



Mini Review

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Drug Resistance in *Helicobacter pylori*

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Abstract

Helicobacter pylori being worldwide in distribution can cause several gastric complications such as gastritis, peptic ulcer diseases and gastric cancer. The risk for the development of gastric complications may be decreased by eradicating the bacteria by antibiotic treatment. However, high rate of treatment failure has been observed, primarily because of the point mutations observed in the antibiotic targets. In this review, we have briefly summarized the resistance mediated by the point mutations of common antibiotic targets.

Keywords: Antibiotic resistance; *Helicobacter pylori*; Mutations

Introduction

Helicobacter pylori (*H. pylori*) is a stomach pathogen that colonizes approximately 50% world's population [1]. However, the prevalence of *H. pylori* infection tends to differ both within and between the countries. The higher infection rate up to 80% in developing countries in comparison to 20-50% infection rate in developed countries reflects the dependence of prevalence of infection on socio-economic status of the countries [2,3]. The exact route of transmission of this bacterium is not known yet but evidence supports the fecal or oral transmission of bacterium from person to person between the family members [4-6]. Once the bacterium enters the stomach it causes chronic infection because it is highly adapted to the environmental stresses encountered [7]. Once the chronic infection is established it can lead to the several gastrointestinal diseases such as gastritis, peptic ulcer, gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [8]. *H. pylori* infection is the primary risk factor for the development of gastric cancer which is the third highest cause of cancer morbidity worldwide [9]. The risk of peptic ulcer and gastric cancer development may be reduced by successful eradication of *H. pylori* [10,11]. However, the increasing antibiotic resistance in *H. pylori* has posed an emerging challenge to achieve the goal of eradication therapy [12].

Therapeutic Regimens

Although many therapeutic regimens such as amoxicillin, clarithromycin, levofloxacin, tetracyclin, metronidazole are in current use either alone or in combinations but the effective

antibiotic therapy seems to be difficult worldwide due to the resistant mediated failure which is the main factor affecting the efficacy of current therapeutic regimens [13]. The consumption of antibiotics in general populations reflects the prevalence of antibiotic resistant bacteria which differs in different geographic areas [14,15]. Currently, triple therapy based treatment which includes a proton pump inhibitor and two antibiotics (amoxicillin and clarithromycin) is most commonly recommended [16-18]. However, in recent years the decreased effectiveness of the triple therapy has been reported with eradication rates lower than 80% [19-21]. It is evident from the several studies that the main cause of treatment failure is clarithromycin resistant [22]. However, in developing countries re-infection has also the great contribution in treatment failure and probably more extensive if re-infected with clarithromycin resistant strains.

Mechanism of Antimicrobial Resistance in *H. pylori*

Initially after the introduction of antimicrobials for the treatment it was believed that the evolution of resistance was not likely to be happened. Previously it was assumed that the frequency of mutations resulting resistance in bacteria was negligible [23]. The antibiotic resistance mediated by the mutations in antibiotic targets is by far the most common mechanism in *H. pylori*.

Amoxicillin Resistance

Amoxicillin, a derivative of ampicillin and a beta-lactam antibiotic, was discovered in 1958 and came into medical use in

1972 [24,25]. Penicillin binding proteins (PBPs) are the bacterial peptidoglycan synthesizing enzymes having trans-peptidase activity in the C-terminal region [26]. Beta-lactam antibiotics (amoxicillin) acts by inhibiting the synthesis of cell wall by binding with PBPs and halting its trans-peptidase activity [27]. Several studies have depicted the substitution of one amino acid to another in the PBP1 leading to the resistance to the action of amoxicillin. The substitution of serine (S) at 414 to arginine (R) (S414R) in PBP1 was found to significantly increase the MIC (>0.5-1mg/L) and amoxicillin resistance [28]. Qureshi et al. [29] demonstrated that the substitution of amino acid at position 469 (V to M), 473 (F to L) and 543 (S to R) can affect the susceptibility of *H. pylori* to amoxicillin.

Clarithromycin Resistance

Clarithromycin is a bacteriostatic antibiotic belonging to the group of macrolide that inhibits the growth of bacteria by inhibiting the protein synthesis. Clarithromycin is one of the essential components of the standard triple therapy [17]. However, its continuous use for the treatment of other infectious diseases such as respiratory tract infections has diminished its efficacy against *H. pylori* infections [30]. The major mutations implicated in the clarithromycin resistant are A2143G, A2142G and A2142C as depicted by several studies [31-33]. A recent study conducted by Chen et al. in clinical isolates from the United States also revealed the role of these mutations in mediating clarithromycin resistance in majority of the isolates. They reported that the mutations A2143G, A2142G and A2142C mediated the resistance in 82%, 14% and 4% of isolates respectively [32]. In addition to A2143G in 23S rRNA gene, we also confirmed mutations responsible for increased MIC values such as one mutation in *infB*, a translation initiation factor encoding gene (G160A) and two mutations in *rpl22*, a ribosomal protein 22 encoding gene (9bp insertion or 3bp deletion) [34].

Levofloxacin Resistance

Levofloxacin is a member of the fluoroquinolone antibiotics with a potent and broad-spectrum activity against Gram-negative bacterial pathogens which targets the bacterial DNA gyrase resulting in the impairment of DNA replication [35,36]. The most common mechanism of high level levofloxacin resistance in *H. pylori* is the point mutation in the DNA gyrase (*gyrA* and *gyrB*). The point mutation in *gyrA* at amino acid 87 and 91 is the most common mutations documented leading to the fluoroquinolone resistance in *H. pylori*. The common mutations in amino acid are asparagine (N) at position 87 to lysine (L) or tyrosine (Y) (N87L or Y), aspartic acid (D) at 91 to glycine (G) or asparagine (N) or tyrosine (Y) (D91G or N or Y) [37,38]. Recently, we also reported the common mutations in *gyrA* in levofloxacin resistant strains such as amino acid N at position 87 to lysine (K) or Isoleucine (I) or tyrosine (Y) (N87K or I or Y) and amino acid D at 91 to N or Y or G (D91N or Y or G) [34,39]. The mutation in *gyrB* is not so common mechanism for the antibiotic resistance. However, a novel mutation at position 463 in *gyrB* leading to the

fluoroquinolone resistance was proposed by Rimbara et al. [40].

Metronidazole Resistance

In a recent meta-analysis conducted in Asia-Pacific region, 44% of the *H. pylori* isolates were reported metronidazole resistance [41]. Metronidazole, a pro-drug which contains a nitro group in its imidazole ring, is activated by reduction of its nitro group which leads to the production of helicoidal DNA-damaging compounds such as nitroso- and hydroxyl amine. The oxygen-insensitive NADPH nitroreductase (RdxA), NADPH-flavin-oxidoreductase (FrxA) and ferredoxin like enzymes (FrxB) performs the reducing activity of metronidazole in *H. pylori* [42]. Teh et al. [43] detected mutations as the common mechanism for the metronidazole resistant. Out of 37 metronidazole resistant strains insertion or deletion type of mutation was noticed in 33 strains [43]. They also reported that 10.8% of metronidazole resistant strains did not contain any mutations in either *rdxA* or *frxA* depicting that mutations in *frxB* or other mechanism rather in commonly reported may have role. Recently, we reported similar mutations in *rdxA* and *frxA* in clinical isolates from Indonesia and Nepal [34,39]. In search for the novel genetic mutations for metronidazole resistance using next generation sequencing we detected the single nucleotide polymorphism in addition to the insertion-deletion in *rdxA* in metronidazole resistant strains. We suggested that the mutations in *frxA* are able to increase the metronidazole resistance only when there are mutations in *rdxA* [44].

Tetracycline Resistance

The antibiotic tetracycline is a broad-spectrum antibiotic belonging to the first generation tetracyclines [45]. This antibiotic is a broad-spectrum agent exhibiting bacteriostatic activity against wide range of Gram-positive as well as Gram-negative bacteria. Mutation in the 16S ribosomal subunit at positions 965-967 (AGA) is reported to be responsible for the tetracycline resistance [46,47]. Single and double mutations are associated with low and intermediate MIC values while simultaneous triple mutations are associated with high MIC values [48]. In a study conducted by Wu et al. [49] 54% of tetracycline resistant strains carried single nucleotide substitution such as A965C, A965G, A965T, A967C or A967T and with slightly increased MIC values [49]. Nonaka et al. [48] suggested that the guanine (G) at position 966 plays more important role for the primary site of tetracycline binding and its substitution with other nucleotide results in the high MIC value.

Role of Bacterial Virulence Factors in Antibiotic Mediated Clearance

In *H. pylori* the specific genotype also have been claimed to be involved in the antibiotic mediated bacterial clearance. In several reports, it was found that the strains with *vacA* s2m2 and *cagA*-negative status were more resistant to clarithromycin than that of *vacA* s1m1/*vacA* s1m2 and *cagA*-positive status [50]. We previously suggested that the patients infected with more

virulent strains (*vacA* s1m1 and *cagA*-positive status) show high rate of antibiotic mediated bacterial clearance because of the enhanced inflammatory process and blood flow with increased diffusion of antibiotics to the site of infection [51].

Conclusion

Taken together, the above mentioned information suggests that *H. pylori* is one of the bacteria which frequently becomes resistant to common antibiotics by point mutations in the antibiotic target genes. A continuous effort is required to search for the novel mutations and for the identification of their role in antibiotic resistance.

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