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Antibiotic Resistance in *Pseudomonas aeruginosa* in Iraq: A Narrative Review

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Abstract

***Pseudomonas aeruginosa*, a Gram-negative bacterium, causes a range of infections, including those affecting the skin and soft tissues, pneumonia, and sepsis. Its significance lies in its capacity to develop resistance to numerous antibiotic classes. In Iraq, infections caused by Pseudomonas are prevalent, especially within healthcare settings. Studies indicate a concerning level of antibiotic resistance in this microorganism. Information regarding the genetic basis of this resistance is limited in Iraq, with existing research typically involving small sample sizes. The growing resistance to β-lactams in Iraq is a serious concern, especially the extended-spectrum β-lactamases (ESBLs). Metallo-β-lactamases (MBLs) such as VIM and NDM are causing a rise in the resistance to carbapenems. The limited data about the resistance patterns to quinolones and aminoglycosides is another barrier. The high prevalence of *Pseudomonas aeruginosa* combined with limited data on its resistance pathways in Iraq highlights the need for continued surveillance, stronger infection control measures, and the development of more targeted treatment options to address this challenging pathogen.**

***Keywords*:** *Antibiotic resistance, Pseudomonas aeruginosa, Sensitivity, ESBL, MBL, Iraq.*

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I. INTRODUCTION

Pseudomonas aeruginosa (*P. aeruginosa*) is a Gram-negative bacterium that can cause a wide range of infections, such as respiratory, urinary, and wound infections (Qin *et al.*, 2022). It is recognized by The World Health Organization (WHO) as a significant public health threat due to its high resistance levels (Naghavi *et al.*, 2024; Pang *et al.*, 2019). Such a microorganism poses a particular risk for patients with immunocompromised status and hospitalized patients (Qin *et al.*, 2022). *P. aeruginosa* is responsible for about 10% of hospital-acquired infections in the United States (Reynolds and Kollef, 2021). Such an infection is associated with deleterious outcomes and may increase the mortality rates because the bacteria tolerate a wide range of antibiotics, including β-lactams, quinolones, and aminoglycosides. (Elfadadny *et al.*, 2024). Besides, hospital-acquired infection with *P. aeruginosa* may result in longer hospital stays and higher costs (Qin *et al.*, 2022). On the other hand, this bacterium can cause a range of community-acquired infections such as otitis externa, skin and soft tissue infections, and urinary tract infections (Pérez-Crespo *et al.*, 2022). It is important to mention that the resistance pattern of *P. aeruginosa* varies from one country to another and from one region to another within the same country (Alatoom *et al.*, 2024). In the post-COVID-19 era, more attention should be paid to the resistance pattern of microorganisms, particularly those with known high resistance rates, such as *P. aeruginosa* (Hussein, 2022; Hussein *et al.*, 2020). Antibiotic misuse and resistance are serious problems in Iraq. A recent review of literature documents high resistance rates in most of the studies, with most hospitalized patients receiving antibiotics irrationally, while culture and sensitivity tests were rarely requested (Al-Jumaili and Ahmed, 2024). The global rise of antibiotic resistance rates combined with

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insufficient data about the resistance patterns and genetic makeup of such resistance in Iraq prevents a targeted approach to tackle this problem (Ali and Assafi, 2024; Assafi *et al.*, 2015; Hussein *et al.*, 2019; Mohammed *et al.*, 2020; Naqid *et al.*, 2020c). This narrative review aimed to assess and explore the available data about the resistance patterns of *P. aeruginosa* in Iraq and the genetic makeup of the resistance.

II. Methods

We aimed to conduct a review about *P. aeruginosa* focusing on antibiotic resistance, sensitivity patterns, and relevant genetic factors. We searched the literature using specific keywords, namely "*Pseudomonas aeruginosa*," "antibiotic resistance," "sensitivity," "Iraq," and "genes." Such terms were used to ensure a focus on relevant studies addressing antibiotic resistance mechanisms and genes specific to *P. aeruginosa* isolates found in Iraq. We used two primary databases: Google Scholar and PubMed. Our search was limited to articles published in English, and studies focused on *P. aeruginosa* in Iraq were included.

After the search was conducted, initially, the titles and abstracts of retrieved articles were assessed for relevance. Such articles were then reviewed to evaluate their alignment with the scope of this review. Non-relevant studies, review articles without primary data, other species of Pseudomonas, and papers addressing topics outside the scope of P. aeruginosa resistance in Iraq were excluded.

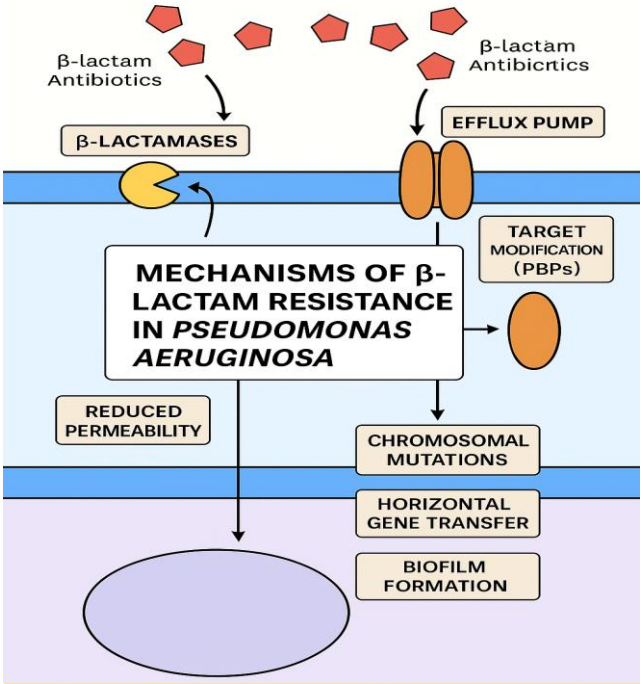

Figure 1. Mechanisms of β-lactam resistance in *P. aeruginosa.*

In such an approach, a curated selection of articles was obtained, providing a good basis for a comprehensive review of antibiotic resistance trends in *P. aeruginosa* specific to the region of Iraq.

III. Beta-Lactam Resistance

P. aeruginosa has developed several strategies to survive against β-lactam antibiotics. These mechanisms are illustrated in Figure 1. Different types enzymes are produced from different gene families and we will discuss some of them in this review.

A. Cefotaximase-Munich (CTX-M) genes

This is a collection of genes that efficiently hydrolyze cefotaxime, leading to the designation Cefotaximase (CTX), with M representing Munich, the initial location where this gene was identified (Zhao and Hu, 2013). A majority of these genes do not effectively hydrolyze ceftazidime (Zhao and and Hu, 2013). A study from Iran found that 23.95% of the 96 clinical isolates of *P. aeruginosa* had *CTX-M* gene (Bahrami *et al.*, 2018). Another Iranian study (Sales *et al.*, 2017) reported similar findings, while research in China and Saudi Arabia identified the *CTX-M* gene in 14.3% (Chen *et al.*, 2015) and 10.7% (Ahmed *et al.*, 2015) of isolates, respectively. Information on this gene group is limited in Iraq. A study carried out in Iraq's Basrah City discovered that 18.94% of 81 clinical samples contained the *CTX-M* gene (Alkhulaifi and Khairallah, 2023).

B. Temoniera (TEM) gene

The *Temoniera* (*TEM*) gene is the beta-lactamase most commonly expressed by Gram-negative species that confers ampicillin and penicillin resistance. Its name comes from the patient in whom the bacteria were first discovered in Greece (Rawat and Nair, 2010). A cross-sectional study in Sudan found that 44.2% of the isolates were expressing the *TEM* gene (Abdelrahman *et al.*, 2021). In Iran, 13.9% of the analyzed isolates exhibited this gene (Bahrami*, et al.*, 2018). In burn patients, the sole research performed in Iraq indicated that 66.7% of the isolates had the *TEM* gene (Aljanabi *et al.*, 2018). The Iraqi sample's high gene prevalence might be attributed to the study's sampling methods and small sample size.

C. The sulhydryl variable (SHV) gene

Sulfhydryl variable (*SHV*) gene was named because of its inhibition by p-chloromercuribenzoate varied depending on the substrate used in the assay. Nonetheless, subsequent research employing purified enzymes did not reproduce these results (Paterson and Bonomo, 2005). Numerous papers have documented the worldwide prevalence of this enzyme in *P. aeruginosa*-infected patients. Bokaeian *et al.* discovered *SHV* in 6.6% of the isolates. Furthermore, Imani Foolad *et al.* discovered *SHV* in 37.5% of isolates, whereas Alam *et al.* identified it in 52.4% of isolates. In their isolates, Dong *et al.* found no *SHV* (Bokaeian *et al.*, 2015; Dong *et al.*, 2008; Alam *et al.*, 2018; Imani Foolad et al., 2010). Research carried out in Turkey discovered that 10.57% of 123 *P. aeruginosa* isolates possessed the *SHV* gene (Bahmani and

Ramazanzadeh, 2013). Once more, information regarding this gene is limited in Iraq. One study conducted on burn patients in Duhok city, Iraq, found that 11.1% of the isolates had the *SHV* gene (Polse *et al.*, 2023).

D. Oxacillinases (OXA)

Oxacillinases (*OXA*) are beta-lactamase enzymes that are capable of breaking down oxacillin and a range of other beta-lactams including penicillins, cephalosporins, and carbapenems. Several types of these enzymes are present in Pseudomonas species, including *OXA-10* and *OXA-50*. Reports of *OXA* in *P. aeruginosa* have emerged globally, with a distinct geographic distribution pattern; for example, *OXA-10* is common in Iran and Turkey (Aghazadeh *et al.*, 2016). A study done in Erbil, Northern Iraq, discovered that 38.2% of the 89 clinical isolates tested positive for the *OXA-10* gene (Ganjo and Mansoor, 2020). A separate study conducted in Duhok, Iraq, detected *blaOXA-10* in 59.26% of the tested isolates (Polse *et al.*, 2023). Comparable results were found in an Iranian study revealing 37.3% of ESBL producers had *blaOXA-10* gene (Amirkamali *et al.*, 2017).

E. Vietnamese extended-spectrum β-lactamase (VEB)

This is an enzyme produced by *P. aeruginosa* that confers resistance against a broad spectrum of beta-lactam antibiotics covering penicillins, cephalosporins, and aztreonam. It was initially discovered in Vietnam. Later research detected *VEB*-producing bacteria in different regions of Asia and subsequently in Europe, Middle East, and, North and South America (Poirel *et al.*, 2008). Nonetheless, the occurrence differs greatly between and even within countries *(Poirel et al*., 2008).

An Iranian study isolated 59 samples of *P. aeruginosa* that are produce ESBL and found that13.3% of them exhibited *VEB* gene (Amirkamali *et al.*, 2017). Moreover, in another Iranian study, 31.34% of the 148 isolates were *VEB* producers (Mirsalehian *et al.*, 2010), whereas research in Qatar revealed that 50% of *P. aeruginosa* isolates had *VEB* genes (Sid Ahmed *et al.*, 2020). In Iraq, a research performed in Erbil found 30% of the isolates expressed the *VEB* gene (van Burgh *et al.*, 2018). Another research in central Iraq showed that 4.4% of the isolates tested expressed *VEB* gene (Al-jumaily and Turkie, 2018) (Table 1).

F. Pseudomonas extended resistance (PER-1) enzyme

Pseudomonas extended resistance (*PER-1*) enzyme has the ability to break down a broad spectrum of beta-lactam antibiotics, such as penicillins, cephalosporins, and monobactams (Danel *et al.*, 1995). An Iranian study investigating 56 strains of *P. aeruginosa*, 27.5% of them contained *PER-1* gene (Akhi *et al.*, 2012). Comparable findings in a research implemented in Saudi Arabia, where 22.4% of the 28 isolates expressed *PER-1* gene (Ahmed*, et al.*, 2015). A study conducted in Basarah city, Southern Iraq, on samples from various clinical specimens, found the rate of *PER-1* is 4.21% of the 95 resistant strains isolated (Alkhulaifi and Khairallah, 2023). On the other hand, a study conducted on 71 clinical isolates in Duhok, Northern Iraq found that 44.44% were *BlaPER* producers (Polse*, et al.*, 2023) (Table1). The huge difference in the rates of *PER-1* in Iraq might be attributed to reginal difference, sample size and study design.

G. Ampicillin chromosomal (AMPC) genes

AmpC β-lactamase have the ability to hydrolyze cephalosporins and β-lactamases inhibitors, which differentiates it from ESBL (Torrens *et al.*, 2019; Zhao and Hu, 2010). *AmpC* can be induced when the bacteria are exposed to specific β-lactam compounds (Torrens*, et al.*, 2019; Zhao and Hu, 2010). Antibiotics that do not induce *AmpC* are more successful in combating this β-lactamase (Zhao and Hu, 2010). Some mutations can lead to hyperexpression of *AmpC*, even in response to weak antibiotic inducers of *AmpC* (Zhao and Hu, 2010). When the inducing agent is eliminated, the excessive production of *AmpC* stops (Lister *et al.*, 2009). In certain scenarios however, mutations may arise in the regulatory genes responsible for *AmpC* expression. The loss of regulation can lead to an excessive enzyme production that does not cease upon stopping the inducing agent. An Iranian study has shown 68.6% of isolates to be positive for the *BlaAmpC* gene (Rafiee *et al.*, 2014). Researchers in the USA studied 76 clinical isolates and found that 18.4% possessed the *BlaAmpC* gene (Tam *et al.*, 2007). A different research conducted in Spain discovered that 24.2% of the 190 isolates exhibited *AmpC* overexpression (Cabot *et al.*, 2011). Once more, data regarding this gene in Iraq is minimal with only a limited number of studies and small sample sizes. In a research study carried out in Babel, Iraq, nine isolates were collected, and each contained the *AmpC* gene. Another research carried out in Al-Muthanna, Iraq investigated 36 samples of *P. aeruginosa* from burn patients and demonstrated 33.3% positivity rate for the *BlaAmpC* gene (Al-garawyi, 2020) (Table 1).

H. Metallo-β-lactamases enzymes

These enzymes utilize zinc ions to break down wide range of beta-lactams including carbapenems, however monobactam antibiotics remain effective. This enzyme can withstand β-lactamase inhibitors like clavulanate (Palzkill, 2013). *Verona integron-mediated metallo-β-lactamases* (*VIM*) and *New Delhi metallo-lactamase* (*NDM*) genes are linked to Metallo-β-lactamases. A systematic review carried out in Iran analyzed 10 articles comprising 1972 *P. aeruginosa* samples, revealing a *BlaVIM* prevalence of 13% (Sedighi *et al.*, 2014). In the United Arab Emirates (UAE), 39% of the 95 isolates of *P. aeruginosa* that are resistant to carbapenems had *BlaIMP* (Zowawi *et al.*, 2018). In Diyala, Iraq, a study showed 56.25% of the 81 clinical isolates to have *BlaVIM* gene (Alsaadi *et al.*, 2020) (Table 1). A research done in Najaf, Iraq showed 36.4% of the 22 clinical isolates possess the *BlaNDM* gene (Chayad *et al.*, 2020) (Table 1).

Table 1. Mechanisms of beta-lactam resistance in *P. aeruginosa* in Iraq

Gene Name	Description	Prevalence
CTX-M	Hydrolyzes cefotaxime; ineffective against ceftazidime.	18.94% in Basrah City.
TEM	Commonly associated with ampicillin and penicillin resistance.	66.7% in burn patients in Iraq.
SHV	Variable inhibition; global prevalence reported.	11.1% in Duhok City.
OXA	Hydrolyzes oxacillin, cephalosporins, and carbapenems; specific geographical distribution.	38.2% in Erbil; 59.26% among ESBL producers in Duhok.
VEB	confers resistance against a broad spectrum of beta-lactam antibiotics	30% in Erbil; 4.4% in another Iraqi study.
PER-1	Hydrolyzes various β-lactam antibiotics, including monobactams.	4.21% in Basrah; 44.44% in Duhok.
AmpC	Efficient at hydrolyzing cephalosporins; can be inducible or hyperexpressed.	33.3% in Al-Muthanna
Metallo-β-lactamases	Requires zinc ions to hydrolyze β-lactams; includes *VIM* and *NDM* genes.	56.25% of isolates in Diyala (*VIM*); 36.4% in Najaf (*NDM*).
IMP	Confers resistance to imipenem.	46% in Babylon burn swabs.

I. Imipenemase (IMP)

Imipenemase (IMP) is a different beta-lactamase enzyme that hydrolyzes imipenem. An Iranian meta-analysis of 36 clinical studies found the average carriage rate of BlaIMP was 12.5% (Ghasemian *et al.*, 2018). Additionally, a study in Turkey investigated 1421 samples of *P. aeruginosa* during 2007 to 2017 period and saw 26.8% expressed the BlaIMP gene (Isik *et al.*, 2021). A study done in Babylon, middle of Iraq found that 46% of the 137 samples of burn swabs confirmed BlaIMP gene (Alghreri *et al.*, 2022) (Table 1).

IV. QUINOLONE RESISTANCE

Quinolones, such as ciprofloxacin and levofloxacin, work by inhibiting type II topoisomerase which is responsible for the topological configuration of DNA. (Akasaka *et al*., 2001). *P. aeruginosa* employs different mechanisms to endure quinolone antibiotics (Figure 2). These include reduced permeability, function of efflux pumps, mutated target sites and plasmid mediated resistance.

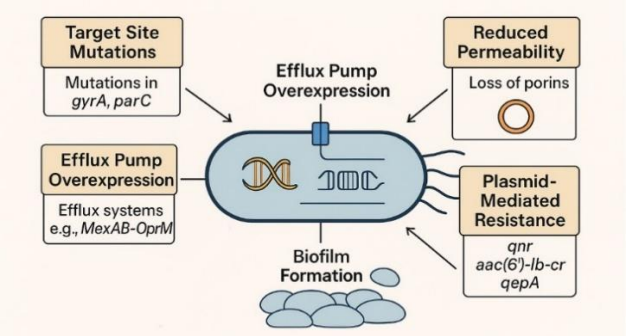

Figure 2. Mechanisms of quinolone resistance in *P. aeruginosa*

A. DNA gyrase and topoisomerase

DNA gyrase and topoisomerase is the targeted site for antibiotic resistance by different mechanisms. In bacteria, DNA gyrase and topoisomerase IV are the two main enzymes that fall under the category of Type II topoisomerases. They regulate DNA replication and transcription, specifically. DNA gyrase consists of two subunits (A and B) which are translated from *gyrA* and *gyrB* genes (Akasaka *et al.*, 2001). On the other hand, topoisomerase IV is composed of two subunits which are translated from *parC* and *parE* genes. Quinolone resistance in *P. aeruginosa* is primarily due to alteration of a region of these two enzymes called the quinolone resistance-determining region (QRDR). Other mechanisms include reduced cell wall permeability and multidrug efflux pumps (Akasaka e*t al*., 2001).

Subunit A of DNA gyrase cuts and reattaches the double-stranded DNA of the host, whereas subunit B functions as an ATPase. Quinolone attaches to subunit A thus interfering with bacterial reproduction (Sada *et al.*, 2022). In a study from Lebanon, *gyrA* mutation was identified in 50% of the 38 isolates (Salma *et al.*, 2013). Another Iranian study conducted in Tabriz found 31.25% rate of *gyrA* mutations in the collected samples (Nouri *et al.*, 2016). Previous studies from Iraq showed elevated resistance rates to this quinolone antibiotics (Naqid *et al.*, 2020a; Naqid *et al.*, 2020b). Nonetheless, data on *gyrA* and *gyrB* mutations in Iraq are limited with only a few studies that included small sample sizes. A study carried out on 50 samples of *P. aeruginosa* in Baghdad, Iraq had 17 ciprofloxacin resistant strains of which 35.2% exhibiting *gyrA* mutation (Hassan *et al.*, 2019). Another study conducted in Babylon, Iraq included 16 cases infected with *P. aeruginosa* from which 93.75% had *gyrA* mutation, 37.5% had *gyrB* mutation, and 62.5% had *ParC* mutation (Raheem, 2021). Topoisomerase plays a key role in relaxing supercoiling in DNA and in separating kinetoplast DNA. The *ParC* and *ParE* genes show homology with *gyrA* and *gyrB* at 36% and 40%, respectively (Akasaka *et al.*, 1999). In an Iranian study recruiting 100 cases of *P. aeruginosa*, it was found that 64% were resistant to ciprofloxacin. Subsequent PCR testing showed 68.75% of the resistant strains had a mutated *ParC* gene (Nouri*, et al.*, 2016). Research in Baghdad, Iraq reported 52 isolates of *P. aeruginosa,* where *ParC* mutation was found in 57.7% isolates (Abdulameer and Abdulhassan, 2021).

B. Multidrug efflux pumps (Mex)

These pumps induce multidrug resistance in different bacteria. Such pumps are part of the resistance-nodulation-division (RND) family and act as a drug/antibiotic antiporter in the outer membrane, extruding specific substrates (Godoy *et al.*, 2010). Mex are a tripartite protein complex made up of a periplasmic membrane fusion protein (PMFP) for instance MexA or MexX, a resistance-nodulation-division transporter (RNDt) for instance MexB or MexY, and a channel-forming outer membrane factor (OMF) for instance OprM or OpN (Lorusso *et al.*, 2022). As an example, MexAB-OprM is a Mex pump where MexA represents a PMFP, MexB acts as

RNDt, and OprM acts as OMF. Once there is an increase in antibiotics concentration close to the protein complex, MexB experiences a conformational change which triggers the extrusion of the drug through a channel formed by MexA and OprM across the periplasmic and outer membranes (Lorusso, *et al.*, 2022). Such a process is controlled by repressor genes known as *MexR*, *NalC*, and *NalD* (Lorusso, *et al.*, 2022). In an Iranian study, *MexA*, *MexB*, and *OprM* genes were identified in 55.5%, 53.3%, and 35.5% of the 45 clinical isolates, respectively (Babak *et al.*, 2016). A study in Babylon, Iraq investigating 79 cases of *P. aeruginosa* by PCR, reported *MexA*, *MexB*, and *OprM* genes at 83.5%, 63.29%, and 48.1% of isolates, respectively (AL-Zwaid and Al-Dahmoshi, 2022) (Table 2). Antibiotic induction controls the MexXY-OprM expression, which is determined by repressor genes including *MexZ*, *ParRS*, and *ArmZ* (Lorusso, *et al.*, 2022). In another study from Iraq, it was found that *MexX*, *MexY*, and *OprM* genes were found in 43%, 51.89%, and 48.1% of the 79 isolates, respectively (Ali and Ghassan, 2024) (Table 2).

Table 2. Mechanisms of quinolone resistance in *P. aeruginosa* in Iraq

Mechanism	Description	Evidence
QRDR mutation of DNA Gyrase (*gyrA*, *gyrB*)	Reduce the binding efficacy of quinolones, thereby decreasing drug effectiveness.	Iraq: 35.2% *gyrA* mutation in Baghdad, 93.75% *gyrA* in Babylon
QRDR mutation of Topoisomerase IV (*parC*, *parE*)	Decrease quinolone binding, affecting bacterial DNA replication.	Iraq: 62.5% *parC* mutation in Babylon, 57.7% *parC* mutation in Baghdad
Multidrug efflux pumps (*MexAB-OprM*, *MexXY-OprM*)	Extrude quinolones out of the cell. *MexAB-OprM* and *MexXY-OprM* are tripartite systems regulated by genes such as *MexR*, *NalC*, and *MexZ*.	Iraq: 83.5% *MexA*, 63.29% *MexB*, 48.1% *OprM* in Babylon; 43% *MexX*, 51.89% *MexY* in Baghdad

V. AMINOGLYCOSIDE RESISTANCE

Aminoglycosides work by inhibiting ribosomal protein synthesis in bacteria. The mechanisms of resistance against aminoglycoside antibiotics in *P. aeruginosa* include inactivation by modifying enzymes, alterations in ribosomal structure and loss of permeability (Kallová *et al.*, 1997).

A. Modifying enzymes

P. aeruginosa inactivates aminoglycosides through enzyme modification via three enzymes: aminoglycoside phosphoryltransferase (APH), which causes phosphorylation; aminoglycoside acetyltransferase (AAC), which leads to acetylation; and aminoglycoside nucleotidyltransferase (ANT), which results in adenylation (Poole, 2005). The enzyme AAC acetylates the 1,2',3,6' amino groups in aminoglycosides, including gentamicin, tobramycin and amikacin (Poole, 2005). ACC enzyme is of different types that have different subtypes and variants (Table 3).

Table 3. AAC enzymes and aminoglycoside resistance in *P. aeruginosa*

Enzyme	Subtype / Variant	Antibiotics Affected	Notes
AAC(3')	1a, 1b, 1c	Gentamicin	Contributes significantly to gentamicin resistance
AAC(6')	-	Kanamycin, netilmicin, tobramycin	General resistance
AAC(6')-I	-	+ Amikacin	Additional resistance to amikacin
AAC(6')-Ia	Subtype of *AAC(6')-I*	Amikacin	Confers amikacin resistance
AAC(6')-Ib / Ib'	Variants of *AAC(6')-I*	Tobramycin	Affects resistance differently due to amino acid changes
AAC(6')-II	-	+ Gentamicin	Commonest subtype in *P. aeruginosa*
Fused gene	*AAC(3')-I-AAC(6')-Ib*	Kanamycin, tobramycin, gentamicin	Hybrid gene with enzymatic activity on multiple aminoglycosides
Short *AAC(6')* variants	*AAC(6')-29a, AAC(6')-29b*	Most *AAC (6')-I* targets (except netilmicin)	*AAC (6')-29b* has weak enzymatic activity but sequesters aminoglycosides

A research study carried out in Iran showed that the *AAC(6')-1b* gene was identified in 71.2% of the samples tested (Panahi *et al.*, 2020). Previous studies from Iraq showed raised resistance levels to aminoglycosides (Naqid *et al.*, 2020a; Naqid *et al.*, 2020b; Hussein *et al.*, 2018). In a study conducted in Baghdad, Iraq, recruiting 50 cases of *P. aeruginosa*, it was shown that 42% of isolates were resistant to aminoglycoside, with *AAC(3)-I* and *AAC(6)-Ib* in 64.2% and 42.8% of those cases, respectively (Al-Jubori *et al.*, 2015). Another study from AL-Diywanyia, Iraq, has reported the rates of *AAC(6')-Ib*, *ACC(3)-II*, *ACC(6')-I*, *AAC(3')I*, and *AAC(6')-IIb* at 87.5%, 31.25%, 21.88%, 15.63%, and 8.33% in the resistant strains, respectively (Dakhl and Alwan, 2015) (Table 3). APH enzymes act by attaching a phosphate group to the hydroxyl group in aminoglycoside molecules. APH(3') has two variants conferring resistance to kanamycin, neomycin, and streptomycin (Poole, 2005). In a study conducted in Iran, Hamadan city, 12.6% of isolates expressed APHA-1 enzyme while 16% expressed APHA-2 enzyme (Alikhani *et al.*, 2017). In India, APH(3') was identified in 10.1% of the samples (Chaudhary and Payasi, 2014), whereas in Iraq, it was identified in 7.1% of the samples (Al-Jubori *et al*., 2015).

ANT enzymes act by adenylating aminoglycosides. A common variant is ANT (2")-I, that works against tobramycin and gentamicin but does not affect amikacin or netilmicin. ANT(3") shows efficacy against streptomycin, while ANT(4')-II is effective against amikacin and tobramycin

(Poole, 2005). In India, the rate of ANT was 18.9% in the tested sample (Chaudhary and Payasi, 2014). In another study from Saudi Arabia, ANT(3")-I was found in 33.3% of the resistant strains (El-Far and Abukhatwah, 2023). In Baghdad, Iraq, researchers investigated 50 isolates, 56% were highly resistant with ANT(4)-IIb expressed in 28.5% of the resistant strains (Al-Jubori*, et al.*, 2015) (Table 4).

B. Ribosomal alteration

P. aeruginosa can methylate its own 16S ribosomal subunit by the action of 16S rRNA methyltransferase (16S RMTase) with multiple variants, preventing aminoglycosides from binding to the ribosome (Taylor *et al.*, 2022). A study carried out in the UK performed whole genome sequencing of 211 *P. aeruginosa* samples. Results showed 16S RMTase was present in 8.6% of the sample. It's variants, *rmtB4*, *rmtD3* and *rmtF2* were detected in 21.1%, 47.4%, and 15.8% of resistant strains, respectively (Taylor*, et al.*, 2022). No research has examined the prevalence of ribosomal alterations in *P. aeruginosa* in Iraq, indicating a gap in the literature to be explored.

Table 4. Mechanisms of aminoglycoside resistance in *P. aeruginosa* in Iraq

Mechanism	Description	Prevalence in Iraq
Aminoglycoside phosphoryltransferase (APH)	Phosphorylates specific amino groups	Baghdad: APH (3') in 7.1% of samples
Aminoglycoside acetyltransferase (AAC)	Acetylating specific amino groups	Baghdad: AAC(3)-I 64.2%, AAC(6)-Ib 42.8%. Al-Diwanyia: AAC(6')-Ib 87.5%, ACC(3)-II 31.25%, ACC(6')-I 21.88%, AAC(3')I, 15.63%, AAC(6')-IIb 8.33% of resistant cases.
Aminoglycoside nucleotidyltransferase (ANT)	Adenylates specific amino groups	Baghdad: ANT(4')-IIb in 28.5% of highly resistant strains
Ribosomal alteration	Methylation of the 16S rRNA ribosome subunit, preventing aminoglycoside binding to ribosome.	Not studied in Iraq

VI. Conclusion

The rising prevalence of β-lactam resistance in *P. aeruginosa* brings a significant challenge to the success of present antimicrobial therapies. The widespread presence of β-lactamases, including *OXA-10*, *VEB*, and the prevalent *TEM*-type ESBLs in burn patients, restricts treatment alternatives even more. The concerning rise of carbapenem resistance caused by metallo-β-lactamases such as *VIM* and *NDM*, along with notable resistance to aminoglycosides and quinolones, underscores the development of multidrug-resistant strains.

The limited scope and depth of local studies restrict a full understanding of resistance patterns and mechanisms. To address this, Iraq needs a national surveillance system to monitor resistance trends and guide treatment decisions. Strengthening infection control practices and implementing antimicrobial stewardship programs are crucial to reduce the spread and misuse of antibiotics. Improving laboratory capacity for accurate diagnostics and molecular testing will support targeted therapies and research. Additionally, education for healthcare professionals and the public on antibiotic use and resistance is essential. Coordinated action combining these strategies is vital to preserve antibiotic effectiveness, improve patient care and stem the spread of these formidable pathogens.

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