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Mechanisms of *Helicobacter pylori* Resistance to Antibiotics

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Abstract

Background: *Helicobacter pylori* is the most frequent human bacterial infection worldwide; it is prevalent in approximately half of the world's population. *H.pylori* poses a major health risk because it possesses distinct virulence factors and highly resistant to antibiotics. Multidrug resistance (MDR) and single-drug resistance are two distinct resistance profiles. Chromosome mutations influence antibiotic activity via target-mediated pathways. Inadequate drug absorption, efflux pumps activity, biofilm development, and cocci formation represent supplementary biological mechanisms by which *H.pylori* acquires drug resistance. The overexpression of efflux pumps genes in mutant isolates is readily detectable in post-therapy courses.

Objective: Characterization of the biological and molecular mechanisms contributing to the development of antibiotic resistance in *H.pylori*.

Conclusion: An alarming rate of drug-resistant *H.pylori* is on the rise. Primary and acquired resistance to clarithromycin and metronidazole has increased globally. Bacterial factors including biofilms, efflux pumps, and molecular mechanism are in association with *H.pylori* resistance. It is important to continue to monitor the resistance profiles of *H.pylori* isolates.

Keywords: *Helicobacter pylori*, MDR, Efflux pump, Biofilm, antibiotic resistance.

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Introduction

Helicobacter pylori is a micro-aerobic, curved, Gram-negative bacteria, a fastidious finicky microorganism that demands complex growth media including blood or serum to serve as a supplementary source of nutrients compared to other intestinal microorganisms [1]. *H.pylori* is highly adapted to its role as a gastric pathogen that causes wide infections ranging from asymptomatic gastritis and peptic ulcer disease to gastric malignancy [2]. *H.pylori* is one of the 12 most important antibiotic-resistant organisms to target while developing new medications, according to the WHO [3]. Clarithromycin and metronidazole resistance, both acquired and primary, has increased worldwide in recent years.

Since antibiotic susceptibility testing is not feasible, therapy selection is empirical. The eradication protocol consists of two antibiotics taken as well as proton pump inhibitors (PPIs) to substantially reduce release of gastric acid [4]. Main therapeutic medicines include bismuth, clarithromycin, amoxicillin, tetracycline, and metronidazole;

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first-line conventional regimens comprise PPI, clarithromycin, amoxicillin, or metronidazole [2].

In general, antimicrobial resistance mechanisms can be broadly classified into four categories: drug uptake limitation, drug target modification, drug inactivation through enzyme modification, and active drug efflux pumps. Even *H.pylori* possesses a diverse array of efflux pump types, as do the majority of bacteria. Bacterial efflux pumps can be grouped based on their structure and source of energy into five families: the ABC (ATP-binding cassette) family, the MATE (multidrug and toxic compound extrusion) family, the SMR (small multidrug resistance) family, the MFS (major facilitator superfamily), and the RND (resistance-nodulation-cell division) family [5]. The RND family is the most common, this family has three members: inner membrane efflux proteins (IEPs), periplasmic efflux proteins (PEPs), and outer membrane efflux proteins (OMEPs) [6]. The hefABC, hefDEF, and hefGHI super families of RND efflux systems were identified [7].

Post-therapy detection of efflux pump overexpression in mutant isolates provides confirmation of their roles in the development of drug resistance in pathogenic bacteria [8].

H.pylori Antimicrobial Resistance

Single-Drug Resistance Profiles and Bimolecular Mechanisms

Antimicrobial resistance is significantly higher in developing nations than in industrialized nations [9]. The World Health Organization (WHO) has released a list of the twelve most dangerous bacterial species to the general public as "priority pathogens," classifying them into three priority levels: crucial, elevated, and moderate [10]. The worldwide prevalence of *H.pylori* antibiotic resistance has escalated to concerning degrees, which has a substantial detrimental effect on the effectiveness of empirical treatments. The following antibiotics are used during infection.

Clarithromycin

The macrolide antibiotic clarithromycin (CLR) has bacteriostatic activity. *H.pylori* is effectively treated with clarithromycin owing to its high absorption in gastric mucus and stability in acidic environments [11]. By traversing the bacterial cell wall, it reversibly bonds to domain V of the 23S rRNA located on the 50S subunit of the ribosome. This interaction effectively obstructs the translocation of aminoacyl transfer RNA and the formation of polypeptides [12].

The resistance of *Helicobacter pylori* to clarithromycin is predominantly attributed to point mutations that occur in the V domain of 23S rRNA. These mutations result in a change in ribosome structure that inhibits the attachment of clarithromycin to 23S rRNA, consequently diminishing the efficiency of protein synthesis [13].

Metronidazole

Metronidazole (MET) is an antibiotic that has strong bactericidal activity. It is a member of the nitroimidazole family and is classified as a pro-drug, that becomes active when reduced under the influence of nitro reductase, nitroso derivatives, nitro anion radicals, and hydroxylamines are all products of its nitro group [14]. These byproducts have the potential to disrupt the bacterial DNA helix's structural integrity [15]. The production of nucleic acid is inhibited as a

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result of the interaction between metronidazole and the nitro reductase. It is possible that another nitro reductase produced by *H.pylori* is responsible for activating the biocidal effect of metronidazole [16]. The key mechanism that contributes to the development of metronidazole resistance is the inactivation of nitro reductases, which are responsible for the synthesis of antibacterial metabolites that destroy bacterial DNA [17]. Genomic rearrangements such as insertions, deletions, frameshift mutations, missense mutations, or premature truncations nearly usually cause this inactivation in the *rdx*A gene, which codes for nitro reductase [18]. Another factor that has been linked to *H.pylori* resistance to metronidazole is a point mutation in the flavinreductase A (*frx*A) gene. Metronidazole resistance is multifactorial and has not been definitively proven because it can develop in the absence of inactivation of NADPH nitroreductases *rdx*A and frxA. Furthermore, it has been found that *H.pylori* strains resistant to MTZ have increased expression of two efflux pump genes, *hp1165* and *hef*A, suggesting a connection between the RND family efflux pump system and MTZ resistance which explains the resistance observed in clinical isolates with intact *rdx*A and *frx*A [19].

Levofloxacin

The third-generation fluoroquinolone levofloxacin (LVX) is an antibiotic. Because it blocks DNA gyrase, levofloxacin prevents the replication of chromosomes, making it a bactericide. Point mutations in the *gyr*A and *gyr*B loci, which encode DNA gyrase subunits, have been linked to resistance to levofloxacin in *H.pylori*, at the quinolone-resistance determining region (QRDR) of the *gyr*A gene, mutations at codons 87 and 91 are both the most common and well-studied (20).

Tetracycline

Bacteriostatic tetracycline (TET) reversibly binds to the 30S subunit of *H.pylori* ribosomes that contain 16S rRNA in order to inhibit protein synthesis [21]. Tetracycline-resistant *H.pylori* is unusual,between 2011 and 2021, resistance to TET- was observed in only 0.87 percent of *H.pylori* strains in the United States [22]. Resistance is caused by mutations in the binding site of the medication [23]. The fact that some *H.pylori* isolates are resistant to treatment despite lacking a mutation in the 16*SrRNA* gene is indicative of a multifactorial resistance involving multiple mechanisms. These include a lowered susceptibility to antibiotics due to a tighter membrane, altered ribosomal binding, drug breakdown by enzyme, and an active efflux pump [13].

Amoxicillin

Antibiotic β-lactam amoxicillin (AMX) possesses bactericidal characteristics. Amoxicillin inhibits the synthesis of peptidoglycan, thereby preventing the development of bacterial cell walls. The majority of *H.pylori* resistance to amoxicillin results from mutations in the penicillin-binding proteins PBP1, PBP2, and PBP3[24]. PBPs are a class of proteins that have an affinity for b-lactams, which helps in the creation of the peptidoglycan layer of bacterial cell walls as well as in its maintenance. The most crucial strategy for resistance to amoxicillin has been identified as mutations in PBP1A that reduce its affinity for the drug [25]. PBP1 is a PBP with transglycosylase and transpeptidase activity

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and a high molecular weight, unlike the others [26]. AMX resistance is also contributed to by the creation of beta-lactamase enzyme. The presence of beta-lactamase activity was detected in a highly resistant *H.pylori* strain [27].

Multidrug Resistance Mechanisms and Profiles

Multidrug-resistant (MDR) *Helicobacter pylori* isolates are those that exhibit resistance to two or more classes of antibiotics [28]. MDR is correlated with antibiotic misuse, high antibiotic consumption, treatment failures, and bacterial factors including mutations, efflux pumps, and biofilms [29]. A microorganism's cell membrane is home to a protein-based carrier system called an efflux pump. Typically, they have correlations with multiple drug resistance due to their ability to extrude several kinds of antibiotics in bacteria [30]. Although they are typically encoded by genes located on chromosomes, transposable elements can play a role in their expression in certain bacteria. The regulation of efflux pump gene expression is accomplished through complex and multifaceted mechanisms. These regulators are situated upstream of the operon that encodes these genes in the form of repressors [31] .

Five types of bacterial efflux pumps exist. ATP-binding cassette (ABC) hydrolyzes ATP to generate energy. The proton motive force powers the multidrug and toxin extrusion (MATE) family, which includes the Na+/H+ drug antiport systems, the major facilitator superfamily (MFS), the small multidrug resistance (SMR) family, the resistance-nodulation-cell division (RND) superfamily, and the proteobacterial antimicrobial compound efflux (PACE) family [32]. RND family transporters, which play an essential part in the efflux pump system, are responsible for the efflux of a number of antibiotics, including CLR, AMX, and TET. The RND family features a combined apparatus that is composed of three parts [33]. It consists of a periplasmic membrane-fusion (adaptor) protein, an outer membrane protein channel, and a cytoplasmic-bound trimer membrane pumas, as illustrated in Figure (1). Their energy source is the proton motive force, which they actively use to extrude substrates [34].

A multidrug-resistant strain of *H.pylori* develops when the *hef*A gene is overexpressed, which promotes antibiotic efflux via the efflux pump system. In addition, the variation in MATE family member hp1184 and hp1181 expression levels between MDR and sensitive strains indicates that active efflux may be associated with additional efflux pump families [35].There are three different RND families: hefABC, hefDEF, and hefGHI. The efflux pump's outer membrane protein is encoded by *Tol*C homologs *hef*A, *hef*D, and *hef*G [5].

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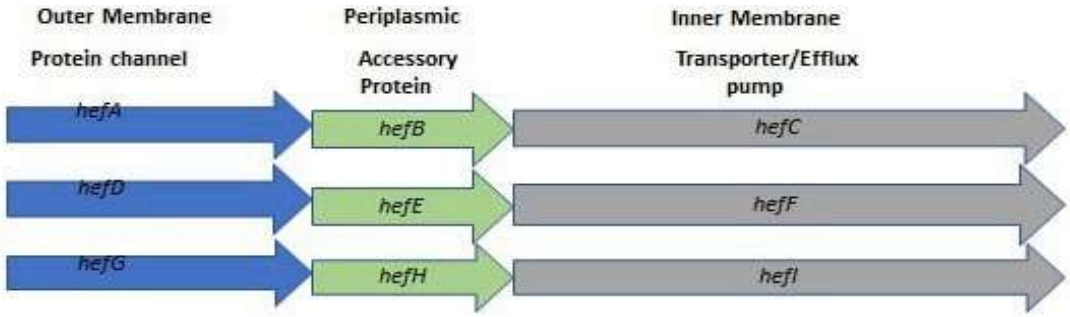

Figure (1): Efflux Pump Operon.

Multi-drug resistance transporters (MDTs) are comprised of certain RND efflux pumps along with other families. Facilitating the movement of molecules from the cytoplasm to the periplasm and outer membrane, these transporters are responsible for extracellular efflux [36]. Certain transporters establish a strong association between the outer membrane protein TolC and the RND subunits AcrB, AcrD, AcrF, and MFS (EmrB) via periplasmic binders AcrA, AcrE, and EmrA [37] as shown in Figure(2). The development of multidrug resistance (MDR) in planktonic cells isattributed to MDTs [38].

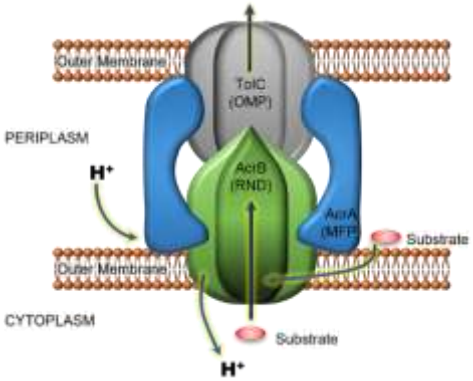

Figure (2): *TOl*C gene structure.

An additional crucial mechanism of MDR is *H.pylori* biofilm formation [39]. Biofilms consist of sessile bacteria that produce a protective matrix, forming complex microbial communities [40]. Attached to the cell surface, this biofilm made *H.pylori* 100-1,000 times more drug-resistant than in the planktonic state [41].

Management of *H.pylori* Infections

The treatment of *Helicobacter pylori* infection faces significant obstacles, Since antibiotic susceptibility testing is not practical, empirical therapy selection is utilized [42]. Hence, an escalation in antibiotic resistance may potentially disrupt the abundance and variety of gastrointestinal microbiota [43]. Combination therapy involving multiple antibiotics is advised due to the ease with which *H.pylori* develops resistance to singular antibiotics. The selection of a first-line treatment regimen is influenced by a number of variables, involving local antibiotic resistance prevalence and patient characteristics like

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age, comorbidities, and medication sensitivities [44]. Bismuth, a proton pump inhibitor, tetracycline, and metronidazole make up the bismuth quadruple treatment, was found to be the best effective treatment after being subjected to a network meta-analysis of numerous first-line treatment regimens. However, in comparison to triple therapy, this treatment has a greater risk of side effects and is more complicated to administer [45].

Conclusions

Clinical eradication therapy has encountered numerous obstacles due to the escalating rates of *H.pylori* resistance in recent decades. *H.pylori* resistance is associated with bacterial factors including biofilms, efflux pumps, and mutations. Mutations in genes associated with nucleic acid synthesis, rRNA coding, and cell wall synthesis are key methods for *H.pylori* in preventing bactericidal effects. Biofilm generation and the efflux pump mechanism both play a role in the emergence of multidrug-resistant bacteria. Given the rising resistance rate of *H.pylori* to conventional antibiotics. Since antibiotic susceptibility testing is not feasible, therapy selection is empirical. Selecting and monitoring medications is crucial for effective clinical eradication treatment. The considerable decline in the effectiveness of *H.pylori* treatments may lead to clinical complications including gastric cancer and peptic ulcers, as infections persist longer.

Recommendations

Screening as well as treatment of *H.pylori* to reducing consequences and antibiotic resistance.

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Ethical clearance: Receiving ethical approval from the Mustansiriyah University /College of Science's research tasks and ethics committee on January 1, 2022 (Ref.: BCSMU/1221/0004 M). This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2023AYA810).

Conflict of interest: Nil

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آليات مقاومة الملوية البوابية للمضادات الحيوية

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الملخص

خلفية الدراسة: تعد الملوية البوابية العدوى البكتيرية الأكثر شيوعا في العالم، وهي منتشرة فيما يقرب من نصف سكان العالم. تشكل الملوية البوابية خطراً صحياً كبيراً لامتلاكها عوامل ضراوة مميزة ومقاومة عالية للمضادات الحيوية. المقاومة للأدوية المتعددة ومقاومة الدواء الفردي هما نوعان مميزان لمقاومة الملوية البوابية. تؤثر طفرات الكروموسوم على نشاط المضادات الحيوية عبر المسارات المستهدفة وكذلك امتلاكها آليات بيولوجية كالامتصاص الغير كافي للدواء، نشاط مضخات الدفق، تطور الأغشية الحيوية، وتحولها الى الشكل الكروي تكتسب من خلالها المقاومة للأدوية. يمكن اكتشاف الإفراط في التعبير الجيني لمضخات الدفق في العزلات الطافرة بسهولة ما بعد العلاج.

اهداف الدراسة: لتوصيف الآليات البيولوجية والجزيئية التي تساهم في تطوير مقاومة المضادات الحيوية في الملوية البوابية.

الاستنتاجات: إن المعدل المقلق لبكتيريا الملوية البوابية المقاومة للأدوية آخذ في الارتفاع. لقد زادت المقاومة الأولية والمكتسبة لكلاريثروميسين وميترونيدازول على مستوى العالم .ترتبط العوامل البكتيرية بما في ذلك الأغشية الحيوية ومضخات الدفق والآلية الجزيئية بمقاومة بكتيريا الملوية البوابية. من المهم الاستمرار في مراقبة تطور المقاومة لعزلات الملوية البوابية.

الكلمات المفتاحية: الملوية البوابية، مقاومة المضادات الحيوية، مضخة التدفق، الأغشية الحيوية، مقاومة المضادات الحيوية.

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