

Mechanisms of Antibiotic Resistance and Developments in Therapeutic Strategies to Combat *Klebsiella pneumoniae* Infection

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Abstract: Infections with drug-resistant bacteria have become one of the greatest public health challenges, and *K. pneumoniae* is among the top six drug-resistant bacteria. *K. pneumoniae* often causes nosocomial infections, leading to illnesses such as pneumonia, liver abscesses, soft tissue infections, urinary tract infections, bacteremia, and in some cases death. As the pathogen continues to evolve and its multidrug resistance increases, *K. pneumoniae* poses a direct threat to humans. Drug resistance in *K. pneumoniae* may occur due to the formation of biofilms, efflux pumps, and the production of β -lactamases. In many cases, resistance is further enhanced by enzymatic modification and loss of porins. Drug resistance to *K. pneumoniae* has led to a decline in the effectiveness of conventional therapies against this pathogen. Therefore, there is an urgent need to accelerate the development of new antibiotics and explore new therapeutic approaches such as antimicrobial peptides, phages, traditional Chinese medicine, immunotherapy, Antimicrobial nanoparticle technology, antisense oligonucleotides and gene editing technologies. In this review, we discuss the mechanisms of drug resistance in *K. pneumoniae* and compare several new potential therapeutic strategies to overcome drug resistance in the treatment of *K. pneumoniae* infections.

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

Introduction

Klebsiella pneumoniae (*K. pneumoniae*) is a gram-negative bacterium found primarily in the respiratory tract and intestines of humans, often causes nosocomial infections, leading to illnesses such as pneumonia, liver abscesses, soft tissue infections, urinary tract infections, bacteremia, and in some cases death.^{1–3} Due to the irrational use of some antibiotics and the evolution of bacteria, drug-resistant bacterial infections have become one of the greatest public health challenges. In 2019, more than 1.2 million people died from drug-resistant bacterial infections, exceeding the number of deaths caused by HIV/AIDS or malaria. *K. pneumoniae* is also one of the six major drug-resistant bacteria.^{2,3} The World Health Organization recognizes that extended-spectrum β -lactam (ESBL) and carbapenem-resistant *K. pneumoniae* (CRKP) pose significant public health threats. Currently, CRKP has been reported in Greece, China, Eastern Europe, Argentina and the Philippines.⁴ In Europe alone, this strain type is reported to cause over 90,000 infections and over 7000 deaths annually, accounting for 25% of deaths caused by multidrug-resistant (MDR) bacterial infections.⁵ The global resistance rate of MDR bacteria is increasing. The detection rate of CRKP is increasing from less than 0.1% to 24.6% in the United States. The resistance rate of *K. pneumoniae* isolates in Greek hospital wards reaches 52.4%. The China Antibiotic Surveillance Network (CHINET) shows that the resistance rate of *K. pneumoniae* to carbapenems increased from 2.4% to 32.8%.⁶

This increased resistance has severely limited therapeutic options and makes combating infections with multidrug-resistant (MDR) and extremely drug-resistant (XDR) *K. pneumoniae* a global challenge.^{7–9} The search for innovative therapeutic strategies has become particularly urgent. *K. pneumoniae* poses an immediate threat to humans and is

becoming increasingly multi-resistant as the pathogen continues to develop. However, there are no approved treatments or vaccines other than traditional antibiotics, and there is an urgent need to accelerate the development of new antibiotics and explore new therapeutic approaches. In recent years, the number of published manuscripts on novel therapeutic strategies for *K. pneumoniae* has increased dramatically. In this review, we present the mechanisms of antibiotic resistance in *K. pneumoniae* and compare several new potential therapeutic strategies to overcome resistance in the treatment of *K. pneumoniae* infections.

Mechanisms of Antibiotic Resistance

Antibiotic resistance in *K. pneumoniae* is achieved through multiple mechanisms that enhance antimicrobial resistance through biofilm formation while also undergoing frequent horizontal transfer of antibiotic resistance genes;⁷ Production of a variety of β -lactamases, including broad-spectrum β -lactamases (eg TEM-30, TEM-31, TEM-50) and AmpC β -lactamases, capable of antibiotics, including clavulanate, vincristine and tazobactam, neutralize and sulbactam. Mutations in KPC enzymes, AmpC, efflux pumps, and outer membrane permeability result in resistance to β -lactam/ β -lactamase inhibitor; Furthermore, mutations in efflux pumps (eg, AcrAB, KdeA, CepA, etc.) result in resistance to a variety of drugs, including mucins, tigecycline, and ceftazidime-avibactam.¹⁰ Aminoglycoside acetyltransferases (eg aac(3)-II and aac(6')-Ib) and plasmid-mediated quinolone resistance are key factors in the resistance of *K. pneumoniae* to these drugs; Reduced membrane permeability, evidenced by the deletion or mutation of the pore proteins OmpK35 and OmpK36, as well as modification of the lipopolysaccharide structure (via phosphoethanolamine, galactosamine, etc.) have also been associated with resistance to peptide antibiotics. The various mechanisms by which *K. pneumoniae* develops resistance to multiple antibiotics and the associated resistance genes are summarized in Table 1.

Biofilm Formation

Biofilms are highly resistant to antimicrobial drugs and immune responses and help organisms to attach to microbial communities, including proteins, extracellular DNA and extracellular polysaccharides, on living or non-living surfaces, providing a protective lifestyle for bacteria.¹⁹

K. pneumoniae usually forms biofilms on the surfaces of medical devices and objects. *K. pneumoniae* can protect bacteria from adverse conditions in the host body (eg, hypoxia and nutrient deficiency) as well as antimicrobial drugs through the formation of biofilms,²⁰ which increase their persistence on the organism's tissue surface and on medical devices. Biofilms increase bacterial resistance and are closely associated with high rates of resistance in clinical isolates of *K. pneumoniae*, with resistance to antimicrobial drugs being 10 to 1000 times higher in the biofilm state of *K. pneumoniae* than in the planktonic state.²¹ This increases the pressure on diagnosis and treatment.²² *K. pneumoniae* biofilm-forming strains isolated from medical devices were found to be 10–25 times more resistant to ceftazidime, ciprofloxacin, and gentamicin than free-living strains.²³ Biofilm formation in *K. pneumoniae* is closely related to the luxS gene, and luxS, together with genes such as micF, ompK36 and ramA, can regulate the biofilm formation.²⁴ Some

Table 1 *K. pneumoniae* Resistance to Multiple Antibiotics and the Associated Resistance Genes

Mechanism	Genes Name	Antibiotics	Refs
Biofilm formation	AmpR	Amikacin, ampicillin, cephalosporins, cefepime, cefoperazone, ceftazidime, ciprofloxacin, gentamicin, netilmicin, meropenem, piperacillin-tazobactam	[11]
Producing β -lactamases	TEM, SHV, CTX-M, OXA	Carbapenems penicillins, cephalosporins, monobactams	[12,13]
Enzymatic modification	AACs, ArmA, RmtB, RmtC	β -lactams, lincosamide, aminoglycosides, streptogramins, quinolones	[14,15]
Efflux pumps	AcrAB, KdeA, CepA	Tetracyclines, quinolones, fluoroquinolones, nitrofurantoin, chloramphenicol, polymixins, macrolids, aminoglycosides, cephalosporins, chlorhexidine, rifampin, copper/silver	[16,17]
Reducing membrane permeability	OmpK35, OmpK36	β -lactams, quinolones, chloramphenicol, colistin, aminoglycosides, nalidixic acid, tetracycline	[18]

researchers have also found that the *acrA* gene is upregulated to some extent during biofilm production²⁵ and that a certain concentration of efflux pump inhibitor can promote the formation of *K. pneumoniae* biofilm.

Producing β -Lactamases

β -lactams, including carbapenems, cephalosporins, and penicillins, are widely used due to their therapeutic efficacy and wide range of options. In recent decades, the number of β -lactam-resistant bacteria (eg, cephalosporin-resistant Enterobacteriaceae) has increased rapidly worldwide. The production of β -lactamases is the main cause of resistance to this class of antimicrobials.²⁶

K. pneumoniae produces extended-spectrum beta-lactamases (ESBLs) that are capable of hydrolyzing a variety of antibiotics such as penicillin and cephalosporins. Since the first report of penicillin resistance in *K. pneumoniae* in the 1960s, there are now more than 200 ESBLs, most of which can hydrolyze via serine residues and a small number of which use zinc ions to destroy the β -lactam ring.² Carbapenemase is a type of ESBLs, and carbapenemase production is the most common mechanism resistance of *K. pneumoniae* to carbapenem antibiotics. Currently, carbapenemases are mainly divided into three categories: A, B and D. Class A includes KPC, SPM and SME; Class B includes metallo- β -lactamases such as NDM, VIM and IMP; and class D consists primarily of OXA, with classes A and D being serine carbapenemases. The genes encoding carbapenemases are mainly located on plasmids and spread through horizontal transmission, easily leading to nosocomial infection outbreaks.²⁷ The AmpC enzyme is also a type of β -lactamase that evolved through the translocation of the AmpC gene from the chromosome to the plasmid.²⁸ It not only hydrolyzes broad-spectrum β -lactam antibiotics, but also resists the inhibitory effect of β -lactamase inhibitors such as clavulanic acid, but the enzyme cannot hydrolyze carbapenems. However, if *K. pneumoniae* produces ESBLs or AmpC together with altered membrane pore proteins, then this is also an important mechanism for its resistance to carbapenem antibiotics.

Enzymatic Modification

Bacteria use a number of molecular strategies such as DNA mutations and protein translation modifications to resist antibiotics, so that they cannot interfere with bacterial metabolism and can be degraded intracellularly.²⁹ Among the mechanisms of the main resistance of *K. pneumoniae* bacteria to aminoglycoside antibiotics, the most widespread is resistance mediated by aminoglycoside acetyltransferases enzymes which effectively prevents the binding of aminoglycoside antibiotics to the ribosome and deprives them of antibacterial activity. Aminoglycoside-acetyltransferase enzymes are present in the bacterial cytoplasm, which can be classified into (AACs), nucleotidyltransferases (ANTs), and phosphotransferases (APHs), etc. According to their modifying activity.¹⁴ The genes of aminoglycoside acetyltransferases enzymes are encoded by plasmids and transposons that can be easily transferred between strains, resulting in increased bacterial resistance to aminoglycoside antimicrobials.³⁰ The most common aminoglycoside acetyltransferase enzymes in *K. pneumoniae* isolates are the enzymes *aac*(3)-II and *aac*(6')-Ib.³¹ Furthermore, modification of 16S rRNA methyltransferases is a high-level aminoglycoside resistance mechanism in Gram-negative pathogens,³² and the prevalence of 16S rRNA methylase in clinical isolates of *K. pneumoniae* has been reported to be quite high. Genes encoding aminoglycoside acetyltransferase enzymes and 16S rRNA methylases (ArmA, RmtB and RmtC) are transferred to other organisms via mobile genetic elements linked to other resistance determinants such as ESBLs and carbapenemases, leading to the emergence of multidrug-resistant tribes leads.³³

Efflux Pumps

Drug efflux pumps are active transport proteins that can actively excrete various antibiotics and other compounds from bacteria after substrate-induced activation of the efflux pump gene,^{1,34} thereby reducing the concentration of drugs in bacteria and thus generating drug resistance, and they include five families (SMR, MFS, RND, ABC and MATE families).

Currently, the efflux system of *K. pneumoniae* is dominated by the AcrAB-TolC system and the OqxAB system in the RND family, while the AcrAB-TolC system is dominant and β -lactam antibiotics, macrolide antibiotics, fluoroquinolone antibiotics, tetracycline antibiotics, amido-alcohol antibiotics etc. and disinfectants. The repressive regulatory genes of this system, *acrR* and *ramR*, carry deletion mutations that lead to overexpression of the AcrAB-TolC efflux pump, which

in turn plays a key role in pan-resistance of *K. pneumoniae*.^{35,36} Autosomal transfer of the OqxAB gene to the plasmid can result in a ten-fold increase in its efflux pump expression level,³⁷ and over expression of OqxAB reduces the susceptibility of *K. pneumoniae* to a variety of antimicrobial drugs by four-fold or more, resulting in the development of drug resistance.³⁸

Reducing Membrane Permeability

Altered membrane permeability affects drug influx and hinders the interaction between the drug and its intracellular target, leading to resistance. Outer membrane proteins (OMP) or porins are trimeric protein channels on the outer membrane of gram-negative bacteria through which antimicrobial drugs can enter the bacterium and bind the corresponding proteins to act.³⁹ When a mutation occurs in the bacterium that causes the outer membrane pore proteins to be absent or reduced, this results in a reduction in the number of antimicrobial drug molecules that can enter the bacterium, which can lead to bacterial drug resistance.⁴⁰

K. pneumoniae primarily expresses two nonspecific porins, OmpK35 and OmpK36, which allow passive diffusion of hydrophilic small molecules and antimicrobial drugs (eg, β -lactams and fluoroquinolones) into the bacterium to exert antimicrobial effects. Since porin expression can be influenced by factors such as coding sequence or promoter site mutations or insertional deletions, resulting in deletion or alteration of porins, antimicrobial resistance can occur by preventing entry of antimicrobial agents into the bacterium. The expression of OmpK35 and OmpK36 porins in *K. pneumoniae* is inversely associated with ESBL production and confers resistance to cephalosporins, meropenem, ertapenem, ciprofloxacin and chloramphenicol.⁴¹ Strains lacking OmpK35 and OmpK36 also show high levels of resistance to antimicrobial drugs.⁴² Experiments in animal models of peritonitis have shown that deficiency of OmpK35/36 proteins reduces pathogenicity and increases resistance to various antibiotics.⁴³

Therapeutic Strategies

Treatment of carbapenem-resistant *K. pneumoniae* (CRKP) infections is a major challenge, with polymyxins, tigecycline, fosfomycin and aminoglycosides being the main treatment agents.⁴⁴ However, increasing antibiotic resistance and difficulties in developing new antibiotics have made the search for new therapeutic strategies an urgent task for the medical community.⁴⁵ CRKP exhibits a high level of resistance to aminoglycosides and carbapenems, although carbapenems are still an effective option for the treatment of CRKP that does not produce carbapenemases.⁴⁵ Antimicrobial combination therapies, particularly polymyxin-based combinations, have shown significant synergistic effects.^{46,47} Compared with traditional treatment regimens, new antibiotics and their synergistic combinations that have been marketed or approved in the later stages of the procedure have shown superior efficacy and safety.

Referring to the 2022 Infectious Diseases Society of America guidelines for the treatment of ultra-broad-spectrum β -lactamase-producing Enterobacteriaceae bacteria, carbapenem-resistant Enterobacteriaceae bacteria, and refractory drug-resistant *Pseudomonas aeruginosa* infections, the Conventional therapeutic regimens for *K. pneumoniae* summarized in Table 2. Given the increasing multidrug resistance in *K. pneumoniae*, it is essential to take new measures to combat drug-resistant bacteria, including the development of novel drugs and non-antibiotic alternatives that are both effective against infectious diseases and safe. The different treatment alternatives are described in Table 3 and Figure 1.

Novel Antibiotics

Several studies have focused on finding drugs that act synergistically with polymyxins, such as sertraline, levopromazine, the LpxC inhibitor Chir-090, and selective estrogen receptor modulators.^{64–66} Meanwhile, the design and development of novel polymyxin analogues such as CB-182804 and Queensland aim to improve the activity and safety of polymyxins.^{67,68} Furthermore, the synthesis of novel antibiotics such as avibactam, plazomicin, eravacycline and cefiderocol as well as the development of synthetic peptides have provided new ideas for the treatment of CRKP infections.

Prazosin is a new semi-synthetic aminoglycoside antibiotic with better antibacterial activity against *Klebsiella pneumoniae*, which produces carbapenemases or ESBLs, which improves efficacy and reduces toxicity compared to mucomycin.⁶⁹ Cefdinir is a new iron-carrying cephalosporin that enters the bacterial cell via an iron transport protein.

Table 2 Recommended Dosage of Antibiotics for Treating Infections Caused by *K. Pneumoniae*

Drug	Dose Administration Route	Target Pathogen
Amikacin	Cystitis: 15 mg/kg/dose IV once; All other infections: 20 mg/kg/dose IV once; Adjusting subsequent dosing and dosing intervals based on pharmacokinetic evaluation results	ESBL-KP, AmpC-KP, CRKP
Cefadil	2 g IV every 8 hours, infusion time exceeding 3 hours	CRKP
Ceftazidime avibactam	2.5 g IV every 8 hours, infusion time exceeding 3 hours	CRKP
Ceftazidime Avibactam combined with Amtrazumab	Cefotaxime avibactam: 2.5 g IV every 8 hours, infusion time exceeding 3 hours, if possible, used together with Ceftazidime Avibactam Combination of Amtrazumab: 2 g IV every 8 hours, infusion time exceeding 3 hours, if possible, used together with Ceftazidime Avibactam	Metalloenzyme producing-CRKP
Ciprofloxacin	400 mg IV every 8–12 hours or 500–750 mg PO every 12 hours	ESBL-KP, AmpC-KP
Polymyxin E	Reference International Consensus Guide	CRKP
Elaclycline	1 mg/kg/dose IV every 12 hours	CRKP
Ertapenem	1 g IV every 24 hours, infusion exceeding 30 minutes	ESBL-KP, AmpC-KP
Fosfomycin	Cystitis: 3 g PO × 1 dose;	ESBL-KP
Gentamicin	Cystitis: 5 mg/kg/dose IV once; All other infections: 7 mg/kg/dose IV once; Adjust subsequent dosage and dosing interval based on pharmacokinetic evaluation results	ESBL-KP, AmpC-KP, CRKP
Imipenem-cilastatin	Cystitis (standard infusion): 500 mg IV every 6 hours, infusion exceeding 30 minutes All other ESBL-KP or AmpC-KP causes infection: 500 mg IV every 6 hours, infusion exceeding 30 minutes; All CRE and CRAB lead to infection: 500 mg IV every 6 hours, infusion for more than 3 hours	ESBL-KP, AmpC-KP, CRKP
Imipenem cilastatin rilibatam	1.25 g IV every 6 hours, infusion for more than 30 minutes	CRKP
Levofloxacin	750 mg IV/PO every 24 hours	ESBL-KP, AmpC-KP, CRKP
Meropenem	Cystitis (standard infusion): 1 g IV every 8 hours, infusion exceeding 30 minutes All other ESBL-KP or AmpC-KP infections: 1–2 g IV every 8 hours, infusion for more than 30 minutes; all other CRE and CRAB infections: 2 g IV every 8 hours, infusion for more than 3 hours	ESBL-KP, AmpC-KP, CRKP
Meropenem Farobartan	4 g IV every 8 hours, infusion for more than 3 hours	CRKP
Furantoin	Cystitis: Large crystals/monohydrate (capsule), 100 mg PO every 12 hours Cystitis: Oral suspension, 50 mg every 6 hours	ESBL-KP, AmpC-KP
Plazomicin	Cystitis: 15 mg/kg IV once All other infections: 15 mg/kg IV once; Adjusting subsequent dosing and dosing intervals based on pharmacokinetic evaluation results	ESBL-KP, AmpC-KP, CRKP
Tigecycline	200 mg IV per dose, followed by 100 mg IV every 12 hours	CRKP
Tobramycin	Cystitis: 5 mg/kg/dose IV once All other infections: 7 mg/kg/dose IV once; Based on pharmacokinetic evaluation results, adjust the dosage and interval of administration for <i>Pseudomonas aeruginosa</i>	ESBL-KP, AmpC-KP, CRKP
Trimethoprim sulfamethoxazole	Cystitis: 160 mg (calculated as trimethoprim) IV/PO every 12 hours Other infections: 8–10 mg/kg/day (calculated based on trimethoprim), with IV/PO evenly distributed every 8–12 hours; Maximum daily dose of trimethoprim 960 mg	ESBL-KP, AmpC-KP, CRKP

Compared to ceftazidime or cefepime, it binds to free iron and increases its concentration in the bacterial periplasm, is extremely stable against carbapenemases and avoids resistance caused by mutations in the pore protein channel and overproduction of the efflux pump.⁷⁰

The advent of bacterial genomics has opened the door to the discovery of new antibiotics. A recent study used a subtractive genomics approach to identify the bacterial DNA adenine methyltransferase of *K. pneumoniae* as a new drug target from hypothetical proteins. This suggests that it is theoretically possible to find important target proteins in *K. pneumoniae* using computational analysis methods.⁴⁸ Although inhibiting these protein targets in vitro is challenging and requires overcoming obstacles in penetrating cellular constraints, this study succeeded in identifying potential new antibiotics, konembin, through a combination of computational drug design and bioinformatics approaches. In addition,

Table 3 A Account of Alternative Treatments for *K. pneumoniae* Infections Available

	Therapies/Strategies	Benefit Over the Other Therapies	Reference
1	Novel Antibiotics	There is resistance to pore proteins, and there are non- β -lactam alternatives available for the treatment of multi-drug resistant bacterial infections.	[48–50]
2	Antimicrobial peptides	Compared with conventional antibiotics, AMPs have the advantages of broad-spectrum antibacterial activity, low drug resistance, high cellular selectivity, low level of pathogen resistance, and relatively short amino acid sequences.	[51,52]
3	Phages	The phage resource pool is rich and diverse, so there is no need to worry about bacteria developing resistance, and phages have phage lytic enzymes that can damage bacteria. Phage therapy has not yet been found to have significant side effects, is highly specific for pathogens, and has less impact on the normal microbial population of the human gut. Another advantage of phages is that they can spread rapidly through the body and organs, such as the brain, prostate, and bones, which are usually beyond the reach of antibiotics.	[53–55]
4	Traditional Chinese Medicine	It has multi-targeted antimicrobial action, low resistance to infection, and modulates the body's immune function, providing unique antimicrobial advantages against multi-drug resistant (MDR) bacteria.	[56,57]
5	Immunotherapy	Effective in preventing <i>Klebsiella pneumoniae</i> infections, the vaccine has multiple targets for triggering host-specific antibody or T-cell activation and reduces the incidence of drug resistance through multiple mechanisms, making it more suitable for preventing community-acquired or hospital-acquired infections.	[58–60]
6	Antimicrobial Nanoparticle Technology	The combination of nanomaterial-loaded antibiotics and photothermal therapy can be performed at low doses of antibiotics with efficient antimicrobial capacity.	[61]
7	Antisense Oligonucleotides and Gene Editing Technologies	Gene-edited recombinant resistance boxes allow for the removal of bacterial resistance genes.	[62,63]

microbial secondary metabolites found by the traditional route from ecosystems have shown potential for the discovery of new antibiotics, such as the antibiotic ludunin produced by *Staphylococcus lugdunensis*, which has been shown to have an inhibitory effect against gram-positive pathogens, including *S. aureus*.⁴⁹ The application of microbiomics has also led to the discovery of new molecules with antimicrobial activity, such as tetracycline against methicillin-resistant *Staphylococcus aureus* soil microbiota and humin, which inhibits the enzyme lipid II flippase and acts synergistically with certain β -lactam antibiotics.⁵⁰

Antimicrobial Peptides

Antimicrobial peptides (AMPs) are broad-spectrum, positively charged antimicrobial host defense peptides produced by all organisms in nature and represent a potential source of new drugs for the treatment of *K. pneumoniae* infections. Recent studies have shown that AMPs have made significant progress in combating pneumonia caused by this bacterium. As a class of immune effector molecules, AMPs act through a variety of mechanisms, including membrane permeability, inhibition of protein, DNA and RNA synthesis, and degradation of genetic material.⁵¹ This has led to AMPs having a broad spectrum of activity against pathogenic microorganisms. As a class of small-molecule peptides or small-molecule proteins, the antimicrobial mechanisms of AMPs include causing cell wall damage and cell membrane damage, influencing the activity of key enzymes for the synthesis and metabolism of biomolecules, and triggering immunoregulatory inhibitory mechanisms. As a result, antimicrobial peptides not only kill bacteria directly, but also mobilize the body's own immune cells to participate in the regulation of inflammation.⁵² This unique antimicrobial mechanism makes AMPs a promising class of antimicrobial agents against Gram-positive and negative multidrug-resistant bacteria.

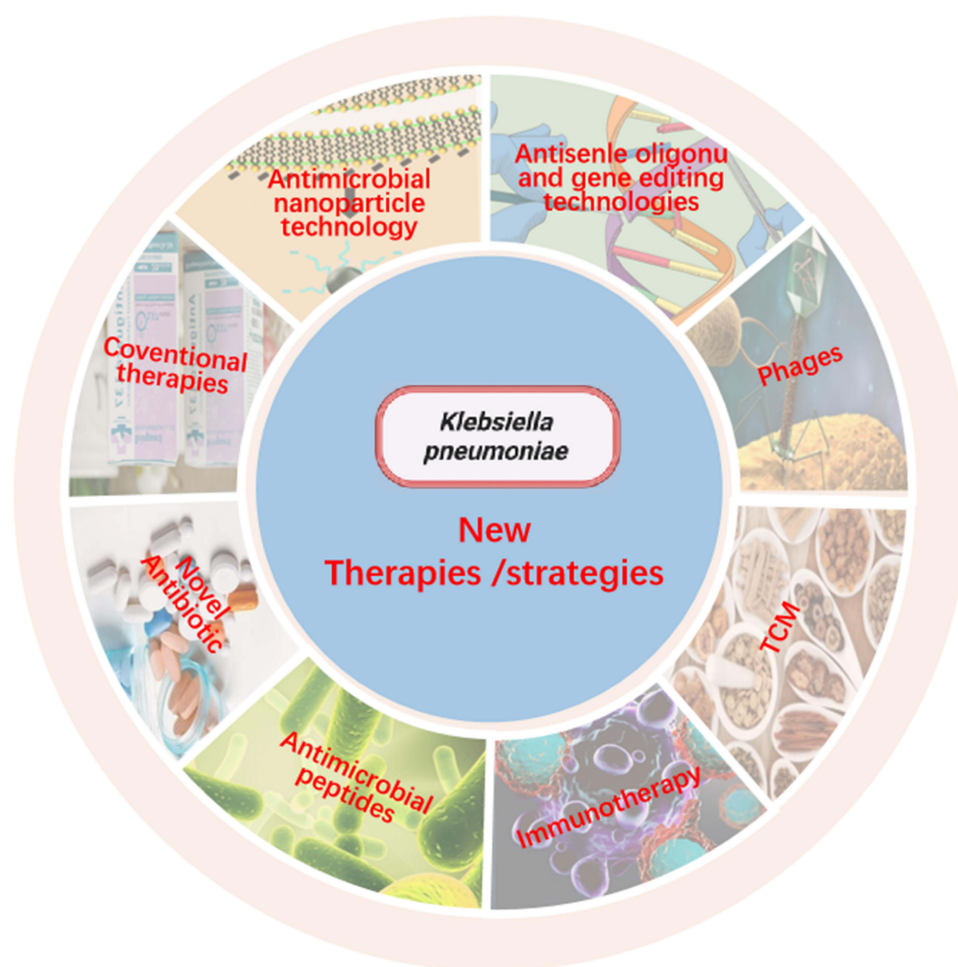


Figure 1 Novel Therapies/Strategies for the treatment of *K. pneumoniae* infections.

It has been found that AMPs can act synergistically when combined with difficult-to-penetrating bacteria or antibiotics in the context of membrane modifications, thereby improving therapeutic efficacy. For example, combination with mucomycin reduced the minimum inhibitory concentration (MIC) of mucomycin against MDR-*K. pneumoniae* strains by up to 11-fold without increasing the hemolytic effect of mucomycin on sheep erythrocytes, suggesting that the combination could improve the safety of mucomycin and the possible use of mucomycin could improve mucomycin therapy by using lower levels. Expand mucomycin concentrations and/or shorter treatment regimens.⁷¹ AMPs also induced synergistic antimicrobial susceptibility of ST258 *K. pneumoniae* strains to rifampicin and azithromycin, suggesting that AMPs may act as antimicrobial enhancers.⁷²

Although AMPs have shown remarkable activity in antimicrobial therapy, their application still faces several challenges, including lack of stability, susceptibility to hydrolysis by proteases, low activity under physiological conditions, and high production cost. Therefore, optimizing the structure of AMPs to improve their biological activity, extend half-life, and reduce cytotoxicity has become a current research focus in the field of AMPs. Although less than 50 AMPs have been enrolled in clinical trials worldwide, the listed AMP drugs such as anidulafungin, baclofungin, caspofungin, daptomycin, etc. provide useful experience and inspiration for the future application of AMPs.

Phages

Phages are viruses that infect and lyse bacteria and have the potential to treat severe drug-resistant bacterial infections. Phage therapy for *K. pneumoniae* infections is still in the early stages of research, with sepsis and pneumonia being the most studied in vivo models for phage therapy of *K. pneumoniae* infections.⁷³

One of the major virulence factors that make *K. pneumoniae* immune to immune responses is podoplanin polysaccharides. Phages can be designed to specifically target podoplanin polysaccharides in *K. pneumoniae*. Phages provide a targeted approach to weaken *K. pneumoniae* defenses such as biofilms and reduce their virulence. The use of phages holds promise for the treatment of CRKP infections. Certain phages, such as phage vB_kpnM_17-11, have demonstrated promising efficacy against *K. pneumoniae* infections in vitro and in vivo, with in vitro assays demonstrating a 105-fold reduction in the number of KPs by vB_kpnM_17-11. In a mouse model of infection, phage treatment improved survival;⁵³ it was demonstrated that phage pKp11 and pKp383 lysed 51 strains of multidrug-resistant *K. pneumoniae* (including strains ST11 and ST383), providing an effective treatment for the early stages of pneumonia in a mouse model of infection without significant side effects.⁵⁴ Scientists at the National Institutes of Health (NIH) successfully treated mice infected with multidrug-resistant *K. pneumoniae* ST258 using two different phage viruses, alone and in combination. These findings are encouraging and show successful therapeutic effects in animal models.⁵⁵

Phage depolymerases are proteins that specifically degrade bacterial surface polysaccharides, specifically recognize bacterial pod types, remove bacterial biofilms, and effectively reduce bacterial virulence.⁵³ In recent years, phage and phage depolymerization enzymes have shown promise in the treatment of CRKP infections. However, phage therapy faces limitations in clinical application due to the lack of standardized guidelines and the variable nature of phage-bacteria interactions. Despite these challenges, more and more researchers are realizing the therapeutic value of phages and it is believed that phage therapy will play an important role in clinical settings in the future as research continues to progress.

Traditional Chinese Medicine

The antimicrobial effects of Traditional Chinese medicines (TCM) against *K. pneumoniae* have been confirmed by several studies, such as the inhibitory effect of baicalein from *Scutellaria baicalensis* on the growth and biofilm formation of highly virulent *K. pneumoniae*,⁷⁴ and the synergistic effect of baicalein combined with imipenem on CRKP, as well as the ability to reduce the resistance of CRKP to imipenem.⁷⁵ Studies on baicalein, the active ingredient in the root bark of *Paeonia lactiflora*, showed that it had significant antibacterial and antibiofilm activity against *K. pneumoniae*. Paeoniflorin effectively inhibited the growth of *K. pneumoniae* with a minimum inhibitory concentration (MIC) of 64 µg/mL. It was found to disrupt the integrity of bacterial cell membranes and alter cell morphology. In addition, paeoniflorin showed potent effects in inhibiting bacterial adhesion and biofilm formation, which are key factors in the process of bacterial infection. It also disperses mature biofilms; therefore, the current study suggests that bryonoxin is a promising new antibacterial and anti-biofilm agent for the treatment of infections caused by *K. pneumoniae*.⁵⁶

Huanglianin is an important alkaloid extracted from the plants such as *Cortex Eucommiae*, *Phellodendron Bark*, and *Rhizoma Coptidis*, and it is recognised as an antibacterial drug in traditional Chinese medicine. Huanglianin can inhibit the formation of *K. pneumoniae* biofilm by down-regulating the expression of the genes for type I and type III bacterial hairs, reducing the surface adhesion ability of *K. pneumoniae*, and thus effectively inhibiting the formation of *K. pneumoniae* biofilm. Recent studies have explored the mechanisms of Chinese herbal medicines against *K. pneumoniae* resistance, revealing their multiple modes of action. Herbal medicines are able to inhibit β -lactamase (an enzyme used by bacteria to resist β -lactam antibiotics), counteract biofilm formation (which protects the structure of the bacterial community), counteract the effects of endotoxin (a component of the outer membrane of Gram-negative bacteria such as *K. pneumoniae*), and inhibit the exocytosis pump (a mechanism used by bacteria to excrete antibiotics and other harmful substances). By understanding these mechanisms, the effects of herbal medicines can be accurately assessed to inform the selection of appropriate antibiotic therapy in the future.⁵⁷

K. pneumoniae, especially those pan-resistant strains, pose a major challenge in clinical treatment due to their high resistance rates. TCM has attracted widespread attention as a novel approach against multi-drug resistant bacteria, either alone or in combination with western drugs, due to its low resistance and broad-spectrum antimicrobial effect against multiple targets of action.

Immunotherapy

In response to the problem of drug resistance in *K. pneumoniae*, especially in the context of the epidemic of drug-resistant bacterial infections and drug-resistant strains faced globally, the production of vaccines and antibodies based on active and passive immunization has provided new ideas for the prevention and treatment of infections with multidrug-resistant bacteria. Immunotherapy has emerged as a promising means to break the dead-end cycle of antibiotic resistance-new antibiotic development-new antibiotic resistance.

Vaccine studies for *K. pneumoniae* infections are currently in the research and development phase, using strategies involving whole cell vaccines, outer membrane vesicles (OMVs), ribosomes, polysaccharides, lipopolysaccharides (LPS) and protein vaccine formulations.⁵⁸ The goal of these approaches is to induce antibodies and cell-mediated immune responses to effectively combat *K. pneumoniae* as a pathogen.⁵⁸ Although overcoming challenges such as the diversity of *K. pneumoniae* strains remains a key issue, preclinical studies have shown that vaccine-induced antimicrobial antibodies are protective against *K. pneumoniae* infection.⁵⁹ In addition, monoclonal antibodies have been explored as one of the strategies against drug-resistant bacteria. About 10 monoclonal antibodies are in clinical trials, of which three have been approved for marketing.⁶⁰ Despite the encouraging progress in the development of vaccines, the diversity of *K. pneumoniae* strains presents significant challenges that need to be overcome to create effective vaccines. Ongoing research is essential to find effective vaccines that offer protection, especially against this increasingly resistant pathogen.

Antimicrobial Nanoparticle Technology

Studies have shown that metal nanoparticles (eg, silver, zinc oxide, magnesium, nitrogen oxide, etc.) possess antimicrobial activity, and their mechanisms of action include induction of oxidative stress, non-oxidative mechanisms, and interactions of released metal ions with functional groups of proteins and nucleic acids. Factors such as the size, zeta potential, charge, surface morphology and crystal structure of the nanoparticles determine their antimicrobial activity.⁷⁶

Common types of antimicrobial nanoparticles include silver nanoparticles, metal oxide nanoparticles, photothermal conversion nanoparticles, and antibiotic conjugated nanoparticles. These nanoparticles achieve their antimicrobial effects in a variety of ways, including disrupting bacterial cell membranes, interacting with bacterial DNA or proteins, and indirectly initiating ROS production.⁶¹

Researchers explored the antibacterial and antibiofilm efficiency of zinc ferrate nanoparticles (ZnFeO NPs) against *K. pneumoniae*. The results showed that ZnFeO nanoparticles exhibited excellent antimicrobial efficiency, inducing reactive oxygen species (ROS)-induced bacterial damage, as well as significant results in anti-biofilm.⁷⁷ The therapeutic possibilities of ZnFeO NPs in antimicrobial applications, especially their overcoming of challenges related to biofilm infectivity. This offers promising avenues for finding more effective and sustainable antimicrobial practices.

Overall, antimicrobial nanoparticle technology shows potential efficacy in the treatment of *K. pneumoniae* infections, offering promising avenues for overcoming drug resistance and providing new therapeutic options.

Antisense Oligonucleotides and Gene Editing Technologies

Research on antisense oligonucleotides and gene editing technologies in the treatment of *K. pneumoniae* infections has shown impressive progress. By classifying and applying different types of antisense oligonucleotides, researchers have successfully achieved the inhibition of gene expression in *K. pneumoniae*, specifically including the inhibition of gene expression by RNA silencing, especially the generation of resistance to antibiotics.⁷⁸ In order to overcome the problem of antisense oligonucleotides reaching sufficiently high concentrations in bacteria, cell-penetrating peptide (CPP) was introduced, a strategy that is expected to improve the effective delivery of oligonucleotides in cells and provide a new direction for the development of antimicrobial agents.⁷⁸

On the other hand, gene editing technologies, especially the CRISPR/Cas system, have been applied to programmable modification of the *K. pneumoniae* genome. The CRISPR/Cas system is capable of re-sensitizing bacteria to antibiotics by selectively eliminating drug-resistant genes, and even by eliminating plasmids containing drug-resistant genes.⁶² This provides a promising solution for the treatment of drug-resistant *K. pneumoniae* infections. However, despite the

remarkable progress, the CRISPR/Cas system still faces a series of challenges for in vivo application, including the problems of efficient delivery to bacteria and the side effects of potential off-target modifications, which need to be solved by future intensive research.^{62,63} Therefore, antisense oligonucleotide and gene editing technologies provide new ideas and possibilities for the treatment of *K. pneumoniae* infections, offering promising solutions to tackle the drug resistance problem.

Other Emerging Strategies

In terms of new strategies to treat *K. pneumoniae* infections, researchers have employed a variety of innovations to address the serious challenge of antimicrobial drug resistance. These new strategies include host-directed therapy (HDT), virulence factor inhibitors, QS inhibitors, and nanoenzymes.⁷⁹ HDT, a promising alternative therapy to antibiotics, has the potential to eradicate pathogenic bacteria by targeting host factors and eliminating intracellular replication of pathogenic bacteria while stimulating the host immune response to the pathogen.⁷⁹ Virulence factor inhibitors, particularly molecules targeting pathogen virulence factors, are expected to disarm bacteria, slow down the development of resistance, and reduce the pathogenicity of the strain.

On the other hand, QS inhibitors achieve antimicrobial effects by inhibiting signaling molecular communication between bacteria and realizing the regulation of physiological processes, such as bacterial metabolism, virulence, and biofilm formation.⁸⁰ Nanoenzymes, as a new generation of artificial mimetic enzymes, combine the unique physico-chemical properties of nanomaterials with enzyme-like catalytic activity, and have the advantages of structural stability, broad antimicrobial spectrum, and low production cost. The introduction of these new strategies offers diverse options for the treatment of *K. pneumoniae* infections and is expected to address the problem of antibiotic resistance.

In addition, there are intervention strategies for the treatment of *K. pneumoniae* infections that target specific virulence factors, including determinants involved in host cell attachment, host immune modulation, and biofilm regulation.^{81–83} Research and development of these strategies is expected to provide more effective means of treating drug-resistant *K. pneumoniae* infections.

Conclusion

With the widespread use of antibiotics in recent decades, the incidence of multidrug-resistant *K. pneumoniae* isolates has increased frequently worldwide, posing a major threat to public health. *K. pneumoniae* is a priority pathogen for research and development of new therapeutic approaches, but its innovation remains a challenge. In this paper, the mechanisms and effects of emerging therapeutic strategies for *K. pneumoniae* in recent years are summarized. Potential therapies were also characterized in Figure 1. The application of these new technologies and their synergistic application with various antimicrobial compounds may be a new direction for future research. In addition, preventive measures are more important than therapeutic measures. Early detection, early diagnosis and early treatment, reduction and avoidance of high-risk factors for CRKP infection, as well as increased management of antimicrobials and drug resistance monitoring, can play a multiplying role in controlling the spread of *K. pneumoniae* infection.

Disclosure

The authors report no conflicts of interest in this work.

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