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Review

Antibiotic Resistance and Virulence Mechanisms in *Klebsiella pneumoniae*: Understanding for Better Interventions

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Abstract

Klebsiella pneumoniae is a prominent pathogen implicated in a wide range of infections, including pneumonia, urinary tract infections, and septicemia. Its ability to acquire and disseminate antibiotic resistance, coupled with the rising prevalence of hypervirulent strains, represents a significant public health threat. Understanding the molecular basis of drug resistance can guide the design and development of effective treatment strategies. Antimicrobial resistance (AMR) in these bacteria is a complicated process and cannot be attributed to only a single resistance mechanism. *K. pneumoniae* develops resistance to antibiotics through a variety of mechanisms, ranging from single molecular mechanisms to complex interactions, where molecular synergy exacerbates resistance. This review summarizes the current understanding of the molecular mechanisms that contribute to the drug resistance and virulence of this pathogen. Key antibiotic resistance mechanisms include drug inactivation via B-lactamases and carbapenemases, membrane remodeling, efflux pump systems, such as AcrAB-TolC and OqxAB, and biofilm formation facilitated by quorum sensing. Additionally, the role of ribosomal changes in resistance was highlighted. This review also examines the mechanisms of virulence, emphasizing fimbriae, iron acquisition systems, and immune evasion strategies. Understanding these mechanisms of drug resistance and virulence is crucial for remodeling existing antibiotics and developing new therapeutic strategies.

Keywords: molecular mechanisms; membrane remodeling; drug resistance; virulence; *Klebsiella pneumoniae*; carbapenemase; ribosomal changes

1. Introduction

Klebsiella pneumoniae (K. pneumoniae) is a ubiquitous, rod-shaped, capsulated, facultative anaerobic, non-motile, gram-negative bacterium. The genome size of this bacterium ranges from 5.1 to 5.6 Mb [1,2]. Genetic variation among different strains of this species can be attributed to genome rearrangements, which often result from the inversion of chromosomes, mobile genetic elements, plasmids, and the presence of genes specific to strains. *K. pneumoniae* was initially described in 1882 by Carl Friedlander as a bacterium recovered from the lungs of patients who died of pneumonia and is known as the Friedlander bacterium [3]. Later, the Klebsiella genus was named by German microbiologist Edwin Klebs, assigning the current name *K. pneumoniae* [4]. *K. pneumoniae is* found in different environments, including the soil, water, and the gastrointestinal and respiratory tracts of humans and animals. *K. pneumoniae* can colonize healthcare environments and medical devices. This bacterium is a great public health challenge because of its increasing pathogenicity, virulence, and emergence of antimicrobial resistance. The association of *K. pneumoniae* with invasive procedures and its ability to form biofilms increases the risk of infection and complicates the treatment options [5,6].

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Historically, this bacterium has been associated with infections in immunocompromised individuals. However, the emergence of antibiotic-resistant strains and increased virulence has presented dual risks in healthy and immunocompetent individuals [3,7–9]. The increasing number of infections and the emergence of MDR strains of this bacterium have attracted attention.

The prevalence of multidrug-resistant (MDR) *K. pneumoniae* strains is increasing. While various molecular mechanisms contribute to resistance, the production of extended-spectrum beta-lactamases (ESBLs) and carbapenemases is the primary driver of drug resistance in this pathogen. Another concern associated with this bacterium is its pathogenicity, which results from the complex interaction of various virulence factors that enable colonization and immune evasion, and facilitate systemic spread [10]. These virulence factors include lipopolysaccharides, iron uptake systems, capsules, exopolysaccharides associated with mucoviscosity, and adhesins [11]. Reports indicate *that K. pneumoniae* isolates are increasingly displaying MDR characteristics, with a rapid increase in global resistance rates for carbapenems [12]. The dual challenges of increased virulence and drug resistance to currently available antibiotics highlight the urgent need for innovative treatment options such as promising phage therapy [13,14].

1.2. Antimicrobial Resistance in K. pneumoniae

Antimicrobial resistance (AMR) has been recognized as a significant public health crisis. AMR is characterized by the ability of microorganisms to resist medications intended to kill them [15]. The World Health Organization (WHO) has identified AMR as a critical threat to public health. If there are no new antibiotics or novel therapeutic options, it is estimated that by 2050, infections related to AMR could lead to the death of 10 million people [16]. *K. pneumoniae* rapidly develops resistance to antibiotics. By 2024, carbapenem-resistant *K. pneumoniae* had risen to the top position on the WHO bacterial priority pathogen list (BPPL), highlighting an alarming increase in resistance among these pathogens[17]. The WHO has prioritized Klebsiella pneumoniae as a critical pathogen due to its ability to acquire AMR genes, rendering it resistant to multiple classes of antibiotics. Current studies reveal that more than half of *K. pneumoniae* isolates are resistant to key antibiotics like third-generation cephalosporins and carbapenems, underscoring the urgent need for enhanced surveillance, novel treatment strategies, and effective antimicrobial stewardship [18–20].

2. Molecular Mechanisms of Drug Resistance in *K. pneumoniae*

The emergence of multidrug-resistant (MDR) strains of Klebsiella pneumoniae constitutes a significant public health challenge due to the pathogen's multifaceted and dynamic resistance mechanisms. Unlike simpler models of antimicrobial resistance (AMR), resistance in *K. pneumoniae* arises from an intricate interplay of molecular strategies, which collectively amplify the bacterium's ability to withstand diverse antibiotic classes (Figure 1). This complexity arises not only from individual resistance determinants but also from synergistic interactions between mechanisms, underlining the pathogen's adaptive versatility (**Figure 1**) [19,20]. A primary mode of resistance involves modification of antibiotic targets, thereby reducing drug affinity and efficacy. Complementarily, *K. pneumoniae* frequently expresses a spectrum of drug-inactivating enzymes, such as β-lactamases, which hydrolyze antibiotic molecules, rendering them ineffective [21–23]. The genetic basis of these enzymatic factors is notably versatile, with resistance genes encoded both chromosomally and on mobile plasmids. The latter route facilitates horizontal gene transfer (HGT), which has been pivotal in disseminating resistance traits across clinical isolates.

Plasmid acquisition is particularly consequential, as it enables the concurrent carriage of multiple resistance genes, fostering the development of extensively drug-resistant (XDR) strains. For instance, co-localization of genes such as *blaNDM* and fluoroquinolone resistance determinants within single plasmids has been repeatedly documented in nosocomial isolates, highlighting the role of plasmids as reservoirs for resistance cassettes that complicate treatment strategies [24].

Efflux pump systems, primarily chromosomally encoded in *K. pneumoniae*, provide an additional layer of resistance by decreasing intracellular drug concentrations through active extrusion. These

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pumps are tightly regulated at the genetic level. They can synergize with plasmid-borne resistance genes to enhance resistance phenotypes, demonstrating a dual genetic control framework that underscores the pathogen's adaptability under antibiotic selective pressure. This synergy between chromosomal and plasmid-mediated mechanisms exemplifies the evolutionary plasticity of *K. pneumoniae*, which is further accelerated by mobile genetic elements facilitating rapid genetic recombination and adaptation [25,26]. The presence of multiple resistance genes on a single plasmid has been documented, contributing to the development of extensively drug-resistant (XDR) strains. For example, studies have shown the presence of carbapenemase and fluoroquinolone resistance genes, as well as blaAmpC and fluoroquinolone resistance genes, within plasmids acquired by bacteria that frequently lead to hospital-acquired infections. Efflux pump systems, which are chromosomally encoded, play a significant role in antibiotic resistance by altering the permeability of the cell membrane to drugs. These pumps are a key mechanism contributing to the drug resistance observed in *K. pneumoniae* [27].

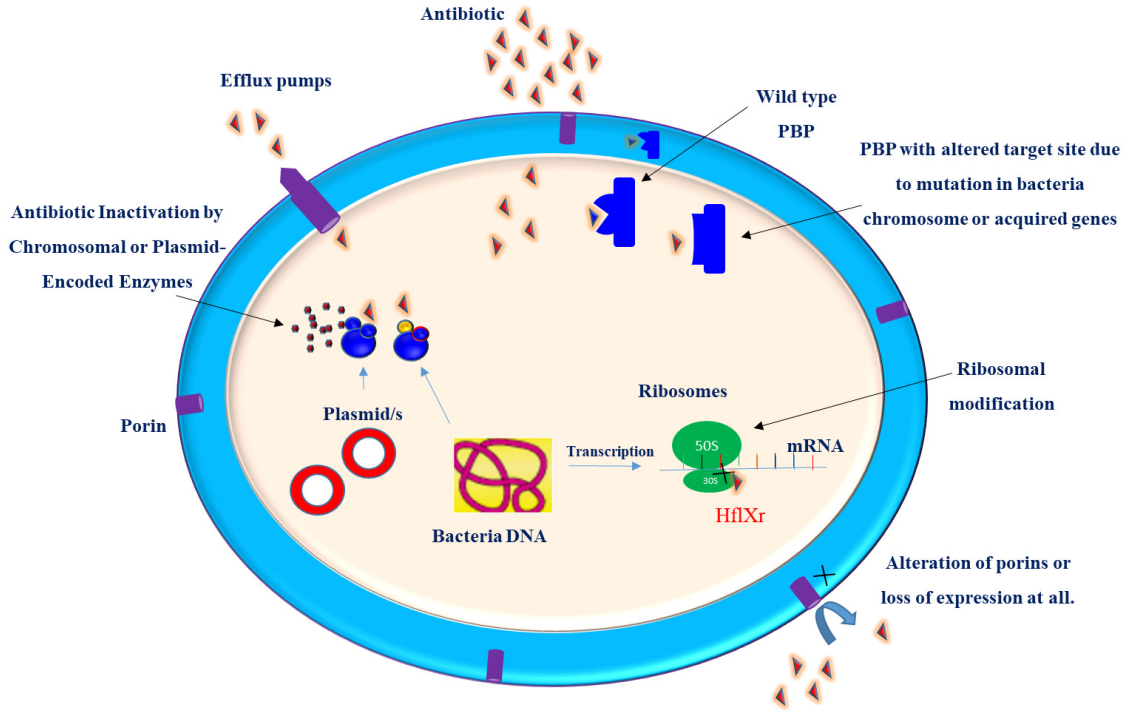

Figure 1. Generalized illustration of mechanisms involved in antimicrobial resistance.

2.1. Drug Inactivation and Target Modification

K. pneumoniae can resist antibiotics by hydrolyzing enzymes, such as B-lactamases, AmpC B-lactamases, and carbapenemases. These Enzymes hydrolyze critical parts of the antibiotics. The primary resistance mechanism involves the production of β-lactamases, enzymes that hydrolyze and inactivate β-lactam antibiotics [28]. B-lactams are a widely used class of antibiotics. After the discovery of benzylpenicillin in the 1920s by Alexander Fleming, numerous penicillin derivatives and related B-lactam classes, including monobactams, cephalosporins, cephamycins, and carbapenems, have been developed. The development was aimed either at expanding the spectrum of activity to cover new species or to combat emerged resistance [29]. B-lactams are commonly used to treat infections caused by *K. pneumoniae*. B -Lactams work by inhibiting penicillin-binding protein (PBPs) (**Figure 1)**, enzymes responsible for cell wall synthesis [30,31].

Without proper peptidoglycan cross-linking, cells experience an uncontrolled influx, leading to swelling and lysis. Even minor disruptions in cross-linking can trigger structural instability, causing membrane blebbing and eventual rupture. Therefore, the precise architecture of peptidoglycan is

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essential for bacterial survival, acting as both a structural component and an osmotic barrier [32,33]. A key target in the peptidoglycan synthesis pathway is the PBPs, transpeptidases responsible for catalyzing the final cross-linking step in the peptidoglycan assembly. B-lactams mimic the D-Ala-D-Ala terminus of peptidoglycan precursors and act as suicide substrates [34]. B-Lactams irreversibly bind to PBPs and inhibit transpeptidase activity. This disruption prevented peptidoglycan cross-linking. This weakens the bacterial cell wall and leads to cell death through osmotic lysis. The effectiveness of B-lactams is attributed to their covalent interactions with PBPs across all bacterial species [30]. Bacteria develop resistance to β-lactam antibiotics by modifying penicillin-binding proteins (PBPs) at the molecular level, which reduces the binding affinity of these antibiotics. In *K. pneumoniae*, this resistance primarily arises from mutations in the genes encoding PBPs, leading to structural changes that decrease their ability to bind β-lactams effectively [30,31]. The loss or structural modification of outer membrane proteins (OMPs) is another mechanism that confers resistance to *K. pneumoniae*. The outer membrane acts as a barrier that antibiotic molecules must cross before binding to penicillin-binding proteins (PBPs). Antibiotics must pass through the porins, specifically OmpK35 and OmpK36. However, the expression levels of these porins are frequently modified, leading to a reduction in membrane permeability. This decrease limits the influx of antibiotics into the bacterial cell, thereby reducing their intracellular concentrations and effectiveness. As a result, such alterations in porin abundance directly contribute to the development of antibiotic resistance by preventing sufficient drug accumulation within the bacteria [35,36]. Together, these multilayered defenses create a formidable barrier against treatment, underscoring the urgent need for integrated molecular surveillance and novel therapeutic strategies to manage emerging multidrug-resistant *K. pneumoniae* infections.

2.1.1. B-Lactamases

B-lactamases are enzymes that are capable of hydrolyzing B-lactam antibiotics. The dominant mechanism of resistance in *K. pneumoniae* involves the production of an extended spectrum of B-lactamases (ESBLs) and AmpC B-lactamases, which are often found on mobile genetic elements, allowing for rapid spread among bacterial populations [37,38]. B-lactamases are categorized into ESBLs, cephalosporinases (AmpC), and carbapenemases [39]. The production of these enzymes in *K. pneumoniae* confers resistance to carbapenems, penicillins, and cephalosporins. ESBLs include cefotaximase (CTX), Temoneria (TEM), sulfhydryl variable (SHV), and oxacillinase (OXA). AmpC confers resistance to first-to third-generation cephalosporins and enzyme inhibitors. AmpC can be either chromosomal- or plasmid-mediated. Currently, more than 40 genetic variants of AMPC have the potential for rapid plasmid-mediated spread among strains [20]. Production of carbapenemase enzymes is another mechanism of resistance in *K. pneumoniae*, leading to the development of carbapenem-resistant *K. pneumoniae* (CRKP). These enzymes reduce the sensitivity to carbapenem-class antibiotics [39].

Temoneria (TEM)-1 is the first reported B-lactamase. TEM was described in 1965, followed by the identification of sulphydryl variable (SHV)-1 B-Lactamase [40]. These enzymes help bacteria survive penicillin treatment. Subsequently, derivatives of TEM and SHV-type B-lactamase, classified as ESBL, were detected. These variants demonstrate hydrolysis of oxyimino B-lactam antibiotics due to minor molecular changes in their active sites [41,42].

Notably, this type of resistance was observed in *K. pneumoniae* shortly after the introduction of third-generation cephalosporins in 1982 [40]. Historically, SHVs or TEMs have been the dominant B-lactamases. However, there has been a shift, with CTX-M being the most commonly detected ESBL worldwide. The distribution of ESBL-producing *K. pneumoniae,* which encodes CTX-M, has increased significantly over the years [43]. Outbreaks of ESBL-producing *K. pneumoniae* in hospitals have posed a threat for several years, dating back to the first report in the 1980s in France [40]. The production of diverse B-lactamases in *K. pneumoniae*, including ESBLs, AmpC cephalosporinases, and carbapenemases, constitutes the primary mechanism driving resistance to critical β-lactam antibiotics (Table 1). The evolving landscape of these enzymes, from the early TEM and SHV variants to the

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widespread CTX-M types, highlights the dynamic adaptation of *K. pneumoniae* to antimicrobial pressure. The rapid dissemination of these genes via mobile genetic elements exacerbates the challenge of treating infections caused by multidrug-resistant strains, underscoring the urgent need for continuous surveillance, stewardship, and the development of novel therapeutic strategies.

2.1.2. Carbapenemases

Carbapenemases are bacterial enzymes that break down carbapenem antibiotics, causing significant treatment challenges. Among these, the "Big Five" carbapenemases *K. pneumoniae* carbapenemase (KPC) (class A), Imipenemase (IMP), Verona integron-encoded metallo-β-lactamase (VIM), New Delhi metallo-β-lactamase (NDM) (class B metallo-β-lactamases), and OXA-48-like oxacillinases (class D) are of particular clinical concern due to their widespread distribution and their role in conferring resistance in Gram-negative bacteria such as *K. pneumoniae* [39]. Carbapenemases are B-lactamases with versatile hydrolytic activity. Many of these enzymes can hydrolyze nearly all B-lactams, making them largely resistant to the currently available B-lactam antibiotics. Carbapenemases are categorized into A, B, and D molecular classes of B-lactamases. Molecular classes A and D use serine-dependent hydrolytic mechanisms, whereas class B comprises metallo-B-lactamases that incorporate zinc into their active site [39]. The term carbapenem-hydrolyzing enzymes is preferable over “carbapenemases," as carbapenems represent only one part of the substrate spectrum. The mechanism of action of Carbapenem-hydrolyzing enzymes acts through the action of catalytic sites, such as serine or zinc. According to Amber’s classification of B-lactamases, carbapenem-hydrolyzing enzymes are classified into molecular classes A, B, and D [44]. Each class comprises multiple enzyme families and their respective subfamilies. Among these enzymes, IMP, VIM, KPC, NDM, and OXA are particularly significant in clinical settings [45,46]. These enzymes are encoded both chromosomally and on plasmid genes, resulting in variability among carbapenemases. Plasmid-encoded carbapenemase genes can be horizontally transferred between related bacterial genera, facilitating the rapid spread of carbapenemase-producing bacteria [24]. Carbapenemases are enzymes that hydrolyze carbapenem antibiotics, posing significant challenges to the effective treatment of infections caused by Gram-negative bacteria such as *K. pneumoniae*. The “Big Five” carbapenemases are especially concerning due to their widespread presence and broad-spectrum hydrolytic activity against almost all β-lactam antibiotics (Table 1). These enzymes employ serine-dependent (classes A and D) or zinc-dependent (class B) catalytic mechanisms, reflecting their molecular diversity. Because their substrate range extends beyond carbapenems, the term carbapenem-hydrolyzing enzymes more accurately describes them. Their genetic encoding on both chromosomes and plasmids facilitates horizontal gene transfer, accelerating the spread of carbapenem resistance among bacterial populations and complicating infection control efforts globally.

2.1.2.1. Serine Carbapenemases (Molecular Class A Carbapenemases)

Serine carbapenemases constitute a group of B-lactamases (functional group 2f) that utilize serine residues for their hydrolytic activity [46,47]. These enzymes effectively degrade a wide range of β-lactam antibiotics, including carbapenems, using serine residues in their active site. These enzymes effectively degrade antibiotics, including cephalosporins, carbapenems, penicillins, and monobactams. Serine carbapenemases are not inhibited by metal-chelating agents such as ethylenediaminetetraacetic Acid (EDTA) [46,47]. These enzymes are commonly identified in *K. pneumoniae* clinical isolates of *K. pneumoniae*. The well-characterized groups of serine carbapenemases include KPC (*K. pneumoniae* carbapenemase), IMI/NMC (Imipenem-hydrolyzing B-Lactamase/Non-Metallo Carbapenemase), SME (*Serratia marcescens* enzyme), and GES (Guiana ESBL). In addition, SHV-38 and SFC-1 (*Serratia fonticola* carbapenemase-1) represent emerging variants. SHV-38, SFC-1, IMI/NMC, and SME are typically chromosomal, whereas KPC and GES are often plasmid-mediated, facilitating rapid horizontal transmission among bacterial populations [24,39].

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2.1.2.2. Molecular Class B Carbapenemases /Metallo- B-Lactamases (MBLs)

MBLs are zinc-dependent enzymes that hydrolyze carbapenems and nearly all B-lactams [48,49]. MBLs can be categorized into three subclasses: B1, B2, and B3. Each subclass has unique characteristics. Class B1 MBLs, including NDM, VIM, IMP, GIM, and SIM, are the most clinically significant and require two zinc ions for catalysis [45,46]. These enzymes are frequently plasmid-mediated, enabling rapid *K. pneumoniae*. Class B2 MBLs are active mono-zinc proteins [50]. CphA from Aeromonas species utilizes only one zinc ion (Zn^{+2}) for catalysis and demonstrates a high specificity for carbapenems. Notably, the Zn1 site in B2 MBLs is non-catalytic and can inhibit activity when occupied. Class B3 MBLs, which include L1 from *Stenotrophomonas maltophilia*, AIM-1 from *P. aeruginosa*, and BcII from Bacillus cereus, also require two zinc ions but are structurally and phylogenetically distinct from B1 and B2 enzymes. B3 MBLs possess active site motifs, such as HHH/DHH, and show greater sequence diversity [51]. In contrast to B1 MBLs, B3 MBLs are often encoded chromosomally. MBLs can evade inhibition by B-lactamase inhibitors such as clavulanate, and MBLs can be inhibited by chelating agents such as EDTA [52,53]. Unlike serine β-lactamases, MBLs are not inhibited by traditional β-lactamase inhibitors, but can be targeted by metal chelators such as EDTA, highlighting the need for novel therapeutic approaches to overcome MBL-mediated resistance.

2.1.2.3. Molecular Class D Carbapenemases (OXA Carbapenemase)

Class D carbapenemases, commonly referred to as oxacillinase (OXA) carbapenemases, are serine-dependent enzymes that hydrolyze carbapenems and B-lactam antibiotics [54]. OXA is a carbapenem-hydrolyzing enzyme classified into a family of molecular class D serine-dependent enzymes. OXA was first reported in 2003 in Turkey [55]. These enzymes have a wide genetic diversity and are encoded by plasmids. Class D carbapenemases utilize a serine residue for their catalytic activity and exhibit resistance to inhibition by EDTA, clavulanate, and tazobactam, owing to their serine-based mechanism. Class D carbapenemases have been identified predominantly in *K. pneumoniae*. The OXA group consisted of more than 489 variants, 37 of which were classified as clinically significant carbapenemases. Among these, OXA-48, including its variants (OXA-181 and OXA-232), is particularly noteworthy and often associated with outbreaks in healthcare environments [56,57]. In contrast to plasmid-mediated carbapenemases (e.g., KPC), OXA enzymes are primarily encoded chromosomally, although plasmid-borne variants have been reported. Their capacity to circumvent conventional inhibitors and propagate through horizontal gene transfer highlights their significance in the context of multidrug-resistant infection [24].

The five most significant carbapenemases, known as "the Big Five," are KPC, IMP, VIM, NDM, and OXA [58]. These enzymes are commonly found in *K. pneumoniae* and other pathogenic bacteria. Their ability to spread via plasmids and chromosomes, especially variants like OXA-48, makes them a critical factor in the rise of multidrug-resistant *K. pneumoniae* infections, and underscores the challenge in managing last-resort carbapenem therapy.

2.1.2.4. *K. pneumoniae* Carbapenemase (KPC)

This is the most clinically reported type of molecular class A carbapenemase. KPC was first identified in North Carolina, USA, in 1996 [59]. KPC is now globally distributed, with reports from all continents and regions [60–67]. Reports have identified over 150 different blaKPC-coding genes [68]. The most prevalent KPC variants are KPC-2 and KPC-3. Newer variants that confer resistance to ceftazidime/avibactam (CZA), such as KPC-80, KPC-97, KPC-81, and KPC-96, have also been reported [69]. This variation is caused by the accumulation of mutations in active site loops, such as the Ω-loop and Lys270-loop [68]. Although KPC has been repeatedly reported in *K. pneumoniae*, it has also been isolated from other Enterobacterales, including Enterobacter spp., *Klebsiella oxytoca*, *E. coli*, *Serratia marcescens*, *Citrobacter freundii*, *Salmonella enterica*, *Proteus mirabilis*, *and P. aeruginosa* [70–73]. The widespread emergence and diversification of KPC enzymes significantly threaten the effectiveness of current β-lactam and carbapenem therapies, complicating infection management

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worldwide. Urgent development of novel inhibitors and robust surveillance systems is essential to control the spread and impact of KPC-producing pathogens.

2.1.2.5. Imipenemase (IMP)

IMPs are carbapenemases classified as a family of molecular class B MBLs that utilize zinc ions (Zn^{2+}) for their catalytic effect, allowing them to confer resistance to carbapenems, particularly imipenem and meropenem [74]. IMP was first identified in Japan as IMP-1, which has since diversified into 88 variants, with the majority being found in Asia [74–76]. IMP are increasingly identified in *K. pneumoniae*, significantly contributing to its multidrug resistance. In *K. pneumoniae*, IMP carbapenemases are typically encoded on plasmids, enabling rapid horizontal gene transfer within and between bacterial populations [77]. These enzymes inactivate nearly all B-lactams, except monobactams, such as aztreonam, rendering carbapenems ineffective. The IMP-43 and IMP-44 variants demonstrated increased catalytic efficiency against carbapenems compared to the IMP-7 and IMP-11 variants. This highlights the growing threat posed by IMP carbapenemase [78]. The global dissemination of IMP-producing pathogens, facilitated by plasmid-mediated horizontal gene transfer, exacerbates resistance and complicates treatment [74,79]. The presence of IMP enzymes in K. pneumoniae undermines the effectiveness of carbapenems, often regarded as last-resort antibiotics for severe infections caused by this pathogen. This enzymatic resistance severely restricts treatment options and is linked to increased morbidity and mortality in infected patients. Therefore, monitoring and controlling the spread of IMP-producing *K. pneumoniae* is essential for infection prevention and effective antimicrobial stewardship.

2.1.2.6. Verona Integron-Encoded Metallo-B-Lactamases (VIMs)

VIMs are carbapenem-hydrolyzing enzymes classified into a family of molecular class B MBLs that utilize zinc ions (Zn^{2+}) for their catalytic activity [80,81]. VIMs are encoded by integron *blaVIM* genes found in plasmids. These enzymes are among the most widespread metallo-B-lactamases (MBLs) worldwide and demonstrate a wide range of hydrolytic activities against cephamycins, penicillins, cephalosporins, and carbapenems. VIMs are not effective against monobactams such as aztreonam. VIM was first reported in 1999 in Verona [82], since it has been reported in regions including the Far East, USA, Europe, and South America [83]. Variants of VIM, VIM-1, and VIM-2 were most frequently reported. These carbapenemases are primarily associated with *K. pneumoniae*. The global spread of VIM-producing bacteria is facilitated by mobile genetic elements within the class 1 integrons. This enables horizontal gene transfer across various bacterial species. Recent studies have highlighted the emergence of novel variants, such as VIM-84 in Asia and Europe, which further complicate the management of multidrug-resistant infections [84,85].

2.1.2.7. New Delhi Metallo-B-Lactamases (NDM)

NDM are hydrolytic enzyme classified into a family of molecular class B carbapenemases (MBLs). NDM was first reported in 2008 in a Swedish patient of Indian descent, who had been treated in New Delhi, India [86,87]. The first NDM variant was isolated from *K. pneumoniae* as NDM-1. Since then, NDM has been disseminated globally. These enzymes hydrolyze almost all B-lactams and carbapenems. These enzymes do not hydrolyze or inactivate monobactams such as aztreonam. NDM carbapenemases are plasmid-mediated and can be shared among bacterial species via horizontal gene transfer. Although aztreonam is still effective against NDM-producing strains, the coexistence of other resistance mechanisms such as ESBLs may reduce its efficacy in some cases [88].

Table 1. Summary of β-Lactamase and Carbapenemase Classes and Key Features.

Enzyme Class	Molecular Class	Representative Enzymes	Substrate Specificity	Inhibition	Ref
Serine-B-lactamases (Class A)	A	KPC,TEM, SHV, CTX-M	Penicillins, cephalosporins, carbapenems (KPC)	Inhibited by clavulanic acid, sulbactam	[46,47]
Metallo-B-lactamases (Class B)	B	IMP, NDM, VIM, SPM, GIM	Broad spectrum including carbapenems, not monobactams	Inhibited by metal chelators (e.g., EDTA)	[45,46]
Serine-B-lactamases (Class C)	C	AmpC-type enzymes	Cephalosporins, penicillins	Not inhibited by clavulanic acid	[39,142]
Oxacillinases (Class D)	D	OXA-48-like carbapenemases, OXA-23, OXA-24/40, OXA-58, OXA-1, OXA-10	Penicillins, cephalosporins, carbapenems (OXA-48 group)	Variable inhibition by clavulanic acid	[54]
Extended-Spectrum-B-Lactamases (ESBLs)	Mostly Class A	CTX-M, SHV variants, TEM variants	Expanded activity against third-generation cephalosporins	Inhibited by clavulanic acid	[41,42]
Carbapenemases (Functional Group)	Classes A, B, D	KPC (A), IMP, VIM, NDM (B), OXA-48-like (D)	Hydrolyze carbapenems and other Î²-lactams	Varies by class (see above)	[45,46,59,74,80,81]

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2.1.3. Resistance to Colistin, Aminoglycosides, and Fluoroquinolones

In addition to its primary resistance mechanisms, *K.pneumonia* has several secondary pathways that enhance its multidrug-resistant profile and create significant challenges for effective treatment. One notable mechanism is the presence of plasmid-borne mcr genes [89], which pose a critical threat by conferring resistance to colistin, a last-resort antibiotic. These genes code for phosphoethanolamine transferase enzymes that chemically modify the lipid A component of the bacterial outer membrane lipopolysaccharide. This modification decreases colistin binding, reducing its bactericidal effectiveness. The plasmid location of mcr genes enables horizontal gene transfer among bacterial populations, promoting the rapid dissemination of colistin resistance in both clinical and environmental *K. pneumoniae* isolates.

Aminoglycoside resistance in *K. pneumoniae* is primarily driven by aminoglycoside-modifying enzymes, which include acetyltransferases (such as aac(3)-II and aac(6')-Ib), nucleotidyltransferases, and phosphotransferases [19]. These enzymes inactivate aminoglycosides through processes like acetylation, adenylation, or phosphorylation, effectively neutralizing the antibiotic. The genes for these enzymes are often located on transferable genetic elements, such as plasmids and transposons, facilitating their spread among bacterial populations. Furthermore, 16S rRNA methyltransferases, like ArmA and RmtB, provide high-level resistance by methylating the ribosomal target of aminoglycosides, which prevents the drugs from binding effectively.

Fluoroquinolone resistance mainly results from point mutations in the quinolone resistance-determining regions (QRDRs) of the genes encoding DNA gyrase (gyrA) and topoisomerase IV (parC) [90,91]. These mutations modify the target enzymes, preventing fluoroquinolones from effectively binding and inhibiting their activity. Resistance is further increased by efflux pumps, such as AcrAB-TolC and OqxAB, which actively remove fluoroquinolones from the bacterial cell, reducing intracellular drug concentrations. Additionally, plasmid-mediated quinolone resistance (PMQR) genes can work in conjunction with chromosomal mutations and efflux mechanisms to elevate resistance levels [91]. Collectively, these mechanisms;-plasmid-mediated colistin resistance, enzymatic drug modification by aminoglycoside-modifying enzymes, and target alteration plus efflux in fluoroquinolone resistance contribute substantially to the multidrug-resistant threat posed by *K. pneumoniae*. Understanding and monitoring these pathways are crucial for developing effective therapeutic strategies and containment policies to combat infections caused by this formidable pathogen.

2.2. Membrane Remodeling

The cell envelope is crucial for the adaptation and survival of the bacteria. The cell envelope of gram-negative bacteria possesses three important layers: the outer membrane (OM), peptidoglycan, and inner membrane [33]. Porin proteins exist in the outer membrane. They are called outer membrane porins and act as protein channels [35]. These porins allow the transport of small nutrients, antibiotics, iron, and hydrophilic molecules across the outer membrane. Porins also serve as bacteriocins and phage receptor proteins, and in association with lipopolysaccharide and peptidoglycan, maintain the integrity of the cell. Earlier studies have indicated a dual role for these proteins in virulence and drug resistance [35]. Extensive studies related to porin characterization have been conducted on the E. *coli* laboratory strain K-12. OmpC and OmpF porins are well known and have been characterized in this strain. In *E. coli,* the port of OmpF is narrower than that of OmpC, which makes it easier for molecules to pass through the latter. In *K. pneumoniae* two well-known active major outer membrane porins, OmpK35 and OmpK36, have been identified in *K. pneumoniae*. OmpK35 and OmpK36 were homologous to OmpC and OmpF, respectively. OmpK35 and OmpK36 allow antibiotics to penetrate the *K. pneumoniae* cell wall. This experiment was initially shown in various studies that cloned the ectopic expression of OmpK35 or OmpK36 in deficient strains lacking both OmpK35 and OmpK36. These studies indicate that cephalosporins pass through OmpK35 more efficiently than through OmpK36. These studies also showed that OmpK35 is not expressed in media

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with high osmolality. This agrees with the theory that OmpF is preferentially expressed in a medium with low osmolality, whereas OmpC is highly abundant at high osmolality [35]. Most *K. pneumoniae* strains that produce ESBL express only OmpK36, whereas the majority of non-ESBL-producing *K. pneumoniae* were found to express both OmpK35 and OmpK36 [35]. ESBL-producing *K. pneumoniae* typically lacks one of these porins, making it more likely to develop resistance by losing the expression of the remaining porins. Both clinical and experimental evidence show that the loss of porins in *K. pneumoniae* that produces ESBLs increases resistance to oxyimino cephalosporins and cefoxitin and decreases susceptibility to fluoroquinolones [92,93].

Coordinated OMP membrane folding and insertion are facilitated by the B-barrel assembly machinery (BAM) complex [94]. The BAM complex of gram-negative bacteria is composed of the outer membrane protein BamA, also known as Omp85 or YaeT, and lipoproteins, such as BamB (YfgL), BamC (NIpB), BamD (YfiO), and BamE (SmpA) [95]. In the BAM complex, BamA is the core molecular component that plays a crucial role in assembling outer membrane proteins (OMPs). Other lipoproteins, including BamA, BamC, BamD, and BamE, directly or indirectly interact with BamA anchored to the periplasmic side of the outer membrane [96]. The absence of BamA causes misfolding of the outer membrane of the B-barrel, preventing its proper insertion into the bacterial outer membrane. This misfolding damages the outer membrane structure, ultimately leading to bacterial cell death [96]. The assembly of porins into the outer membrane of bacteria at the molecular level, combined with molecular knowledge of the signals that determine which porin-encoding genes are activated in response to specific stimuli, such as antibiotics [35,97]. Targeting molecules such as BAM on the bacterial outer membrane surface could serve as promising sites for drug development.

2.3. Efflux Pump Systems

Efflux pumps are transport proteins localized in the bacterial membrane. Efflux pumps regulate the internal cellular environment by fluxing toxic substances, including antibiotics. Most efflux pump systems are activated by stimuli (i.e., substrate-induced activation). This mechanism reduces the concentration of antibiotics within the bacteria and contributes to the development of drug resistance. Multidrug efflux pumps contribute to increased resistance to various antimicrobial agents, including antibiotics, dyes, antiseptics, and detergents. In *K. pneumoniae,* several multidrug efflux pumps have been identified in *K. pneumoniae*, including AcrAB, AxAB, EefAB, KexD, KmrA, KdeA, and CepA [98]. Among these, the dominant efflux pump systems are AcrAB-ToIC and OqxAB from the RND family. AcrAB, OqxAB, EefAB, and KexD belong to the RND family. The RND-type efflux pump system is composed of three parts: outer membrane, inner membrane, and periplasmic protein. The RND-type efflux pump, along with its function in intrinsic resistance, is also thought to play a role in bacterial colonization of the intestinal tract by releasing virulence factors [98]. The AcrAB-ToIC system is also known for fluxing B-lactam antibiotics, macrolides, fluoroquinolones, tetracycline, and amido-alcohol antibiotics. The regulatory genes *acrR* and *ramR* associated with this system often contain mutations that favor overexpression of the AcrAB-ToIC efflux pump [99]. This efflux plays an important role in the drug resistance observed in *K. pneumoniae.* Autosomal transfer of OqxAB to a plasmid can increase the expression of the efflux pump, which further increases drug resistance.

2.4. Quorum Sensing and Biofilm Formation

A biofilm is a collection of bacteria embedded in self-produced molecules known as an extracellular polymeric matrix. Biofilm formation is a multistage process that includes the attachment of free bacteria to the surface or other cells, followed by the formation of microcolonies, maturation, and dispersion, which allows the biofilm to spread and colonize new surfaces [100]. Biofilms are formed when many bacterial cells aggregate in extracellular mucus composed of a polysaccharide matrix, lipids, and proteins secreted by bacteria. Biofilms may be comprised of a single bacterial species or a mixture of other microorganisms [101]. Bacteria form biofilms in response to external pressure, including high osmotic pressure, low PH, oxidative stress, and antimicrobial exposure. The mechanism by which bacterial cells communicate their population density is known as quorum

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sensing (QS), also called density sensing. This process regulates various biological behaviors in bacteria by adjusting gene expression based on the population density. As the density of the bacterial population increases, bacterial cells begin to produce signaling molecules that trigger various cellular mechanisms, such as the expression of virulence factors, antibiotic tolerance, biofilm formation, and the development of drug resistance [102]. This coordination allows bacteria to activate this mechanism only in the presence of maximum environmental stress; conditions that threaten their survival and require a collective adaptive response [98,103,104].

In *K. pneumoniae*, QS is essential for regulating biofilm formation, the expression of virulence factors, and antimicrobial resistance. This bacterium primarily utilizes acyl-homoserine lactones (AHLs) as QS signaling molecules, which coordinate group behaviors crucial for its survival and pathogenicity. QS enhances the production of extracellular polymeric substances that comprise the biofilm matrix, facilitating strong biofilm development on both living tissues and medical devices [105]. Biofilm formation in *K. pneumoniae* is strongly linked to its ability to evade host immune responses and resist antibiotic treatment, contributing to persistent infections such as pneumonia, urinary tract infections, and bloodstream infections. The biofilm matrix acts as a physical barrier that limits antibiotic penetration and facilitates horizontal gene transfer of resistance genes, including those encoding carbapenemases [106]. Moreover, QS-regulated biofilm formation increases the expression of capsular polysaccharides and fimbrial adhesins in K. pneumoniae, both of which are key virulence determinants that promote adherence and immune evasion. Disrupting QS signaling pathways in K. pneumoniae has shown promise as a therapeutic strategy to inhibit biofilm formation and reduce virulence, underscoring the impact of QS on its pathogenic potential [106]. During critical stress conditions such as nutrient limitation, immune attack, oxidative stress, desiccation, or antibiotic exposure, bacteria require strong defenses. The bacterial capsule, a protective polysaccharide layer, helps shield cells from these threats by preventing phagocytosis, reducing water loss, and limiting antibiotic entry. Quorum sensing allows bacteria to detect when their population and stress levels are sufficient to trigger the energy-demanding production of capsules, ensuring coordinated formation that enhances survival and virulence under high-risk conditions. The activity of the bacterial community is regulated by the expression of autoinducers. Autoinducers vary among different bacteria. For instance, gram-negative bacteria, including *K. pneumoniae*, rely on acyl-homoserine lactones, which are small molecules. Gram-positive bacteria use auto-inducing peptides that activate the kinase activities of their receptors [103].

3. Molecular Mechanisms of Virulence and Pathogenicity in *K. pneumoniae*

Although *K. pneumoniae* is historically known to cause infection in immunocompromised individuals, there are increasing reports of virulent strains capable of causing disease in healthy individuals [3,7–9,11,18,66,107]. The pathogenicity of *K. pneumoniae* depends on the presence and type of its virulence factors of *K. pneumoniae*. Infections caused by *K. pneumoniae* include respiratory tract infection (RTI), urinary tract infection (UTI), bloodstream infection (BSI), and wound site infections. *K. pneumoniae* strains are traditionally known to have low virulence and a high degree of antibiotic resistance; therefore, these infections are difficult to treat. Hypervirulent strains are highly pathogenic and can cause community-acquired infections. Hypervirulent strains mainly cause meningitis and liver abscesses [18,107,108]. Although hypervirulent strains commonly cause community-acquired infections, studies have reported that hospital outbreaks are associated with hypervirulent *K. pneumoniae.* Although the convergence of MDR and hypervirulence is emerging, hypervirulent strains are more susceptible to antibiotic treatment than classical strains. Well-known and characterized virulence factors in *K. pneumoniae* are fimbriae, capsules, siderophores, iron uptake systems, and the ability to metabolize allantoin [109,110].

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3.1. Fimbriae

Gram-negative bacteria and some gram-positive bacteria have fimbriae that help them adhere to the surface and other cells [111]. Although the clusters were under-characterized, from genome analysis of *K. pneumoniae* there estimated ten types of fimbriae. Seven gene clusters were identified and named *kpa* to *kpg* [112]. The operon responsible for the expression of *E. coli* common pilus (ECP), a well-studied and characterized E. coli fimbriae, has been reported in *K. pneumoniae.* The well-known and characterized fimbriae in *K. pneumoniae* are types 1 and 3, which serve as structural and adhesive molecules. *K. pneumoniae* virulence is enhanced by the presence of fimbriae. Fimbriae facilitate adherence to surfaces and host tissues. Type 1 and type 3 fimbriae are membrane-anchored and divided into adhesive and structural subunits. The subunits contain specific genes in the form of gene clusters, *fim* (*fimABCDEFGHIK*) and *mrk* (*mrkABCDF),* in type 1 and type 3 fimbriae, respectively, [11,113]. Adhesive subunits in the extremities are involved in virulence. *K. pneumoniae* uses the *fimH* gene to express the FimH adhesive subunit, which is important for recognizing and adhering to the mannosylated regions of glycoproteins in the urothelium (uroplaquin Ia). *FimH* gene-expressing *K. pneumoniae* is considered uropathogenic, as the urothelium is an uroplasmic-rich tissue [11,114]. The mrkA and mrkD genes of type 3 fimbriae express the adhesive subunits of type 3 fimbriae. *K. pneumoniae* fimbriae in this class are known to mediate biofilm formation, which was demonstrated in gene knockout studies by comparing the wild-type and *mrk*-deficient mutant strains. Studies have also shown the co-presence of type 1 and type 3 fimbriae, which increases virulence, and mrkD adhesins with FimH. Studies have reported that the prevalence of *mrkD* is 100% among biofilm-producing *K. pneumoniae* isolates [11,115]. Understanding the genetic regulation and interplay of fimbrial gene clusters offers valuable insight for developing new strategies to prevent and treat biofilm-associated infections.

3.2. Iron Acquisition Systems

Iron is an essential metabolic cofactor for both eukaryotes and prokaryotes. There is natural competition for this metal between the host cells and bacterial pathogens. Iron is vital to organismal growth and development [116]. Iron acts as a cofactor for essential enzymes involved in oxidative metabolism and is a crucial component of oxygen transport proteins. Although iron is abundant in nature, its presence in the oxidized state (Fe3+) reduces the free iron available for microbial use. The concentration of free iron in the natural environment is approximately 1×10^{-18} mo/L, which is very low compared with the 1×10^{-6} mo/L required by most microbes [117].

The ability of many pathogens to proliferate is restricted by iron availability. The iron concentration required for bacterial growth is higher than that required for its free availability in mammalian hosts [116]. Studies conducted in a siderophore mutant *E. coli* strain were found to acquire 0.05 μM, increasing the iron concentration from 2 μM to improve growth in this strain [118]. This creates selective pressure that promotes the evolution of systems that can overcome iron sequestration in hosts. Although mammalian cells defend against this mechanism by sequestering Fe^{3+} in binding proteins and ferritin [119], *K. pneumoniae* has a mechanism to overcome the limited iron in the host environment. In response to host defence mechanisms that limit iron access, *K. pneumoniae* secretes siderophore proteins to extract $Fe3^{+}$ from tissues, cells, and proteins. Siderophores are small molecules known for their strong ability to bind iron, which is crucial for the life forms that require this metal. *K. pneumoniae* secreted siderophores have a strong affinity for iron chelates and transport iron to bacteria, which is essential for their development and metabolism. Since these siderophores have a greater affinity for absorbing iron than the host, this is one of the pathogenicity factors [119]. The ligand-gated porins in these bacteria actively acquire ferric siderophores and other iron-containing molecules such as heme. *K. pneumoniae* produces important siderophores such as enterobactin, which is encoded by the gene cluster entABCDEF. The Enterobactin *entB gene* is the most frequently reported [120,121]. Another prevalent siderophore in *K. pneumoniae* is yersiniabactin, which is found in nearly all hypervirulent strains. The ybtAEPQSTUX gene cluster, irp1, and irp2 are responsible for the expression of yersiniabactin [122]. The frequently reported genes include *irp1,*

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irp2, ybtA, and ybtS. Another important siderophore found in hypervirulent *K. pneumoniae*, aerobactin, is rare in the classical *K. pneumoniae* strains. Aerobactins are expressed in the iucABCD gene cluster [123]. The prevalence of these siderophores is high in hypervirulent *K. pneumoniae* [124], and they can serve as virulence markers. The ability of *K. pneumoniae* to produce diverse siderophores allows it to overcome host iron sequestration. This underscores the importance of iron acquisition systems as key virulence factors. These systems also represent potential targets for therapeutic intervention in infections caused by this pathogen.

3.3. Capsule

The capsule is the most widely studied virulence factor in *K. pneumoniae.* The capsule contains an extracellular polysaccharide matrix. Capsules enhance cellular fitness by protecting against harmful stimuli, such as antibiotics, and facilitate competitive interactions with other bacterial species. Capsules are also known to increase virulence, especially in human hosts [104]. *K. pneumoniae* uses its capsules to evade immune phagocytosis and to protect itself from biocidal molecules. The capsular polysaccharide (CPS) is a crucial virulence factor that contributes to the hypervirulent phenotype of *K. pneumoniae*. Variations in the composition and structure of CPS affect the virulence of these bacteria. Although the host immune defense system consists of an innate immune system that provides first-line defense against invading foreign antigens, *K. pneumoniae* CPS has immune evasion mechanisms that enhance survival, colonization, and dissemination. Factors, such as lipopolysaccharides (LPS) and CPS, contribute to survival and pathogenicity [125,126]. CPS (K antigen) and LPS (O antigen) are key components of the outer membrane of *K. pneumoniae*. These molecules play an important role in host interactions. *K. pneumoniae* contains LPS that are anchored to its membrane. LPS is composed of three structural components: the Lipid A oligosaccharide core and the terminal side chain of the O antigen. Lipid A anchors the bacterial cell membrane and is synthesized by the *Ipx* gene cluster [125,127]. The host immune system recognizes LPS predominantly through lipid A, which binds strongly to Toll-like receptor 4 (TLR4). This recognition leads to the activation of innate immune responses. However, the modification of this molecule hinders *K. pneumoniae* by immune cells [125]. The core oligosaccharide connects lipid A to O antigen. The waa locus contains genes that encode the core oligosaccharides. The O antigen is attached to the core oligosaccharide via the WaaL ligase, which is encoded by the *waaL* gene. The O antigen is composed of a polymer of repeating units of oligosaccharides located in the outer part of LPS. The wb gene cluster regulates the synthesis, assembly, and transfer of diverse O antigens. Among the nine *K. pneumoniae* identified, the differences arose from variations in the sequence and composition of the sugar monomers. Diverse repeats of O antigens contribute to the structural variations in LPS [128]. LPS is important for both the virulence and drug resistance of these bacteria. *K. pneumoniae* develops resistance to polymyxin by altering the LPS structure, as polymyxin primarily targets the negatively charged lipid A [129].

K. pneumoniae produces an acidic CPS that plays a crucial role in its survival within the host. Historically, *K. pneumoniae* has been categorized based on its (K antigen) serotyping, with 79 capsule types currently identified [130]. Differences in the capsule types of *K. pneumoniae* are due to variations in the nucleotide sequences and the number of genes. Studies have proposed a new classification system for CPS that relies on the sequencing of conserved *wzi/wzc* genes located in the cps locus [131–133]. The CPS of *K. pneumoniae* is recognized as a key virulence factor, owing to its ability to inhibit phagocytosis. The severity of infection associated with this bacterium is also linked to the presence of strains possessing specific K antigens or CPS types. For instance, the CPS of K1 and K2 expressing *K. pneumoniae* strains is associated with pyogenic liver abscesses, and they were found to be resistant to serum complement [125,134]. Understanding the genetic regulation and diversity of CPS and LPS highlights their roles in pathogenicity and antimicrobial resistance. This knowledge emphasizes their potential as targets for therapeutic intervention.

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4. Novel Therapeutic Strategies

Recent experimental and preclinical studies have highlighted promising novel therapeutic strategies against multidrug-resistant *K. pneumoniae*. Phage therapy, which employs bacteriophages specific to *K. pneumoniae*, has shown remarkable efficacy in disrupting biofilms and reducing bacterial loads in infected animal models (Table 2). For example, phage cocktails that combine multiple bacteriophages have significantly increased survival rates in mice infected with drug-resistant strains, while also lowering bacterial burden in tissues and blood [135,136]. Additionally, individual phages targeting specific *K. pneumoniae* serotypes have demonstrated therapeutic potential in surgical site infection models, improving survival rates and decreasing inflammation. Importantly, combining phages with antibiotics like meropenem or imipenem has enhanced bacterial clearance and reduced the development of resistance [137–139].

Anti-biofilm agents complement these therapies by inhibiting biofilm formation or promoting biofilm dispersal, thereby restoring antibiotic susceptibility and aiding immune system clearance. Antimicrobial peptides (AMPs), which are naturally occurring small cationic peptides, disrupt bacterial membranes and modulate host immunity [15,140] . Studies indicate that AMPs can work synergistically with conventional antibiotics against *K. pneumoniae*, leading to reduced dosages and diminished resistance emergence. Furthermore, nanoparticle-based approaches enable targeted delivery of antimicrobials and provide intrinsic antibacterial activity through the generation of reactive oxygen species and membrane disruption, thereby enhancing drug penetration and overcoming resistance barriers [141]. Collectively, these strategies form a multifaceted arsenal against MDR *K. pneumoniae*, offering promising advances for more effective clinical interventions. Continued research and clinical validation of these approaches are vital to address the growing threat posed by drug-resistant *K. pneumoniae* infections.

Table 2. Successful phage therapies against MDR *K. pneumoniae*.

Study / Report	Model / Patient	Phage Therapy Details	Outcome / Success Summary	Ref.
φNK5 phage in a mouse model of *K. pneumoniae* liver infection	Mouse model (liver abscess)	Single dose φNK5, intragastric or intraperitoneal	Protected mice from death, cleared bacteria, reduced liver damage	[135]
Personalized phage therapy for prosthetic knee infection	Human patient with prosthetic knee infection	De novo isolated phages φ2 and φ4, used alone	Infection controlled, clinical improvement, tolerated well	[136]
Phage cocktail Katrice-16 against MDR *K. pneumoniae* ST16	In vitro and preclinical	Cocktail of 8 lytic phages	High in vitro activity against MDR *K. pneumoniae*, potential for human use	[143]
Treated pneumonia caused by MDR *K. pneumoniae*	A human patient with pneumonia	Increasing doses of nebulized phages over 16 days, combined with antibiotics initially	Clinical improvement, bacterial load reduction, and discharge from hospital	[144]
Dual-phage cocktail in mice for *K. pneumoniae* infection	Mouse model	Dual-phage cocktail	Improved survival rates compared to single phage therapy	

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Treated pneumonia caused by MDR *K. pneumoniae*	Murine pneumonia model	Phages pKp11 and pKp383 targeting ST11 and ST383 MDR *K. pneumoniae*	Effective treatment of pneumonia	[145]
Phage cocktail therapy for burn wound infections (includes *K. pneumoniae*)	Animal model	Phage cocktail	Remarkable therapeutic efficacy and tolerance	[146]
Phage therapy in refractory pneumonia caused by MDR *K. pneumoniae*	Clinical case reports	Phage therapy alone or combined with antibiotics	Promising treatment outcomes in refractory pneumonia	[147]
Phage cocktails reduce inflammation in mouse mammary gland infection	Mouse model	Phage cocktail	Reduced bacterial load and inflammatory factors	[148]
Phage therapy for carbapenem-resistant *K. pneumoniae* in a trauma patient	Human patient	Phage cocktail targeting *K. pneumoniae*	Avoided amputation, clinical improvement	[144]
Phage therapy for *K. pneumoniae* infections in burn wounds	Animal model	Phage cocktail	Improved survival and infection control	[149]

5. Conclusion

The molecular basis of *K. pneumoniae* virulence and mechanisms of drug resistance are multifaceted and complex. Understanding the molecular mechanisms involved can help to predict novel therapeutic targets. The production of B-lactamases and carbapenemases renders last-resort drugs ineffective. Genetic variations in these enzymes complicate treatment options. Different enzymes exhibit varying resistance profiles and are often associated with specific geographic regions. Additionally, certain virulence factors play dual roles in influencing virulence and antibiotic resistance. For example, the ability to form biofilms enhances resistance mechanisms and promotes colonization and infection. *K. pneumoniae* uses lipid A for virulence and resistance. Moreover, genes associated with virulence, such as those encoding adhesins and siderophores, help the bacterium evade the host immune system and persist in the presence of antimicrobial agents. The increasing prevalence of MDR and hypervirulent strains highlights the need for novel therapeutic strategies. Future research should focus on exploring novel therapeutic strategies, including developing anti-biofilm agents, combining traditional antibiotics with natural compounds, and advancing therapies such as phage therapy, antimicrobial peptides, and nanoparticles to combat resistant and hypervirulent bacterial strains. Such innovative approaches show significant potential for effectively tackling resistant *K. pneumoniae* infections and enhancing patient outcomes.

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