Infection and Drug Resistance

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REVIEW

A Comprehensive Overview of Klebsiella Pneumoniae: Resistance Dynamics, Clinical Manifestations, and Therapeutic Options

Shan-Shan Jin^{1,2,*}, Wei-Qin Wang^{1,*}, Yi-Han Jiang^{1,*}, Yue-Tian Yu³, Rui-Lan Wang^{1,2}

¹Department of Critical Care Medicine, Shanghai General Hospital, Shanghai Jiaotong University, School of Medicine, Shanghai, People's Republic of China; ²Department of Critical Care Medicine, Shanghai General Hospital of Nanjing Medical University, Shanghai, People's Republic of China; ³Department of Critical Care Medicine, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Rui-Lan Wang, Email wangyusun@hotmail.com

Abstract: *Klebsiella pneumoniae* (Kp) is a notable pathogen responsible for various infections. The emergence of hypervirulent and carbapenem-resistant strains has raised global concern. Many novel approaches were developed to combat the current severe situation of antibiotic resistance, and clinical guidelines have also provided corresponding recommendations. This review highlights the critical aspects of Kp, including classification, virulence factors, systemic dissemination, drug resistance progression and the new therapeutic strategies to combat this evolving threat.

Keywords: *Klebsiella pneumoniae*, virulence, hypervirulent, carbapenem resistant, evolution, metastatic spread, colonization, capsule types, virulence plasmid

Introduction

Klebsiella pneumoniae (Kp) is a Gram-negative, encapsulated bacterium belonging to the *Enterobacteriaceae* family. It was initially identified by Carl Friedländer in 1882 as a pathogen causing pneumonia.¹ Commonly found in the environment, Kp typically colonizes the human gastrointestinal tract and oropharyngeal mucosal surfaces.^{2–4} The ability of Kp to acquire new resistance genes has facilitated its evolution and pathogenicity.⁵ Kp has become a major concern in the healthcare settings due to its high incidence and significant drug resistance, particularly in hospital settings among immunocompromised and hospitalized patients.^{6,7} The global distribution of hypervirulent strains of Kp adds another layer of complexity, as these strains demonstrate the ability to cause invasive infections in both hospital and community settings.^{8,9} For the scope of this review, we concentrate on a comprehensive understanding on the pathogenicity, resistance mechanisms, treatment options, and control strategies of Kp.

Classification and Typing

The genus Klebsiella, named after Edwin Klebs (1834–1913), includes 27 child taxa.¹⁰ One child taxa: *Klebsiella pneumoniae*, relevant to human infections. Based on the a genomic analysis, it is divided into three distinct phylogroups: KpI (*Klebsiella pneumoniae*), KpII (*K. quasipneumoniae*), and KpIII (*K. variicola*).^{2,11,12} Following the classification of Ørskov, *Klebsiella pneumoniae* is divided into three subspecies: *Klebsiella pneumoniae subsp. pneumoniae, Klebsiella pneumoniae, klebsiella pneumoniae subsp. ozaenae, and Klebsiella pneumoniae subsp. rhinoscleromatis*.¹³ These strains affect animals and plants and are common in various environments.¹⁴ Kp is classified into two pathotypes in clinical practice: classical Kp (cKp) and hypervirulent Kp (hvKp).^{8,13} Differentiating between cKp and hvKp has been a challenge in the past due to the difficulties in tracing their evolutionary history, with insights often being derived indirectly from case reports or retrospective cohort studies.¹⁵ An advancements in whole-genome sequencing(WGS) of Kp on a large scale have started

Jin et al

to uncover genomic distinctions between hvKp and cKp. For the characteristics of hvKp and cKp, refer to Table 1. There has been a global rise in antibiotic-resistant hvKp isolates.^{16–19} Prior studies have highlighted that multi-drug resistant Kp (MDR-Kp) and hvKp are notably distinct. For example, MDR-Kp is primarily associated with clonal groups (CGs) 258, 15, and 147, whereas hvKp strains are commonly identified in CGs 23, 86, and 380, with a predominant presence of the K1 and K2 serotypes.²⁰

cKp and Its Antimicrobial Resistance (AMR) Genes

Clinicians are quite familiar with cKp, which typically infects patients with comorbidities, those who are immunocompromised, or those with compromised barriers such as intravascular devices, endotracheal tubes, or surgical wounds, in healthcare settings; it is an opportunistic pathogen.⁷ Studies in the mid-20th century highlighted the cKp 's capacity to cause urinary tract infections, pneumonia, and sepsis, leading to a deeper understanding of its clinical significance.⁶ In the 1910s, Toennissen was the first researcher to draw attention to the serologic specificity of Klebsiella capsules.²¹ Kp is characterized by a prominent polysaccharide capsule, and serological typing is based on the structural diversity of the capsule polysaccharides (K antigens) and lipopolysaccharides (O antigens), with 77 different K antigens and 8 O antigens identified.¹³ The identified clones of Kp include eight MDR clones, namely clonal group (CG) 15, CG20, CG29, CG37, CG147, CG101, CG258, and CG307, as well as six hypervirulent clones, which are CG23, CG25, CG65, CG66, CG86,

Characteristics	Classical Kp (cKp)	Hypervirulent Kp(hvKp)
Clonal group (CG)	CG 15, CG 20, CG 29, CG 37, CG 147, CG 101, CG 258, CG307	CG 23, CG 25, CG 65, CG 66, CG 86, CG 380
Multilocus Sequence Typing (MLST)	ST 11, ST 258	ST 23, ST 65, ST 66, ST 86
Serotypes	Non-K1K2	K1, K2, K20, K54, K62
Host	Older immunocompromised patients	All ages including young healthy adults (Prone to Diabetes or Alcoholism)
Place of infection	Nosocomial	Community
Infectious sites	Usually single	Usually multiple
Rare infection sites	No	Yes, invasive syndrome: liver abscess with extrahepatic complications, especially CNS involvement, necrotising fasciitis, or endophthalmitis; splenic abscess and et al
Co-infection	Often	Rare
Capsular Polysaccharide (CPS)	Thinner	Thicker
Siderophores	Enterobactin	Enterobactin, yersiniabactin,salmochelin, and aerobactin
Hypermucoviscosity	Sometimes	Often
Plasmid-encoded genes	Plasmid-encoded Resistance genes : Carbapenem Resistance-Encoding Plasmids, ESBL plasmids and et al	Plasmid-encoded virulence genes : pLVPK(219-kb), pK2044 (224,152 bp), Kp52.145 plasmid II (pKpST66-2) (121-kb), pKP35_vir (191-kb)
Hypervirulence-encoding genes	No	iroB, iroN, iucA, iutA, peg-344, rmpA, rmpA2, clbA, clbB, entB
Carbapenem-resistant hypervirulent Kp	Hv-CRKp: acquisition of virulence plasmids by non-KI/K2 CRKp	CR-hvKp : acquisition of carbapenem-resistance genes by hvKp

Table I The Differentiation of Classical and Hypervirulent Kp Strains

Abbreviations: CRKp, carbapenem-resistant Kp; CR-hvkKp, carbapenem-resistant hypervirulent Kp.

and CG380.²² In Europe and America, the most common type of cKp is ST258, while in the Asia-Pacific region, it is predominantly sequence type (ST) 11.²³ ST 23, 65, 66, and 86 are identified as being associated with hvKp strains.^{24,25} The study revealed that the high-risk ST11 KL64 CRKp subclone, which emerged in the Americas in 1996 and spread globally, demonstrated significant expansion and survival advantages, particularly the BMPPS single-nucleotide polymorphism (SNP) clade, associated with high mortality and strong anti-phagocytic and competitive traits in vitro.²⁶ There is a rise in KL64 CRKp prevalence (59.5%) and a decline in KL47 CRKp, providing valuable information on CRKp serotype trends.²⁷

Timeline of Resistance Development in cKp

The history of cKp's resistance to antibiotics spans several decades, beginning with the emergence of penicillin resistance soon after its widespread use in the mid-20th century. By the 1970s and 1980s, resistance to broader-spectrum antibiotics, including first-generation cephalosporins and aminoglycosides, was increasingly reported in hospital settings.²⁸ The discovery of extended-spectrum beta-lactamases (ESBLs) and carbapenemases in cKp strains marked critical points in the bacterium's history, indicating a worrying trend in its ability to evade even the most potent antibiotics.²⁹ The initial key event in this evolutionary trajectory was the identification of ESBLs (particularly Temoniera β -lactamase (TEM), Sulfhydryl Variable β lactamase (SHV), and Cefotaximase β -lactamase (CTX-M) types) in the 1980s. There was a notable rise in the prevalence of ESBL-producing strains of cKp.^{30–33} The situation was further exacerbated in the 1990s with the emergence of carbapenemresistant strains.³⁴ Carbapenems were introduced as a powerful class of beta-lactam antibiotics effective against a broad spectrum of bacteria, including those resistant to other beta-lactams. However, the advent of carbapenemases, enzymes that hydrolyze carbapenems, rendered these drugs ineffective against CRKp. The most notorious of these carbapenemases is the Klebsiella pneumoniae carbapenemase (KPC), which was first identified in North Carolina in 2001 and has since spread globally.⁵ Other carbapenemases, such as the New Delhi Metallo-beta-lactamase-1 (NDM-1), have also been identified, further complicating the treatment of cKp infections.³⁵ The emergence of these AMR genes signified a critical shift in the approach to managing cKp infections and prompted the need for new antibiotics and alternative therapeutic strategies. A review discussed the variants of KPC and the blaKPC mutation related to ceftazidime-avibactam (CZA). To date, over 145 bla_{KPC} variants have been reported globally, with most of the new variants identified in the past three years.³⁶ In vitro studies mimicking in vivo KPC mutations with CZA indicate that insufficient avibactam concentrations are more likely to induce resistance in strains against CZA, and the mutation is reversible.³⁷

Factors Contributing to the Evolution of Resistance

Several factors have contributed to the rapid evolution of AMR in cKp. Firstly, environmental factors, including the presence of antibiotics in water systems and soil, have also contributed to the selection pressure leading to the emergence of resistant strains.³⁸ The global environmental reservoirs of carbapenemase-producing genes—KPC, NDM, Oxacillinase-48 (OXA-48), and verona integron-encoded metallo-β-lactamase (VIM)—are found in diverse matrices such as wastewater, natural and recreational waters, animals, and food products.³⁹ A study in China found nine NDM-5-producing, multidrug-resistant bacteria in a vegetable production area. Samples from vegetables, soil, water, sediments, and farmer feces showed clonal transmission of carbapenem-resistant bacteria within greenhouse soils, with highly transmissible IncX3 plasmids detected. These plasmids were also found in farm workers' feces, indicating potential transfer from the environment to humans.⁴⁰ Secondly, the ability of cKp to form biofilms on medical devices has posed challenges in eradicating the bacteria and has been a significant factor in the persistence and spread of AMR genes in healthcare settings.⁴¹ The persistence and spread of AMR genes in healthcare settings are further exacerbated by inadequate infection control practices. The failure to implement and adhere to strict infection control measures, such as hand hygiene, equipment sterilization, and patient isolation, facilitates the transmission of cKp within healthcare facilities.⁴² Furthermore, antibiotic use in both clinical and agricultural settings has significantly contributed to AMR.⁴³ A study reported a patient of hy-CRKP-associated infection, detailing the in-host evolution of resistance to tigecycline and polymyxin during clinical therapy, with mutations identified in the genes ramR, lon, pmrB, phoQ, and mgrB.⁴⁴ Heteroresistance (PHR) is a resistance phenotype where subpopulations of a bacterial isolate show significantly reduced sensitivity to antimicrobial agents compared to the main population. Polymyxin B(POLB) PHR in CRKp found that many

undetected PHR strains evolved into fully resistant (FR) strains after POLB treatment, driven by higher mgrB mutations in ST11 strains and a shift to pmrAB mutations.⁴⁵

HvKp and hvKp-Specific Factors

The Emergence of hvKp

HvKp is characterized by its hypermucoviscosity (HMV), a physical trait associated with increased virulence and the ability to cause more severe infections than the cKp. The first clinical identification of hvKp occurred in 1986 when Liu et al reported cases of invasive Kp infections characterized by hepatic abscess and septic endophthalmitis.⁴⁶ The evolutionary trajectory of hvKp can be traced back to the late 19th century with the initial description of Kp by Carl Friedländer in 1882. Friedländer 's bacillus is known for causing severe pneumonia. It accounts for only 0.5 to 5% of community-acquired pneumonias.^{47,48} HvKp is linked to various extrapulmonary infections, including renal and hepatic abscesses, osteomyelitis, cavernous sinus thrombosis, meningitis, brain abscess, splenic infection, spontaneous bacterial peritonitis and soft tissue abscesses.⁴⁹ According to Schroeter, J., Kp subsp. pneumoniae was discovered in 1886.^{50–54} The clinical and biological manifestations of Friedlander's bacillus are extremely similar to those of hvKp. Meanwhile, research by Lam et al in 2018 suggests ST23 hvKp originated around 1878, supporting the idea that Friedlander's bacillus was the first hvKp strain.²³ Studies have confirmed that several biomarkers and quantitative siderophore production can accurately predict hvKp strains, enhancing our understanding and effective response to these more aggressive infections.^{55–57}

Virulence Factors of hvKp

Virulence Genes of hvKp

Research indicates that the genes iroB, iroN, iucA, iutA, peg-344, rmpA, and rmpA2 are the most precise markers for identifying hvKp. Additionally, genes such as clbA, clbB and entB are also considered to play a role in enhancing the invasiveness of Kp.^{58,59} The iroB and iroN genes are components of the iroBCDEN gene cluster, which are responsible for the biosynthesis of the siderophore salmochelins.^{60,61} Similarly, the iucA and iutA genes, forming part of the iucABCD-iutA gene cluster, are essential for the biosynthesis of the siderophore aerobactin.^{61,62} Peg-344 functions as a metabolic transporter and is highly associated with the virulence of hvKp.⁶¹ RmpA and rmpA2 are regulatory genes that enhance capsule production, with rmpA specifically linked to the HMV characteristic of hvKp.^{61,62} Two genes (clbA and clbB) of the pks colibactin gene cluster have been related to biosynthesis of colibactin.⁶³

These biomarkers significantly validate the usefulness of these virulence genes for effectively distinguishing between hvKp and cKp. Enterobactin is the product of $entB^7$ (Figure 1).



Figure I Virulence factors of cKp and hvKp.

Other Virulence Factors

Other virulence factors also include capsular polysaccharide (CPS), siderophores, HMV, fimbriae, lipopolysaccharide (LPS), plasmids; see Table 2 for details.

CR-hvKp

Advancements in WGS have allowed for the tracking of hvKp spread and evolution, revealing the complex interplay between antibiotic resistance and virulence. These strains have begun to acquire ESBLs and carbapenemase genes, which could potentially lead to a convergence of hypervirulence and multidrug resistance, posing a severe threat to public health.⁷⁶ There has been a growing number of reports highlighting the emergence of hypervirulent Kp strains that are resistant to multiple drugs.^{77,78} HvKp strains can exhibit the ability to integrate resistance genes into their virulence

Virulence Factors	Discription
CPS	CPS is a complex polysaccharide layer that surrounds the bacterial cell, significantly differing in composition and thickness compared to cKp. CPS acts as a physical barrier and is to aid in immune evasion. The capsules are encoded by wzi, wza, wzb, wzc, wzx, and wzy. ⁶⁴ CPS plays a vital role in biofilm formation. Robust biofilms is associated with chronic infections and poses significant challenges in clinical settings, such as in the case of indwelling medical devices like catheters and prosthetic joints. ⁶⁵
Siderophores	The types of siderophores present in hvKp, including yersiniabactin, aerobactin, and salmochelin, are distinguished by their high affinity for iron and their unique roles in pathogenesis. ¹⁵ Enterobactin is an iron-chelating siderophore shared by both cKp and hvKp. Salmochelins, synthesized by the iroBCDEN gene cluster, are C-glucosylated form of enterobactin. ⁶⁰ Aerobactin is produced by the iucA gene. Both iutA and iucA are essential for the creation and assimilation of aerobactin. The iutA gene is responsible for encoding the aerobactin receptor protein. The iucA is tasked with encoding aerobactin synthase. ⁶⁶ Yersiniabactin is encoded by loci ybt of the pks gene cluster which was embedded in integrative conjugative elements (ICE). ^{67,68}
нмv	HMV phenotype is encoded by genes located in the chromosomal rmp locus of virulence plasmid. This trait enhances the bacterium's ability to evade the host immune system, particularly by resisting phagocytosis. The thick, mucoid capsule impedes the action of phagocytes and other components of the innate immune system, allowing hvKp to survive and proliferate within the host. Using "hypermucoviscous" to describe hvKp strains presents difficulties due to its lack of sensitivity and specificity; not every hvKp strain shows HMV, and the phenotype is sometimes seen in cKp strains. ¹⁵
Fimbriae	Type I fimbriae including FimA and FimH are characterized by their ability to mediate the adhesion of Kp to receptors present on the surface of host cells, facilitating colonization and subsequent infection, especially in the urinary tract. Type I fimbriae expression, triggered by Fim gene clusters, is prominent in UTIs, and is notably diminished in lung or gastrointestinal infections in murine models, highlighting the specificity of fimbrial function in different infection sites. ^{69,70} Type 3 fimbriae, encoded by the mrk gene cluster(mrkABCDF), are implicated in the adhesion to epithelial and endothelial cells. The primary contribution of type 3 fimbriae lies in their capacity to mediate biofilm formation on abiotic surfaces, such as indwelling medical devices including catheters. However, The interplay between fimbrial expression and other virulence factors, such as the hypercapsule phenotype observed in hypermucoviscous K1 serotype isolates of Kp, complicates the pathogenesis landscape. The hypercapsule, characterized by its significant mucoviscosity, may mask the fimbriae, potentially impeding initial adhesion to host cells. This phenomenon indicates a complex regulatory network governing the expression and function of virulence factors in Kp, balancing adhesin-mediated adhesion with capsule-mediated immune evasion. ⁷¹
LPS	The structure of LPS typically includes three parts: the O-antigen, core oligosaccharide, and lipid A. ⁷² The OI antigen is often associated with KI and K2 capsule types, commonly observed in hvKp strains. ¹⁵ The O-antigen is a key focus in vaccine development, leading to the creation of conjugate vaccines that link O-antigen polysaccharides to carrier proteins.
Plasmids	Plasmids, as extrachromosomal DNA elements, contain specific genes that markedly amplify the virulence of hvKp. Two dominant virulence plasmids pLVPK(219-kb) which harbor hypervirulence-associated genes iuc, iro, rmpA, and rmpA2 and Kp52.145 plasmid II (pKpST66-2) (121-kb) which harbor genes iuc2, iro2, and rmpA are the best-characterized virulence factors of hvKp. ^{73,74} A study indicates that a newly identified virulence plasmid(pKP35_vir) (191-kb) harbors virulence genes such as rmpADC, iroBCDN (iro1), and the ybt locus (ybt4). This novel virulence plasmid has appeared in various countries, including China, Australia, and the United States. Its emergence could potentially pose a threat to public health. ⁷⁵

Table 2 Virulence Factors of hvKp

plasmids, such as the earliest well-known pLVPK-like virulence plasmid pVir-CR-hvKP4 (178,154 bp).⁷⁶ The "superbug" like carbapenem-resistant hypervirulent Kp (CR-hvKp) is known for its enhanced virulence, significant carbapenem antibiotic resistance, and global spread through three main mechanisms. First, hvKp transforms into CR-hvKp by acquiring plasmids that contain carbapenem resistance genes; Second, CRKp evolves into CR-hvKp after absorbing virulence plasmids; Third, Kp turns into CR-hvKp by obtaining a fusion plasmid that includes both virulence and carbapenem resistance genes, demonstrating the complex genetic changes that boost the robustness of this pathogen.⁷⁹ The clinical use of tigecycline for treating CRKp infections has contributed to the widespread dissemination of CR-hvKP in healthcare settings.⁸⁰

Colonization, Systemic Dissemination and Zoonotic Infections

Colonization and Development of Infection

The potential onset of infection might be influenced by the number of colonizing Kp strains, host factors, and the virulence levels of hvKp. Although acquiring Kp and undergoing colonization are critical phases, they do not necessarily lead to infection. In Western countries, the prevalence of Kp colonization in the colons of healthy people ranges from 5% to 35%.¹⁵ In Asian countries, the rates of Kp colonization in stool samples of healthy adults vary from 18.8% to 87.7%.⁸¹ Individuals colonized with hvKp are at a markedly increased risk of infection. A Chinese study observed a colonization rate of Kp in the stool of ICU admission patients at 28.0% (68/243), with 54% (37/68) being CRKp isolates. The occurrence of subsequent CRKp infections in the CRKp carrier group (45.9%, 17/37) was significantly higher compared to the group without Kp.⁸² The primary colonization sites include nasopharyngeal colonization (15%)⁶ and gastrointest-inal colonization (23%),⁸³ while colonization in other areas is considered transient. Nasopharyngeal colonization has been linked to alcohol consumption.⁸⁴ Higher rates of nasopharyngeal colonization are associated with poorer sanitation conditions, increased contamination of food and water, age, smoking, alcohol use, and residing in rural communities.⁸⁵

The colonization and infection by Kp are also closely related to its interactions with other microorganisms, which may include cross-feeding and mutually beneficial symbiotic relationships between Klebsiella and other microbes. A study found that co-culturing A. baumannii and Kp leads to the formation of biofilms and changes in cell shapes, which enhances antibiotic resistance.⁸⁶ The biofilms formed in co-culture are thicker and exhibit unique structural adaptations, with both bacteria displaying elongated cells due to reduced expression of cell division genes. This mutualistic relationship is evident not only among Gram-negative bacteria but also between Gram-negative and Grampositive bacteria. A study reported the spread of the NDM-5-positive IncX3 plasmid (known as pX3_NDM-5) within microbial communities in hospital wastewater in Fuzhou, China and the transfer of plasmids between Gram-negative and Gram-positive bacteria.⁸⁷ It may reveal the plasmid's exceptional ability to cross bacterial phylum boundaries.

Environment and Zoonotic Infections by Kp

Emerging infections caused by Kp are influenced by intricate "host-bacteria-environment" interactions, occurring unpredictably.⁸⁸ Food has been identified as a potential source of Kp infection, with an increasing number of cases where Kp is detected in various food items, marking its emergence as a pathogen in the food industry. Research from around the globe indicates that Kp can contaminate both meat and dairy products, leading to both spoilage and health concerns. Milk samples have tested positive for MDR Kp,⁸⁹ and CRKp strains have been found in chicken samples collected from farms in western Algeria, highlighting the risk of transmission through food consumption.⁹⁰ A study on the bacteriological quality of bottled waters in Iraq, found contaminants like E. coli, P. aeruginosa, and Kp. Notably, Kp showed sensitivity to all antibiotics tested, except ceftriaxone.⁹¹

Kp has the ability to infect a wide range of nonhuman hosts. Resistant bacteria may be transferred from animals to humans. A randomized controlled trial (RCT) from New Zealand found that hvKp infections severely impacted the survival rates of New Zealand sea lion pups on Enderby Island.⁹² During 2016–2018, 150 sea lion pups were studied, and 69 pups died, with only a small fraction of pups, 26.1% (18/69), showing symptoms before death, revealing rapid disease progression with hvKp infections. In Thailand, infections caused by Kp led to the deaths of four African marmosets,⁹³ from which 24 isolates were identified. One isolate was determined to be of ST 65, containing virulence and antibiotic resistance genes akin to those observed in human infections. Phylogenetic studies have demonstrated the widespread

dissemination of the ST65 strain globally. Pets like cats and dogs are key reservoirs and could be vital in transmitting Kp.^{94,95}

The environment serves as a critical reservoir for the acquisition of Kp by humans, either through colonization or infection, as Kp is commonly found in water, soil, sewage, and on plant surfaces. The widespread and non-medical use of antibiotics, encompassing their application in meat production, agricultural practices to avert crop losses, and the treatment of diseases in aquaculture, significantly fuels the emergence of drug-resistant pathogens. In hospitals, Kp can be transmitted through multiple channels, including direct person-to-person contact between healthcare workers and patients, with healthcare workers' hands being a notable vector. Additionally, contaminated surfaces and medical instruments have been recognized as transmission pathways, underscoring the multifaceted nature of Kp spread and the challenges in controlling its transmission.⁹⁶ Research from China reveals that CRKp in ICUs can contaminate environmental surfaces surrounding patients and then further spread among patients, ICU staff, and the environment. Environmental reservoirs for CRKp transmission in ICU settings, including gauze pads around endotracheal tubes, nasal catheters, oxygen masks, suction machines, bed linens near pillows, floors beside beds, bed rails, mobile nursing cart handrails, and the outer surfaces of bedside drainage bags, are frequently touched by healthcare workers during routine patient care.⁹⁷

Clinical Manifestation

Pneumonia

Community-acquired pneumonia caused by Kp infection predominantly affects males, with the primary transmission route being the respiratory tract.^{98–100} The patients may present with symptoms of hemoptysis, and in severe cases, there might be bloody sputum or red jelly-like sputum. The occurrence rate of hemoptysis can be as high as 58.3% (Figure 2).^{100–104} CT imaging characteristics of primary severe community-acquired pneumonia caused by hvKp include extensive consolidation in the lungs at the early stages of the disease. As the stages of the progresses, different manifestations such as pleural effusion, lung cavitation, and necrotic changes may appear. CT imaging findings in septicemic pulmonary embolism patients with Kp infection include peripheral wedge-shaped density, multiple nodular lesions, multifocal pulmonary parenchymal infiltrates, patchy ground-glass opacities, focal consolidation, and lung abscesses among other distinctive features.^{99,103}

Liver Abscess

Clinical manifestations of the liver abcesses often include fever and/or chills, general malaise, changes in mental status, and may be accompanied by gastrointestinal symptoms (such as right upper quadrant pain, indigestion, diarrhea, vomiting, and nausea), as well as symptoms of jaundice.^{105–107} Patients with invasive Klebsiella pneumoniae liver abscess syndrome (IKPLAS) have a significantly higher incidence of mental disorders, possibly due to systemic complications, including septic pneumonia, meningitis, and other metastatic infections. Host risk factors include diabetes, chronic gallbladder disease, cancer, alcohol abuse, chronic renal failure, etc. Studies have shown that diabetes patients with poor blood sugar control are more prone to IKPLAS and metastatic infections.^{108,109} Abdominal CT typically reveals a solid, thin-walled, low-density focus without edge enhancement, which is often located in the right lobe of the liver.¹⁰⁷ IKPLAS may be further complicated by thrombophlebitis, making it important to differentiate its CT presentation from that of hepatocellular carcinoma with vascular thrombosis. The rapid invasion by hypervirulent strains does not allow enough time for the liver parenchyma to completely break down into homogeneous pus. Instead, a mixture of immature pus and debris may be produced, leading to a lower volume of pus being aspirated during the initial drainage compared to other pyogenic abscesses.^{110–113}

Urinary Tract Infection

The primary sites of urinary tract infections caused by Kp include the prostate, urethra, kidneys, and bladder.^{114,115} Clinical manifestations mainly include fever, possibly accompanied by chills, abdominal pain, frequent urination, urinary retention, urgency, nocturia, difficulty urinating, incontinence, dribbling, and significant hematuria. Some patients may also present with systemic symptoms such as hypotension, difficulty breathing, and changes in mental status. Patients



Figure 2 Common infection sites of Kp.

may experience localized pain in areas such as the pubic region, perineum, area around the rectum, testicular region, or flank.^{115–117} The pathways of infection include direct invasion through urethral infections, direct spread or lymphatic spread from intestinal bacteria, and hematogenous dissemination.^{114,117} The main risk factors include: infections are more common in men than women, especially in male patients over the age of 60. Other risk factors include prolonged hospitalization with multiple chronic diseases (such as hypoalbuminemia, solid tumors, and congestive heart failure), and patients with catheters and invasive devices (such as central venous catheters and thoracoabdominal drainage tubes). The most common findings of laboratory investigations were leukocytosis and pyuria.¹¹⁵

Endophthalmitis

The most typical presentation of endogenous Klebsiella pneumoniae endophthalmitis (EKE) is painful ocular swelling, redness, and sudden onset of blurred vision.¹¹⁸ Between 13% to 25% of patients experience bilateral involvement.¹¹⁹ Due to the rapid onset of the condition, some patients may suffer irreversible blindness even before the systemic infection process is identified. The most common source of infection for EKE is IKPLAS.¹¹⁹ Risk factors for poor visual outcomes in patients with IKPLAS-associated EKE include initial vision worse than counting fingers (CF), eye pain, hypopyon, ocular hypertension, positive intraocular fluid culture, subretinal abscess, unilateral eye involvement, delayed visit to an ophthalmologist, initial ocular symptoms preceding systemic symptoms, and corneal edema.^{119–122} Among these, initial vision worse than CF and initial ocular symptoms preceding systemic symptoms are independent significant factors that affect the prognosis for poor vision.^{119,121}

Bacteremia Infection

Jin et al

Bacteremia is an extremely common complication of Kp site-specific infection. The main clinical symptoms include: fever or chills, low blood pressure, difficulty breathing, and confusion.^{123,124} A distinctive characteristic of hvKp bacteremia is the notably high number of cases where an immediate infectious source is not evident. Those with hvKp bacteremia tend to exhibit positive blood cultures prior to the identification or cultivation of the primary infection site, more so than individuals with Kp infections.¹²³ Although hvKp can lead to a variety of severe clinical symptoms, the occurrence of endocarditis as a manifestation of hvKp disease remains exceedingly uncommon.¹²⁵

Central Nervous System Disease

Kp was identified as the causative pathogen in 10.6%, 13.8%, and 16.8% of all cases, culture-confirmed cases, and cases of monomicrobial adult brain abscess, respectively.¹²⁶ In Western countries, adult brain meningitis (ABM) related to Kp infections are more commonly associated with hospital-acquired infections(HAI), often in patients with prior neurosurgical conditions.^{126–130} Diabetes Mellitus (DM) and liver disease, particularly cirrhosis, emerge as the most prevalent underlying conditions in this specific group experiencing central nervous system infections.¹³¹ Other less frequent underlying conditions include liver cirrhosis, alcoholism, cancer, end-stage renal disease, with some cases preceding a neurosurgical state.¹³¹ The clinical manifestations of Kp-related brain abscess and meningitis include the following symptoms and signs: sudden severe persistent headache, intermittent nausea, vomiting, fever, abnormal hearing, and a feeling of swelling in the right ear.^{131–134} Brain MRI revealed the following characteristic findings: an abnormal high signal in the head of the left caudate nucleus, low signal on T1-weighted sequences, high signal on T2-weighted sequences, slightly high signal on FLAIR sequences, and restricted diffusion at the corresponding location on diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps. Ring enhancement was observed on intracranial SPGR and meningeal CUBE enhanced imaging, consistent with the thickness adjacent to the anterior horn of the left lateral ventricle, and linear enhancement of the left occipital meninges was observed, suggesting a high probability of brain abscess and meningitis.¹³²

Musculoskeletal and Soft Tissue Infection

Kp-induced complicated skin and soft tissue infections (cSSTIs) involving the limbs are characterized by the following clinical features and outcomes in patients: a predominance of male patients, with a higher incidence of cirrhosis, malignancy, and alcohol abuse.¹³⁵ Compared to cSSTIs caused by other bacteria, those caused by Kp are more likely to present with fever, shock, bacteremia, gas formation, osteomyelitis, metastatic infection, and require longer hospital stays.¹³⁵ Kp cSSTIs may also lead to metastatic infections, such as liver abscesses, endophthalmitis, urinary tract infections, and soft tissue infections. These infections may be accompanied by bacteremia and require surgical intervention. For patients with cirrhosis, the clinical association with Kp infections may be related to impaired immune function, leading to bacterial translocation and colonization in the limbs.¹³⁵

Therapeutic Strategies: Recommendation from Guidelines

Treating infections caused by Kp requires prompt identification of the pathogen and initiation of antimicrobial therapy. The treatment of multidrug-resistant Kp, particularly strains resistant to carbapenems, is challenging. Various clinical guidelines have sequentially offered appropriate treatment strategies.^{136–138}

The Infectious Diseases Society of America (IDSA)¹³⁶ recommends trimethoprim-sulfamethoxazole, ciprofloxacin, or levofloxacin as first-choice antibiotics for ESBL-producing Enterobacterales (ESBL-E) infections in the urinary tract, with alternatives like ertapenem or meropenem for resistant cases. Aminoglycosides are an option for certain situations. For CRE, the same first-choice antibiotics apply, with CZA and meropenem-vaborbactam as additional options. For infections outside the urinary tract, CZA or cefiderocol is preferred, especially for NDMs -producing CRE. POLB and colistin are generally not recommended but might be used as a backup option for simple CRE cystitis cases. European Society of Clinical Microbiology and Infectious Diseases (ESCMID)¹³⁷ guidelines recommend carbapenems (imipenem or meropenem) for severe infections by third-generation cephalosporin-resistant Enterobacterales (3GCephRE) with bloodstream infections, with alternatives like piperacillin-tazobactam for less severe cases. For CRE, meropenem-

vaborbactam or CZA are considered, with cefiderocol for resistant strains. Combination therapies are advised for severe infections.

A guideline¹³⁸ from China advises opting for POLB combination therapy instead of single-agent POLB for treating CRE infections in patients who need POLB. It is recommended to use inhaled POLB alongside intravenous administration for those with CRE pneumonia. For CRE infections linked to serine carbapenemase producers like KPC and OXA-48, the guideline suggests using CZA. When dealing with infections caused by NDM-producing CRE, a combination of CZA and aztreonam is preferred over other treatment options. For treating CRE infections in patients who can tolerate aminoglycosides, therapy that includes amikacin or similar aminoglycosides is advised. If the CRE strain is responsive to fosfomycin or if combining it with other agents is more effective, using fosfomycin-based combination therapy via intravenous route is recommended.

Novel Approaches to Antibiotic Resistance

Vaccines and Monoclonal Antibodies

Vaccines that focus on surface polysaccharide antigens like CPS (also known as the K antigen) or LPS (known as the O antigen) are seen as a viable alternative to traditional antimicrobials in the fight against multidrug-resistant pathogens.^{139,140} Both vaccines and monoclonal antibodies (mAbs) have demonstrated effectiveness in protecting against Kp in animal studies.¹⁴¹ Bahy et al confirmed that both single and combined LPS based vaccines can effectively protect against and reduce the incidence of Kp lower respiratory tract infections (LRTIs).¹⁴² Dey et al designed a multi-peptide CPS based vaccine that can evoke strong immune responses to combat Kp.¹⁴³ In addition to focusing on surface polysaccharide antigens, vaccines against Kp can also be developed targeting other immunogenic proteins. Naveed et al identified eight immunogenic proteins from the annotation of the whole proteome to construct mRNA and multi-epitope vaccines.¹⁴⁴

By transferring active antibodies specific to a disease to an infected subject via passive immunization, the O-antigen, fimbriae, and siderophores may also play a crucial role in combating Kp infections.¹⁴⁵ mAbs that target Type 3 fimbriae were utilized to inhibit biofilm formation. Wang, Q. et al investigated mAbs that are specific to non-polysaccharide antigens like MrkA, which is the primary component of Type 3 fimbriae.¹⁴⁶ These vaccines can effectively combat community-acquired pneumonia, HAI, and lung-associated infections caused by Kp. mAbs targeted O-antigens that were identified in humans were found to be extremely protective against murine pneumonia and bacteremia.¹⁴⁷ In murine pneumonia, treatment with mAbs in combination with meropenem provided greater protection against drug-resistant strains than treatment with meropenem or mAb alone. The investigation of siderophore receptor proteins (SRPs) has also transpired. The utilization of SRPs to immunize heifers before calving reduced the likelihood of Kp mastitis by 76.9%.¹⁴⁸ This study has shown that the Kleb-SRP vaccine, when administered before the commencement of a lactation cycle, is effective against coliform mastitis in general (including all coliforms) and Klebsiella mastitis specifically. Further vaccines included conjugate vaccines, nanovaccines, live attenuated vaccines, and heat-killed microorganisms, in addition to those already mentioned.¹⁴⁰

Antivirulence Compounds

Antivirulence compounds can inhibit virulence factors, reducing the ability of bacterial pathogens to cause harm. Treatment could involve the use of antivirulence molecules alone or in combination with antimicrobial agents. Siddiqui et al¹⁴⁹ have shown that the synthesis of enrofloxacin derivatives 2–17 can effectively prevent biofilm formation by Kp.

Novel Nanoparticles

A range of diseases can be induced by biofilm-forming microbes; in fact, 65–80% of infections are linked to biofilmrelated microorganisms.¹⁵⁰ Antibiotics were unable to penetrate the biofilm and eliminate the bacteria. Atlas et al examined the efficacy of apramycin and apramycin formulated with nanoparticles (DXT-SCPN-Apra).¹⁵¹ The findings revealed that DXT-SCPN-Apra effectively inhibited the growth of Kp within the initial six hours of bacterial exposure and restricted the formation of Kp biofilms. Silver nanoparticles (Ag NPs) have been utilized specifically in agriculture and medicine. Ag NPs inhibit the growth and propagation of numerous bacteria and fungi, including Pseudomonas aeruginosa, Escherichia coli, Kp, and Candida albicans, through the binding of Ag/Ag+ with biomolecules located within the microbial cells. There is speculation that Ag NPs may generate reactive oxygen species and free radicals, which subsequently induce apoptosis and impede the replication of cells by causing cell death.¹⁵² Wang et al develop D-alpha tocopheryl polyethylene glycol succinate-modified and S-thanatin peptide-functionalized nanorods based on calcium phosphate nanoparticles for the treatment of pneumonia brought on by Kp that is resistant to tigecycline.¹⁵³ The nanorods can increase the accumulation of tigecycline in bacteria. Nanorods effectively decrease the number of white blood cells and neutrophils, diminish bacterial colonies, and improve neutrophil infiltration events, resulting in a substantial increase in the survival rate of mice with pneumonia. Research indicates that the manufacturing of zinc oxide nanoparticles (ZnO-NP) is considered to be substantially safer and more environmentally friendly. These nanoparticles have a greater ability to pass through the surface of Kp, surpassing cefepime, meropenem, and imipenem. ZnO-NP exhibit powerful antibacterial abilities and are being investigated for their potential as effective antibacterial agents that do not have harmful effects on human cells.^{154,155}

Bacteriophages

Bacteriophages, being viruses that attack bacteria, naturally occur in environments where bacteria are commonly found. The excessive use of antibiotics can lead to the emergence and dissemination of antibiotic-resistant bacteria. This phenomenon is particularly concerning with specific types of Kp, which are evolving to withstand antibiotic treatments, rendering such infections harder to manage. Employing bacteriophages as a means to combat pathogens presents an alternative strategy that does not rely on antibiotics, potentially providing a solution for treating infections resistant to multiple drugs. At 25°C, phage vB_KpP_HS106 decreased MDR Kp by roughly 1.6 log₁₀CFU/mL in milk and by almost 2 log₁₀CFU/cm3 in chicken. Thus, phage vB_KpP_HS106 has great potential as a substitute for antibiotics in the biocontrol of MDR Kp in food.¹⁵⁶ Fayez et al extracted the phage vB_Kpn_ZC2 (abbreviated as ZCKP2) from sewage water. In terms of antibacterial action, ZCKP2 consistently produced clear zones of inhibition around bacteria and other hosts, demonstrating sustained effectiveness in killing bacteria over time.¹⁵⁷ Three virulent bacteriophages were identified with narrow specificity against Kp of capsule type K23, capable of safeguarding Galleria mellonella larvae in a model infection involving a multidrug-resistant Kp strain¹⁵⁸. These discoveries support the potential of bacteriophages as valuable assets in antimicrobial treatments.

These innovative strategies for tackling antibiotic resistance have not progressed to the stage of clinical application in humans, requiring additional validation through in vitro and in vivo studies (Figure 3).

Control Strategies: AMR

Decreasing the intensity of antibiotic use may be one of the most effective strategies to curb AMR, removing antibiotics quickly reduces AMR.¹⁵⁹ It's essential to establish programs for preventing and controlling infections, protect key antibiotics, and bring forth new vaccines and advanced antibiotics. Equally important are strategies to avoid infections acquired in hospitals, such as proactive screening for carriers of CRKp, adopting comprehensive intervention plans that may include isolating patients in single rooms or specific cohorts, and positioning handwashing stations away from direct patient care areas.¹³⁸ CRKp can rapidly spread through competitive transmission in a newly opened ICU, with 3.5% of patients carrying CRKp upon admission and an additional 16.3% acquiring CRKp subsequently. CRKp was found in the ICU environment up to 10 weeks later.¹⁶⁰ Fundamental practices like regular cleaning of the environment and thorough cleaning after patient discharge are essential to reduce the spread driven by environmental contamination. A study from China documented 65 CRKp-HAI cases and seven outbreaks.¹⁶¹ From 95 unique CRKp samples, 32 came from a patient in a small, isolated ward. Analysis showed five CRKp transmission events and two outbreaks, but no ICU transmissions over five years. The small-ward ICU setup with strict infection control effectively prevented CRKp spread. Handwashing sinks at inappropriate locations and incorrect application are seen as factors contributing to the spread of drug-resistant bacteria in the ICU. Feng et al identified handwashing sinks as a transmission reservoir for CRKp within the ICU, pinpointing a particular sink as the origin of CRKp colonization/ infection among patients, rather than patient-to-patient spread of a single clone. The finding highlights the critical role



Figure 3 Novel Approaches to MDR Kp.

of handwashing sinks in the dissemination of multi-drug-resistant organisms. Implementing sink management practices, such as banning the disposal of body fluids in them and enforcing daily chlorine disinfection, effectively halted the transmission.

Conclusion

Kp is a significant pathogen responsible for severe infections. This review comprehensively examines various aspects of Kp. We have explored the transmission dynamics, highlighting the role of horizontal gene transfer in disseminating resistance genes among different Kp strains. Our discussion on therapeutic strategies underscores the necessity of developing novel antibacterial agents and implementing combination therapies to effectively overcome resistance. Overall, effectively combating Kp infections requires a thorough understanding of pathogenesis and resistance mechanisms, coupled with the implementation of optimized strategies to manage and prevent the spread of resistant Kp strains.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. SSJ, WQW, and YHJ participated in drafting and revising the article.

YTY contributed to critically reviewing the article. RLW gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and accepts accountability for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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