Biomedical and Biopharmaceutical Research
Abbreviation: Biomed. Biopharm. Res.
Volume: 22: Issue: 02 |Year: 2025
Page Number: 654-662

Antibiotic Resistance in Klebsiella pneumoniae: New Insights into Mechanisms and Drug Development

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Article Received:27-06-2025

Article Accepted:28-07-2025

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ABSTRACT

Klebsiella pneumoniae, a major cause of hospital- and community-acquired infections, has become increasingly resistant to multiple antibiotics, posing a serious public health challenge worldwide. This review comprehensively examines the diverse mechanisms underlying antibiotic resistance in K. pneumoniae, including the production of β-lactamases such as ESBLs and carbapenemases, alterations in outer membrane porins, activation of efflux pumps, and biofilm formation. These mechanisms contribute to the bacterium's ability to evade the effects of a broad spectrum of antimicrobial agents, leading to multidrug-resistant (MDR) and extensively drug-resistant (XDR) phenotypes. The emergence and global dissemination of carbapenem-resistant K. pneumoniae strains are particularly concerning due to limited therapeutic options and high mortality rates. Additionally, this review highlights the impact of resistance on clinical outcomes and the challenges posed by the limited development of new antibiotics. Understanding the molecular basis of antibiotic resistance in K. pneumoniae is essential for guiding effective treatment strategies and fostering the development of novel antimicrobial agents.

Keywords: Multidrug resistant-Klebsiella pneumonia, MDR, XDR, Antimicrobial stewardship

1. INTRODUCTION;

Klebsiella pneumoniae is a widespread, Gram-negative, facultative anaerobic bacterium [1]. It inhabits a variety of environments, including the respiratory and gastrointestinal tracts of both humans and animals [1]. Over 95% of infections caused by Klebsiella species are attributed to K. pneumoniae. These infections can lead to a range of clinical conditions, particularly in individuals with compromised immune systems. Notably, K. pneumoniae infections are frequently encountered in healthcare settings around the world [1].

Of growing concern is the emergence of genetically altered strains of K. pneumoniae that display either enhanced virulence or resistance to antibiotics [1]. The global rise and spread of multidrug-resistant (MDR) organisms, including K. pneumoniae, is a critical issue under active scientific investigation. MDR strains of K. pneumoniae pose a significant threat to public health due to their ability to limit available treatment options.

Two key mechanisms underlie antibiotic resistance in K. pneumoniae. One involves the production of extended-spectrum β-lactamases (ESBLs), which confer resistance to cephalosporins and monobactams [1]. The other involves carbapenemase enzymes, which make the bacteria resistant to nearly all β-lactam antibiotics, including carbapenems [1]. These resistant strains have led to more than 90,000 infections and 7,000 deaths in the European region alone [2].

To manage infections caused by carbapenem-resistant K. pneumoniae (CRKp), clinicians often resort to last-line antibiotics such as colistin and tigecycline [3]. However, these drugs tend to be effective only when combined with other agents, rather than as standalone therapies.

However, the use of colistin and tigecycline is associated with several adverse effects, including kidney toxicity [4]. Alarmingly, new strains of Klebsiella pneumoniae that produce extended-spectrum β-lactamases (ESBLs) or are carbapenem-resistant (CRKp) are increasingly becoming resistant even to these last-resort antibiotics. Traditional treatment options have largely failed to eliminate these pathogens, making multidrug-resistant (MDR) infections a serious threat to global health and the economy.

Compounding the issue is a marked decline in the development of new antimicrobial agents since the golden age of antibiotic discovery. Contributing factors include rising resistance, reduced profitability, and regulatory hurdles. As a result, there is an urgent need for the discovery of new therapeutic agents to combat this growing crisis.

Moreover, our understanding of both innate and acquired resistance mechanisms in K. pneumoniae remains incomplete. Therefore, it is critically important to continuously explore innovative strategies for tackling K. pneumoniae, while also expanding our knowledge of the molecular mechanisms behind its resistance to currently available drugs.

This review aims to present a detailed analysis of how K. pneumoniae resists antibiotic treatment. It further highlights the molecular elements responsible for both natural and acquired resistance. Additionally, this work explores emerging pharmacological targets that could provide valuable insights into more effective treatments for K. pneumoniae infections.

2. MAIN TEXT

2.1 Antimicrobial Resistance

2.1.1 Intrinsic Resistance

Klebsiella pneumoniae naturally exhibits resistance to antibiotics, making conventional therapies less effective. This intrinsic resistance is driven by several key mechanisms, including the production of enzymes that deactivate or alter antibiotics, the loss of porin channels that reduce drug entry, the increased activity of efflux pumps that expel antibiotics from the cell, and the formation of protective biofilms (see Fig. 1) [5, 6]. A detailed overview of these innate resistance mechanisms is provided in Table 1.

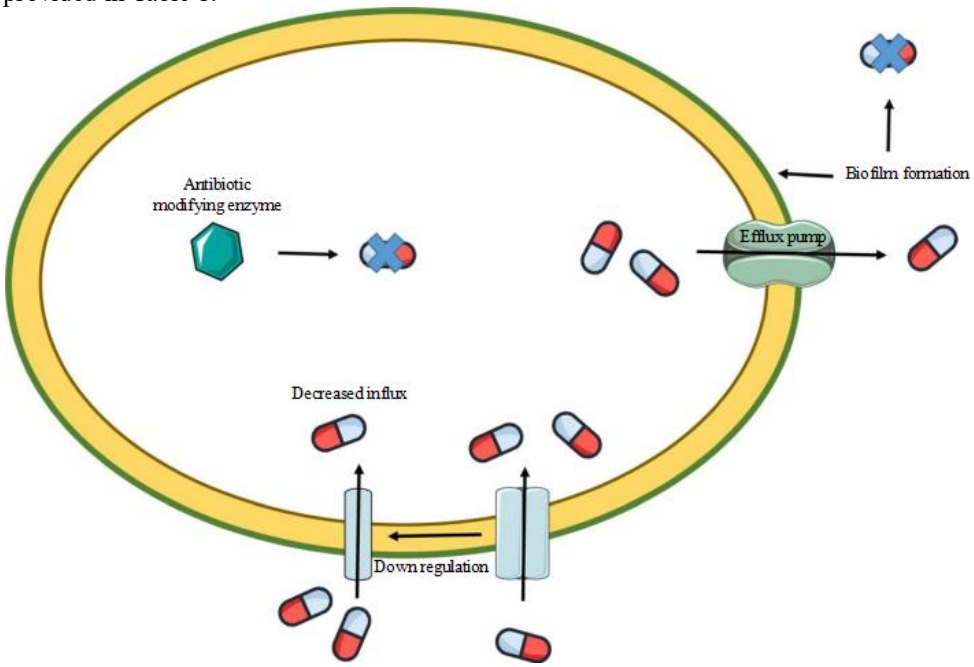

Fig. 1 Mechanisms of K. pneumoniae innate antibiotic resistance

Table 1. Intrinsic Mechanisms of Antibiotic Resistance in Klebsiella pneumoniae

Resistance Mechanism	Associated Antibiotic Classes	References
Enzymatic modification or inactivation	β-Lactam antibiotics	[9–12, 15, 16]
Reduced drug uptake (decreased influx)	β-Lactams and fluoroquinolones	[7]
Active drug expulsion via efflux pumps	β-Lactams, macrolides, fluoroquinolones, and tetracyclines	[7]
Biofilm development	Aminoglycosides, penicillins, and quinolones	[8]

2.1.2 Antibiotic-Modifying or Inactivating Enzymes

Klebsiella pneumoniae commonly develops resistance to antibiotics through the modification or inactivation of these drugs. β-lactam antibiotics are widely used in clinical settings to treat infections caused by K. pneumoniae. These antibiotics function by forming covalent bonds with penicillin-binding proteins (PBPs), which play a crucial role in the cross-linking of peptidoglycan layers during bacterial cell wall synthesis [9]. In response, K. pneumoniae produces β-lactamase enzymes that hydrolyze the β-lactam ring, rendering the antibiotics ineffective—a major resistance mechanism.

There are three main categories of β-lactamases: cephalosporinases (AmpC), extended-spectrum β-lactamases (ESBLs), and carbapenemases [10–13]. ESBLs are typically plasmid-encoded, and genes like blaSHV-2 and blaTEM-3 have been identified in K. pneumoniae [14, 15], representing mutated forms carried by mobile genetic elements [15]. Clavulanic acid can inhibit ESBL activity, particularly against carbapenems, leading to the classification of these enzymes as "extended-spectrum." Among ESBLs, CTX-M-type has increasingly replaced TEM and SHV types due to the ease of gene acquisition through plasmids and transposons.

Moreover, horizontal gene transfer has facilitated the spread of other ESBL genes, such as blaPER, blaSFO, blaTLA, blaOXA, blaGES, blaVEB, and blaKLUC-5 [16]. Carbapenems have traditionally been the drugs of choice for treating

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infections caused by ESBL-producing bacteria [14]. AmpC β-lactamases, in contrast, confer resistance to a broad range of antibiotics including first- to third-generation cephalosporins, cephamycins, and β-lactamase inhibitors [12]. Over 40 different AmpC variants have been identified, many of which can spread rapidly across bacterial strains through plasmid-mediated transfer [14].

2.1.3 Bacterial Influx

The outer membrane of Klebsiella pneumoniae is rich in proteins known as porins, which play a crucial role in regulating the movement of molecules across the membrane by forming channel-like structures [17]. These channels allow small, hydrophilic molecules—typically less than 600 Da in size—such as β-lactams and fluoroquinolones, to pass through the lipid bilayer [17]. In addition to facilitating molecular transport, porins act as receptors for bacteriocins and bacteriophages, thus playing a protective role for the bacterial cell [18]. Furthermore, these pore-forming proteins contribute to the pathogen's virulence by assisting in adhesion, invasion, and resistance to host serum defenses [18].

In strains producing extended-spectrum β-lactamases (ESBLs), the absence or loss of porins may reduce antibiotic entry and promote the selection of other resistance mechanisms [19]. Under host-like conditions, porins in K. pneumoniae also help stabilize the outer membrane and provide resistance against immune defenses such as defensins and other antimicrobial peptides [20]. Changes in the type, expression level, or functional activity of porins can significantly impair drug uptake by the bacterial cell [20]. Key porins involved in intrinsic resistance in K. pneumoniae include LamB, OmpK26, PhoE, OmpK35, OmpK36, and KpnO [7].

2.1.4 Efflux Pump

Efflux pumps serve as a major bacterial defense mechanism that helps K. pneumoniae adapt to and survive in hostile environments, particularly in the presence of antibiotics. These membrane-bound transport systems actively expel antimicrobial agents out of the bacterial cell, thereby lowering the intracellular concentration of drugs and contributing to antibiotic resistance [21–23]. Resistance may arise due to overproduction of efflux pumps in response to increased drug levels or due to mutations that enhance pump efficiency [24].

Genome sequencing has revealed that K. pneumoniae carries over 30 genes or operons encoding multidrug resistance (MDR) efflux systems on its chromosome [25]. These include members of several families such as the major facilitator superfamily (MFS), resistance-nodulation-division (RND), small multidrug resistance (SMR), and multidrug and toxic compound extrusion (MATE) systems [20]. Among them, the RND family plays a key role in both intrinsic and acquired antibiotic resistance.

Two proteins, TolC and AcrA, are known to interact with multiple efflux systems in both the RND and MFS families, showcasing their broad compatibility [26]. The most well-characterized efflux pump in K. pneumoniae is the AcrAB-TolC system. This complex is responsible for the active, energy-dependent expulsion of various antibiotics from the cell [20]. AcrAB-TolC can handle both negatively and positively charged substrates, requiring only a hydrophobic region to insert the drug into the phospholipid membrane for transport [20]. This pump effectively exports multiple antibiotic classes, including β-lactams, macrolides, fluoroquinolones, and tetracyclines [20].

2.1.5 Biofilm Formation

Klebsiella pneumoniae has a strong ability to form biofilms, a process in which surface structures like capsules and pili are significantly involved [21]. Biofilms create a protective environment that limits antibiotic penetration by reducing bacterial growth rates, supporting the survival of persister cells, and facilitating the exchange of genetic material [21]. These biofilms form when bacteria adhere to either living or non-living surfaces and produce an extracellular polymeric matrix composed of polysaccharides, proteins, and extracellular DNA [22].

This matrix acts as a barrier to osmotic pressure and contributes to the organism's resistance to antimicrobial agents. In K. pneumoniae, biofilm formation has been shown to decrease susceptibility to several antibiotics, including gentamicin, ampicillin, and ciprofloxacin [8]. Furthermore, biofilm development has also been associated with the emergence of resistance to colistin, a last-resort antibiotic [23].

2.1.6 Acquired Resistance

β-lactam antibiotics are widely used for the treatment of Klebsiella pneumoniae infections. However, in cases involving multidrug-resistant or prolonged infections caused by K. pneumoniae, alternative antibiotics become necessary. Unfortunately, resistance can also emerge against these alternatives during clinical use. Table 2 outlines the key mechanisms of acquired resistance in K. pneumoniae.

Rather than arising mainly from chromosomal mutations, resistance in K. pneumoniae is largely driven by horizontally acquired antimicrobial resistance (AMR) genes. These genes are typically carried on plasmids but may also be incorporated into the bacterial chromosome.

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Table 2. Acquired Mechanisms of Antibiotic Resistance in K. pneumoniae

Resistance Genes	Associated Antibiotic Class	References
bla genes (blaSHV, blaTEM, blaCTX, blaKLUC-5, blaSFO, blaGES, blaPER, blaVEB, blaTLA, blaKPC, blaNDM, blaVIM, blaIMP, blaOXA, blaCMY, blaDHA, blaFOX, blaMOX), and others including aac, aph, ant, AcrAB-TolC, kpnEF, and KpnO	β-lactam antibiotics	[8, 32, 33, 40, 41]
AcrAB-TolC, OqxAB, RarA, RamA, RamR, AcrR, rpsJ, 16S rRNA methylase, and tetA	Tigecycline	[7]
DNA gyrase, topoisomerase IV, mpK36, acrAB, kdeA, OqxAB, and aa(6')-Ib-cr	Quinolones	[7]
phoPQ, pmrA, pmrD, mcr-1, and mgrB	Polymyxins	[7]
Fos	Fosfomycin	[7]

2.1.7 Carbapenem Resistance

The extensive use of carbapenems has been driven by the increasing prevalence of ESBL-producing K. pneumoniae, largely due to selective pressure. Among the most concerning mechanisms of multidrug resistance are carbapenemases encoded on plasmids. The serine-based class A β-lactamase known as KPC (Klebsiella pneumoniae carbapenemase) is the most common and clinically threatening carbapenemase. This enzyme is linked with the clonal group CG258, particularly the ST258 and ST11 strains. ST258 is more commonly found in Europe and the Americas, while ST11 is widespread in Asia.

The blaKPC gene is mobilized by the Tn4401 transposon, which facilitates its integration into other plasmids and supports clonal spread. The global dissemination of such resistance genes has led to high mortality rates and therapeutic challenges in managing carbapenemase-producing Enterobacteriaceae. Notably, most β-lactamase inhibitors are ineffective against KPC, complicating treatment.

Additionally, resistance is further intensified by the chromosomal integration of carbapenemase genes initially present on plasmids. This adaptability makes CRKP (carbapenem-resistant K. pneumoniae) a major clinical concern.

K. pneumoniae can also spread AmpC-type cephalosporinase enzymes by acquiring β-lactamase genes on mobile plasmids. The presence of blaAmpC, as well as mechanisms like gene overexpression or mutations enhancing efflux (similar to blaACT-1), contributes to β-lactam resistance. Increased gene copy numbers or strong promoters on plasmids facilitate high expression, resulting in carbapenem resistance. Some K. pneumoniae isolates may harbor multiple β-lactamase genes—such as SHV, AmpC, and KPC—which together heighten resistance. Although enzymes like VIM, NDM, and IMP do not independently confer resistance to aztreonam, when co-expressed with ESBL or AmpC, they can lead to resistance even against this drug.

2.1.8 Aminoglycoside Resistance

Resistance to aminoglycosides in K. pneumoniae is often mediated by plasmid-borne genes from the armA family. While drug-modifying enzymes can reduce the activity of aminoglycosides, 16S rRNA methylases provide broad resistance to nearly all drugs in this class.

Resistance can also be influenced by chromosomal changes, including mutations affecting the AcrAB-TolC and KpnEF efflux systems, or deletions of the KpnO outer membrane protein. These changes impair membrane permeability. For instance, strains with altered efflux pumps show high resistance to tobramycin and gentamicin, while KpnO deletion leads to increased resistance to vancomycin and moderate resistance to streptomycin. This suggests that aminoglycosides rely on specific membrane channels to enter the cell. Loss of the KpnO protein has also been associated with resistance to tobramycin, streptomycin, and spectinomycin.

2.1.9 Tetracycline Resistance

Tigecycline, a next-generation tetracycline antibiotic, exhibits broad-spectrum activity against ESBL-producing bacteria [37]. Resistance to tigecycline primarily involves chromosomally encoded mechanisms, including efflux pumps like OqxAB, AdeABC, mutated Tet(A), KpgABC, and alterations in ribosomal proteins. These mechanisms impact cell membrane permeability and ribosomal binding sites [14]. The **rpsJ** gene, which encodes ribosomal protein S10—part of the 30S ribosomal subunit—lies near the tigecycline and tetracycline binding site. In one of three resistant K. pneumoniae strains, a point mutation in the **rpsJ** gene was identified near the tigecycline binding site on the 30S subunit [38]. This suggests that modifications in the S10 protein might represent a novel resistance pathway. Ribosomal proteins S3, S13, and S10 are located near the tetracycline binding site, with S3 being crucial for maintaining structural integrity [39]. Structural changes in S3 could also contribute to tigecycline resistance. Studies indicate that **rpsJ** mutations can confer resistance without involving efflux mechanisms [14].

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2.1.10 Quinolone Resistance

Quinolones function by inhibiting bacterial topoisomerases, thereby blocking DNA replication [40]. Resistance in K. pneumoniae arises through mutations in target genes, upregulation of multidrug efflux pumps, and alterations in involved enzymes and proteins [40]. Chromosomally mediated resistance includes modifications to DNA gyrase and topoisomerase IV, the primary quinolone targets. The **OqxAB** efflux pump, often encoded on plasmids, contributes to quinolone resistance in various bacteria [41]. Additional plasmid-mediated resistance mechanisms in Enterobacteriaceae include proteins that shield DNA gyrase and topoisomerase IV from quinolones. A notable resistance gene, **aac(6')-Ib-cr**, modifies quinolones and other substrates, reducing their efficacy [42]. Recently, this gene has also been detected on the chromosome. Its expression promotes chromosomal mutations that lead to low to moderate quinolone resistance [41].

2.1.11 Resistance to Other Antibiotics

Resistance to polymyxins in K. pneumoniae is typically due to mutations in regulatory genes like **mgrB**, which modulates lipid A synthesis—polymyxin's bacterial target—thereby decreasing drug affinity [43–45]. While the **mcr-1** gene is uncommon in K. pneumoniae bloodstream infections in China, it is frequently found in E. coli, and the first U.S. case was reported in 2016 [46].

Fosfomycin, an older antibiotic being repurposed for treating multidrug-resistant infections, is facing rising resistance. Mechanisms include overexpression or amino acid substitutions in **MurA**, decreased or absent expression of transporters **GlpT** and **UhpT**, and presence of the **fos** gene encoding a glutathione S-transferase that deactivates fosfomycin [48]. The **fosA3** gene has been identified as a major contributor to fosfomycin resistance in carbapenem-resistant K. pneumoniae (CRKp). Its plasmid-mediated transfer is commonly seen in hospital settings [49]. In fosfomycin-resistant CRKp strains lacking **fosA3**, mutations in **MurA** or the **glpT** transporter were observed [49].

2.1.12 Potential Drug Targets in K. pneumoniae

The growing threat of multidrug-resistant and hypervirulent K. pneumoniae strains, alongside diminishing antibiotic effectiveness, underscores the urgent need for new treatment strategies [50]. Novel drug targets can be identified using whole-genome sequencing and subtractive genomics to exclude human-homologous proteins, minimizing cross-reactivity and side effects [51]. Tools like BLASTp and BLAT help identify pathogen-specific proteins, while databases of essential genes and KEGG pathway analyses assist in pinpointing critical survival-related pathways [52, 53]. Promising targets often participate in essential biosynthetic processes such as peptidoglycan, fatty acid, LPS, and purine nucleotide synthesis.

Enzymes **FabB**, **FabI**, and **FabH**, integral to fatty acid biosynthesis, are attractive drug targets. **FabI** is especially promising for antibacterial drug development, catalyzing the reduction of enoyl-ACP during fatty acid elongation [54]. **FabB** facilitates elongation by incorporating malonyl-ACP-derived carbon atoms into acyl chains [55]. **FabH** initiates fatty acid synthesis by transferring acetyl-CoA to malonyl-ACP and regulates the type of fatty acids synthesized [56, 57].

Additionally, **LpxA**, **LpxB**, **LpxC**, and **LpxD**—enzymes involved in LPS biosynthesis—are also important drug targets [58, 59]. The **MurG** and **MurF** enzymes are essential for peptidoglycan synthesis and cell wall assembly [60, 61]. **Aspartate semialdehyde dehydrogenase**, crucial for synthesizing several amino acids (lysine, threonine, methionine, homoserine), also serves as a viable target.

SecA, a membrane-associated ATPase, is essential for Sec-dependent protein translocation. It forms a complex with **SecYEG** and **YajC**, playing a key role in secretion of proteins and virulence factors [62]. Its membrane localization makes it accessible to inhibitors without needing cytoplasmic entry [63].

Other potential targets include histidine kinase **EvgS** from the two-component system EvgS/EvgA, which mediates acid and drug resistance in E. coli [64, 65]. Upon mild acidification, EvgS phosphorylates EvgA, activating acid-resistance genes. **TolC**, involved in exporting antibiotics, toxins, and dyes, supports bacterial survival by enabling efflux of harmful substances [65, 66]. The two-component sensor kinase **QseC**, activated by host hormones like epinephrine and norepinephrine, also presents a compelling target for novel therapies [67].

CONCLUSION

Klebsiella pneumoniae poses a significant and growing threat to global health due to its multifaceted antibiotic resistance mechanisms, including enzyme production, porin loss, efflux pumps, and biofilm formation. The rise of multidrug-resistant and carbapenem-resistant strains severely limits treatment options and contributes to high morbidity and mortality. Compounded by a slowdown in new antibiotic development, there is an urgent need for continued research into the molecular basis of resistance and innovative therapeutic strategies. Understanding these resistance mechanisms is critical to developing effective drugs and managing infections caused by this formidable pathogen.

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