the synthesis of the cell wall, resulting in expansion and cracking of *H. pylori* cells [12].

AMX is one of the most commonly used antibiotics but has a low antibiotic resistance rate throughout the world. The global average AMX-resistance rate was 2.6% in the past 10 years. The primary antibiotic resistance to AMX in Asia, Europe, Africa and Americas was 2.8%, 0, 70.4% and 4.8% respectively [9].

AMX resistance is associated with PBPs. Qureshi et al. isolated five strains with higher levels of resistance and sequenced whole genome. The results indicated mutations in *pbp1*, *hefC*, *hopC*, *hofH*, and possibly *pbp2* contributed to *H. pylori* high-level AMX resistance [17]. *HefC* and *hofH* are associated with the efflux pump system whereas *hopC* is an outer membrane protein. High levels of AMX resistance are associated with the production of beta-lactamase in *H. pylori* [12].

2.5. Multidrug resistance in *Helicobacter pylori*

2.5.1 Multidrug resistance profiles

Multidrug resistance (MDR) in *H. pylori* is defined as resistance to two or more antibiotics from different classes. Globally, the rising prevalence of MDR in *H. pylori* has become a significant concern, leading to treatment failures and reduced eradication rates.

Lv et al. conducted a comprehensive analysis of the phenotypes and genotypes of 140 *H. pylori* strains using whole-genome sequencing. Among these strains, the most prevalent dual antibiotic resistance pattern was CLA +MTZ, observed in 39.3% of the isolates. In contrast, the dual resistance rates for CLA +LEV and LEV + MTZ were significantly lower, at 0.7% and 36.4%, respectively. Additionally, a triple resistance pattern involving CLA + LEV + MTZ was identified in 25.0% of the strains [18].

Another single-center retrospective observational study conducted in China revealed that the top 3 most common patterns of secondary antibiotic resistance were CLA+LEV+MTZ (36.44%), AMX+CLA+LEV+MTZ (17.00%), CLA+MTZ (15.38%). The proportion of MDR isolates increased quickly as the number of treatment failures accumulated [19]. The increasing prevalence of MDR in *H. pylori* strains, along with their diverse resistance patterns, poses a growing challenge to eradication efforts worldwide. Effective treatment of *H. pylori* infections remains a complex and pressing issue.

2.5.2 Factors associated with MDR

Factors associated with MDR are national antibiotic consumption, antibiotic misuses, treatment failures, and bacterial factors, such as mutations, efflux pumps, and biofilms. In many countries, national antibiotic consumption and antibiotic misuse significantly increase the drug resistance rate of bacteria and are closely related to the development of MDR strains [15]. An evaluation of primary antibiotic resistance in 24 centers from 18 European countries confirmed the positive correlation

between macrolide and quinolone consumption in the community and corresponding *H. pylori* resistance [20].

Xie et al. indicated that patients who had failed multiple courses of therapy exhibited a significantly higher MDR rate of 83.72%, compared to treatment-naïve patients, who had an MDR rate of 39.19%. The proportion of MDR patterns such as AMX+CLA+LEV+MTZ, CLA+LEV+MTZ, AMX+CLA+MTZ, and CLA+MTZ elevated significantly with the number of treatment failures accumulated, which showed in the Figure 1. Therefore, treatment failure is a key factor in the development of *H. pylori* resistance [19].

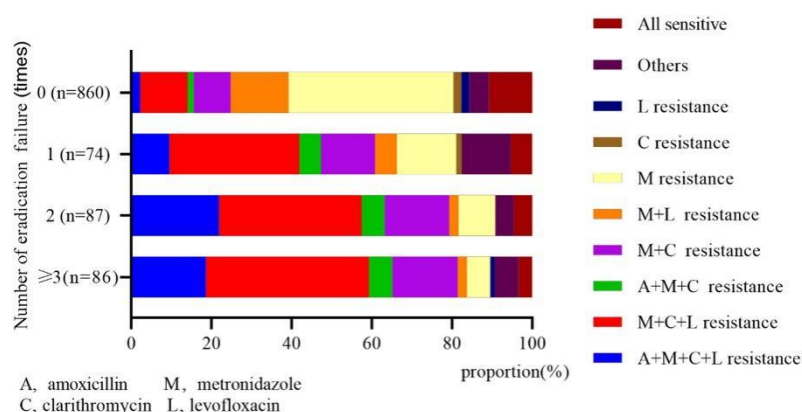


Fig. 1 The proportion of antibiotic resistance patterns [19].

Gene mutations play a crucial role in single-drug antibiotic resistance. Additionally, research indicates that the A1378G mutation in HP0399 and the A149G mutation in FabH may be associated with tetracycline resistance and multidrug resistance, respectively, which provides new directions for the role of mutations in antibiotic resistance [21].

Data shows that Hp1174 (glucose/galactose transporter [gluP]), an efflux pump of the major facilitator superfamily (MFS), is highly expressed in biofilm-forming and MDR of *H. pylori* [22]. The efflux pump gene *hefA* also plays an important role in MDR of *H. pylori* [23].

3. Strategies for combating antibiotic resistance in *H. pylori*

Global researchers are now focusing on the development of other effective strategies to combat antibiotic-resistant bacteria in recent years in addition to the development of new antibiotics. These strategies include efflux pump inhibitors (EPI), efflux enzyme inhibitors, oxidative treatment, alteration of cell membrane permeability, nanomaterials, multi-omics technology, bacteriophage therapy, and antibody-antibiotic conjugates [24].

Notably, a range of non-pharmacological therapies targeting *H. pylori* have been developed, including probiotic therapy, hyperbaric oxygen therapy, antibacterial photodynamic therapy, nanomaterials, antimicrobial peptide therapy, phage therapy and modified lysins, offering promising alternatives to traditional antibiotic-based treatments [25].

Among this strategy, the increasing evidence indicates that nanoscale materials and technologies with unique antimicrobials have great promise in treating pathogenic bacteria. An oral nanomedicine (RHL/PC@EPI/R-Ag NPs) loaded with the urease inhibitor EPI and antibacterial agent R-Ag NPs was successfully prepared with efficient drug delivery, acid responsiveness, mucus penetration, urease inhibition, rapid bactericidal activity, and good biocompatibility. It could enhance the eradication rate of *H. pylori* in vivo and reduce the gastrointestinal inflammation and drug resistance problems caused by the triple therapy [26]. The recent findings implied that CH Schiff base (CH-Py-Cl)/Se nanocomposite and NCT/MBS/Se NPs demonstrated the high activity against *H. pylori* [27]. In addition, an innovative biocidal nano formulation included chitosan nanoparticles (NCT), broccoli seeds mucilage (MBS) and Se nanoparticles, called NCT/MBS/Se NPs, also exhibited remarkable efficacy in comparison to the standard antibiotic (AMX)[28].

Probiotic therapy has been shown to enhance the eradication rate of *H. pylori* infections and reduce associated side effects. Meanwhile, the use of probiotics may aid in the treatment of *H. pylori*-related diseases by inhibiting the pathogen, strengthening the gastric mucosal barrier, and competing with the bacteria for adhesion. However, neither single-strain nor multi-strain probiotic supplementation has achieved satisfactory eradication rates, thus limiting their role to adjunctive therapy for *H. pylori* infections [29]. Recently, fecal microbiota transplantation (FMT) has emerged as a promising approach, replenishing deficient microbial communities (including bacteria, fungi, and phages) and their metabolites to eradicate *H. pylori*. FMT, whether used as a standalone or adjunctive therapy, has demonstrated beneficial effects in eradicating *H. pylori* infections and preventing adverse events. Nevertheless, both FMT and probiotic therapy require further clinical evidence and in-depth research to validate their efficacy and safety [30].

Antibacterial Photodynamic Therapy (APDT), a new type of antibacterial therapy, is based on three substances including photosensitisers (PS), oxygen and light at the appropriate wavelength. The generation of reactive oxygen species (ROS) by APDT induces a super-oxidative process that results in damage to bacterial DNA, RNA, proteins and lipids, leading to bacterial death [31]. Im et al. proposed a system that consisted of multiple 3'-sialyllactose (3SL)-conjugated, poly-l-lysine-based photosensitizer (p3SLP). p3SLP can selectively recognize and interact with sialic acid-binding adhesin (SabA) in the *H. pylori* membrane and destroy biological molecules through the ROS that is generated under laser irradiation. It is noteworthy that p3SLP showed antibacterial therapeutic effects similar to those of antibiotic-based therapy because PDT is less likely to cause the drug resistance due to the different bactericidal mechanisms of antibiotics [32]. Currently, the use of PDT in the treatment of *H. pylori* can be divided into two parts: PDT alone and PDT in combination with other methods. PDT has unique advantages in targeting drug-resistant strains of *H. pylori*, but there are still some challenges that need to be solved, such as enhancing the selectivity of PDT against *H. pylori*, increasing the depth of light penetration [31].

Beyond developing novel treatment approaches, to combat antibiotic resistance, governments must implement robust policies to regulate antibiotic consumption, strengthen antibiotic stewardship, monitor resistance trends, and incentivize the development of new drugs. Healthcare institutions should optimize antibiotic use and promote alternative therapies. Simultaneously, raising public awareness about rational drug use and encouraging healthy lifestyles are essential steps toward enhancing immunity and reducing reliance on antibiotics [33].

4. Conclusion

Antibiotic resistance has grown into a serious worldwide health concern. Resistance is driven by a variety of processes, including biofilm development, genetic changes and so on. Resistant pathogens, including multidrug-resistant organisms, not only compromise treatment outcomes, but also impose severe economic and clinical burdens, such as prolonged hospital stays. Researchers are actively exploring novel non-antibiotic therapies for *H. pylori*, including probiotic therapy, hyperbaric oxygen therapy, antimicrobial photodynamic therapy, nanomaterials, antimicrobial peptide therapy, phage therapy, and modified lysins. However, further research is essential to validate their efficacy and safety. Meanwhile, addressing the global challenge of antibiotic resistance in *H. pylori* requires a concerted effort from governments, healthcare institutions, and the public to implement comprehensive strategies and promote responsible antibiotic use. A coordinated global effort, grounded in innovation, collaboration, and sustainability, is essential to safeguard the effectiveness of current antibiotics and to drive the development of new therapeutic strategies that can effectively address this urgent health challenge.

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