Molecular Epidemiology and Resistance Mechanisms of Extensively Drug-Resistant Gram-Negative Bacteria: Challenges and Emerging Therapeutic Strategies

Bikom Chandra Singha1*, Abul Kalam Azad[2]

Abstract

A Background: The emergence of extensively drug-resistant (XDR) gram-negative bacteria poses a major global health challenge, contributing to increased mortality, prolonged hospital stays, and escalating healthcare costs. Over the past two decades, advances in whole-genome sequencing and genotyping have improved our understanding of the development and spread of antibiotic resistance. Resistance in XDR infections arises from mechanisms such as target site mutations, enzymatic degradation of antibiotics, and alterations in membrane permeability. Methods: This study examines the epidemiology and molecular resistance mechanisms of three clinically significant gram-negative pathogens: XDR *Pseudomonas aeruginosa*, XDR Acinetobacter baumannii, and carbapenem-resistant Enterobacteriaceae (CRE). Literature-based evidence and molecular findings were analyzed to identify resistance patterns, emerging clones, and therapeutic challenges. Results: The findings indicate that these pathogens, classified as "critical threats" by the World Health Organization, often necessitate last-resort antibiotics such as polymyxins and novel β-lactam/β-lactamase inhibitor combinations. resistance. Strengthening antibiotic stewardship and advancing targeted therapies are essential to mitigate treatment challenges and control the spread of these pathogens. Resistance mechanisms differ among species but commonly involve enzymatic activity, genetic mutations, and permeability changes. Molecular diagnostics have shown promise in guiding combination therapies, particularly against metallo-β-lactamase-producing CRE, though routine use remains limited. Several novel antimicrobials—including ceftolozane-tazobactam, plazomicin, vaborbactam, and avibactam offer alternative therapeutic options. Conclusion: The growing threat of XDR gram-negative bacteria underscores the urgent need for ongoing global surveillance, improved diagnostic strategies, and deeper investigation into the molecular epidemiology of

Keywords: Extensively drug-resistant bacteria, Gram-negative pathogens, Antibiotic resistance mechanisms, Molecular epidemiology, Novel antimicrobials

Significance | This study demonstrated molecular epidemiology and resistance mechanisms of XDR gram-negative bacteria, guiding diagnostics, surveillance, and targeted therapies.

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Editor Md. Moyen Uddin PK, Ph.D, And accepted by the Editorial Board March 19, 2025 (received for review Jan 01, 2025)

1. Introduction

Gram-negative bacteria have a thin peptidoglycan cell wall sandwiched between their inner and outer membranes. Gram-

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Please cite this article.
Singha, B. C., Azad, A. K. (2025). "Molecular Epidemiology and Resistance Mechanisms of Extensively Drug-Resistant Gram-Negative Bacteria: Challenges and Emerging Therapeutic Strategies", Paradise, 1(1),1-9,10358

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positive bacteria, on the other hand, have a thick peptidoglycan cell wall. Gram-negative bacteria are common in nature and can infect the circulation, biliary system, lower respiratory tract, and urinary tract, among other parts of the body (Tumbarello et al., 2012). Over the past 20 years, gram-negative bacterial resistance has dramatically grown, mostly as a result of the selection pressure of antibiotic usage. Since antibiotic resistance in gram-negative bacterial infections has been linked to higher mortality and higher healthcare costs in comparison to infections with more susceptible bacterial strains, this increased resistance has had significant implications for patients, physicians, and the healthcare system as a whole (Pouch et al., 2015). With the use of whole genome sequencing and genotyping of huge collections of clinical bacterial isolates, our understanding of the emergence of antibiotic resistance has significantly increased. Numerous methods have been demonstrated by bacteria to break down antibiotics, alter the target location of an antibiotic, or control the amount of antibiotic that enters or exits the bacterial cell (Gasink et al., 2009). It is essential to comprehend the epidemiology and mechanics behind these resistance mechanisms. In the widest sense, knowing the processes underlying antibiotic resistance helps us understand how resistance develops and how bacteria transmit to patient. Since several new drugs have been developed to get around established resistance mechanisms, the pharmaceutical industry has also benefited from the research of resistance mechanisms. These agents were often created by altering medication classes that had already received FDA approval for use as antibiotics in the United States. Examples include the novel aminoglycoside plazomicin, the novel cephalosporin ceftolozane (which was used with tazobactam), and novel β-lactamase inhibitors like avibactam, vaborbactam, and relebactam that were combined with already-approved β-lactam antibiotics to form aztreonam (Patel et al., 2008).

Even while regular genotyping to identify the causes of bacterial resistance is not yet widely used in clinical settings, it can be helpful in some circumstances. For instance, metallo-β-lactamases (MBL) found in carbapenem-resistant Enterobacteriaceae (CRE) frequently have a complicated molecular background with many β-lactamases (Thaden et al., 2016). Understanding the specific resistance mechanisms that exist in a bacterial strain can result in directed combination therapy that is effective, even when a single antibiotic may not be able to overcome all resistance mechanisms. Data indicates that treating MBL-producing CRE may benefit from this kind of treatment (Evans et al., 2006). Therefore, a comprehensive understanding of gram-negative bacterial resistance mechanisms helps with drug discovery, impacts antibiotic therapy in some situations, and provides basic information of how resistance arises and spreads. The fundamental mechanisms of resistance and worldwide epidemiology of the most important antibiotic-resistant gram-negative bacteria in clinical settings are our goals in this review: *Pseudomonas aeruginosa* that is extensively drug resistant (XDR), Acinetobacter baumannii that is XDR, and carbapenem-resistant Enterobacteriaceae. The World Health Organization has classified these three pathogens as "critical" threats. Since the treatment of these pathogens frequently involves the use of alternatives to β-lactam antibiotics, including polymyxins, it is crucial to comprehend the epidemiology and resistance mechanisms of these bacteria.

2. Mechanisms and Epidemiology of Antibiotic Resistance in Carbapenem-Resistant Enterobacteriaceae (CRE)

2.1 Overview of Resistance Mechanisms in CRE

It is challenging to treat infections caused by carbapenem-resistant Enterobacteriaceae (CRE), which employ a variety of tactics to avoid the effects of carbapenem medications. The development of efflux pumps that actively expel antibiotics, the enzymatic breakdown of carbapenems through the formation of carbapenemase, and reduced outer membrane permeability as a result of poring mutations are the main resistance mechanisms (Hu et al., 2010). The most important mechanism that contributes to resistance among them is the synthesis of carbapenemase. The Ambler classification system divides carbapenemases and other β-lactamases into Classes A, B, and D according to their molecular structure. Enzymes in each class have the ability to hydrolyze carbapenems, giving them resistance to these antibiotics used as a last option.

2.2 Risk Factors for CRE Infections

Despite large regional variations in frequency and resistance mechanisms, CRE infections pose an increasing danger to global health. While CRE infections are still rare in Scandinavia, they are widespread in nations like Italy and Greece. The Northeast and Great Lakes areas of the United States account for the majority of CRE cases (Lautenbach et al., 2001). Traveling abroad to places where CRE is common raises the risk of infection, especially for people who already have a medical condition. Immunosuppression, advanced age, extended hospital stays, admission to the intensive care unit (ICU), mechanical ventilation, and organ transplantation are additional significant risk factors. Furthermore, the risk of CRE colonization and infection is greatly increased by prior exposure to broad-spectrum antibiotics, particularly carbapenems.

2.3 Class A Carbapenemases

Serine-based enzymes known as class A carbapenemases hydrolyze a variety of β-lactam antibiotics, such as cephalosporin's, carbapenems, and penicillins. Klebsiella pneumoniae carbapenemase (KPC), which is common in the US and has aided in the quick spread of CRE infections, is the most clinically relevant Class (Billard-Pomares et al., 2013). Although they are less frequently seen in clinical settings, imipenemase non-metallo carbapenemase-A (IMI/NMC-A) and the Serratia marcescens

enzyme (SME) are also members of this category (Kapmaz et al., 2016). SME and IMI/NMC-A are chromosomally encoded, which restricts their distribution in contrast to KPC, which is encoded on highly transmissible plasmids. Since its first discovery in the United States in 1996, KPC-producing Enterobacteriaceae have become much more common worldwide, with reports coming from Europe, South America, the Middle East, and Asia. K. pneumoniae sequence type (ST) 258 clonal proliferation has been a key factor in the global spread of strains that produce KPC.

2.4 Class B Carbapenemases

Class B carbapenemases, also known as metallo-β-lactamases (MBLs), require zinc as a cofactor to hydrolyze β-lactam antibiotics. Conventional β-lactamase inhibitors like clavulanate, tazobactam, or avibactam do not inhibit MBLs, in contrast to Class A carbapenemases. Nonetheless, certain investigational medicines have demonstrated promise against MBL-producing CRE, such as cefiderocol and the monobactam-β-lactamase inhibitor combination aztreonam-avibactam (Tanguy et al., 2017). The imipenemase (IMP) family, New Delhi metallo-β-lactamase (NDM), and Verona integron-encoded metallo-β-lactamase (VIM) are the most clinically significant MBLs. In South Asia, especially in Bangladesh, Pakistan, and India, Enterobacteriaceae that produce NDM are prevalent. Concerns of broad spread have been raised by the discovery that the gene encoding NDM-1 is present in both clinical isolates and environmental samples. Although there have been more reports of NDM-producing bacteria in North America and Europe, their incidence is still much lower than in South Asia.

2.5 Class D Carbapenemases

Class D carbapenemases, primarily represented by OXA-48-like enzymes, are another significant contributor to carbapenem resistance in Enterobacteriaceae. While carbapenems are slightly hydrolyzed by these β-lactamases and typically spare the extended-spectrum cephalosporin's. OXA-48-like carbapenemases were first discovered in Turkey in 2001, and they are now prevalent in areas of Europe, especially Malta and Turkey, with more and more cases being reported in France, Spain, and Belgium. Unlike KPC and NDM, OXA-48-like enzymes have limited prevalence in the United States (Moffatt et al., 2010). Plasmid-mediated horizontal gene transfer is the main mechanism by which these carbapenemases propagate, making infection control measures even more challenging.

2.6 Efflux Pumps and Their Role in Carbapenem Resistance

Efflux pumps aggressively remove antibiotics from the bacterial cell, which contributes to carbapenem resistance in Enterobacteriaceae in addition to enzymatic breakdown. By lowering intracellular antibiotic concentrations, the AcrAB-TolC efflux system, a member of the resistance-nodulation-division (RND) family, contributes significantly to multidrug resistance. Efflux pumps are linked to resistance to other antibiotic classes, such as macrolides, tetracyclines, and fluoroquinolones, in addition to carbapenem resistance. It is unknown, therefore, how much efflux pump overexpression affects the worldwide epidemiology of CRE.

2.7 Porin Mutations and Their Contribution to Resistance

Proteins called poring make it easier for antibiotics to enter bacterial cells. Porin-encoding gene mutations, including those in ompK35 and ompK36, inhibit the absorption of antibiotics by decreasing outer membrane permeability (Turton et al., 2006). Although porin mutations by themselves cannot give carbapenem resistance, they can greatly increase resistance when paired with the generation of β-lactamase. Porin mutations are frequently seen in CRE bacteria that produce AmpC or CTX-M-type β-lactamases, which further reduces their resistance to carbapenems. Treatment choices are further complicated by the high prevalence of porin mutations among carbapenem-resistant K. pneumoniae isolates reported in U.S. studies.

2.8 Colistin Resistance in CRE

Colistin is one of the polymyxins that are frequently used as a last option to treat CRE infections. However, changes to the bacterial lipopolysaccharide (LPS) layer are the cause of the growing worry about colistin resistance. These changes hinder colistin's ability to connect to bacterial cells, including increased capsule synthesis and loss or modification of LPS. Furthermore, some Enterobacteriaceae species have been shown to possess plasmid-mediated resistance, which is provided by the mcr-1 gene. This raises concerns regarding the possibility of broad spread. Colistin-resistant CRE's rise emphasizes the pressing need for improved monitoring and innovative antimicrobial approaches.

3. Mechanisms and Epidemiology of Antibiotic Resistance in XDR *Pseudomonas aeruginosa*

3.1 Overview of Mechanisms of Resistance in XDR P. aeruginosa

Pseudomonas aeruginosa is naturally resistant to a variety of antibiotics, such as trimethoprim-sulfamethoxazole, rifampin, tetracycline, chloramphenicol, and several β-lactams. The observed natural resistance can be primarily ascribed to the low permeability of the membrane and the existence of efflux pumps. Nonetheless, extensively drug-resistant (XDR) *P. aeruginosa* arises from the incorporation of further resistance mechanisms, leading to vulnerability to merely one or two categories of antipseudomonal antibiotics (Seward & Towner, 1998). The primary mechanisms contributing to this resistance are the overexpression of efflux pumps, mutations in porins, modifications to antibiotic targets, and the synthesis of enzymes that inactivate drugs. The interplay of these mechanisms results in the XDR phenotype, rendering infections from these strains especially difficult to manage.

3.2 Prevalence of and Risk Factors for XDR P. aeruginosa

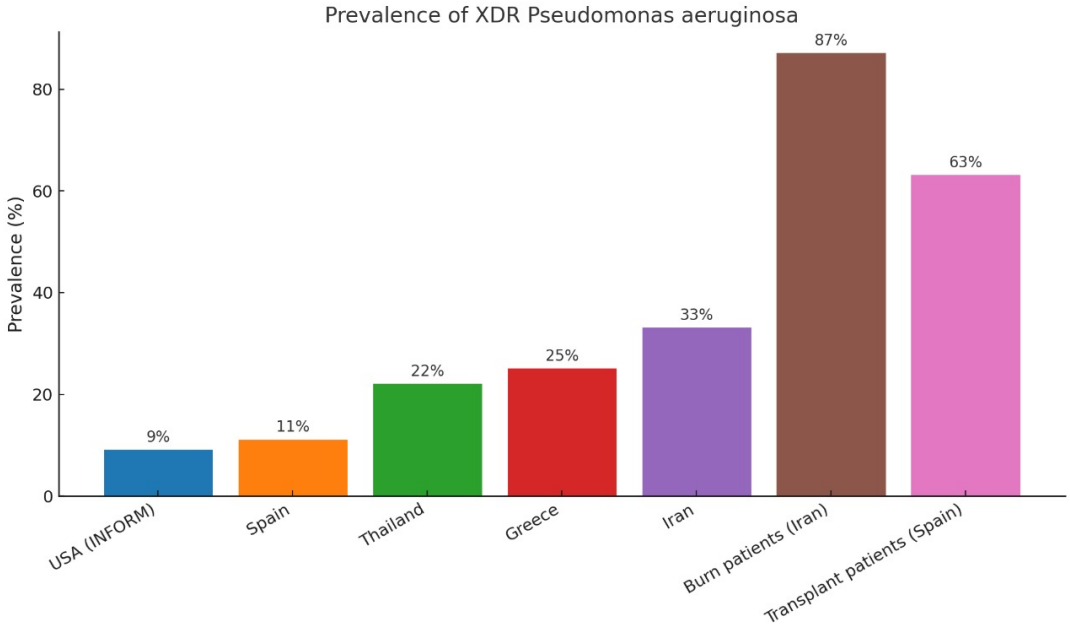


Figure 1. Prevalence of XDR *Pseudomonas aeruginosa* in Different Regions and High-Risk Populations

The worldwide occurrence of XDR *P. aeruginosa* presents challenges in quantification, primarily due to insufficient surveillance data and the variety of resistance mechanisms at play Figure 1. According to a report from the International Network for Optimal Resistance Monitoring (INFORM) in the United States, 9% of *P. aeruginosa* isolates from 79 medical centers displayed the XDR phenotype. Similar or greater prevalence percentages, such as 11% in Spain, 22% in Thailand, 25% in Greece, and 33% in Iran, have been reported in other research (Vila et al., 1997). The prevalence in high-risk populations is notably concerning; for example, in burn patients in Iran, 87% of isolates were classified as XDR, and similarly, 63% of isolates from solid organ transplant patients in Spain displayed the same phenotype (Ansaldi et al., 2011). Prior exposure to fluoroquinolones or carbapenems, complete parenteral nutrition, hematological malignancies, mechanical ventilation, and high illness severity as measured by the APACHE-II score are some of the risk factors that lead to the acquisition of XDR *P. aeruginosa* infections.

3.3 Efflux Pumps and Their Role in Resistance

By aggressively eliminating drugs from bacterial cells and lowering their intracellular concentration, efflux pumps contribute significantly to antibiotic resistance. One of the main causes of *P. aeruginosa*' s multidrug resistance is the MexA-MexB-OprM efflux pathway, which gives the bacteria resistance to aminoglycosides, fluoroquinolones, and β-lactam antibiotics. Antibiotic exposure typically results in the upregulation of these efflux pumps, which is commonly linked to changes in regulatory genes (Hu et al., 2010). Although little is known about the worldwide epidemiology of efflux pump-mediated resistance in XDR *P. aeruginosa*, it is obvious that these mechanisms are crucial to the emergence of resistance.

3.4 Porin Mutations and Their Impact on Carbapenem Resistance

The passage of antibiotics into bacterial cells is made possible by porins. Resistance develops in *P. aeruginosa* when the OprD porin is lost because it drastically lowers the absorption of carbapenems, especially imipenem (Cabot et al., 2012). The bacteria become resistant to several antibiotic classes, such as meropenem, ceftazidime, ureidopenicillins, carboxypenicillins, quinolones, tetracycline, and chloramphenicol, when OprD mutations are coupled with efflux pump overexpression Figure 2. The global development of carbapenem resistance is further fueled by OprD mutations, which are specifically linked to high-risk *P. aeruginosa* clones like ST75.Antibiotic target site mutations can cause *P. aeruginosa* to become resistant. For instance, mutations in the parC and gyrA genes, which encode DNA gyrase and topoisomerase IV, respectively, are frequently the cause of fluoroquinolone resistance. Bacterial DNA replication depends on these enzymes, and changes in them decrease fluoroquinolone binding, which results in resistance. Similarly, methyl transferases like RmtA, RmtD, and ArmA may alter the 16S rRNA target, resulting in aminoglycoside resistance (Bodro et al., 2014). This resistance is conferred to all therapeutically effective aminoglycosides. Another rising issue is colistin resistance, which occurs when the structure of the bacterial lipopolysaccharide (LPS) is changed by changes in regulatory genes such as pmrAB and phoPQ. This prevents colistin from binding and makes the antibiotic useless.

3.6 Antibiotic Degradation by Enzymatic Inactivation

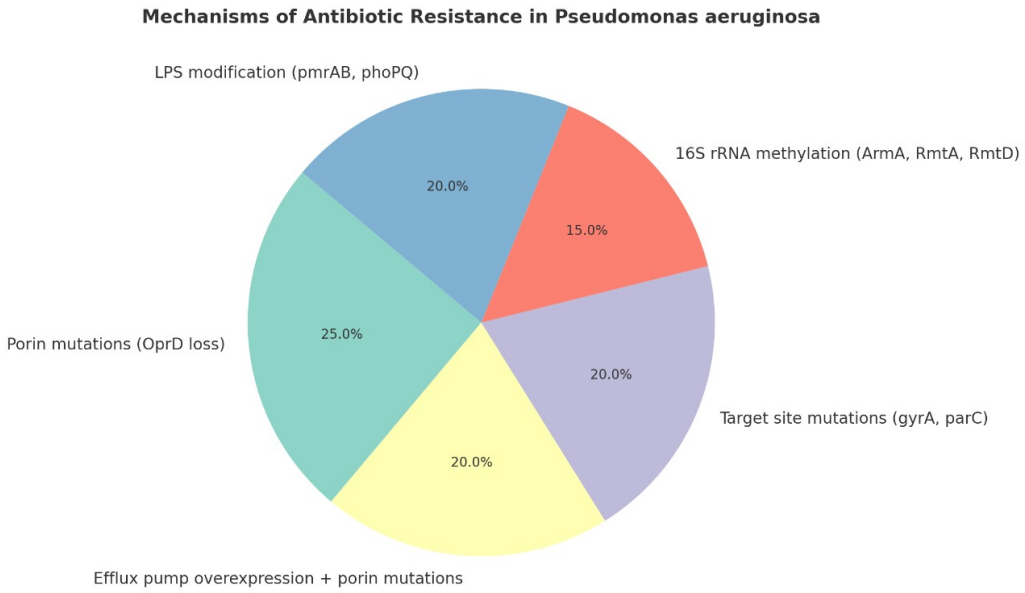


Figure 2. Porin Mutations and Their Impact on Carbapenem Resistance

Antimicrobial resistance in *Pseudomonas aeruginosa* is largely driven by the upregulation of intrinsic enzymes or the horizontal transfer of drug-inactivating enzymes. Chromosomally encoded class C AmpC cephalosporinases are naturally present in *P. aeruginosa*. Resistance to penicillins, monobactams, and cephalosporins can arise from mutations that increase the expression of AmpC enzymes or lead to hyper-inducible AmpC synthesis (Afzal-Shah et al., 2001). Beyond intrinsic mechanisms, resistance can be broadened through the horizontal acquisition of multiple β-lactamases from classes A, B, and D. Some of these enzymes are strongly associated with globally distributed "high-risk" *P. aeruginosa* clones. Narrow-spectrum β-lactamases, such as PSE (Pseudomonas-specific enzyme)-1, PSE-4, and certain OXA-type enzymes, confer resistance to antipseudomonal penicillins and cefoperazone, though they do not provide protection against monobactams, carbapenems, or antipseudomonal cephalosporins.In contrast, broad-spectrum β-lactamases such as PER-1, VEB-1, GES-1, GES-2, and selected OXA variants enable resistance to antipseudomonal penicillins, cephalosporins, and monobactams, but remain ineffective against carbapenems. More concerning are metallo-β-lactamases (MBLs), including IMP, SPM (São Paulo metallo-β-lactamase), GIM (German imipenemase), and VIM enzymes, which confer resistance to nearly all antipseudomonal β-lactams except monobactams (Mulet et al., 2013).Resistance to aminoglycosides can also be acquired via horizontal gene transfer of aminoglycoside-modifying enzymes (AMEs). These enzymes phosphorylate, adenylate, or acetylate the antibiotic, thereby reducing its ability to bind to the ribosomal subunit. Among them, AAC(6′)-II, which mediates resistance to tobramycin, gentamicin, and netilmicin, and ANT(2″)-I, which mediates resistance to gentamicin and tobramycin, are the most common in *P. aeruginosa*. Importantly, novel aminoglycosides such as plazomicin retain efficacy against strains carrying these AMEs, due to structural modifications that prevent enzymatic inactivation.

3.7 Clonal Structure of XDR P. aeruginosa

Although isolates with the XDR phenotype tend to exhibit a more clonal structure, *Pseudomonas aeruginosa* overall demonstrates considerable genetic diversity. In one investigation, nearly 90% of all XDR *P. aeruginosa* isolates belonged to three major "high-risk" clones: ST111, ST175, or ST235. Among these, ST235 is the most widely distributed, having been reported on five continents. ST111 is also globally present, with the exception of Oceania, whereas ST175 is more commonly found in Europe and is rarely identified elsewhere. Despite their clonal relatedness, resistance mechanisms within these high-risk clones vary substantially (Mulet et al., 2013). For example, ST235 isolates are associated with an extraordinary diversity of resistance determinants, with at least 39 distinct β-lactamases identified across clinical isolates. These include class A enzyme such as extended-spectrum β-lactamases (ESBLs) of the PER and GES families, as well as class B carbapenemase, particularly VIM-1, which is widespread geographically. Of particular concern are ST235 isolates detected in South America that harbor the KPC-2 enzyme, further expanding their resistance profile (Clancy et al., 2013).ST111 isolates also carry multiple β-lactamases, though the diversity is somewhat lower than in ST235. These include ESBLs from the GES and VEB families, with VIM-2 representing the most frequently observed carbapenemase. Similar to ST235, KPC-2 has also been reported in ST111 isolates from South America. Unlike

Table 1. Mechanisms of Antibiotic Resistance in XDR Acinetobacter baumannii

Mechanism	Molecular Basis (Genes/Enzymes)	Antibiotics Affected
Efflux pumps	AdeABC, AdeIJK, TetA, TetB	Fluoroquinolones, aminoglycosides, tetracyclines, chloramphenicol, trimethoprim, tigecycline
Decreased outer membrane permeability	OmpA mutations, porin loss	Chloramphenicol, aztreonam, nalidixic acid, carbapenems
Target site mutations	gyrA, parC	Fluoroquinolones
LPS modification/loss	Mutations in lipid A biosynthesis enzymes	Colistin
Aminoglycoside-modifying enzymes (AMEs)	Acetyltransferases, nucleotidyltransferases, phosphotransferases	Aminoglycosides
16S rRNA methylation	ArmA, RmtA–G, NpmA	Aminoglycosides
β-lactamases	AmpC cephalosporinase, OXA-type carbapenemases (OXA-23, OXA-40, OXA-58, OXA-72), Class A KPC, Class B MBLs (IMP, VIM, NDM, SIM)	β-lactams, cephalosporins, carbapenems

ST235 and ST111, the XDR phenotype in ST175 is often linked to non-enzymatic mechanisms such as porin Ord inactivation, AmpC overproduction, and efflux pump overexpression. However, VIM-2 carbapenemase are still commonly encountered in this clone, underscoring the convergent evolution of resistance mechanisms across different lineages of *P. aeruginosa*.

4. Mechanisms and Epidemiology of Antibiotic Resistance in XDR Acinetobacter baumannii

4.1 Mechanisms of Resistance in XDR A. baumannii

In the hospital setting, antibiotics frequently exert strong selection pressure on *A. baumannii*, an opportunistic and nosocomial infection. To ensure its survival and spread, this might lead to chromosomal changes and the horizontal transfer of resistance genes. *A. baumannii* has an innate resistance to a number of antimicrobial classes, including as streptogamins, glycopeptides, lincosamides, and macrolides. Numerous mechanisms, including as efflux pumps, porin expression, antibiotic target mutations, and drug-inactivating enzymes (Sections 4.3–4.5), can give rise to XDR *A. baumannii*.

4.2 Prevalence of and Risk Factors for XDR A. baumannii Infection

A. baumannii is a significant contributor to healthcare-associated infections. It is difficult to estimate the prevalence of XDR *A. baumannii* since the XDR phenotype may not be the primary focus of extensive multicenter research concerning antibiotic resistance in this pathogen. However, as carbapenem-resistant isolates are frequently XDR, carbapenem resistance is considered one of the defining characteristics of XDR *A. baumannii*. Reported incidence rates indicate that carbapenem-resistant *A. baumannii* accounts for a large proportion of urinary tract infections associated with catheters and bacteremia linked with central lines (Correa et al., 2015). In Europe, nearly half of clinical isolates were resistant to carbapenems, with significant regional variation, particularly high in the Baltic and southern European nations. Similarly, elevated resistance rates have been documented in other regions, including Latin America and parts of southern and southeast Asia.Risk factors for colonization or infection with XDR A Table 1. baumannii include prior antibiotic use (especially carbapenems, third-generation cephalosporins, or fluoroquinolones), presence of indwelling central lines, mechanical ventilation, tracheostomy, recent surgical procedures, and prolonged stays in intensive care units.

4.3 Outbreaks of XDR A. baumannii Infection

XDR *A. baumannii* outbreaks frequently occur in intensive care units. High levels of antibiotic resistance are driven by the rapid acquisition of diverse resistance mechanisms and the strong selection pressure created by the use of broad-spectrum antibiotics in these settings. Another contributing factor is the remarkable ability of *A. baumannii* to persist on inanimate surfaces for extended periods. For example, viable bacteria have been recovered from hospital bed rails even several days after an infected patient's discharge.Many intensive care unit outbreaks have been traced to contamination sources such as the hands of medical staff or respiratory equipment. Epidemics of *A. baumannii* in ICUs have been reported across Europe, South America, Africa, Asia, the Middle East, and the United States. In addition, the transfer of colonized or infected patients between healthcare facilities has facilitated the spread of outbreaks both between institutions and on a global scale. By contrast, community-acquired infections with XDR *A. baumannii* remain extremely rare.

4.4 Efflux Pumps and Decreased Outer Membrane Permeability

One of *A. baumannii*'s main resistance mechanisms is increased efflux pump activity. In particular, resistance to a number of antibiotic families, including as fluoroquinolones, aminoglycosides, trimethoprim, tetracyclines, and chloramphenicol, is made possible

Table 2. Epidemiology and Risk Factors of XDR Acinetobacter baumannii

Feature	Substantial Points
Prevalence	High in Europe (Baltic & Southern regions), Latin America, South & Southeast Asia; ~50% carbapenem resistance in some European isolates
Outbreak settings	Intensive care units (ICUs), ventilator-associated pneumonia, bloodstream infections (central lines), catheter-associated urinary tract infections
Transmission routes	Contaminated surfaces (bed rails, equipment), hands of healthcare workers, patient transfer between facilities
Risk factors	Prior broad-spectrum antibiotic use (carbapenems, cephalosporins, fluoroquinolones), invasive devices, prolonged ICU stay, mechanical ventilation, tracheostomy, surgery
Global spread	Reported across Europe, Asia, Middle East, South America, Africa, USA; community-acquired infections remain rare

by overexpression of the adeABC resistance-nodulation-cell division (RND) efflux mechanism. High level carbapenem resistance is attained when *A. baumannii* carrying carbapenem-hydrolyzing oxacillinases overexpress the adeABC efflux pump. Resistance to tigecycline may be conferred via a second efflux system-adeIJK (Weiner et al., 2016). This is especially true when co-expression of adeIJK and adeABC occurs. The tet genes encode efflux pumps, which are usually linked to mobile genetic elements. TetA and TetB provide resistance to tetracycline and minocycline, respectively. One important porin of *A. baumannii* is the outer membrane protein OmpA. Chloramphenicol, aztreonam, and nalidixic acid resistance can be attained by mutations that target the ompA gene, which may also reduce outer membrane permeability.

4.5 Mutations in Antibiotic Target Sites

Mutations in the DNA gyrase and DNA topoisomerase subunits, gyrA and parC, respectively, might result in resistance to fluoroquinolones by reducing the fluoroquinolones' affinity for their targets. It has been shown that gyrA and parC gene mutations are quite common in a global collection of fluoroquinolone-resistant. It is unknown how other resistance mechanisms, such as efflux pump overexpression, contribute to the worldwide fluoroquinolone resistance epidemic. A part of lipopolysaccharide (LPS) may result in colistin resistance through reduced colistin binding due to mutations in the enzymes involved in LPS production, which alter or eliminate the lipid Table 2. Acetyltransferases, nucleotidyltransferases, and phosphotransferases are examples of aminoglycoside-modifying enzymes that can be obtained by plasmid exchange, transposons, or class 1 integrons. To provide resistance to aminoglycosides, these enzymes can exist alone or in combination (Catalano et al., 1999). The bacterial 16S rRNA is bound and inhibited by aminoglycosides, as explained in Section 3.5. Another efficient resistance mechanism is alteration of the target 16S. For instance, substantial levels of resistance to all aminoglycosides, including amikacin, are caused by 16S rRNA methyl transferases, which have been identified in *A. baumannii*. By preventing aminoglycosides from attaching to their site of action, ArmA, a 16S rRNA methyltransferase that is well-characterized in *A. baumannii*, provides resistance. ArmA has been found all over the world. Less is known about the worldwide epidemiology of the other 16S methylases, such as RmtA, RmtB, RmtC, RmtD, RmtE, RmtF, RmtG, and NpmA (Brigante et al., 2012). Notably, because of their relationship with transposable structures and placement on transferable plasmids, isolates that include 16S rRNA methylases also frequently have ESBLs or MBLs.

4.6 Antibiotic Degradation

The chromosomal AmpC cephalosporinase, which is naturally present in *A. baumannii*, hydrolyzes cephalosporins at a low level. Penicillins and carbapenems are also hydrolyzed at a low level by the class D oxacillinase, OXA-51-like enzyme that *A. baumannii* naturally has. Clinically substantial cephalosporin resistance occurs when ISAba1, a potent transcriptional promotor, is inserted upstream of the ampC cephalosporinase or OXA-51-like gene (Robledo et al., 2009). Furthermore, *A. baumannii*'s acquisition of carbapenemases has been thoroughly documented. In particular, the most often found carbapenemases in *A. baumannii* are class D enzymes, which can be chromosomally or plasmid encoded and include OXA-23-, OXA-40-, and OXA-58-like enzymes. The most prevalent carbapenem-hydrolyzing enzymes found in *A. baumannii* globally are OXA-23-like enzymes, which are also frequently responsible for nosocomial outbreaks of *A. baumannii* that are resistant to carbapenem. Usually, transposons Tn2006 and Tn2007 are linked to these enzymes. Other carbapenemase-active class D β-lactamases have more regional distributions; for example, OXA-25, OXA-26, and OXA-40 are primarily found in Europe, whereas OXA-72 is primarily found in Asia (Tada et al., 2014). Class A and B β-lactamases are less frequently implicated in carbapenem resistance in *A. baumannii*. Extremely uncommon, class A KPC-producing A. (HéRitier et al., 2002). Although the IMP- and VIM-type enzymes are the most often isolated and extensively dispersed, *A. baumannii* has been shown to have Class B IMP-, VIM-, SIM-(Seoul imipenemase), and NDM-type enzymes.

5. Conclusions

Due to a variety of resistance mechanisms, including as enzymatic degradation, efflux pumps, and target site changes, extensively drug-resistant (XDR) Gram-negative bacteria are rapidly becoming more prevalent, which poses a serious threat to world health. The development of new medicinal approaches and antimicrobial stewardship initiatives have benefited from our increased understanding of these pathways because to advancements in molecular tools like whole-genome sequencing and genotyping. Treatment of XDR infections is still quite complicated, even with the advent of novel antimicrobials like next-generation aminoglycosides and β-lactam/β-lactamase inhibitor combos. Targeted therapy may be improved by the incorporation of molecular diagnostics into clinical settings, especially for infections that produce metallo-β-lactamases (MBLs), for which there are currently few available treatments. A multimodal strategy is required for successfully dealing with XDR Gram-negative infections (Catalano et al., 1999b). This entails prioritizing research into novel antimicrobial drugs, implementing antimicrobial stewardship programs, and bolstering infection control measures. Furthermore, proactive measures to lessen the burden of XDR infections on healthcare systems throughout the world would need ongoing global surveillance and a better understanding of how resistance has evolved.

Author contributions

B.C.S. and A.K.A. contributed equally to the conceptualization, writing, and critical revision of this review article.

Acknowledgment

Author is grateful to department

Competing financial interests

The authors have no conflict of interest.

Generative AI statement

The authors declare that Gen AI was used in the creation of this manuscript. Generative AI was used in the preparation of this manuscript in a limited and strictly controlled manner. Specifically, it assisted during the initial organization of thematic sections and helped identify general areas of literature for further manual exploration. All writing, analysis, interpretation, and synthesis of content were performed by the authors. All references in the current version have been manually reviewed and verified. The final manuscript has been completely revised to ensure originality, accuracy, and integrity, fully aligning with Frontiers' ethical policies on the responsible use of generative AI.

Data availability statement

The data supporting the findings of this study are derived from publicly available literature included in the systematic review and cited accordingly in the reference list.

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