Texila International Journal of Public Health
ISSN: 2520-3134
DOI: 10.21522/TIJPH.2013.13.01.Art084

Carbapenem Resistant *Klebsiella pneumoniae* Cases from India: An Overview of Current Knowledge

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Abstract

Carbapenem-resistant Klebsiella pneumoniae (CRKP) is a significant public health concern in India. Our current review attempts a qualitative summary of observational studies published in the last ten years. The key resistance mechanisms identified include carbapenemase enzymes like New Delhi Metallo-beta-lactamase (NDM-1), Oxacillinase-48 (OXA-48), and Klebsiella pneumoniae carbapenemase (KPC), as well as non-enzymatic factors such as efflux pump overexpression and alterations in outer membrane porins (OmpK35, OmpK36). Horizontal gene transfer via plasmids and transposons was also observed to accelerate the dissemination of resistance genes. Carbapenem resistance rates in India have surged from 9% in 2008 to approximately 60% by 2024. Environmental contamination from untreated industrial and hospital waste, along with antibiotic overuse, also significantly contributed to the increased spread of CRKp strains and is associated with mortality rates of around 68%. Challenges in the diagnosis of CRKp cases arise from limitations of phenotypic methods and the non-availability of genotypic techniques such as PCR and whole-genome sequencing in resource-constrained settings. Treatment options against CRKp are limited, often relying on last-resort antibiotics like polymyxins and tigecycline, which also have significant side effects and face rising resistance. Emerging therapies, including novel β-lactam/β-lactamase inhibitor combinations and agents like cefiderocol, show a promising option but require further validation. Therefore, an urgent, integrated approach is recommended to combat rising CRKp infections in India, which involves enhancing surveillance systems, strengthening antimicrobial stewardship programs, improving infection control practices within healthcare facilities, and promoting public education on the risks of antibiotic misuse.

Keywords: *Carbapenem, Hypervirulent CRKp, Klebsiella pneumoniae, Multidrug-Resistant.*

Introduction

Klebsiella pneumonia is reported as an important public health threat in India, showing the rapid development of resistance to carbapenem antibiotics, which are currently used as a last resort for the treatment of multidrug-resistant infections. CRKp poses severe challenges in clinical settings, particularly in tertiary care hospitals, where infections are linked with high mortality rates [1]. The main causes for CRKp spread in India the excessive antibiotic use, higher patient volumes, and various genetic resistance mechanisms. There are several molecular mechanisms and genetic pathways that contribute to carbapenem resistance.

According to Indrajith et al., this resistance can primarily be attributed to the production of carbapenemase enzymes, as well as non-enzymatic mechanisms such as efflux pumps and variations in porin proteins. The mechanisms include the production of carbapenemases like New Delhi Metallo-beta-lactamase (NDM-1), Oxacillinase-48 (OXA-

Received: 20.12.2024 ***Accepted: 20.01.2025*** ***Published on: 28.03.2025***
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48), and Klebsiella pneumoniae carbapenemase (KPC). Alterations in outer membrane porins can prevent drugs from entering the cell, while the overexpression of efflux pumps can expel antibiotics, further contributing to resistance [2]. Horizontal gene transfer via mobile genetic elements, including plasmids, also promotes a rapid spread of resistance genes in healthcare settings. Hypervirulent CRKp has recently been identified with hypermucoviscous phenotypes, which further make the situation worse. In addition, various researchers studied these strains, among whom Shankar et al. (2018 published a high mortality case rate of patients infected by the hypermucoviscous CRKp [3, 4]. Similarly, according to Das et al. (2024, virulence variation is induced by antibiotic pressure [5]. Not only India, but the entire world is suffering from these emerging resistance threats.

In the present view, several overlapping layers of mechanisms and factors contribute to the increasing rate of antibiotic resistance in India. Through this review, we will attempt an overview of CRKp infections and their mechanisms by critically reviewing observational studies from India.

Materials and Methods

The current review synthesized observational studies from the past decade that investigated the molecular mechanisms underlying carbapenem resistance in *Klebsiella pneumoniae*. It encompassed various types of observational studies, including cohort studies, case-control studies, case reports, case series, and cross-sectional studies. Literature searches were conducted across major electronic databases, such as PubMed, Scopus, and Google Scholar. Only studies published in English between 2014 and 2024 were taken into final review data extraction.

Results

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 [6]. These infections are mainly nosocomial and have a higher incidence in ICUs with a mortality rate of around 68% [7]. Urban healthcare facilities are said to have the highest resistance rates, although the same trend in the rural setting is increasing [8].

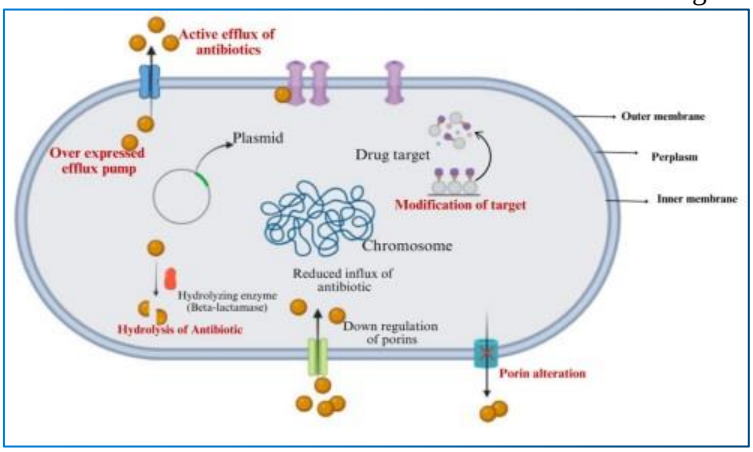

Figure 1. The Various Mechanisms of Carbapenem Resistance in Klebsiella pneumoniae

Beta-lactamase

In India, there is a rise in carbapenemase-producing 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 [9]. 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 [10]. These carbapenemase enzymes—such as *Klebsiella pneumoniae* carbapenemase (kpc), New Delhi metallo-beta-lactamase (ndm), and Verona integron-encoded 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 [Figure 1] [11].

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 [12]. 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 [13]. 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 [14].

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 [15]. Gupta et al. (2010) and Garima et al. (2015) in their study observed that the sub-inhibitory 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 [16, 17]. 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 [18].

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 [19]. 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 [20]. 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 [21]. 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 hyper-virulent strains. They usually cause severe infections with very few treatment options available [22]. 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 [23]. The high transmissibility of CRKp plasmids has been linked with regional outbreaks and multi-hospital transmission events in India [24, 25].

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 [26]. 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 [27]. 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 [28]. 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 [29].

Diagnostic Techniques and Challenges

Diagnostic techniques for detecting carbapenem resistance in Klebsiella pneumoniae are crucial for effective infection management and antibiotic stewardship [29]. 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 [30]. 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 (31). 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 [32]. 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 [33].

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 [33]. 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 [34]. Another rapid and cost-effective method is loop-mediated isothermal amplification (LAMP) is useful for screening specific resistance genes, suitable for less equipped settings [35].

Current Treatment Approaches

The treatment of carbapenem-resistant Klebsiella pneumoniae (CRKP) is a complex challenge due to the increasing prevalence of various resistance mechanisms in bacteria such as efflux pumps, porin alterations, and enzymatic hydrolysis. The choice of therapy depends on the specific resistance profile of the isolation, patient factors, and the severity of infection. A combination therapy approach is often necessary to achieve optimal clinical outcomes [36, 37]. (See Table 1; Current treatment options, table 2; Emerging therapies to combat the resistance).

Table 1. The Commonly Used Treatment Options for CRKp, Including their Mechanisms of Action, Dosing Regimens, and Limitations

Therapeutic Agent	Mechanism of Action	Effectiveness Against	Limitations	References
Polymyxins (Colistin, Polymyxin B)	Disrupts cell membrane	Broad-spectrum, including CRKp	Nephrotoxicity; limited tissue penetration; rising resistance	[38]
Tigecycline	Inhibits protein synthesis	Broad-spectrum, including MDR pathogens	Limited for bloodstream infections; potential GI side effects	[39]

β-Lactam/β-Lactamase Inhibitor Combinations				
Ceftazidime-Avibactam	β-lactamase inhibitor protects ceftazidime	Class A (KPC) and some Class D	Not effective for Class B MBL enzymes	[39]
Meropenem-Vaborbactam	β-lactamase inhibitor enhances meropenem activity	KPC-producing CRKp	Limited against Class B and some Class D carbapenemases	[40]
Imipenem-Relebactam	Non-β-lactam β-lactamase inhibitor combined with carbapenem	KPC and some Class D CRKp	Not effective for Class B carbapenemases	[41]
Cefiderocol	Exploits iron uptake systems for cellular entry	Various Gram-negative pathogens, including CRKp	Limited efficacy against Gram-positive and anaerobic bacteria	[42]
Aztreonam (with Avibactam)	Targets cell wall synthesis; avibactam inhibits other β-lactamases	Class B carbapenemases (e.g., MBLs)	Often combined with avibactam for broader coverage; limited as monotherapy.	[43]

Table 2. Emerging Therapies of CRKP

Therapeutic Agent	Potential Benefits	Current Stage	Reference
Nanoparticles	Disrupts cell membrane and function	Pre-clinical research	[44]
Phage Therapy	Targets specific bacteria for killing	Clinical trials	[45]
Antimicrobial Peptides	Disrupts cell membrane and interacts with intracellular targets	Pre-clinical research	[46]

Current Status and Future Prospects

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) poses a serious threat to patient outcomes and healthcare systems in India, with mortality rates often ranging from 40% to 60%, particularly among critically ill patients in intensive care units. Treatment options are limited, frequently necessitating the use of last-resort antibiotics like colistin, which is not only costly but also associated with severe side effects [48]. This dependency on suboptimal treatments often results in treatment failures, and prolonged hospital stays, and escalates the complications also, adding to the economic burden on both public and private healthcare systems [49].

The need for extensive diagnostic testing to detect resistant strains, alongside the implementation of strict infection control measures, holds significant importance now because these challenges extend beyond individual patients, they impact the entire healthcare system [50]. Hospitals all the time more face the necessity of adopting rigorous infection control practices, which may involve constructing isolation facilities and providing extended nursing care, in addition to this additional laboratory services for strain testing, along with training for additional staff, further increase the resources required to manage CRKp cases effectively [51, 52]. Strengthening infection control practices and ensuring strict adherence to preventive measures are critical to reduce transmission risks in healthcare settings. Additionally, it is essential to reevaluate empirical treatment protocols to align with current resistance

patterns, thereby improving patient outcomes and reducing the spread of CRKp [53]. To combat the escalating threat of CRKp, this recommendation can be considered.

1. Surveillance increase: A robust surveillance system needs to be developed for monitoring the trends of the prevalence and resistance rates of CRKP. It will include data collection from hospitals, laboratories, and public health agencies.
2. New antimicrobial discovery: There is a dire need for investments in research on new antibiotics and other treatments like bacteriophage therapy and antimicrobial peptides against CRKp [54].
3. Antimicrobial stewardship: There should be strength in stewardship programs so that the use of antibiotics may take place at the most effective level with minimum prescription of antibiotics. This will come through the education provided for healthcare professionals to prescribe them effectively and appropriately [55].
4. Infection prevention bettered in the healthcare setting: Improved infection prevention strategies of better care in hospitals include rigid hand hygiene, correct donning and removal of personal protective equipment and adequate isolation procedures among the patients [56].
5. Public education: Educating the public and healthcare providers on the risks of antibiotic resistance through public education campaigns is important to encourage the appropriate use of antibiotics [28].
6. Policy formulation: The involvement of healthcare providers, policymakers, and public health officials in formulating policies and guidelines to manage CRKp infections is essential [57].
7. International collaboration: International collaboration in data sharing, resource sharing, and best practices is necessary to strengthen the global response to rising antibiotic resistance cases [58, 59].

Conclusion

Carbapenem-resistant Klebsiella pneumoniae is a serious challenge to public health in India because of its complex mechanism of resistance and rapid spread through reservoirs in healthcare and the environment. The clinical, genetic, and environmental factors that culminated in the emergence of CRKp are inevitable; hence, there is an urgent need for an integrated approach to tackle this alarming trend of CRKp. The most immediate recommendation all the studies propose is the strengthening of the diagnostic capacities, infection control, and judicious use of antibiotics. Innovative approaches to treatment-including combination and emerging therapies are also proposed, coupled with strategic responses to growing rates of hypervirulent and multidrug-resistant strains. A strategic intervention that defines the merged focus on surveillance of the environment coupled with research in the area of AMR will help in curbing the spread of CRKP.

Conflict of Interest

The authors affirm that none of their known conflicting financial interests or personal connections could have an impact on the research presented in this study.

Acknowledgements

My mentor and faculty at Department of Research, Meenakshi Academy of Higher Education and Research deserve my gratitude.

Authors Contributions

Justy Babu: Composing an initial draft, reviewing and revising it, and conducting a formal analysis. Sathasivam Sivamalar: Writing, editing, and review; supervision; final draft.

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