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Recent discoveries and overview of Carbapenem-Resistant Klebsiella Pneumoniae

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Abstract - *Klebsiella pneumoniae* is a Gram-negative opportunistic pathogen that has emerged as a major cause of healthcare-associated infections worldwide, including pneumonia, bloodstream infections, and urinary tract infections. Its clinical success is driven by a combination of extensive virulence determinants and an exceptional capacity to acquire antimicrobial resistance. Key virulence factors such as the polysaccharide capsule, lipopolysaccharide, fimbrial adhesins, and multiple iron-scavenging systems facilitate colonization, immune evasion, and invasive disease. Of particular concern is the global emergence of hypervirulent *K. pneumoniae* lineages, which cause severe community-onset infections and are increasingly converging with multidrug-resistant phenotypes. Carbapenem-resistant *K. pneumoniae* (CRKP) represents a critical public health threat, fueled by the dissemination of carbapenemase genes including *bla*KPC, *bla*NDM, *bla*OXA-48-like, and *bla*VIM, often carried on mobile genetic elements. In India and other high-burden regions, resistance is further amplified by porin loss, efflux pump overexpression, and horizontal gene transfer, contributing to high morbidity and mortality, particularly in intensive care settings. Environmental contamination, inappropriate antibiotic use, and inadequate infection control practices exacerbate the spread of CRKP. Accurate and timely detection remains challenging, especially in resource-limited settings, where phenotypic assays are widely used despite limited specificity, while molecular techniques offer greater sensitivity but limited accessibility. This review highlights the interplay between virulence, resistance mechanisms, epidemiology, and diagnostic challenges of *K. pneumoniae*, emphasizing the urgent need for integrated surveillance, improved diagnostics, and effective antimicrobial stewardship to curb the growing threat posed by carbapenem-resistant and hypervirulent strains.

Keyword: *Klebsiella pneumoniae*, carbapenem resistance, antimicrobial resistance, Hypervirulent *Klebsiella pneumoniae* (hvKp), Virulence factors.

Introduction:

Klebsiella pneumoniae is a Gram-negative, encapsulated, non-motile, facultatively anaerobic bacillus of the family *Enterobacteriaceae*, commonly colonizing the human gastrointestinal tract and nasopharynx and persisting in healthcare environments. Historically recognized as a cause of severe pneumonia since the late 19th century, it is now a leading opportunistic pathogen in healthcare-associated infections (HAIs), including pneumonia, bloodstream infection, and urinary tract infection (UTI). [1–4] A prominent virulence determinant is the polysaccharide capsule (K antigen), which protects against complement and phagocytosis and contributes to the classic mucoid phenotype. Genomic surveys reveal extensive capsule (K-locus) diversity—well over a hundred distinct K-loci—underscoring immuno-epidemiological heterogeneity and the challenges for typing and vaccine design. [5–7] Lipopolysaccharide (O antigen), multiple fimbrial adhesins, and high-affinity siderophores (enterobactin, yersiniabactin, salmochelin, and aerobactin) further promote epithelial adherence, serum resistance, and iron acquisition in host tissues. [3,8,9] Clinically, *K. pneumoniae* causes a spectrum of community- and healthcare-onset disease. It is a frequent HAI pathogen in catheter-associated UTI and central line–associated bloodstream infection, and an established cause of ventilator-associated pneumonia; UTI and respiratory isolates predominate in surveillance datasets from acute-care settings. [2–4] Since the 1980s, a hypervirulent pathotype (hvKp) has emerged globally, classically linked to community-onset pyogenic liver abscess with metastatic complications (e.g., endophthalmitis, meningitis) in otherwise healthy hosts. These strains often carry large virulence plasmids encoding regulators of mucoidy (rmpA/rmpA2) and siderophore systems (notably aerobactin, salmochelin), and may harbor yersiniabactin (and sometimes colibactin) on integrative elements; K1 and K2 capsular lineages are prototypical. [8–12] Concurrently, *K. pneumoniae* has become a major reservoir of antimicrobial resistance (AMR). Beyond extended-spectrum β-lactamases and AmpC, the acquisition of carbapenemases—most commonly KPC (class A), NDM/IMP/VIM (class B metallo-β-lactamases), and OXA-48-like (class D)—has eroded the effectiveness of last-line carbapenems and complicated therapy and infection control. [13–16] Reflecting its combined burden of virulence and resistance, **carbapenem-resistant *K. pneumoniae* (CRKP)** is ranked at the top of the World Health Organization's 2024 Bacterial Priority Pathogens List and is a central focus of contemporary treatment guidance. [17,18].

Pathogenesis

Colonization and Transmission

Klebsiella pneumoniae is primarily a commensal organism of the human gut, nasopharynx, and skin. Colonization precedes infection, with gut carriage being the major reservoir for endogenous infections in hospitalized patients. Cross-transmission also occurs through contaminated hands of healthcare workers, invasive devices (catheters, ventilators), and environmental surfaces, facilitating nosocomial outbreaks [19–21].

Host Defenses

Respiratory tract: Microaspiration of oropharyngeal secretions leads to pneumonia, especially in ventilated or debilitated patients.

Urinary tract: Indwelling catheters facilitate ascending infection.

Bloodstream: Central venous catheters and translocation from the gut are common sources.

Liver abscesses (hvKp): Bacteremia arising from gut colonization can seed the liver and other organs [22,23].

Key Virulence Factors

Capsule (K antigen):

The thick polysaccharide capsule is the major virulence determinant.

It prevents complement activation, phagocytosis, and antimicrobial peptide activity.

Certain capsule types (K1, K2, K47, K64) are strongly associated with invasive disease [24–27].

Lipopolysaccharide (LPS, O antigen):

Protects against complement-mediated killing.

Contributes to septic shock through endotoxin activity [23,28].

Fimbriae and Adhesins:

Type 1 and type 3 fimbriae mediate adherence to host epithelial cells and abiotic surfaces (biofilms on catheters and ventilators).

Biofilm formation increases persistence and antibiotic tolerance [27].

Siderophores (iron acquisition systems):

K. pneumoniae produces multiple siderophores—**enterobactin, yersiniabactin, salmochelin, and aerobactin**—to scavenge iron in iron-limited host environments.

Hypervirulent strains frequently carry **aerobactin and salmochelin plasmids**, conferring a growth advantage in blood and tissues [28–30].

Hypermucoidy phenotype:

Regulated by **rmpA/rmpA2** genes on virulence plasmids.

Results in a sticky, viscous colony phenotype that resists phagocytosis and serum killing.

Strongly associated with liver abscess and disseminated hvKp infections [22,28].

Other factors:

Colibactin (a genotoxin in some hvKp lineages) causes host DNA damage.

Efflux pumps and porins contribute to resistance but also modulate virulence.

Outer membrane proteins (OmpA, OmpK36) play roles in adhesion and immune evasion [29,30].

Progression of Disease

Lobar pneumonia with necrotizing consolidation (classically described as “currant-jelly sputum”).

Septicemia with high mortality, especially in CRKP infections.

Pyogenic liver abscesses with metastatic complications (endophthalmitis, meningitis, brain abscess) in hvKp infections.

Device-associated infections (catheter-associated UTIs, ventilator-associated pneumonia, central line bacteremia) in hospital settings [20–22].

Epidemiology of *Carbapenem-Resistant Klebsiella pneumoniae (CRKP).*

Global Burden

Klebsiella pneumoniae is one of the leading causes of multidrug-resistant (MDR) infections worldwide. Carbapenem-resistant strains (CRKP) are classified by the

World Health Organization (WHO) as a **critical priority pathogen**, reflecting their rapid global spread and limited treatment options [31]. The burden is particularly high in **healthcare-associated infections** such as ventilator-associated pneumonia, bloodstream infections, urinary tract infections, and surgical site infections [32].

Regional Distribution

United States & Europe:

CRKP accounts for 5–10% of *K. pneumoniae* isolates in hospitals. Surveillance data show higher prevalence in long-term care facilities, where colonization serves as a reservoir for outbreaks [33,34].

Asia-Pacific:

Countries such as China, India, and Southeast Asia report some of the highest CRKP prevalence rates, exceeding 50% in many tertiary hospitals [35,36]. India is considered a **hotspot**, with rapid clonal expansion of carbapenemase-producing lineages [36].

Latin America & Middle East:

Increasing CRKP incidence has been reported, with outbreaks frequently associated with **KPC-producing strains** [37].

Africa:

Limited surveillance data, but emerging reports suggest growing prevalence, often underdiagnosed due to lack of advanced diagnostic facilities [38].

Molecular Epidemiology

The spread of CRKP is strongly associated with **mobile genetic elements** that carry carbapenemase genes. The major carbapenemases include:

KPC (Klebsiella pneumoniae carbapenemase):

First identified in the US; now globally widespread.

NDM (New Delhi metallo-β-lactamase): Initially reported in India; now a dominant mechanism in South Asia and spreading worldwide.

OXA-48-like enzymes: Prevalent in Europe, Middle East, and North Africa.

IMP and VIM enzymes: Reported sporadically in Asia and Europe [39,40].

CRKP lineages such as **ST258, ST11, ST147, and ST307** are globally dominant, often associated with epidemic outbreaks due to their adaptability and ability to acquire multiple resistance genes [40,41].

Risk Factors and Populations Affected

CRKP infections are predominantly **nosocomial** and occur in:

ICU patients with **prolonged hospitalization**. Individuals with **invasive devices** (central lines, urinary catheters, ventilators).

Patients receiving **broad-spectrum antibiotics** (especially carbapenems, cephalosporins, fluoroquinolones).

Immunocompromised patients (transplant recipients, cancer patients) [32,42].

Colonization often precedes infection. Gut carriage of CRKP is a major source of bloodstream and urinary infections, particularly in hospital settings [43].

Morbidity and Mortality

CRKP infections are associated with **high morbidity and mortality rates** (30–70%), especially in cases of septicemia and pneumonia, due to limited treatment options and frequent delays in effective therapy [34,36,42]. Mortality is highest in critically ill and immunocompromised patients.

Mechanisms of Carbapenem Resistance

The rising incidence of CRKp in India presents a formidable challenge to ongoing infection control efforts, particularly in hospitals. Where resistance rates have increased from 9% in 2008 to around 60% by 2024 [44]. These infections are mainly nosocomial and have a higher incidence in ICUs with a mortality rate of around 68% [45]. Urban healthcare facilities are said to have the highest resistance rates, although the same trend in the rural setting is increasing [46].

Beta-lactamase

In India, there is a rise in carbapenemaseproducing Enterobacteriaceae, particularly the New Delhi metallo-beta-lactamase (ndm-1), which was first reported in 2010. This enzyme is now highly prevalent in *Klebsiella pneumoniae* and *Escherichia coli*, leading to increased rates of treatment failure [47]. Other carbapenemases, such as oxa-48 and oxa-181, have also been reported from various regions of India, albeit with lower prevalence. The diversity of these carbapenemase genes found in many bacterial isolates complicates treatment options [48]. These carbapenemase enzymes—such as Klebsiella pneumoniae carbapenemase (kpc), New Delhi metallobeta-

lactamase (ndm), and Verona integronencoded metallo-β-lactamase (vim)—function by hydrolyzing the carbapenem antibiotic, breaking its β-lactam ring and preventing it from binding to penicillin-binding proteins on bacterial cell walls. Without this binding, the antibiotic cannot inhibit cell wall synthesis, allowing the bacteria to survive and proliferate. [49]

Outer Membrane Porins

The outer membrane porins, ompk35 and ompk36 are required for the passage of hydrophilic molecules, such as sugars, ions, and small solutes, they facilitate the uptake of antibiotics in Klebsiella pneumoniae. These proteins generate pores in the outer membrane, and the small molecules, like β-lactam antibiotics, diffuse passively through them. The mutations in genes encoding such porins down-regulate or remove them completely, contributing toward carbapenem resistance. Reduced expression of ompk35 and ompk36 leads to reduced permeability of the outer membrane, which restricts the entry of carbapenems to the periplasmic space [50]. This is particularly troublesome in strains that also have carbapenemases because the reduced influx of antibiotics can make these antibiotics useless, even in the presence of β-lactamase activity. Thus, the interplay of porin loss and carbapenemase production leads to a compounded resistance mechanism that is more difficult to tackle. Regulatory mechanisms also play a significant role in controlling protein expression [51]. The apr/envz two-component system is one of the primary regulators of protein genes in *Klebsiella pneumoniae*. Mutations in or lead to the production of abnormal proteins that are unable to activate protein gene transcription. This regulatory failure increases porin downregulation, further enhancing the resistance phenotype. Additionally, environmental factors, such as sublethal antibiotic concentrations, can alter porin expression. As an adaptive response, the survival of *K. pneumoniae* in the presence of antibiotics promotes the selection of resistant strains [52].

Efflux Pump Overexpression in Indian Isolates

The overexpression of efflux pump genes significantly contributes to resistance, especially the up-regulation of genes such as mmpl5, rv0194, and rv1250 in resistant strains, has been reported recently in India [53]. Gupta et al. (2010) and Garima et al. (2015) in their study observed that the subinhibitory concentration of antibiotics may even up-regulate efflux pumps, which leads to the over-transportation of drugs; therefore, their concentration is reduced inside the cell [54, 55]. So, it does not survive solely due to resistance but complicated drug regimens as well. The overexpression of efflux pumps in Indian isolates calls for targeted inhibition strategies for these pumps thus potentially rejuvenating the effectiveness of existing antibiotics and smoothing treatment outcomes [56].

Genetic Epidemiology and Horizontal Gene Transfer

Genetic epidemiology of CRKp in India implies an important role of certain specific resistance genes, including the blaOXA-48- like and blaNDM-1/5, contributing towards carbapenem resistance localized mainly on plasmids. This localization into plasmids makes the process of (Horizontal Gene Transfer) HGT easily facilitated, leading to its rapid spread between different bacterial strains and even in clinical environments [57]. For instance, derivatives of the blaOXA-48 gene have been recently associated with the ColKP3 plasmid carrying high-risk CRKp clones such as ST14, ST231, and ST147, with each displaying a unique resistance profile. Beyond this, mutations affecting OmpK35 and OmpK36 outer membrane proteins limit the entry of drugs into the cell, exacerbating the treatment challenge [58]. These porin mutations, in combination with ESBL genes such as blaCTX-M-15 and blaSHV-11, result in reduced membrane permeability, which is a synergistic resistance to β-lactam antibiotics. HGT among CRKp strains is mediated by MGEs (Mobile genetic elements) like transposons, integrons, and OMVs (Outer membrane vesicles). These MGEs not only transfer AMR genes but also carry virulence factors, thus enhancing the pathogenic potential of recipient strains. Specifically, OMVs can protect resistance genes from degradation and ensure proper uptake by recipient bacteria as a means of enhancing the spread of multidrug resistance [59]. Moreover, whole genome plus phylogenetic analyses involving Indian CRKp isolates revealed the presence of great genetic diversity, recombination as well as a gene-sharing event that is a testimony to the ability of such adaptability in strains towards changing pressure due to antimicrobial influence. Apart from this, the emergence of hypervirulent CRKp (CR-HvKP) strains in India presents new clinical challenges since these are simultaneously multidrug-resistant and hypervirulent strains. They usually cause severe infections with very few treatment options available [60]. Resistance and virulence factors combined in CRKp make it challenging to comprehend the AMR mechanisms, and in fact, the complexity also extends to other antibiotic classes, including aminoglycosides and fluoroquinolones, through resistance genes like qnrB1 and qnrS1. Such interplay among genetic determinants and phenotypic resistance highlights the crucial role of strong surveillance efforts like resistome profiling and whole genome sequencing [61]. The high transmissibility of CRKp plasmids has been linked with regional outbreaks and multihospital transmission events in India [62, 63].

Clinical and Environmental Factors

Environmental factors, particularly the contamination of water bodies by untreated industrial, hospital, and municipal waste, have been major contributors to the spread of carbapenem-resistant Klebsiella pneumoniae in India [64]. A critical issue was that 60% of the Indian population lacked adequate sanitation facilities, which likely led to the release of resistant pathogens into the environment. The major problem is these people use, rivers and lakes, as drinking water sources, which frequently receive untreated effluents, increasing the risk of bacterial dissemination. Studies have shown that environmental reservoirs, such as hospital effluents and contaminated rivers, are significant sources of multidrug-resistant organisms, including CRKp strains carrying resistance genes like bland-1 and blaoxa-48 [65]. Hospital waste is a primary source of carbapenem-resistant enterobacteriaceae, and river sediments from areas like the Mutha River in Pune revealed high levels of resistance genes, largely due to contamination from pharmaceutical production sites [66]. This environmental spread is exacerbated by the over-the-counter availability and improper use of antibiotics, promoting resistance in both clinical and environmental contexts. Active monitoring of these reservoirs is essential to mitigate the growing health and environmental threats posed by CRKp in India [67].

Diagnostic Techniques and Challenges

Diagnostic techniques for detecting carbapenem resistance in Klebsiella pneumoniae are crucial for effective infection management and antibiotic stewardship [67]. These techniques can be categorized into phenotypic and genotypic methods. Phenotypic methods are practical and commonly used in clinical labs; however, they may lack specificity, but their cost effectiveness and ease of performance in limited resource facilities make them popular. One of such most widely used tests is the Modified Hodge test (MHT), which detects carbapenemase production through growth patterns on agar plates, indicated by a cloverleaf indentation. However, it may yield false positives in ESBL- or amps-positive strains [68]. Another important test of diagnostic utility is the combined disc test which utilizes carbapenem discs with inhibitors to differentiate between carbapenemase types, offering more precise results than MHT (69). The carbapenemase inhibition test (CIT) is another test that combines carbapenem discs with specific inhibitors to confirm enzyme-mediated resistance, distinguishing it from non-enzyme related mechanisms [70]. Another easy-to perform test is the E-test which is a gradient diffusion method that determines the minimum inhibitory concentration for carbapenems, identifying low-level resistance [71]. Genotypic techniques or molecular assays are highly sensitive and specific, serving as the gold standard, especially when phenotypic results become inconclusive. The most sensitive assays are polymerase chain reaction (PCR) which detects specific carbapenemase genes like blaNDM and blaKPC, with multiplex PCR allowing simultaneous detection of multiple genes [71]. Even though more sensitive and comprehensive genetic information on resistance determinants can be derived through whole genome sequencing (WGS) it is typically limited to high-resource settings [72]. Another rapid and cost-effective method is loop-mediated isothermal amplification (LAMP) is useful for screening specific resistance genes, suitable for less equipped settings [73].

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