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Clinical significance of clarithromycin resistance in Helicobacter pylori – A review

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ABSTRACT
Clarithromycin, a macrolide class of antibiotic, has emerged as the most significant antibiotic in the treatment of H. pylori infection [1, 2]. Since its broad adoption in H. pylori therapy but, the rising clarithromycin resistance in H. pylori and its influence on the success of eradication therapy have been raised [3, 4]. The goal of this study is to look at about the clarithromycin resistance in H. pylori, as well as its molecular underpinnings and its clinical implications.
Key words : Clarithromycin, H.pylori, Antibiotic, Resistance

➢ Medicinal Uses of Clarithromycin

Clarithromycin is generally used as an alternative to penicillin in the treatment of strep throat as well as pneumonia and Helicobacter pylori. [5] Various applications include the treatment of toxoplasmosis, cat scratch illness, bartonella infections, and cryptosporidiosis. [5] People who are unable to take penicillin may also use it to avoid bacterial endocarditis. [5] It works well to treat skin and soft tissue infections, upper and lower respiratory tract infections, and Helicobacter pylori infections linked to duodenal ulcers.

➢ Why clarithromycin is a key antibiotic for H. Pylori infection?

The classic microbiologic rule states that after doing susceptibility testing, an infectious agent should be treated with the proper antibiotics. Despite several dangerous pathogenic germs, H. pylori's situation is unique. Notably, if resistant bacteria are present, the success likelihood of a regimen that includes clarithromycin is less than 40%. This dismal result may reflect clarithromycin's undeniable importance as a cornerstone antibiotic in the treatment of H. pylori. The issue with this crucial function is that antimicrobial resistance to this medication is significantly rising, which makes it increasingly difficult to have successful eradication regimens (i.e., consistent treatment success > 90%) with clarithromycin.

➢ Molecular mechanisms of clarithromycin resistance

Versalovic et al. [30] were the first to discover an AG transition mutation in a conserved loop of H. pylori 23S rRNA and its link to clarithromycin resistance. The mutation is most prevalent at two gene sites that correspond to positions 2058 and 2059 of Escherichia coli-23S rRNA, which were renamed 2143 and 2144, respectively, and are now updated as 2142 and 2143 [4,31]. Point mutations can occur at any location and can be either a transition (AG) or a transversion (AC), however the transition is significantly more common [4, 32-35]. Versalovic et al. [32] also found that the A2142G mutation was linked to a higher degree of resistance (MIC > 64 mg/L) than the A2143G mutation. Other research [33, 36] has also backed up these findings. In vitro, macrolide resistance was found to be unstable in some strains of H. pylori [17]. This behaviour has also been seen in vivo, with strains developing resistance after treatment and then reverting to susceptibility after a period of observation [17, 30]. Before and after therapy with clarithromycin alone, Versalovic et al [30] cultivated five genotypically identical isolates from one patient. They discovered that the A2143G mutation was present in the first two post-treatment isolates with low-level clarithromycin resistance, but not in the susceptible pretreatment isolate or the last two post-treatment isolates with restored susceptibility [30]. This raises the possibility that the mutation is unstable [35]. Clarithromycin resistance was maintained after 50 subcultures in vitro, according to Hulten et al [35], which is similar with earlier studies [37]. In H. pylori, cross-resistance between macrolides has been observed

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[12, 17, 30]. H. pylori bacteria that are resistant to clarithromycin are typically also resistant to erythromycin, azithromycin, and roxithromycin, or vice versa. At the molecular level, these findings have been confirmed [36].

➢ **Detection of clarithromycin resistance in H. pylori**

The agar dilution method, broth dilution method, disc diffusion test, and the Epsilometer test (E-test) are now utilised for susceptibility testing of H. pylori to clarithromycin. Antibiotics' minimum inhibitory concentrations (MICs) against bacteria are determined using the agar dilution technique. This procedure is time-consuming and inconvenient to employ on a regular basis. It is, nevertheless, a dependable approach that is frequently used as a reference method for other procedures [17, 38, 39]. Because it is difficult to grow H. pylori in broth, the broth dilution approach is rarely employed. The disc diffusion test is the most straightforward and cost-effective method of determining susceptibility. However, before this exam can be employed, it must be thoroughly standardised [39]. The E-test, which was created in 1988, uses a diffusion-like approach to directly determine a strain's MIC. [40] On one side of a plastic-coated strip is a prefabricated antimicrobial gradient, and on the other is a scale. At the point where the ellipse of growth inhibition crosses the strip, a reading is obtained. Prior to application, standardisation and correlation using the agar dilution procedure are also necessary. This approach is currently widely employed by numerous investigators [12, 13, 15, 16, 18, 22-28]. At this time, no "gold standard" method for testing H. pylori susceptibility to antibiotics such as clarithromycin and metronidazole has been proposed, as there is still a need for standardisation in terms of the appropriate medium, supplementation, inoculum size, incubation atmosphere, appropriate time to read the plates, and the breakpoint that distinguishes resistance and susceptibility [38]. Because macrolide cross-resistance occurs, erythromycin susceptibility testing might help forecast (determine) clarithromycin-resistant H. pylori strains [12, 17]. Many microbiological laboratories use erythromycin susceptibility testing, which is now far less expensive than clarithromycin susceptibility testing. The discovery of a link between point mutations in the 23S rRNA gene and macrolide resistance in H. pylori might lead to a novel method for identifying macrolide-resistant bacteria. Despite the fact that cycle DNA sequencing of 23S rRNA gene amplicons is considered the gold standard, simpler approaches have been developed [38]. A polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP), an oligonucleotide ligation assay (PCR-OLA), a DNA enzyme immunoassay (PCR-DEIA), a reverse hybridisation line probe assay (PCR-LiPA), and a preferential homoduplex formation assay (PCR-PHFA) are some examples [30, 31, 33, 41-43]. PCR-based molecular approaches are faster than microbiological susceptibility testing, and they can be done on stomach biopsies and gastric juice [10, 44, 45].

Indeed, molecular approaches were quickly developed during the past ten years [17] in the lack of a trustworthy culture-based method to provide data on susceptibility testing. Numerous techniques have been created to swiftly detect clarithromycin resistance in colonised H. pylori strains based on the molecular tools tracking the 23S rRNA gene that are now accessible (Table1). Despite the fact that we have made progress, a rapid approach with precise results is still lacking. Real-time PCR can be recommended as the best alternative for usage in hospitals and even smaller institutions when taken as a whole. Many businesses have started producing this equipment recently, and it is now far less expensive than it was ten years ago (almost 10 folds). Therefore, we recommend using this machine to determine the kind of mutations that have occurred. It will be simpler to display the susceptibility profile and 23S rRNA gene.

Methods	Advantages	Disadvantages	PCR-based method	Reference
Real-time PCR	Quick and reliable High specificity, high sensitivity	Relatively expensive	Yes	[21]
PCR-LiPA	Fast and cheap	Moderate specificity and sensitivity	Yes	[22]
DNA	Produce many	Expensive,	Yes	[23]

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sequencing	information	Time-consuming protocol		
3'-mismatch PCR	Fast and high specificity	Produce limited data on the gene, not practically useful	Yes	[24]
RFLP	High specificity, high sensitivity	Risk of contamination Low reproducibility	Yes	[15,25]
FISH	High specificity, high sensitivity	Need invasive approach so not good for children	No	[26,27]

Table 1: Molecular methods to identify mutations induce clarithromycin resistance in clinical Helicobacter pylori isolates (FISH: Fluorescence in situ hybridisation; RFLP: Restriction fragment length polymorphism; PCR-LiPA: PCR line probe assay)

➢ **Clinical relevance of clarithromycin resistance in H. pylori**

Clarithromycin resistance in H. pylori has a significant impact on the efficacy of clarithromycin-based eradication regimens. Dual treatment with an antisecretory drug (e.g., H2 antagonist or proton pump inhibitor) and clarithromycin provides eradication rates of 60% to 80% for susceptible strains but fewer than 40% for resistant strains. For susceptible infections, triple therapy with an antisecretory drug, clarithromycin, and another antibiotic (i.e., amoxycillin or metronidazole) boosts eradication rates to 80 % to 95 %, while rates for resistant strains remain below 40 %. An early investigation found that a combination of ranitidine bismuth citrate and clarithromycin eliminated H. pylori at a rate of 98 % for susceptible strains and 92 % for resistant strains, respectively, although this has yet to be confirmed [13]. The use of metronidazole as a major agent in traditional triple treatment (bismuth, metronidazole, and tetracycline or amoxycillin) or greater usage of this medicine for other illnesses are most likely to blame for this rise. Similarly, the current incidence of clarithromycin-resistant strains in Australia is 6 % to 8%, which is significantly greater than the 1.9 % reported four years ago [11, 12, 48]. Clarithromycin resistance has also been found to be on the rise in Europe and the United States [14,20,27,49]. Prescriptions for macrolides, particularly newer members like spiramycin, roxithromycin, azithromycin, and clarithromycin, are thought to have grown in recent years for the treatment of respiratory infections, sexually transmitted illnesses, and other infectious disorders. As cross-resistance occurs across macrolides, individuals treated with any member of the macrolide family may select macrolide resistant H. pylori organisms (if infected). Overall, H. pylori resistance to clarithromycin is of lower clinical importance than resistance to metronidazole, owing to its low incidence and the possibility of reversibility in some strains. Because of the limited occurrence of clarithromycin resistance, susceptibility testing is not necessary before therapy. In patients who have failed to respond to clarithromycin medication, H. pylori should be cultivated and evaluated for clarithromycin susceptibility. Furthermore, any prior usage of macrolides that were not intended to treat H. pylori infection should be considered when choosing clarithromycin for H. pylori eradication.

CONCLUSIONS

H. pylori that is resistant to clarithromycin is uncommon, although it is on the rise. The resistance is caused by point mutations in the 23S rRNA gene, namely at locations 2142 and 2143 with an AG transition. Despite the fact that current clarithromycin-based triple treatments may eliminate up to 90% of susceptible bacteria, eradication rates for resistant strains might be much lower. Furthermore, failure to respond to clarithromycin-containing regimens is linked to the development of drug resistance, which might explain the rising rate of clarithromycin resistance.

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