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Carbapenem-Resistant *Klebsiella pneumoniae*: Clinical Epidemiology, Resistant Mechanisms, and Therapeutic Challenges

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Abstract

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) represents a critical global health threat, ranked by the WHO as the top priority pathogen requiring urgent new therapeutics. As a leading member of the ESKAPE group, *K. pneumoniae* has evolved from a commensal organism to an extensively drug-resistant (XDR) pathogen capable of causing severe nosocomial infections with high mortality. This review examines the clinical epidemiology, molecular resistance mechanisms, and therapeutic challenges of CRKP. Geographic heterogeneity is evident, with KPC-2 dominating in China and North America, NDM-1 rising in South America, and OXA-48 prevalent in Europe. High-risk clones such as ST11 and ST258 are associated with increased all-cause mortality (pooled OR up to 3.57) and prolonged hospital stays. Resistance arises primarily from carbapenemase production (Class A KPC, Class B MBLs, Class D OXA-48-like) combined with non-enzymatic mechanisms including porin loss (OmpK35/36) and efflux pump overexpression (AcrAB-TolC, OqxAB). Alarmingly, convergence of hypervirulence and resistance in strains carrying siderophores (aerobactin, yersiniabactin) and hypercapsulation is increasing, particularly in Asia. Diagnostic strategies range from phenotypic assays (mCIM, CARBA 5) to whole-genome sequencing. Treatment remains challenging; older agents like colistin and tigecycline show limited efficacy and toxicity, while newer options ceftazidime-avibactam, meropenem-vaborbactam, cefiderocol, and aztreonam-avibactam offer improved outcomes but face emerging resistance through blaKPC mutations and siderophore receptor alterations. Future directions include phage therapy and monoclonal antibodies. Comprehensive infection control, antimicrobial stewardship, and innovative non-antibiotic approaches are essential to curb the escalating burden of CRKP.

1. Introduction

Adaptation of *Klebsiella pneumoniae* from a harmless organism in the human gut and nasopharynx to evolving extensively drug resistant (XDR) pathogens is one of the most important challenges in the contemporary medicine (Sindhushree *et al.,* 2025). Being a primary member of the ESKAPE group, a group of pathogens that includes; *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter*

baumannii, Pseudomonas aeruginosa, and *Enterobacter* species, this bacterium is notable for its versatility (Karampatakis *et al.,* 2024). This versatility is what allows this organism to be a primary source of antimicrobial resistance genes (ARGs) and virulence factors that are often acquired by other unrelated species through horizontal gene transfer (Vinayamohan *et al.,* 2022). The emergence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) globally necessitates the reconsideration of infection control and treatment principles as these strains are resistant to last line antibiotics used to manage multi drug resistant (MDR) infections (Michaelis *et al.,* 2023). The WHO has prioritized CRKP globally due to the fact that it calls for new treatment and diagnostic options, and for this reason it has been listed as the number one organism on the Bacterial Priority Pathogen List (BPL) for which there is an urgent need to develop new therapeutics (Beyer, 2025).

2. Geographic Heterogeneity and High-Risk Genotypes

As part of their global surveillance efforts, researchers study regional variations in the CRKP dominant genotypes. A systematic review and meta-analysis focusing on the most relevant studies through 2025 indicates that the specific carbapenemase produced greatly determines the clinical relevance of CRKP (Zhang *et al.,* 2025). There is a large clinical and statistical impact of the high-risk genotypes, mostly those that produce *Klebsiella pneumoniae* carbapenemase (KPC) and OXA-48-like enzymes. Such high-risk genotypes are linked to a substantial increase in all-cause mortality with a pooled odds ratio (OR) of 3.08 when compared to carbapenem-susceptible strains (Boyd *et al.,* 2022).

Table 1: Regional Prevalence and Dominant Carbapenemase Genotypes

Region	Predominant Carbapenemase	Epidemiological Context	Key Finding
China	KPC-2	ST11 highly prevalent	KPC-Kp incidence ~1.16%; 46% mortality (Feng et al., 2025)
South America	NDM-1, KPC-2	Rapid rise since 2007	CRKP prevalence >20% in 2021 (Krapp *et al.,* 2025)
Europe	OXA-48, VIM, KPC	Romanian ICU studies	Shift from MDR to XDR/PDR (2021–2024) (Beyer, 2025)
North America	KPC-2, KPC-3	ST258 success	Low prevalence of MBLs (<20%) (Beyer, 2025)
Global Meta-Analysis	KPC, OXA-48	Multi-center analysis	KPC-type OR for mortality: 3.57 (Beyer, 2025)

2.1 Mortality Risk Factors and ICU Burden

For individuals who contract CRKP, clinical outcomes are extremely grim.

Mortality from KPC-Kp infections is 46%. That is considerably worse than the 10.4% mortality seen in infections that are carbapenem-resistant but not KPC (Feng *et al.,* 2025). Modeling suggests that even more than 50% of the deaths occur in the first week of diagnosis, confirming the unrelenting and lethal nature of these infections (O'Sullivan *et al.,* 2025).

The independent mortality risk factors concerning CRKP infections are varied, combining host factors and clinical factors. Strong predictors of mortality are older age, history of tracheotomy, presence of septic shock, and lower counts of platelets (Huang *et al.,* 2025). Moreover, the clinical environment matters significantly; being in the ICU doubles one's odds of dying (3.39 OR), and specifically having CRKP bloodstream infection (BSI), one's odds of dying increases by 8.57 (Kong *et al.,* 2025). Healthcare systems are strained even more with LOS (length of stay) being extended: CRKP cases are in the hospital a median 31 days, whereas susceptible strain cases are in a median 19 days. Financial strain is significant, with cost estimates being roughly CRKP cases in the hospital P 2 3 times more than susceptible strain cases (Sun *et al.,* 2023).

3. Molecular Mechanisms of Carbapenem Resistance

The ability of *K. pneumoniae* to survive carbapenem exposure is the result of a sophisticated interplay between acquired enzymatic resistance and chromosomal modifications. While carbapenemase production is the most common mechanism, the synergy between high-level beta-lactamase expression and structural barriers often defines the final resistance phenotype (Karampatakis *et al.,* 2023).

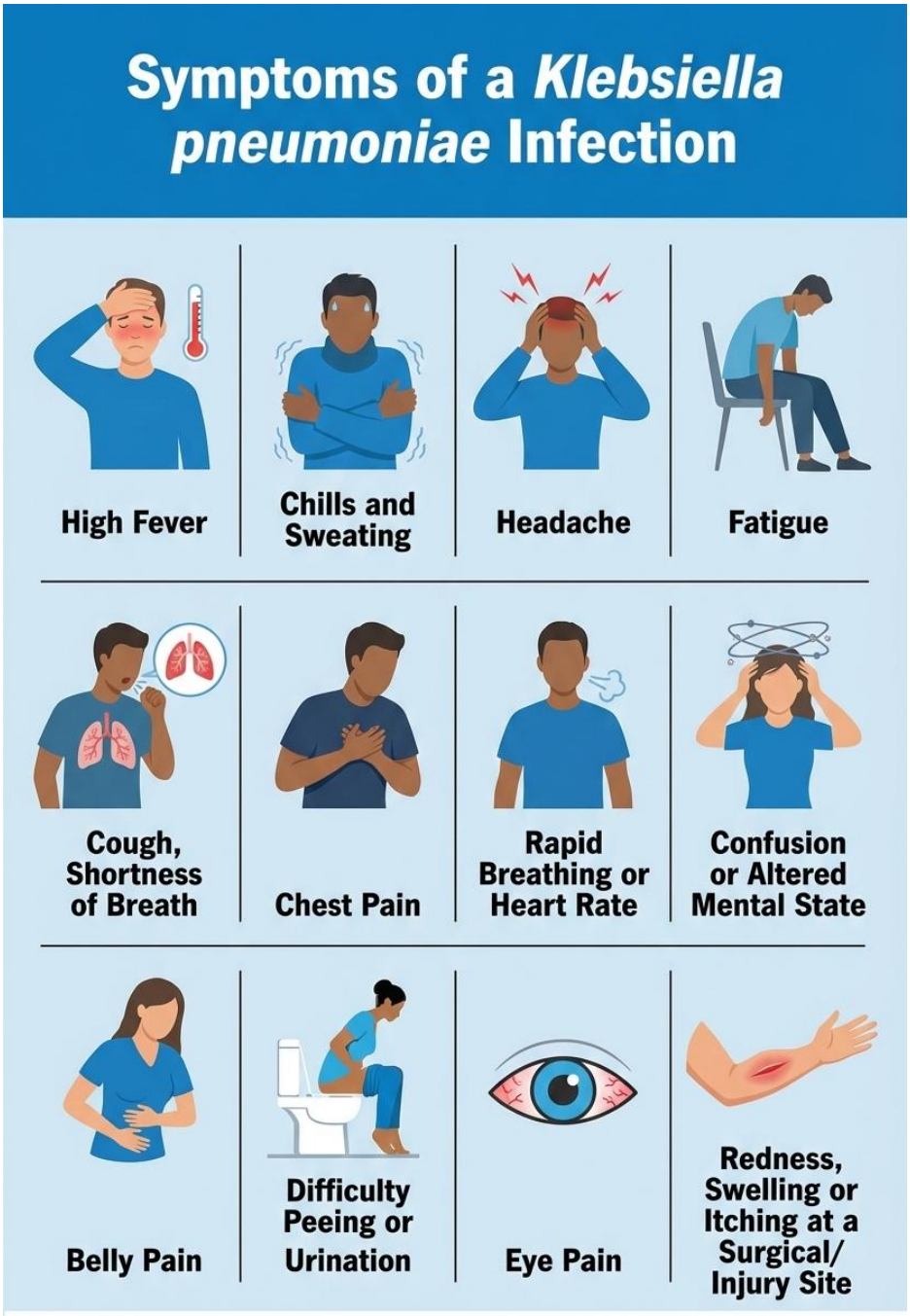

Figure 1: Common Clinical Symptoms of *Klebsiella pneumoniae* Infection

3.1 Enzymatic Degradation: The Role of Carbapenemases

Carbapenemases, like other beta-lactamases, can hydrolyze the beta-lactam ring of key antibiotics like carbapenems, penicillins, and cephalosporins (Akhtar *et al.,* 2022). These enzymes can to be classified into the molecular classes of the Ambler scheme, which includes the following broad categories:

Class A Serine Carbapenemases: The KPC family (KPC-2, KPC-3, etc.) is the most important family of carbapenemases in the clinic. These enzymes can be found on mobile genetic elements like the Tn4401 transposon located on the IncFII and IncL family plasmids (Forero-Hurtado *et al.,* 2023). The KPC enzymes found on the transposon Tn4401 plasmids are particularly problematic due to the fact that the beta-lactamase enzyme inhibitors of older generations like clavulanate and tazobactam have no effect on them, though avibactam, which is a beta-lactamase inhibitors of newer generations, is effective against them (Hobson *et al.,* 2022).

Class B Metallo-beta-lactamases (MBLs): NDM, VIM, and IMP enzymes fall in this category. The do require divalent cations like Zn2+ are also differentiated by their

ability to hydrolyze all beta-lactams except the monobactam aztreonam (Sobia *et al.,* 2022). The genes for these enzymes are found in plasmids and in integrations with aminoglycoside-modifying enzyme and sulfonamide resistance gene cassettes (Krapp *et al.,* 2025).

Class D Oxacillinases: OXA-48-like enzymes represent a particular problem because, while they show little to no carbapenem-hydrolyzing activity by themselves, they can cause clinical resistance via other mechanisms such as porin loss or efflux pump overexpression. They are also noted for their resistance to avibactam in some clinical situations, as well as for their rapid dissemination throughout Europe and the Middle East (Bonnin *et al.,* 2025).

3.2 Structural Mechanisms: Porin Loss and Efflux Pumps

Non-enzymatic resistance mechanisms are important for *K. pneumoniae* survival, and are especially relevant for the non-CP-CRKP strains. As per Hamzaoui *et al.* (2025), the two major outer membrane porins through which the Carbapenems enter the bacteria periplasm are OmpK35 and OmpK36. The reduction and/or complete loss of these porins, which is often caused by insertion sequences or truncations of the ompK35/36 genes, greatly decreases the intracellular concentration of the antibiotic (Davin-Regli *et al.* 2024).

Table 2: Chromosomal and Accessory Mechanisms of Resistance

Resistance Component	Specific Mechanism	Impact on Carbapenem MIC	Key Genetic Regulators
Porins	OmpK35/OmpK36 loss	Reduced drug entry	micF, micC (sRNA) (Sindhushree *et al.,* 2025)
Efflux Pumps	AcrAB-TolC overexpression	Increased drug expulsion	ramR, marR, acrR (Beyer, 2025)
Efflux Pumps	OqxAB upregulation	Multi-drug tolerance	oqxR (Sindhushree *et al.,* 2025)
LPS Modification	mgrB inactivation	Colistin resistance	phoPQ, pmrAB (Beyer, 2025)
Enzyme Hyperproduction	ESBL (CTX-M-15) + porin loss	Carbapenem non-susceptibility	Plasmid-mediated blaCTX-M (Sindhushree *et al.,* 2025)

Pumps that cause efflux actively remove antibiotics from the cytoplasm to the outside of the cell, which makes resistance even worse (Lorusso *et al.,* 2022). The most notable systems in *K. pneumoniae* are the AcrAB-TolC and OqxAB systems. Efflux pump overactivity from mutations in the ramR regulatory gene is often a cause of higher resistance to a wide range of antibiotics, including tetracyclines, fluoroquinolones, and sometimes even carbapenems like ertapenem (Seukep *et al.,* 2022).

4. The Convergence of Hypervirulence and Resistance

One troubling trend regarding the evolution of *K. pneumoniae* is the emergence of strains that are hypervirulent and multi-drug resistant (Aurilio *et al.,* 2022). While classical *K. pneumoniae* (cKp) is usually an opportunistic pathogen, hypervirulent *K.*

pneumoniae (hvKp) can cause potentially fatal community-acquired infections such as liver abscesses, endophthalmitis, and meningitis even in immunocompetent hosts (Angeles-Solano *et al.,* 2025).

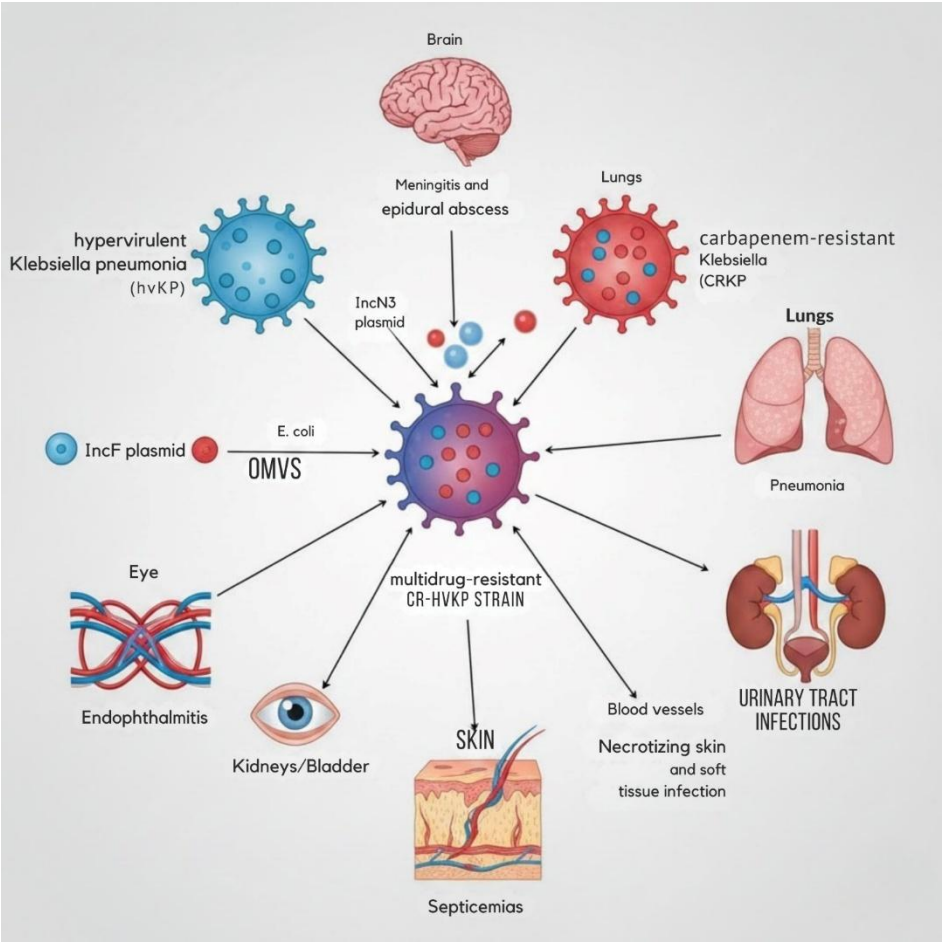

Figure 2: Convergence of Resistance and Hypervirulence in *Klebsiella pneumoniae* Pathogenesis

4.1 Virulence Determinants in hvKp

Distinct elements driving hypervirulent phenotype can be found on large virulence plasmids:

Capsular Overproduction: Hypercapsulation is the most apparent feature of hvKp leading to a hypermucoviscous phenotype in colonies. A thick capsule is capable of blocking C3b deposition on the surface of the bacterium as well as shielding the bacterium from being engulfed by phagocytes (Xu *et al.,* 2024).

Enhanced Siderophore Production: High virulent *Klebsiella pneumonia* (hvKp) are associated with the production of several high-affinity, iron-chelating, and blood survival critical (especially in dispersal tissues) siderophore, aerobactin (which is a product of iuc), salmochelin (iro), and yersiniabactin (ybt) (Abbas *et al.,* 2024).

Biofilm Matrix Dynamics: Biofilms create a safe haven for the CRKP particularly for chronic infection medical devices like catheters and ventilators. virulence factors like fimbriae (Type 1 and Type 3) that are found on the cells are said to be instrumental in the first attachment and structural development of such biofilms (Moussa, 2022).

The combination of these virulence traits with carbapenemase genes (e.g., in the ST11-KPC-2 lineage) has spawned a `superbug' that is immensely concerning as it possesses the ability to inflict high morbidity and mortality, while paradoxically being extremely difficult to treat infection. In the case of China, up to 36% of CRKP isolates have hypervirulence factors, and this shows that such convergence is becoming routine (Beyer, 2025).

5. CRKP Diagnostic Strategies

The cornerstone of effective antimicrobial stewardship and patient management is the rapid and precise identification of CRKP. Two primary types of diagnostics are enzyme activity phenotypic assays and the genotypic detection of specific ARGs (Braun *et al.,* 2025).

5.1 Phenotypic Profiling

Phenotypic testing looks at a bacterium's ability to breakdown carbapenems using hydrolysis in vitro. The Modified Carbapenem Inactivation Method (mCIM) and standard tools are used for carbapenemase detection and for the differentiation of serine and metallo enzymes. Though these methods are fairly sensitive (Verma *et al.,* 2025) , they tend to be slow and require 24 hours of incubation.

Table 3: Comparative Performance of Phenotypic Diagnostic Assays

Phenotypic Test	Target	Strengths	Weaknesses
mCIM/eCIM	General carbapenemase	Accurate class differentiation	24-hour turnaround time (Beyer, 2025)
NG-Test CARBA 5	KPC, NDM, IMP, VIM, OXA-48	Rapid (minutes); no special equipment	Does not detect OXA-23 (Beyer, 2025)
Carba NP Assay	Hydrolytic activity	Rapid; uses pH color change	Can be subjective; requires reagents (Beyer, 2025)
CDI (Immunoassay)	KPC, NDM, OXA-48, VIM	Highest compliance with WGS (99%)	Failed to detect NDM-1 in P. mirabilis (Beyer, 2025)
String Test	Hypermucoviscosity	Simple bedside test for hvKp	Not all hvKp are hypermucoviscous (Sindhushree *et al.,* 2025)

5.2 Genomic and Molecular Detection

The most definitive identification of resistance mechanisms would be through genotypic approaches such as multiplex PCR and whole-genome sequencing (WGS). In terms of mapping specific antibiotic resistance genes (ARGs) to plasmids, WGS via Illumina and Nanopore of Matsumura *et al.* (2025) provides exemplary resolution for this, along with constructing detailed phylogenetic trees. This type of technology is critical in monitoring clonal dissemination of the highly problematic lineages such as ST258 and ST11, as well as detecting novel mutations in the ramR regulatory gene, which is associated with the development of resistance (Campos-Madueno *et al.,* 2024).

6. Management / Therapeutic Challenges of CRKP

Tailoring the use of specific antibiotics to the type of carbapenemase produced after balancing the possible high toxicity and resistant risk is one of the most challenging aspects of managing CRKP infections (Zhu *et al.,* 2024).

6.1 Combined and Conventional Therapies

Even before the first modern BL-BLI combinations, colistin and tigecycline were the first choice for the treatment of CRKP. Colistin's efficacy as monotherapy is highly questionable; some cohorts report nephrotoxicity rates as high as 20% (Samarkos *et al.,* 2022). Mortality analyses on colistin demonstrate no meaningful reductions in mortality; with monotherapy it is 42.6%. Combined mortality is 38%; however, it does significantly increase rates of eradication for the microbes (Rabi *et al.,* 2023).

For some infections, tigecycline is still a suitable choice due to its coverage of most CRKP strains; however, its use in bacteremia is highly limited due to its rapid distribution out of the blood stream. The emergence of pandrug-resistant cases, where even these "last-resort" agents fail, has become a significant threat in the ICU from 2021 to 2024 (Gajic *et al.,* 2025).

6.2 Novel Therapeutic Agents

With the rise of new antibiotics, less harmful and new ways have been discovered to manage CRKP (Karampatakis et al., 2023) include the following:

1. Ceftazidime-Avibactam (CZA) shows positives for treating KPC and OXA-48 producers. Compared to the best available therapy (BAT), clinical studies show better efficacy and cure rates, with the exception of the emerging form of resistance caused by mutation in the blaKPC and porin deficiency (Aslan *et al.,* 2023).

2. Meropenem-Vaborbactam has been formulated to treat KPC producing *Enterobacterales*. Compared to older formulations in its class, this combination has been found to have better clinical cure rates and lower mortality (Bassetti *et al.,* 2025).

3. Cefiderocol, a cephalosporin, is a unique class of antibiotics that have the ability to bypass the traditional routes of entry due to its iron-chelating properties. This antibiotic has activity against all of the Ambler classes, including the MBL sub-class. Effectiveness is also attributed to the lack of mutations in the siderophore receptor, such as cirA (Moon *et al.,* 2025).

4. The first beta-lactam and monobactam combination that has been approved specifically for treatment of CRE infections where other treatment options are not available is Aztreonam-Avibactam (ATM-AVI). He is the marketer of Emblaveo. It has to be the first line option to manage strains that are producing NDM and VIM because aztreonam, which is a beta-lactam, is MBLs and stably avibactam against the beta-lactamases, and additionally is not produced against serine NDM (Hidalgo-Tenorio *et al.,* 2024).

Table 4: Summary of Key Clinical Trials for CRKP and MBL Infections

Clinical Trial	Drug under Study	Indication	Key Result
REVISIT	ATM-AVI + MTZ	cIAI, HAP/VAP	76% cure in cIAI; 46% in HAP/VAP (Beyer, 2025)
ASSEMBLE	ATM-AVI	MBL infections	42% cure vs. 0% in BAT (small cohort) (Beyer, 2025)
REJUVENATE	ATM-AVI	Dose-ranging (cIAI)	PK confirmed efficacy of 2g q6h dose (Beyer, 2025)
GAME-CHANGER	Cefiderocol	Serious GN infections	Confirmed efficacy in BSIs

			and CRE (Beyer, 2025)

7. Adaptation to New Generation Antibiotics

As new classes of therapeutics are released, *K. pneumoniae* rapidly modifies and develops new resistance phenotypes using existing genomic tools (Rahman *et al.,* 2025).

7.1 Development of Resistance to Ceftazidime-Avibactam

Most resistance to CZA involves mutations in the blaKPC gene, particularly in the Omega-loop domain. The variant KPC-31 is associated with the KPC-3 D179Y mutation, and has increased binding to ceftazidime and decreased inhibition by avibactam (Zhang *et al.,* 2025). Mutations in the Omega-loop even restore susceptibility to carbapenems, and this trade off is beneficial for clinical cycling. The loss of porins OmpK35/36, and the overexpression of the AcrAB efflux pump also induce resistance (Chen *et al.,* 2023).

7.2 Cefiderocol Resistance

The resistance mechanisms are varied and complicated. Changes in beta-lactamase activity, the target itself, iron metabolism, and the addition of new iron acquisition proteins also cause resistance (Moon *et al.,* 2025).

Siderophore Receptor Mutations: The most prevalent genomic resistance markers are truncation or missense mutations in the receptors cirA, fiu, fecA, and fhuF. These mutations, in place, prevent the “Trojan horse” mechanism of cefiderocol entry (Tristancho-Baró *et al.,* 2025).

Transcriptional Reprogramming: An example of resistance is the large scale reprogramming and consequent restructuring of the cell's metabolism which drives the cell away from the drug's targeted iron uptake systems (Wang *et al.,* 2022).

Heteroresistance: Cefiderocol heteroresistance in *K. pneumoniae* is characterized by a small subpopulation of cells that remain alive and active even in the presence of high concentrations of the antibiotic. This makes treatment failure and relapse a distinct possibility (Bianco *et al.,* 2024).

8. Future Directions: Phages and Non-Traditional Therapies

The challenges posed by the overreliance on small molecule antibiotics have prompted the search for innovative alternatives, notably the adoption of bacteriophages and monoclonal antibody therapies (Umarje *et al.,* 2023).8.1 Bacteriophage Therapy

Bacteriophages, or phages, are a kind of virus that has the ability to infect and destroy bacterial cells. Phages are a good option as a therapeutic strategy against CRKP for a number of reasons: they have the ability to target specific bacterial strains, they replicate themselves at the infection site, and they possess a biofilm degradation mechanism through the secretion of polysaccharide depolymerases (Gorodnichev *et al.,* 2025). In 2024-2025, some reports describe instances of phage therapy, used in a compassionate-use context, that achieve clinical improvement in 50-70% of the cases, where antibiotics have not worked (Uchechukwu & Shonekan, 2024).

8.2 Monoclonal Antibodies and Small Molecule Pipeline

The creation of mAbs (monoclonal antibodies) directed against specific bacterial enzymes/toxins is also being actively pursued. A number of micorarray-based protein screens have shown the capacity to identify antibody pairs of almost universal sensitivity to members of a wide range of carbapenemases (KPC, NDM, VIM, IMP, OXA) (Braun *et al.,* 2025).

9. Socioeconomic Impact and Health Policy

The ramifications of CRKP are not limited to the healthcare system but extend considerably to the economy as the burden of CRKP is not limited to hospital beds (Yao *et al.,* 2024).

9.1 The Cost of Resistance

The primary medical expenses caused by the resistance of *K. pneumoniae* to carbapenems cannot be described by the costs of the antimicrobial therapy themselves. The additional costs arising from longer stays in the intensive care unit and the need for more supportive non pharmacological therapies, such as dialysis and mechanical ventilation, are even more important (Verma *et al.,* 2025). In a Chinese cohort study, for instance, the patients who had CRKP infections had medical costs that were about twice as much as the costs for the infections that were susceptible (Feng *et al.,* 2025).

9.2 Market Failure and Global Responsibility

Pharmaceutical companies lack the motivation to create new antibiotics since they will likely fall victim to a type of market failure in which new antibiotics will be given to patients that will be treated for little more than a single resistant infection (Moussa, 2022). The “One Health” concept is equally important, as antibiotics used in the more agricultural pesticides and farming practices can create an additional environmental repository of resistance genes that are eventually incorporated into the clinical strains of *K. pneumoniae* (Karampatakis *et al.,* 2023).

9.3 Operational Strain and Strategic Policy Requirements

The operational impact on healthcare infrastructure extends beyond direct costs to include severe constraints on hospital capacity. Comparative analysis reveals that the median length of stay (LOS) for patients with CRKP is prolonged to 31 days, significantly higher than the 19 days observed for patients with susceptible strains, which directly exacerbates bed shortages and resource allocation challenges. While some cohorts indicate a doubling of medical expenses, broader financial models suggest that CRKP cases can incur costs two to three times greater than susceptible infections, creating substantial financial volatility for healthcare institutions. Consequently, future health policy must move beyond reliance on new drugs alone; it requires the implementation of comprehensive infection control, antimicrobial stewardship, and innovative non-antibiotic approaches to effectively mitigate the escalating clinical and economic burden of this pathogen.

10. Conclusion

The genomic mobility of Carbapenem-resistant *Klebsiella pneumoniae* makes it one of the most serious "priority pathogens." It can be rapidly disseminated throughout the world, often with high mortality, and drive converging resistance with hypervirulence. Even though new antibiotics, including ceftazidime-avibactam, meropenem-vaborbactam, cefiderocol, and aztreonam-avibactam, provide a hope for new antimicrobial therapies, they may be suboptimal. Furthermore, with the exception of aztreonam-avibactam, they may be effective against only one or two carbapenemase types. Because of the way *Klebsiella pneumoniae* and other pathogens rapidly evolve; they will likely develop resistance to these last-line antibiotics. Even more new antibiotics will be needed. The implementation of standard diagnostics, prevention of infection, and the surveillance of high-risk clones will be needed to effectively manage the spread of this pathogen. The former two will most likely be in the form of antimicrobial combination therapies. More innovative, non-conventional approaches may need to be employed to manage the superinfection of this pathogen. For example, antibody therapies and bacteriophages may be employed to manage the infection.

Managing the superinfection will be complicated further with resistance that far outstrips the infection. Innovative approaches will need to be balanced with or employed alongside regulation of antibiotics to manage the infection, along with antimicrobial stewardship, less antibiotics in farming, and more creative ways to mitigate the infection and along with innovative approaches to directly promote the improvement of new antibiotics. It is hoped that the combination of new antibiotics and innovative approaches will keep the pathogen at bay.

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