Mini-Review

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Characteristics of antibiotic resistance mechanisms and genes of *Klebsiella pneumoniae*

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Abstract: *Klebsiella pneumoniae* is an important multidrug-resistant (MDR) pathogen that can cause a range of infections in hospitalized patients. With the growing use of antibiotics, MDR *K. pneumoniae* is more prevalent, posing additional difficulties and obstacles in clinical therapy. To provide a valuable reference to deeply understand *K. pneumoniae*, and also to provide the theoretical basis for clinical prevention of such bacteria infections, the antibiotic resistance and mechanism of *K. pneumoniae* are discussed in this article. We conducted a literature review on antibiotic resistance of *K. pneumoniae*. We ran a thorough literature search of PubMed, Web of Science, and Scopus, among other databases. We also thoroughly searched the literature listed in the papers. We searched all antibiotic resistance mechanisms and genes of seven important antibiotics used to treat *K. pneumoniae* infections. Antibiotics such as β-lactams, aminoglycosides, and quinolones are used in the treatment of *K. pneumoniae* infection. With both chromosomal and plasmid-encoded ARGs, this pathogen has diverse resistance genes. Carbapenem resistance genes, enlarged-spectrum β-lactamase genes, and AmpC genes are the most often β-lactamase resistance genes. *K. pneumoniae* is a major contributor to antibiotic resistance worldwide. Understanding *K. pneumoniae* antibiotic resistance mechanisms and molecular characteristics will be important for the design of targeted prevention and novel control strategies against this pathogen.

Keywords: *Klebsiella pneumoniae*, antibiotic resistance, resistance mechanisms

1 Introduction

The gram-negative bacterium *Klebsiella pneumoniae* is a member of the family *Enterobacteriaceae*, closely related to the well-known *Salmonella enterica* and *Escherichia coli* pathogens [1]. *K. pneumoniae* can ferment lactose and has capsular polysaccharides. *K. pneumoniae* is a common hospital-acquired opportunistic pathogen, accounting for about 30% of all gram-negative bacterial infections.

K. pneumoniae can be commensals in a range of environments, including soil, water, a variety of plants, insect species, birds, and animals. Typical *K. pneumoniae* is widely distributed among human and animal mouth, skin, respiratory tract, urogenital tract, and intestine [2,3]. *K. pneumoniae* causes infections through gene or plasmid horizontal transfer [4]. A large percentage of *K. pneumoniae* infections occur in newborns, the elderly, and those with compromised immune systems [2]. It can infect the respiratory tract, the urinary tract, as well as wounds or soft tissues. Even with appropriate antibiotic treatment, the mortality rate of hospital-acquired pneumonia is still more than 50%. The incidence rate and mortality of diseases caused by *K. pneumoniae* are very high, especially for newborns, leukaemia patients, and other immunodeficiency patients. With the growing use of antibiotics, multidrug-resistant (MDR) *K. pneumoniae* has become more common, posing greater difficulties and obstacles in clinical treatment. The World Health Organization recognizes extended-spectrum β-lactam (ESBL)-producing and carbapenem-resistant *K. pneumoniae* (CRKP) as a critical public health threat [5]. Transmission of *K. pneumoniae* is shown in Figure 1.

We deepened all antibiotic resistance mechanisms and genes of seven important antibiotics used to treat *K. pneumoniae* infections. We conducted a literature

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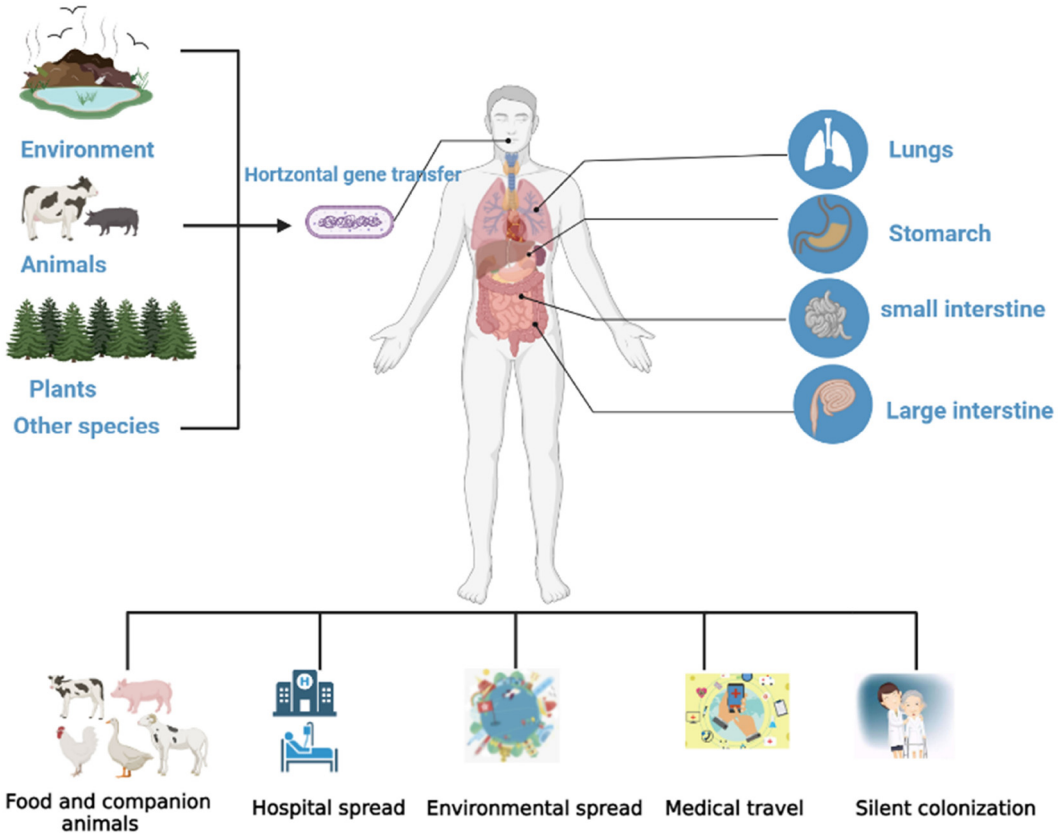

Figure 1: Transmission of *K. pneumoniae*.

evaluation of antibiotic resistance in *K. pneumoniae*. We ran a thorough literature search in PubMed, Web of Science, and Scopus, among other databases. Keywords such as antibiotics or antibiotic resistant or antimicrobial resistant or drug resistant or drug-resistant were searched in various databases, and literatures with keywords such as *K. pneumoniae* or *K. pneumoniaee* were also included. It also contains seven antibiotics, namely *β*-lactam, macrolide, aminoglycoside, lincomycin, chloramphenicol, peptides, and other themes. We also thoroughly deepened the literature listed in the papers.

2 Antibiotic resistance in *K. pneumoniae*

Antibiotics such as aminoglycosides and cephalosporins are commonly used to treat *K. pneumoniae*. The choice of an antimicrobial agent is based on the patient's health, medical history, and disease severity [9,12]. For urinary tract infections caused by MDR-resistant *Klebsiella* species, a combination of amikacin and meropenem has been suggested [6]. *Klebsiella* infections have caused liver fistulas in patients with diabetes mellitus in Taiwan, and third-generation carbapenems have been used to treat them. For patients in clinical settings, antimicrobial resistance (AMR) in MDR *K. pneumoniae* is a major public health concern, restricting treatment options [7]. When compared to individuals who received combination therapy, those who received monotherapy had more treatment failures (49% vs 25%; $p = 0.01$) [8].

Combination therapy can delay the emergence of resistance because the simultaneous use of multiple mechanisms of action increases the pharmacodynamic killing activity of antibiotics [9]. Combination therapy with carbapenems, tetracyclines, polymyxins, and fosfomycin is suggested and frequently utilized due to the increased degree of AMR in *K. pneumoniae* and the rising incidence of CRKP. Repeated exposure to a large range of antimicrobial compounds can trigger the emergence of new MDR phenotypes. With the wide abuse of β-lactam antibiotics and carbapenems in clinical practice, the detection rate of *K. pneumoniae* infection as an opportunistic pathogen is gradually increasing in clinical practice.

K. pneumoniae shows resistance against the main antibiotic classes: carbapenems, cephalosporins, aminoglycosides, and fosfomycin, leading to the therapeutic failure of these agents [10]. The development of antibiotic resistance in *K. pneumoniae* has led to a decline in the effectiveness of traditional treatments against the pathogen. Resistance may occur due to increased efflux, drug inactivation, or altered binding to the target site. Many strains of *K. pneumoniae* produce ESBL or form biofilms, further exacerbating resistance. The antibiotic resistance of *K. pneumoniae* is mainly produced in the following five ways: (1) enzymatic antibiotic inactivation and modification, (2) antibiotic target alteration, (3) porin loss and mutation, (4) increased efflux pump expression of the antibiotic, and (5) biofilm formation [11,12]. The five mechanisms conferring antibiotic resistance to *K. pneumoniae* are shown in Figure 2 and Table 1.

3 Enzymatic antibiotic inactivation and modification

Drug alteration is a major mechanism of resistance against antibiotics *in K. pneumoniae* [13]. β-Lactamase is an important resistance mechanism, which hydrolyses the β-loop of β-lactam. β-Lactamases are divided into ultra-broad-spectrum β-lactamases (ESBLs), cephalosporinases (AmpC), and carbapenemases [14–17]. The expression of these enzymes in *K. pneumoniae* renders it resistant to penicillins, cephalosporins, and carbapenems. ESBLs include SHV, TEM, OXA, CTX, and other types. AmpC is resistant to cephalosporins, cephalomycin, and enzyme inhibitors of the first to the third generation, which can be mediated by chromosomes or plasmids. Up to now, there are more than 40 genotypes of AmpC enzyme, which can spread rapidly among strains by the plasmid. The production of carbapenemases decreases the sensitivity of *K. pneumoniae* to carbapenems, and the emergence of CRKP makes the treatment difficult. According to the Ambler classification, carbapenemases can be classified into classes A, B, and D [18].

4 Antibiotic targets alteration

Fluoroquinolone antibiotics target DNA topoisomerase [19]. Aminoglycoside antibiotics target 16S rRNA. The mechanism of resistance to polymyxin in *K. pneumoniae* usually involves the modification of lipid A [20], and the mechanism of resistance to fosfomycin involves the modification targeting MurA [21]. *K. pneumoniae* causes drug

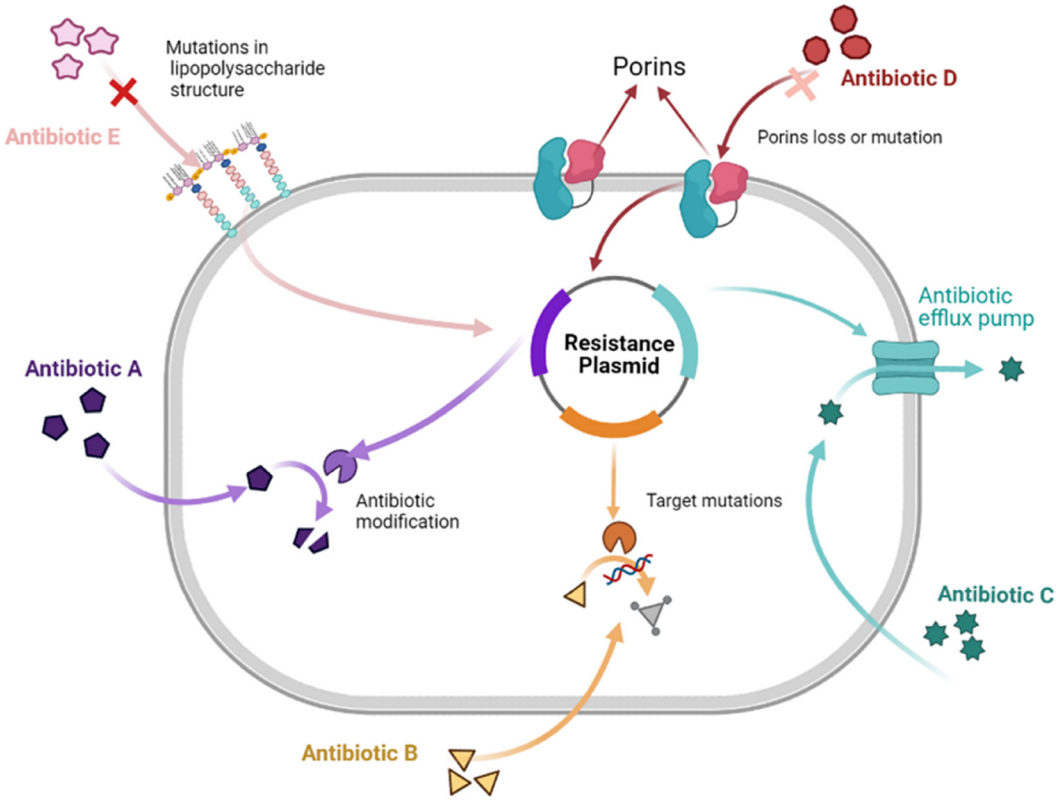

Figure 2: Various mechanisms conferring antibiotic resistance to *K. pneumoniae*.

Table 1: Resistant strategies in *K. pneumoniae*

Resistant strategies in *K. pneumoniae*	Key findings	References
Enzymatic antibiotic inactivation and modification	β-Lactamase is an important resistance mechanism, which is divided into ESBLs, AmpC, and carbapenemases	[13,18]
Antibiotic targets alteration	*K. pneumoniae* causes drug resistance by mutating the target gene or methylating some bases	[19–21]
Porin loss and mutation	*K. pneumoniae* develops resistance by reducing the entry of antimicrobial agents into the bacteria by reducing the outer membrane pore protein	[25,26]
Increased efflux pump expression of the antibiotic	Efflux pumps reduce intracellular drug concentrations by releasing antimicrobial cells outside the cell, thereby reducing susceptibility to multiple antibiotics	[29]
Biofilm formation	Biofilms have osmotic barrier properties and are resistant to antimicrobial agents	[31–33]

resistance by mutating the target gene or methylating some bases so that the corresponding antimicrobial agents cannot bind to the target site.

5 Porin loss and mutation

K. pneumoniae develops resistance by reducing the entry of antimicrobial agents into the bacteria by reducing the outer membrane pore protein. Outer membrane proteins (OMPs) or porins are trimeric transmembrane proteins that are abundantly expressed on the outer membranes of Gram-negative bacteria [22–24]. In *K. pneumoniae*, OmpK35 and OmpK36 are the two major nonspecific porins associated with AMR. LamB, OmpK26, PhoE, and KpnO porins also contribute to intrinsic resistance [25,26].

6 Increased efflux pump expression of the antibiotic

Efflux pumps are membrane proteins involved in substance expulsion that reduce intracellular drug concentrations by releasing antimicrobial cells outside the cell, thereby reducing susceptibility to multiple antibiotics [27,28]. The active efflux system AcrAB-TolC can exocytosis many kinds of antibiotics, including β-lactam, macrolides, fluoroquinolones, and tetracycline, which is an important reason for the MDR *K. pneumoniae* [29,30].

7 Biofilm formation

K. pneumoniae is prone to form biofilms, and structures such as capsular and pili play an important role in the formation of biofilms [31]. Biofilms have osmotic barrier properties and are resistant to antimicrobial agents, and one study showed that *K. pneumoniae* biofilms reduced sensitivity to gentamicin, ampicillin, and ciprofloxacin [32]. Colistin resistance has also been linked to biofilm formation [33].

8 Resistance mechanisms and genes

β-Lactam antibiotics are frequently used to treat *K. pneumoniae* infections. When patients are infected with *K. pneumoniae* that is MDR or extended drug-resistant, they have no choice but to use other antibiotics (aminoglycosides, quinolones, polymyxins, tigecycline, etc.). However, when these antibiotics are used in clinical settings, they can lead to drug resistance. Antibiotic resistance-related genes were carefully summarized, and their functions in *K. pneumoniae* are systematically presented in Table 2.

9 β-Lactamase Resistance Genes

β-Lactamase produced by *K. pneumoniae* hydrolyses the β-lactam ring in antibiotics, resulting in resistance to β-lactam antibiotics. *K. pneumoniae* is naturally resistant to numerous β-lactamase genes attributed to the prevalence of the SHV β-lactamase in the genome sequence, and ampicillin resistance is a defining trait of the organism.

10 ESBLs

ESBLs are plasmid-based antibiotic resistance pathways identified in the accessory genome. In Germany [35], the blaSHV-2 (ESBL) gene in *K. pneumoniae* was found for the

Table 2: Antibiotic resistance-related genes in *K. pneumoniae*

Characteristic	Gene name	Gene functions	References
β-Lactam	*bla*SHV, *bla*TEM, *bla*CTX	ESBLs	[34–36]
	*bla*GES, *bla*SFO, *bla*PER, *bla*TLA, *bla*VEB, *bla*KLUC-5	Lateral gene transfer	[37–40]
	bla KPC *Bla* NDM, *bla* VIM, *bla* IMP, and *bla* OXA	Carbapenemase	[41,42]
	*bla*CMY, *bla*DHA, *bla*FOX, *bla*MOX	AmpC plasmids	[43,44]
Aminoglycoside	aac, ant, aph gene,16S rRNA methylase	Plasmid-encoded	[45–48]
	AcrAB-TolC, kpnEF, KpnO	Efflux pump systems	[49]
Quinolone	DNA gyrase, topoisomerase IV	Quinolone-binding targets	[50]
	OmpK36, acrAB, kdeA, OqxAB, aa(6')-Ib-cr	PMQR	[51–54]
Polymyxin	phoPQ, pmrA, pmrD, and mgrB	Regulative gene	[55–57]
	mcr-1	Via plasmid	[58–60]
Tigecycline	AcrAB-TolC, OqxAB	Efflux pump systems	[61]
	RarA, RamA, RamR, and AcrR	Regulators of efflux pumps	[61]
	rpsJ	Encoding ribosome	[62]
	tetA	Efflux pump systems	[61]
Fosfomycin	fos	Via plasmid	[63]

first time. Soon after, blaTEM-3, a viral vector ESBL mutant gene, was found in France [64]. The enlarged-spectrum action of ESBL genes against β-lactams, including third-generation carbapenems, is inhibited by clavulanic acid [65].

K. pneumoniae that produces ESBL has become a prevalent pathogen in hospital infection outbreaks. CTX-M gradually superseded TEM and SHV as the main genotype of ESBLs owing to the accessibility of plasmids and transposons generating *bla*CTX-M-type ESBLs [36]. Other ESBL genotypes were also transmitted to *K. pneumoniae* by horizontal gene transfer, including *bla*OXA type ESBLs [38] and the uncommon genes *bla* GES, *bla* SFO [37], or *bla* PER, *bla* TLA, *bla* VEB [40], and *bla* KLUC-5 [39]. *K. pneumoniae* that produces ESBL is becoming more common over the world, with endemic rates of up to 50% in some areas [39]. Carbapenems have traditionally been the treatment of choice for treating ESBL-producing bacterial infections.

11 Carbapenem resistance genes

Carbapenem use has increased significantly as a result of the MDR phenotypic characteristics of ESBL-producing *K. pneumoniae* strains. Carbapenem resistance has evolved, possibly as a result of the selective pressure of carbapenems treatment, and *K. pneumoniae* has emerged as the most prevalent carbapenem-resistant *Enterobacteriaceae* (CRE).

The carbapenem enzymes regulated by plasmids are still the most concerned pathway of multidrug resistance. KPC is a serine-based class β-lactamase that is the most common and damaging carbapenemase in *K. pneumoniae*. Clonal group 258 (CG258) is linked to KPCs [66,67]. ST258 (ST258) is found in Europe, America, and Asia, while ST11 is prevalent in Asia [68–72]. *bla* KPC genes are discovered in a specific Tn4401 transposition form and are incorporated onto plasmids of several plasmid types in addition to clonal dissemination [73], making it easier to spread the gene to others [74]. *Bla* NDM, bla_{VIM}, bla_{IMP}, and *bla* OXA are other carbapenemase genes found in *K. pneumoniae* [41]. Ripabelli et al. evaluated resistance to 19 antibiotics in Italy by disk diffusion and agar dilution method. The highly pathogenic variant of NDM-1 was screened for the first time in their study [75]. Such resistance genes can cause a large number of carbapenemase-producing *Enterobacteriaceae* (CPE) to be resistant to many commonly used clinical antibiotics, resulting in the difficult clinical treatment of CPE and high mortality. KPCs are generally resistant to conventional β-lactamase inhibitors, creating a therapeutic issue [76]. These resistances are virtually impossible to regulate due to the translocation of carbapenemase-encoding genes from *K. pneumoniae* plasmids onto the chromosome [41]. In the lack of the carbapenemase gene, *K. pneumoniae* can become carbapenem-resistant, owing to the loss of porin, increased effluent pump, and excessive production of *β*-lactamases such as ESBL and AmpC. Clinically, CRKP infection is a tough problem in the clinic [77].

12 Plasmid-mediated AmpC Genes

Plasmid-mediated AmpC-like cephalosporins evolved and dispersed in these species due to *K. pneumoniae*'s exceptional versatility in adding *β*-lactamase genes onto

transportable plasmids that facilitate the dissemination [43,44]. The *bla* AmpC gene sequences *bla* CMY, DHA, FOX, and MOX are most frequent in *K. pneumoniae*. *K. pneumoniae* had better β-lactam resistance owing to the presence of *bla* AmpC coupled with gene encoding losses or enhanced efflux, similar to *bla*ACT-1. Plasmid genes can be readily abundantly expressed on plasmids due to the increase of many copies or promoter strength, resulting in carbapenem resistance [44].

Multiple-lactamase genes, including AmpC, KPC, SHV, and β-lactamase inhibitors, may be present in some *K. pneumoniae* strains. Multiple-resistant genes carried by the same strain have synergistic effects. For instance, while NDM, Vim, and IMP are not resistant to monocyclic antibiotics like aztreonam, they may develop resistance to aztreonam if ESBL or AmpC is present.

13 Aminoglycoside resistance genes

Aminoglycosides were commonly used in antibacterial chemotherapy from 1940 to 1980 until third-generation cephalosporins, carbapenems, and fluoroquinolones replaced them [78]. *K. pneumoniae* acquired the primary antibiotic resistance mechanisms during this time, including drug-modifying enzymes with varied functions, such as adenylation, acetylation, or phosphorylation as well as all transposon resistance genes from the *aac, aph,* and *ant* gene families [45].

The use of aminoglycosides was limited, which slowed down the emergence of novel resistance genes till the armA gene family expressed 16S rRNA methylase [46]. In *K. pneumoniae*, these genes are plasmid-encoded, and while drug-modifying enzymes inhibit activity [48], 16S rRNA methylase is resistant to almost all aminoglycosides, including plazomicin and newly discovered aminoglycosides [47].

Genes on chromosomes also have a role in the *K. pneumoniae* resistance to aminoglycoside antibiotics, which modify cell permeability through changes in the *AcrAB-TolC* and *KpnEF* efflux pump systems, as well as the loss of the putative porin *KpnO*. The *AcrAB-TolC* and *KpnEF* efflux pump systems changed throughout time, resulting in variable levels of resistance to different aminoglycoside antibiotics. Tobramycin and gentamicin resistance was predominant in the former, whereas tobramycin and vancomycin resistance was predominant in the latter, with gentamicin and streptomycin resistance being minor. This implies that various aminoglycosides correspond to various cell channels. Resistance to tobramycin, streptomycin, and spectinomycin was linked to the loss of the pore protein *KpnO* [49].

14 Quinolone resistance genes

Quinolone antibiotics function by inhibiting topoisomerases, which hinder DNA replication in bacteria. Mutations in the target gene increased MDR efflux production, and mutations to enzymes and proteins all contribute to *K. pneumoniae's* tolerance to fluoroquinolones [79]. Topoisomerase IV and DNA gyrase are quinolone-binding targets with chromosomal resistance mechanisms. ParC and gyrA *K. pneumoniae* mutations were found earlier and also more frequently [50]. Changes in cell permeability in *K. pneumoniae* were linked to drug-resistant strains.

Among the most common are the deficiency of OmpK36 [51], overexpression of the gene acrAB [52], and nonalteration production of kdeA [53]. OqxAB is found in many bacteria and has been linked to plasmid-mediated quinolone resistance (PMQR) [80]. *K. pneumoniae* quinolone resistance has also been linked to efflux pump regulators [81].

The PMQR determinant, which is found in *K. pneumoniae* and other *Enterobacteriaceae* species, is another type of quinolone resistance gene. These genes encode a protein family that protects DNA gyrase and topoisomerase IV from quinolones. In *K. pneumoniae* [82], aa(6')-Ib-cr, another PMQR gene, is thought to be the only one involved in quinolone modification. It can inactivate limited quinolones that contain the enzyme's substrate, as well as other antibiotics. It was recently discovered on chromosomes as well. PMQR gene expression provides mechanisms for low or moderate quinolone resistance, but it also creates favourable conditions for chromosomal genetic changes to emerge [83].

15 Polymyxin resistance gene

The recent appearance of CRE has necessitated a reintroduction of *polymyxins* as a last-line treatment [84]. Polymyxin resistance in *K. pneumoniae* is typically induced by alterations in regulative genes, for instance, *mgr*B, which regularizes the changes of bacterial lipid A, a target of polymyxin antibiotics, lowering polymyxin interaction [55–57].

In 2016, the *mcr*-1 gene conferred colistin resistance via plasmid in an *E. coli* strain from China [85]. This study

illustrates that easily transmissible genes potentially result in pan-resistance. In China, mcr-1 is rarely discovered in *K. pneumoniae* BSI isolates and is more commonly seen in *E. coli*. The first mcr-1 case was discovered in America in 2016. A pan-resistant isolate of *K. pneumoniae* was discovered in September 2016, although colistin resistance was not mediated by *mcr-1* in this isolate [58–60].

16 Tigecycline resistance genes

Tigecycline, as a new tetracycline antibiotic, has a broad-spectrum activity against ESBL-producing strains [86]. It has been accustomed to healing *K. pneumoniae* infection since 2005 and the tigecycline resistance in *K. pneumoniae* was reported shortly after its first use. It is known that the resistance gene of this antibiotic is located on the chromosome, and the mechanism includes the modification of 30S and 16S ribosomal targets of antibiotics and the alteration of cell permeability [61]. The mechanism of antibiotic resistance is mainly related to the Ade-ABC efflux pump, Oqx-AB efflux pump, KpgABC efflux pump, Tet (A) mutant, and ribosomal protein.

Active efflux pump widely exists in the genome of *K. pneumoniae*. It can selectively or nonselectively pump the drugs or substrates in the bacteria out of the body, resulting in the decrease of antibacterial drug concentration in the body and drug resistance. The efflux pump transport systems involved in the resistance of *K. pneumoniae* to tigecycline are the AcrAB-TolC efflux pump, OqxAB efflux pump, KpgABC efflux pump, and Tet (A) efflux pump variants. Among them, the AcrAB TolC efflux pump, OqxAB efflux pump, and KpgABC efflux pump belong to the resistance nodule cell division family, and Tet (A) efflux pump variant belongs to the major facilitator super superfamily.

Ribosomal protein S10 is encoded by the *rpsJ* gene and is a component of the ribosomal 30S subunit. It is located near the main binding site of tetracycline and tigecycline in the ribosomal 30S subunit. Villa et al. [62] obtained three *K. pneumoniae*-resistant strains of tigecycline. One strain indicated that the coding gene *rpsJ* of S10 ribosomal protein adjacent to the target of tigecycline in the ribosomal 30S subunit had a point mutation. The *reps* mutation alone could confer tigecycline resistance to *Enterococcus faecalis* and conducted an adaptability test on six common clinical pathogens [87]. Therefore, the structural change of ribosomal protein S10 is also a potential new mechanism, which deserves attention in the follow-up research. Lupien et al. [88] show that in addition to S10, ribosomal proteins S3 and S13 are also located near the binding domain between tetracycline and ribosomal subunit, and S3 has been proved to have the function of maintaining the structural integrity of the tetracycline-binding site. Similarly, it is inferred that the structural mutation of the S3 protein may also result in tigecycline resistance. Studies have shown that without the involvement of efflux pump, *rpsJ* gene mutation can lead to specific resistance to tigecycline.

17 Fosfomycin resistance genes

Fosfomycin was discovered in 1969 and has a wide range of bactericidal activities [89]. Although fosfomycin is an old antibiotic, it has received renewed interest and is increasingly being used to treat infections caused by MDR bacteria [90]. However, with the increasing use of fosfomycin, resistant strains are being reported [91,92]. Resistance mechanisms of fosfomycin have been reported, including amino acid replacement or overexpression of the fosfomycin target protein MurA, deficient or reduced expression of two transporters (GlpT and UhpT), and the presence of the fos gene encoding a fosfomycin-modified enzyme that inactivates fosfomycin by activating glutathione S-transferase activity [93]. Liu et al. reported that the fosA3 gene is the main mechanism of the resistance of CRKP to fosfomycin, which can be transmitted by plasmid in hospitals. Fosfomycin target protein MurA and glpT transporter mutations were found in fosA3-negative CRKP with fosfomycin resistance [63].

18 Other mechanisms

Tolerance and persistence have long been recognized as helping bacteria survive antibiotic exposure [94]. Persister cells (persistence phenotype) with an epigenetic feature that allows them to be resistant to antibiotics while remaining latent and metabolically inactive [95].

Changes in the number of certain proteins, metabolites, and signal transduction, such as toxic chemical modules, adenosine triphosphate, and guanosine (penta) tetraphosphate, have been associated with the creation of persister formation. Despite contradicting changes in proteins, metabolites, and signal transduction, persistent bacteria form as a result of sluggish growth alone, according to Pontes and Groisman [96]. Persister cells have been seen in bacterial populations before antibiotics were

introduced, sluggish growing or quiescent due to phenotypic switching [97,98]. After the antibiotics are removed, the surviving persisters regenerate into a new heterogeneous population with tolerant and sensitive subpopulations, much like the initial culture [99]. Increased antibiotic concentrations and longer antibiotic treatment reduced *K. pneumoniae* persistence [100]. In the fight against MDR, understanding the molecular processes governing bacterial tolerance and persistence phenotypes is critical, as it will enable the identification of new targets for creating novel anti-infective treatments.

19 Conclusions

In this study, the antibiotic resistance status, antibiotic resistance mechanism, and resistance genes of *K. pneumoniae* were described. In the resistance mechanism, ESBLs, carbapenemase, or AmpC targets alteration, porin loss and mutation, efflux pump overexpression, and horizontal dissemination of mobile gene elements were also studied in many fields. Up to now, the mechanism of antibiotic resistance of *K. pneumoniae* has not been thoroughly studied in many aspects, such as how biofilm formation regulates antibiotic resistance. Addressing the escalating prevalence of AMR, antibacterial drug therapy effect weakened, clinical treatment of severe problems such as no cure, the new drug-resistant bacteria drugs research and development work is imminent.

Novel therapies like phage therapy, nanoparticles, phytotherapy, photodynamic therapy, and antimicrobial peptides are being used to overcome resistance in *K. pneumoniae* infections [101–105]. The mechanisms of antibiotic resistance of *K. pneumoniae* are complex and diverse. We should provide insights into useful strategies to combat this important pathogen. How to prevent and to treat infection has become an urgent problem to be solved. It is important to determine the main antibiotic resistance genotypes for the rational use of antibiotics. Understanding *K. pneumoniae* antibiotic resistance mechanisms and molecular characteristics will be important for the design of targeted prevention and novel control strategies against this pathogen. At the same time, to effectively reduce and control the generation and spread of MDR bacteria, we should actively carry out antibiotic resistance monitoring and timely grasp the mechanism and characteristics of antibiotic resistance.

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