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REVIEW ARTICLE OPEN ACCESS

Antibiotic Resistance in *Proteus mirabilis*: Mechanism, Status, and Public Health Significance

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Abstract

***Proteus mirabilis* is a specific opportunistic pathogen of many infections including urinary tract infections (UTIs). Risk factors are linked with the acquisition of multidrug-resistant (MDR) to 3 or more classes of antimicrobials) strains. The resistance in extended-spectrum alpha-lactamase is rare, but the rising resistance in extended-spectrum beta-lactamase (ESBL) producing strains is a matter of concern. β-lactamases and antibiotic modifying enzymes mainly constitute the ESBLs resistance mechanism by hydrolyzing the antibiotics. Mutation or Porin loss could lead to the reduced permeability of antibiotics, enhanced efflux pump activity hindering the antibiotic access to the target site, antibiotic failure to bind at the target site because of the target modification, and lipopolysaccharide mutation causing the resistance against polymyxin antibiotics. This review aimed to explore various antimicrobial resistance mechanisms in *Proteus mirabilis* and their impact on public health status.**

Keywords: *Proteus mirabilis*, Antibiotic Resistance, Beta-lactams, Cephalosporins, Fluoroquinolones, Tetracyclines, Public Health

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INTRODUCTION

Proteus mirabilis, belonging to the class Gammaproteobacteria and family *Enterobacteriaceae*, is a well-known rod-shaped Gram-negative bacteria that swarm across the agar plates to form characteristic bullseye-shaped motility.[1] *P. mirabilis* strains representing 18 different species have been isolated from various geographical locations.[2] *P. mirabilis* is found in multiple environments such as sewage, soil, water, and especially in the gastrointestinal tract of animals and humans.[3] The patients having long-term indwelling catheters or complicated UTIs also suffer from the infection of this opportunistic pathogen.[4] Several human infections are associated with this bacterium such as infections of the gastrointestinal tract, wounds, eyes, and UTIs especially catheter-associated urinary tract infections (CAUTI).[5] Renal damage and the formation of kidney and bladder stones (urolithiasis) further complicate the *P. mirabilis* related UTIs and CAUTIs.[6] In the urinary tract, *P. mirabilis* mainly forms two types of crystals including apatite and struvite ($CaPO_4$ and $MgNH_3PO_4$), which prevent urine flow.[7] The symptoms of *P. mirabilis* infections such as bacteriuria, acute pyelonephritis, catheter occlusion, and fever could further complicate into bacteremia and sepsis.[8] CAUTI is quite common in nursing homes whereas bacteremia mostly occurs following CAUTI or UTI. *P. mirabilis* associated sepsis and bacteremia comparatively lead to a higher mortality rate than other infections.[9,10]

Antibiotics resistance exhibited in 48% *P. mirabilis* strains complicates the treatment of infections.[11] The resistant strains are rising sharply and current therapies are becoming unable to cope with the situation. This scenario demands the urgent development of new antibiotic targets. Uropathogenic *P. mirabilis* might also be resistant to extended-spectrum beta-lactams, cephalosporins, fluoroquinolones, and aminoglycosides.[11] *P. mirabilis* acquire genes encoding antimicrobial resistance via transferable plasmids, insertion sequences, transposons and integrons. Of these mobile genetic materials, integrons, which are not considered as transferable element, but are usually located on mobile plasmids, and play an important role in facilitating the horizontal gene transfer process of cassettes carrying resistance genes, i.e., integrons help incorporate gene cassettes encoding resistance to β-lactams, aminoglycoside and also plasmid-mediates quinolones resistance genes into recipient *P. mirabilis* cells (Figure 1).[11] Integrons contain an integrase gene, *attI* (recombination site), and a promoter PC for the captured genes' transcription.[12] Integrons link with the mobile DNA elements (plasmids and transposons) to spread resistance determinants. The integrase gene sequence revealed five classes of integrons connected with resistance determinants.[13] Integrons belonging to class 1 are mainly associated with MDR.[14] Several antibiotic resistance determinants are present in *Enterobacteriaceae* strains, which are mediated by the integrons. Plasmid-mediated beta-lactamases gene coding and PMQR (quinolone resistance determinants) are complex integrons, which include ISCR1 and resistance genes through the duplication of the 3′ conserved region in addition to the variable part between 5′ and 3′ covered regions.[15]

Antibiotic resistance mechanisms in *Proteus mirabilis*

Resistance to fluoroquinolones

Fluoroquinolones are commonly used antibiotics in Western Europe, North America, and Japan to treat a broad range of infections including UTIs.[16] European Antimicrobial Resistance Monitoring Network has reported significantly increased resistance to fluoroquinolones in Europe since 2001.[17] Different fluoroquinolones resistance mechanisms have been identified including target enzyme modification in *parC* and *parE* encoded topoisomerase IV, *gyrA* and *gyrB* encoded DNA gyrase, and changes in the outer membrane to reduce drug accumulation through efflux pumps.[18] Gram-negative organisms primarily target DNA gyrase whereas Gram-positive organisms target topoisomerase IV.[19] *gyrA* is the essential target of fluoroquinolones in several *Enterobacteriaceae* species and its mutation is associated with fluoroquinolones resistance.[20] Further mutations in DNA gyrase and topoisomerase IV cause higher resistance to fluoroquinolones.[21] DNA sequence analyses have revealed the genetic characterization of mutations in clinical isolates.

Quinolone resistance determining regions (QRDRs) have been reported to be extremely conserved.[20] QRDRs linked with *P. mirabilis* resistance to fluoroquinolones exhibit substitutions in *parC* (S80) and gyrA (S83) whereas *gyrB* (S464) mutation could result in further higher fluoroquinolones resistance.[22] QRDRs' role in *P. mirabilis* resistance to fluoroquinolones is not well understood, which requires more data to elaborate its resistance mechanism. Levofloxacin-resistant *P. mirabilis* has been studied to investigate the fluoroquinolone resistance mechanism. The results depicted that *parE* (D420) and *gyrA* (E87) mutations are crucial for a higher resistance in *P. mirabilis* clinical isolates, which links ParE QRDRs and resistance to fluoroquinolones.[18] Different spectroscopic techniques have been employed to identify new ciprofloxacin derivatives (hydroxamic acid, amide, and hydrazide) in addition to levofloxacin analogues. Some of these compounds exhibited

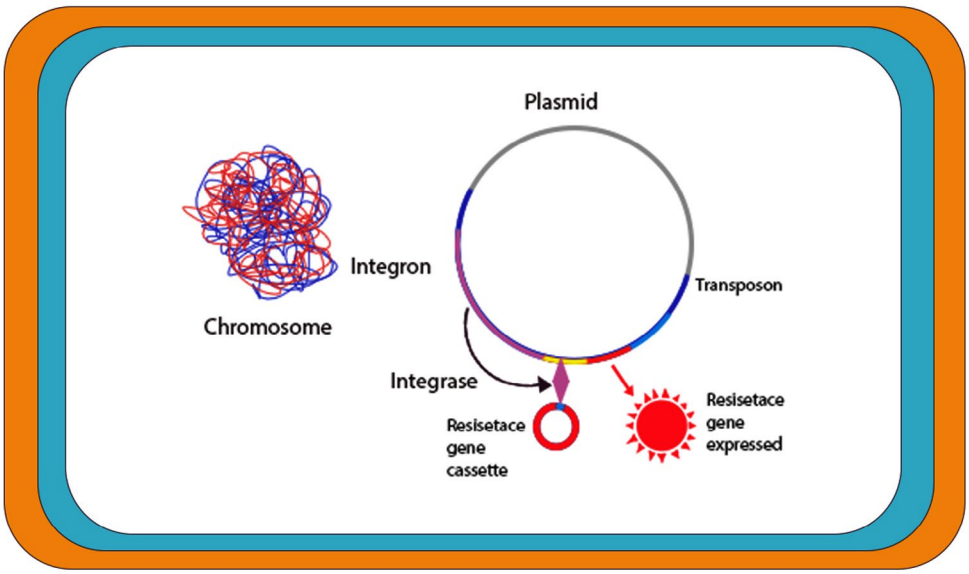

Figure 1. Schematic diagram illustrating the role of integron in drug resistance acquisition in *Proteus mirabilis*

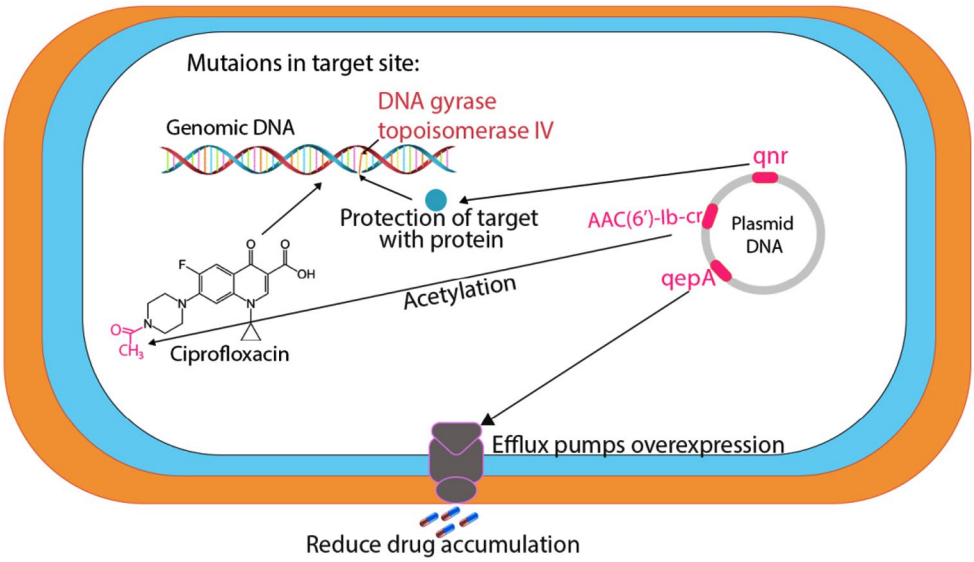

Figure 2. Schematic overview of resistance mechanisms to fluoroquinolones in *Proteus mirabilis*

significant efficacy against urease splitting *P. mirabilis*.[23] Similar to the *GyrA* gene, the role of the *ParC* gene in ciprofloxacin resistance is also important. A couple of mutations in *P. mirabilis GyrA* and *ParC* genes could cause resistance to ciprofloxacin. Moreover, the percentage of quinolones resistance should be considered while aiming for other medical options. Therefore, drug susceptibility testing should be conducted for all patients with comparable infections before starting a specific medicine.[24]

The mutations in target enzymes (*GyrB* (Ser-464) and *ParC* (Ser-80) codons) and *AcrAB* efflux pump were investigated in relation to *P. mirabilis* resistance against fluoroquinolones. However, any relationship between mutation numbers in *ParC, GyrA,* and *GyrB* genes and the degree of *P. mirabilis* resistance to fluoroquinolone was not observed. The role of efflux pumps in fluoroquinolones resistance has been estimated by measuring the minimum inhibitory concentrations (MICs) through an efflux pump inhibitor CCCP. The CCCP (12.5 mM) was integrated with Mueller Hinton agar. Fifty isolates with uninfluenced fluoroquinolones susceptibility in response to CCCP were selected from a total of 100 isolates and characterized in terms of MICs and genotype for Levofloxacin (Figure 2).[18]

Resistance to tetracyclines

Several Gram-positive and Gram-negative bacterial infections are treated with tetracycline antibiotics but high tetracycline resistance rates in *Enterobacteriaceae* have been reported.[25] Tetracycline resistance is presumed to be related to the efflux mechanism. The efflux resistance genes are often associated with the mobile elements such as the class A tetracycline resistance (tet) determinant that was the first to be identified from the RP1/Tn1721 system.[26] Tigecycline (9-t-butylglycylamido derivative of minocycline) belongs to the novel class of tetracyclines that is used to treat Gram-negative bacteria.[27] *Klebsiella pneumoniae* was the first tigecycline-resistant strain of *Enterobacteriaceae* with *rpsJ* mutation encoding Val57Leu on S10.[28] *Enterobacteriaceae*

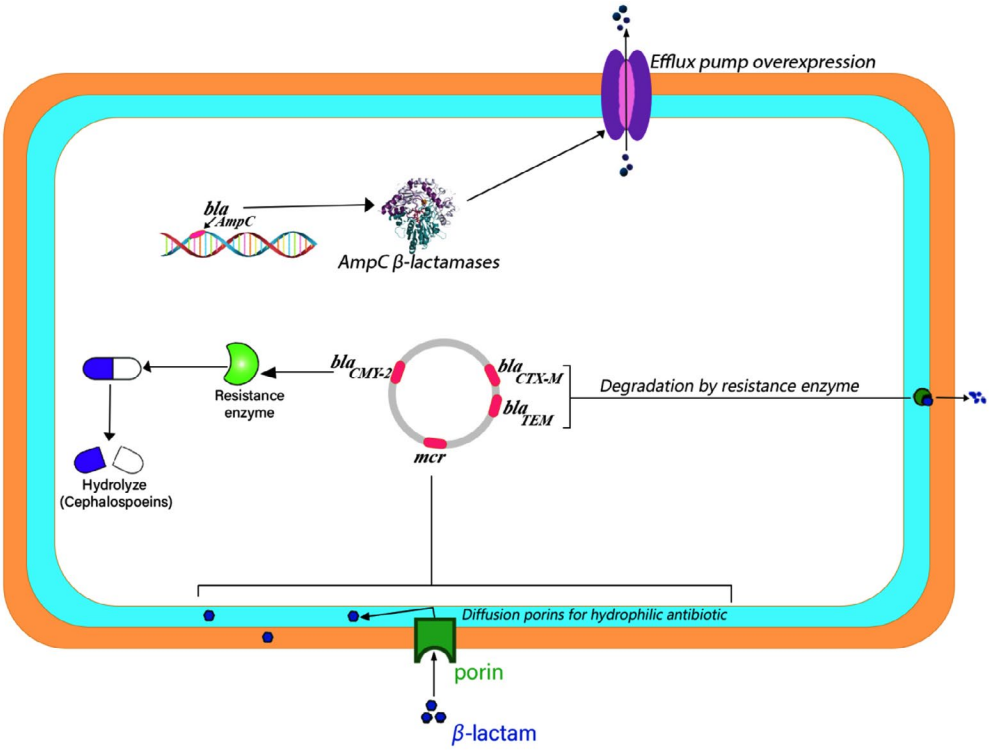

Figure 3. Illustrative diagram of resistance mechanisms to β-lactams and cephalosporins exhibited by *Proteus mirabilis*

tetracycline resistance is mostly considered to be linked with tet (A) to tet (E) gene determinants.[29] *P. mirabilis* possesses a natural resistance against tetracycline that could be the main reason for its rising tolerance.[30] The rise in acquired resistance of *Enterobacteriaceae* demands the development of new antibiotics to effectively treat bacterial infections.

AcrAB efflux pump, which is a member of the resistance-nodulation-division (RND) superfamily is found in *Enterobacteriaceae*. This efflux pump has been reported to be involved in *P. mirabilis* resistance to tigecycline.[31] AcrAB provides intrinsic resistance to several structurally diverse lipophilic compounds, antibiotics, dyes, and inclusive detergents.[32] *P. mirabilis* is a notable exemption to tigecycline activity, which normally exhibits 4 µg/ml MICs in tests. A typical clinical isolate was selected to identify the mechanism of decreased tigecycline sensitivity. Two independent transposon insertion mutants were isolated and inserted into the *P. mirabilis* chromosome. The results revealed a correlation between AcrRAB gene expression and observed MIC changes in various *P. mirabilis* strains. The classical tetracycline resistance determinants could not affect the tigecycline, however, AcrAB efflux pump identification in *P. mirabilis* explained its decreased susceptibility to tigecycline. Fortunately, the study did not report a direct threat of spreading tigecycline resistance.[33] Nontoxic carbon nanoparticles could inhibit Gram-negative bacterial growth when integrated with tetracycline. This combination has generated tenfold higher activities against tetracycline-resistant bacteria as compared to solely tetracycline. The tetracycline-conjugated carbon nanoparticles could inhibit the efflux mechanism of bacteria. Tetracycline is supposed to direct nanoparticles into efflux pumps to block and inhibit their normal functioning. Qin et al.[34] have conducted a study to acquire tigecycline, tetracycline, and colistin-resistant *P. mirabilis* for NDM-1 Plasmid and further characterized PM58 isolate. Molecular investigation elaborated that the PM58 chromosome contains a novel *Salmonella* genomic island 1 and conjugative NDM-1 plasmid.[34,35]

Resistance to β-lactams

Lactamase genes are absent on the *P. mirabilis* chromosome whereas β-lactamase production includes *AmpC* β-lactamases and broad-spectrum β-lactamases.[36] Gene cassette sequence analysis could not relate the resistance patterns and gene cassette content. The resistance patterns to beta-lactam antibiotics were more diverse than depicted by integrin-embedded cassettes. Gene screening revealed the presence

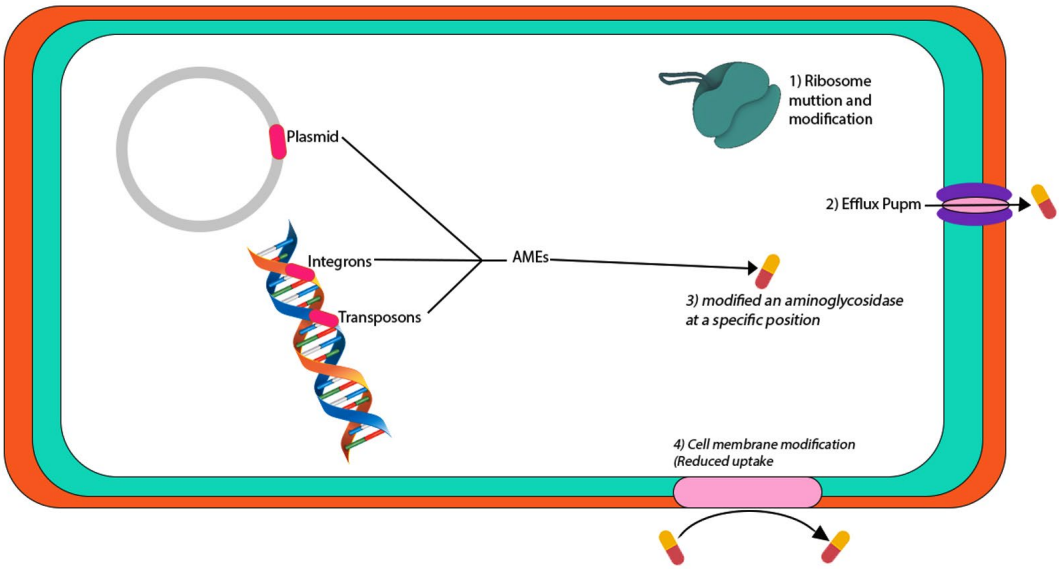

Figure 4. Schematic overview showing aminoglycosides resistance mechanisms in *Proteus mirabilis*

of bla_{TEM} genes in both genomes. bla_{TEM-2} encoding beta-lactamases are effective against early cephalosporins and penicillin. Thus, they could not be attributed to ESBL phenotype. Ye et al.[37] have reported the involvement of another enzyme in ESBL-positive strains. *P. mirabilis* is known to possess CMY-2-like *AmpC* β-lactamases encoding genes, which facilitate to resist against cephamycins and cephalosporins. bla_{CMY} sequence has been reported to conform with *P. mirabilis* bla_{CMY-15}.

Ahn et al.[38] have reported chromosome-borne genes coding for MY-15 in *P. mirabilis* strains in Poland. Colistin serves as a last-resort drug against MDR Gram-negative bacterial infections. *P. mirabilis* is naturally resistant to colistin due to the presence of the *mcr* genes, which are mediated by the plasmid. This bacterium can transmit these genes to other bacteria, which are susceptible to colistin.[39] ESBL enzyme production confirms the wide-spectrum β-lactam antibiotic resistance. However, the presence of these genes does not necessarily generate phenotypical aspects of ESBLs as reported in several studies.[40] Initially, the *CTX-M* gene appears in combination with the *TEM* gene but as the predominant gene spreads it replaces others. The selective pressure posed by the antibiotics misuse might provide a favorable environment for the diffusion of ESBLs among *Enterobacteriaceae* (Figure 3).[41]

Resistance to cephalosporins

Cephalosporins are widely prescribed to treat respiratory, abdominal, and urinary infections. Such broad-scale utilization leads to significant selection pressure on *Enterobacteriaceae* members for resistance. Cephalosporins resistance is either associated with the higher chromosomal '*AmpC*' b-lactamases production in Enterobacter spp. or transferable ESBLs.[42] During a study in China, 2288 clinical isolates (non-repetitive) were collected from five laboratories in four cities to establish cefoselis epidemiological cut-off values (ECOFFs). Disc diffusion and broth micro-dilution methods based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines were followed to determine MICs of Cefoselis and diameters of isolates inhibition zones. MIC ECOFFs were estimated through visual assessment and ECOF Finder software. Distributed cefoselis MICs ranged between 0.008 to >256 mg/L whereas MIC ECOFFs value was noted as 0.125 mg/L. *P. mirabilis* zone diameter ECOFF was observed as 26 mm.[43] bla_{CTX}, bla_{OXA-1}, *tetA*, bla_{CTX-M}, and *sul1* genes were encoded for cephalosporins-resistance.[44, 45]

P. mirabilis isolates exhibited significant resistance (57.1%) to Cephalosporins (ceftazidime and cefotaxime).[45] *P. mirabilis* strains are not frequently found in pneumonia patients but they can cause airborne acute infection of the lower airways (pneumonia) or infections that are transferred through the bloodstream from one body part to others.[46] Cefepime, an antimicrobial agent that is administered to treat pneumonia patients, was found to be the most effective among six antibiotics used against severe Gram-negative bacterial infections.[47] Several studies have confirmed the clinical efficacy of cefepime against drug-resistant organisms.[48] However, the efficacy of ceftazidime has reduced over the past decade because of the extraordinary rise in microbial resistance.[49] Cefotaxime is used against both types of bacteria (Gram-positive and Gram-negative) but *P. mirabilis* resistance to cefotaxime has been reported.[50] Cefuroxime was found to display better efficiency against rod-shaped Gram-negative bacteria than cephalosporins (first-generation).[51] have concluded that carbapenemase genes were not involved in the development of resistance in cephalosporin-resistant strains. The mutations in porin and protein of the outer membrane leading to low antibiotic permeability might have contributed to the resistance of cephalosporin-resistant strains.[52] ESBL confirmatory tests revealed that 15 out of 50 cephalosporin-resistant *Enterobacteriaceae* were ESBL negative depicting that these strains might have acquired cephalosporin resistance via other mechanisms.[53] The *fosA* gene mediated by plasmid could be transferred amidst *Enterobacteriaceae* species and *fosA3* has been reported in 90% of *E. coli* isolates, which produces ESBL to resist fosfomycin (FOM).[54,55] *parC, gyrA,* and *fosA3* mutations might induce resistance to quinolone and further lead to high cross-resistance against fosfomycin (FOM), levofloxacin (LVX), and cephalosporin in UTI-causing bacteria. Ishii et al.[56] have reported considerable *gyrA* and *parC* mutations based cross

resistance of UTI causing bacteria to levofloxacin whereas the presence of *fosA3* was linked to fosfomycin resistance. (Figure 3).[56]

Resistance to aminoglycosides

Broad-spectrum aminoglycosides antibiotics are primarily produced through Actinomyces species to treat Gram-negative and Gram-positive bacteria.[57] Aminoglycosides have served as successful antibiotics but the resistance and toxicity aspects have hindered their application.[58] However, they can still be efficiently used to counter MDR bacterial species.[57] Mechanisms of aminoglycoside resistance and aminoglycoside-modifying enzymes (AMEs) have been detected frequently in bacteria.[59] AMEs initiate resistance by changing aminoglycoside molecules at specific positions. Based on the modifications, these enzymes are known as aminoglycoside acetyltransferases (AACs), phosphotransferases (APHs), nucleotidyltransferases, and adenyltransferases (ANTs).[60] The mobile agents such as plasmids, integrons, or transposons carry the AME coding genes, which often integrate with other resistance mechanisms.[57] Recently, 16S ribosomal RNA (rRNA) methyltransferases have been used to code the aminoglycoside-resistance mechanism as these enzymes contain an aminoglycoside linking site in the ribosome to produce higher resistance against all clinically available aminoglycosides.[61] Sometimes, the isolates already containing β-lactamases or Metallo-β-Lactamase (MBLs) carry 16S rRNA methyltransferases encoding genes.[62] Alteration of membrane protein and ribosome, and raised efflux could be the other mechanisms of aminoglycoside resistance. However, these mechanisms are less spread as compared to AMEs.[63] Plazomicin aminoglycoside (semi-synthetic) is obtained from sisomicin. The modifications in the plazomicin molecule structure make it resistant to AMEs-based alterations.[64]

Carbapenems are highly effective antimicrobial agents to cure hospital-acquired infections (HAIs). However, the development of carbapenemases (GES, VIM, KPC, IMP, OXA-48, and NDM) based resistance has limited their utility.[65] Carbapenemases encoding genes are commonly found in plasmids and they might also contain AMEs encoding genes.[66] AMEs-based enzymatic inefficiency is common aminoglycosides resistance mechanism followed by 16S rRNA methylation that also imparts significantly higher resistance against gentamicin, tobramycin, and amikacin.[67] The studies have reported multiple isolates harbouring bla_{KPC-2}, bla_{NDM-1}, and AMEs encoding genes. The literature depicts the *Klebesiella pneumoniae* carbapenemase (KPC) insistence over the years that led to the emergence of a new carbapenemase known as NDM. The relationship of bla_{KPc-2} and bla_{NDM-1} genes and their association with AME genes in *P. mirabilis* isolates has been described (Figure 4). This association demonstrates a fast *P. mirabilis* evolution to obtain and preserve different genes, which urgently require further in-depth elaboration.[68]

Status of *Proteus mirabilis* resistance to various antimicrobial agents

The first report of ESBL-based resistance in *Proteus* species emerged in 1987.[69] *P. mirabilis* isolates capable of producing ESBL are now more frequently detected in clinical settings. A study in France (1988 to 1990) revealed the presence of only 0.8% ESBL producing *P. mirabilis* strains, which has increased up to 6.9% and 9.5% in France and the USA, respectively.[70-72] The isolation of ESBL-producing *P. mirabilis* strains reached 8.8% during 1997–1999.[73] An Italian survey in 1999 ranked *P. mirabilis* as the second-highest ESBL producer in *Enterobacteriaceae*.[74] In France, urine samples of 3340 patients were found positive for *P. mirabilis* from 1997 to 2002 whereas 45 (1.3%) patients were infected with extended-spectrum b-lactamases producing *P. mirabilis*.[75] In Japan, 45.6% of the *P. mirabilis* strains were found to produce ESBL during 2009-2010.[76] European Committee on Antimicrobial Susceptibility Testing revealed that74% of isolates were resistant to penicillin in 2010 whereas 1.23% of *P. mirabilis* strains were resistant to third-generation cephalosporins.[77,78] In 2019, 8.4% of *P. mirabilis* isolates were noted to be resistant to various antibiotics such as ciprofloxacin, amoxicillin, gentamicin, amoxicillin/clavulanic acid, and cefotaxime. 28.6% of these isolates possessed ESBL genotype ($bla_{CTX-M-2}$) whereas 71.4% had AmpC/ESBL genotype (bla_{CMY-2}/bla_{TEM-1}).[79] Recently (i.e. 2020), 37% of strains produced ESBLs and all ESBLs-producing isolates contained bla_{TEM}. These

isolates were susceptible to cefotaxime/clavulanic, cefoxitin, and imipenem.[80]

Levofloxacine (LVX) resistance average has gradually increased between 2000 and 2005 and a continuous high prevalence (17.5%) has been reported in Europe and Japan since 2004.[81,82] Similarly, a high spreading rate (37.0%) of cefotaxime (CTX)-resistant *P. mirabilis* strain was also noted in 2004. The rise in CTX-resistant *P. mirabilis* up to 45.6% is comparable to that reported in Japan between 2009 and 2010,[76] whereas the spread of FQ-resistant *P. mirabilis* strain increased to 17.5% in Japan.[18] In 2014, the ciprofloxacin resistance in uncomplicated UTIs in some European countries was reported as Germany (20.3%), France (4.8%), Sweden (7.3%), Spain (30.8%), and the UK (15.3%).[83] *P. mirabilis* resistance rate against a novel antimicrobial agent glycylcycline reached up to 13% in Germany in 2016[47,51] whereas *P. mirabilis* resistance to imipenem (3.6%) and meropenem (4%) has also been reported in Iran.[84] Similarly, decreased efficacy of imipenem (61.5%, 90.9) and ceftazidime-avibactam (72.7%, 93.8%) has been noticed in Canada for ESBL as compared to non-ESBL-producing *Enterobacteriaceae* in 2015. The situation has led to the lower response of complicated UTI patients to imipenem and ceftazidime-avibactam.[85]

CONCLUSION

Problems and Future Concerns

The ability of *Proteus mirabilis* to colonize and form crystalline multidrug-resistant (MDR) biofilms is a major reason for recurrent CAUTIs.[86] Multidrug resistance (MDR) in the clinical isolates *P. mirabilis* is leading to public health anxiety and serious wildlife implications. Therefore, wildlife's role in spreading resistance to antimicrobials has become a main topic of interest for researchers.[87] Several studies have been conducted to understand the *P. mirabilis* ability to produce swarm cells but it remains unclarified. Peng et al.[88] have reported that the swarming migration of the *P. mirabilis* strain is a rare feature.[88] A recent study has revealed the appearance of infectious diseases and the mcr-1gene (colistin-resistant) in MDR *Enterobacteriaceae* in the Syrian refugee camps' sewage water.[89] These findings further elevate concerns about the health and sanitary conditions in Syrian camps. Similarly, mcr-1 gene has been detected in *P. mirabilis* samples collected from sewer and domestic waters of Lebanon's war refugee camps. These results are alarming as *P. mirabilis* association with healthcare and community infections has already been established. Furthermore, the mcr gene encodes colistin resistance that serves as a last-resort antibiotic to treat complex Gram-negative bacterial infections.[39]

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

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