The Growing Burden Of *Klebsiella Pneumoniae* Infections In India Healthcare: A Comprehensive Review Of Case Reports

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Abstract
Klebsiella pneumoniae is a critical nosocomial (hospital-acquired) pathogen, with rapidly increasing rates of multidrug resistance (MDR), extensive drug resistance (XDR), and even pan-drug resistance (PDR), posing a severe threat to global healthcare systems and patient safety. This review analysed case reports published between 2014 and 2024 that focused on K. pneumoniae infections. The Joanna Briggs Institute Critical Appraisal Checklist was employed for quality assessment, ultimately including 14 case reports that covered a range of clinical presentations and Klebsiella pneumonia infections.
The identified resistance mechanisms included the production of beta-lactamases, biofilm formation, and the presence of efflux pumps. Notably, many strains demonstrated XDR or pan-drug resistance (PDR), along with hypervirulent characteristics. K. pneumoniae infections often occur as co-infections or healthcare-associated infections (HAIs) related to surgical procedures and prolonged hospital stays. The role of Klebsiella pneumoniae as a secondary pathogen in hospital-acquired infections underscores the significant threat posed by MDR and XDR strains, particularly regarding their ability to develop biofilms in patients with other complications. These findings highlight the critical need for prevention and control measures for K. pneumoniae infections in Indian healthcare settings.

INTRODUCTION

Carl Friedlander was the first person to isolate and describe *Klebsiella pneumoniae* as an encapsulated Gram-negative bacillus for the first time in 1882 (1). The World Health Organization reports that *K. pneumoniae* is one of the key causes of healthcare-acquired infections worldwide, especially among immunocompromised patients (2). A particularly notorious attribute of its virulence, together with its ability to form biofilm, is that it has become increasingly resistant to most classes of antibiotics, a problem not only for treatment efforts but also enhances survival and persistence within the hospital settings, and this is one of the biggest challenges posed by infectious disease management (3).

Raising cases of antibiotic-resistant *K. pneumoniae* in India is an immediate threat to the entire healthcare system because of factors that lead to a heavy burden of bacterial infections, including high population density, uneven standards of hygiene, and an inconsistent policy towards the use of antibiotics (4). In the new reports, we can see a surge of resistant strains to carbapenems and third-generation cephalosporins. This emerging resistance trend not only offers fewer treatment options but also gives rise to outbreaks in healthcare facilities where at times, resources for proper screening and diagnosis are limited (5). However, although this is an area of significant importance, clinically, the evidence about antibiotic resistance in *K. pneumoniae* in the Indian healthcare system is synthesised and fragmented. To bridge this gap, this review brings together existing literature on the profiles of antibiotic resistance in *K. pneumoniae* isolated from clinical settings across India. The current comprehensive review aims to give an overall picture of the current state of knowledge based on case reports and provide recommendations for further research directions.

Methodology

A comprehensive literature search was conducted to identify case reports focusing on *Klebsiella pneumoniae* infections published in the English language from 2014 to 2024. The search was carried out across three major databases: PubMed, Google Scholar, and Scopus. A comprehensive search strategy was employed using both MeSH terms and Boolean operators in PubMed, and relevant keywords in other databases, including "*Klebsiella pneumoniae*," "case reports," "India," "antibiotic resistance," and "Indian healthcare settings". Only case reports that specifically documented *Klebsiella pneumoniae* infections were included in the review. Studies were screened for inclusion based, ensuring that they met the focus of the review on *Klebsiella pneumoniae* infections within Indian healthcare settings.

Each selected case report was quality assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports. Case reports that achieved a score of 75% or higher on the JBI checklist were considered methodologically sound and were included in the review as high-quality studies (6).

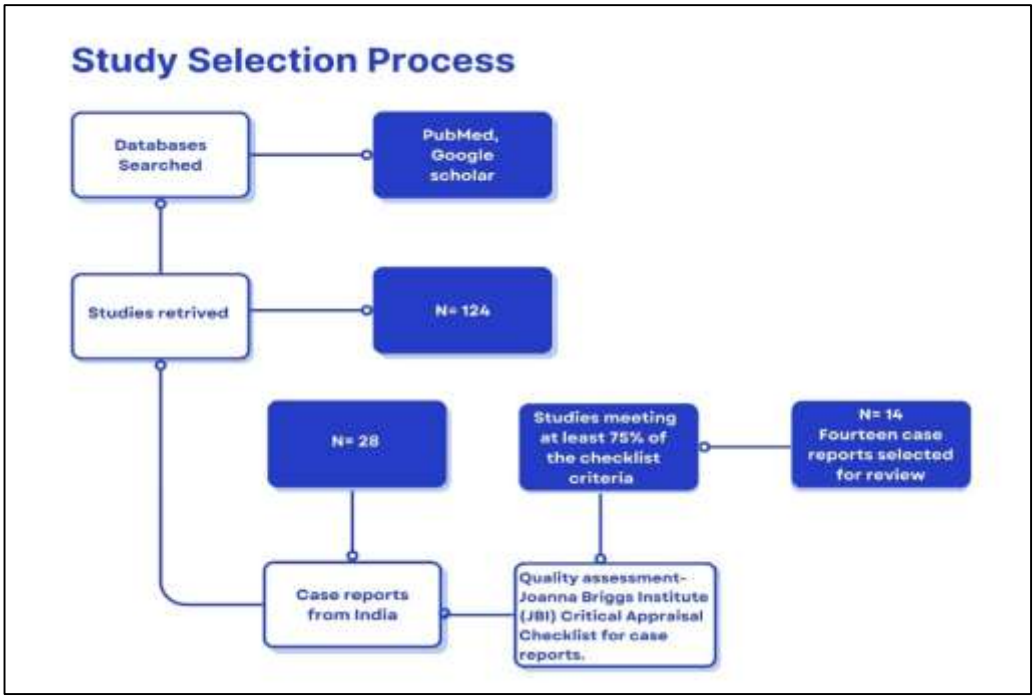

Chart 1: Flowchart presenting different stages of review

Antibiotic resistance in Klebsiella pneumoniae

The antibiotic resistance *in Klebsiella pneumoniae*, is linked with various mechanisms and the most relevant mechanisms are the production of enzymes commonly referred to as beta-Lactamases that hydrolyze or break down antibiotics like beta-lactam - penicillins, monobactams, and cephalosporins. Most of these-extended-spectrum beta-lactamases (ESBLs) and carbapenemases, which include KPC and OXA-48 are significant in breaking down a high variety of antibiotics of the class beta-lactam (7,8). ESBLs hydrolyze penicillins, first, second, third-generation cephalosporins and aztreonam but are often inhibited by clavulanic acid. The primary carbapenemases reported in *Klebsiella pneumoniae* are KPC (*Klebsiella pneumoniae* carbapenemase), OXA-48, and NDM-1 (New Delhi metallo-beta-lactamase-1) (9,10).

The efflux pumps are the other well-known mechanism. These are complex protein systems that work actively to pump antibiotics out of the bacterial cell, which depresses the intracellular concentration of the drug to sub-lethal levels, which allows the bacterium to survive in the antibiotic environment (11). The major families of efflux pumps in bacteria are the resistance-nodulation-division (RND), major facilitator superfamily (MFS), and ATP-binding cassette (ABC) transporters. Each of these pumps uses a different mechanism, such as proton motive force or ATP hydrolysis, to pump drugs out of the bacterial cell (11,12).

Antibiotics act on essential bacterial processes such as cell wall synthesis, protein synthesis, or DNA replication but *Klebsiella pneumoniae* can develop modification of these target sites. Change in Penicillin-Binding Proteins (PBPs) which are the targets for beta-lactam antibiotics, can lead to reduced affinity for these drugs (13). Another target site is the ribosomal proteins, where modifications in the ribosomal RNA or

ribosomal proteins, often mediated by methyltransferases, can prevent antibiotics like tetracyclines and aminoglycosides from binding to the ribosome, thus inhibiting their bacteriostatic or bactericidal effects (14). (See figure 1 summarising different antibiotic resistance mechanisms in *Klebsiella pneumoniae*)

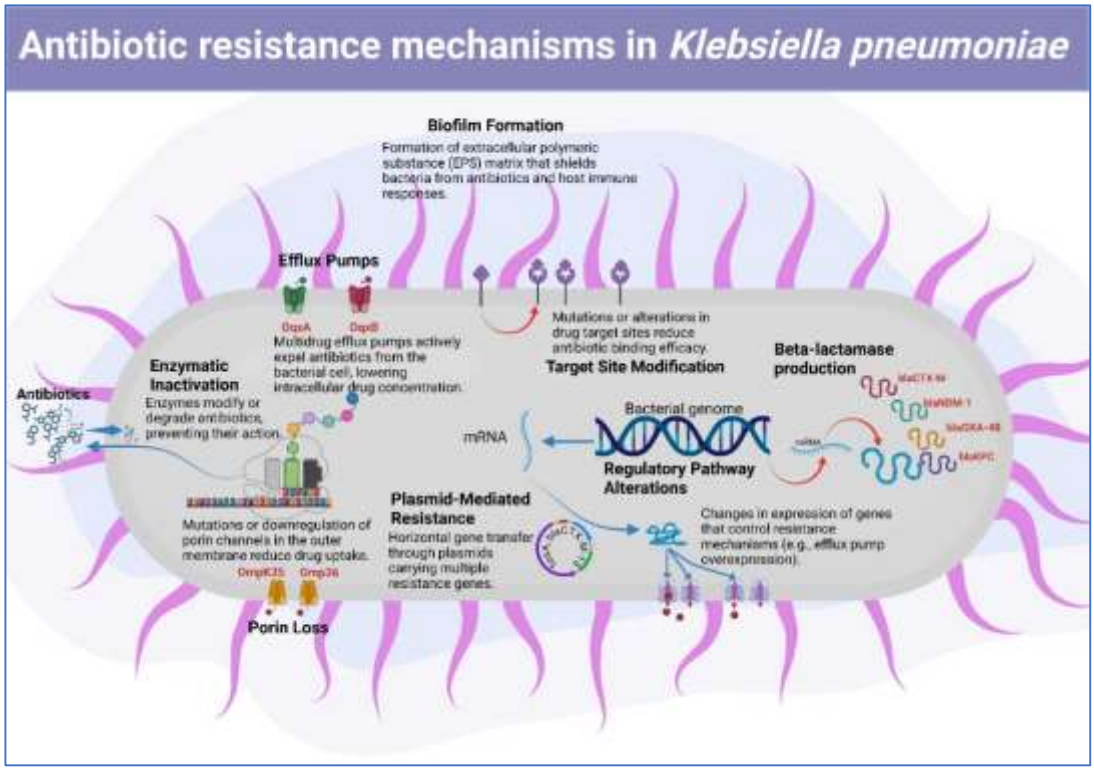

Figure 1: Antibiotic resistance mechanism in klebsiella pneumoniae

Table 1: Summary of fourteen case reports from India reporting *Klebsiella pneumoniae* infections

Author, Year	Case	Samples	Findings
Shankar et al., 2019	A 41-year-old woman with a traumatic brain injury was unresponsive and a tracheostomy was performed to help in breathing.	Tracheal aspirate & Respiratory catheter tip culture	String test negative colistin-resistant *K. quasipneumoniae subsp. similipneumoniae* harboring blaKPC-9 gene
Simner et al., 2018	A 44-year-old man with liver cirrhosis was hospitalized for fall-related injuries with fevers and right upper quadrant pain. Accompanied by an uncomplicated parapneumonic effusion causing respiratory distress..	Blood, Sputum, Renal abscess and Environmental sample culture	Highly mucoid string test positive XDR *Klebsiella pneumoniae* positive for the carbapenemase $bla_{\text{OXA-48}}$-like and the ESBL $bla_{\text{CTX-M-15}}$. Others: $bla_{\text{TEM-1}}$, $bla_{\text{CTX-M-15}}$ and $bla_{\text{OXA-181}}$, *aac(6')Ib-cr, APH(3")Ib, APH(6)Id, rmtF, arr-2, cat, catII, dfrA12, dfrA14, aac(6')Ib-cr, qnrB1,* bla_{SHV11}, *oqxA/oqxB, fosA5*
Bhatia et al., 2024	A 66-year-old male, reformed smoker with COPD. Presented with breathlessness, cough with expectorations and wheezing for 15 days and intermittent episodes of hemopysis for more than 6 months.	Tracheal aspirate and Serial sputum sample culture	Coinfection of *Klebsiella pneumoniae* and Aspergillus
Gupta et al., 2016	A 20-year-old male patient with chief complaints of fever and	Blood culture	MDR *K. pneumoniae* with resistance to carbapenems, colistin and sensitivity to Elores.

	cough since one month, presented to hospital prog ressed to sepsis.		
Shah et al., 2021	A 80 year male with fever and past medical history consisted of chronic obstructive pulmonary disease, pneumonia, tracheostomy, type 2 diabetes mellitus, hypertension, hyperlipidemia, and Parkinson disease. Patient also had an epigastric feeding tube and cholecystectomy tube in place and the patient was treated with colistin for an unknown multidrug-resistant organism	Blood & urine culture	Metallo-beta-lactamase (MBL)-producing *K pneumoniae*
Chrystle et al., 2021	A 63 year old male with a medical history of T2DM and chronic kidney disease diagnosed with lung abscess.	Bronchial lavage culture	*Klebsiella pneumoniae* producing New Delhi metallo-beta lactamase and class D oxacillinase
Dhiman et al., 2023	A 16-year-old girl presented with decreased vision in the right eye preceding an episode of fever with a rash associated with burning micturition.	Blood & corneal scraping culture	ESBL producing *K. pneumoniae*.
Dwidmuthe et al., 2024	A 25-year-old women with sickle cell disease underwent treatment for dengue infection.	Blood & biopsy culture	Hypervirulent *Klebsiella sp*. and was only sensitive to Co-trimoxazole.
Karad et al., 2020	A 64 year old female patient, had a fall and intracranial hemorrhage.	Tracheal aspirate culture	*K. pneumoniae* harboring blaTEM-1 genes susceptible to the first-line treatment agents, including the third and fourth-generation cephalosporins, carbapenems, and aminoglycosides.
Mohit et al., 2019	A 48-year-old male with a case of left eye (LE) choroidal neovascular membrane (CNVM) with subretinal hemorrhage (SRH) for urgent pneumatic displacement.	Urine & vitreous tap culture	*Klebsiella pneumoniae*, sensitive to piperacillin/tazobactum (PPT).
Singh et al., 2021	A 8-year-old male child with tuberculosis on mechanical ventilations.	Tracheal aspirate culture	Carbapenemase-producing multidrug-resistant *Klebsiella pneumoniae*
Dogra et al., 2018	A 35 year old male with sudden, painless diminution of vision in the left eye with fever of 2 days' duration. He was a diagnosed case of alcohol-related necrotizing pancreatitis with a pancreatic pseudocyst and had undergone drainage.	Vitreous tap culture	Multidrug-resistant *Klebsiella pneumoniae* which led to Endogenous endophthalmitis (EE).
Inamasu et al., 2016	A 38-year-old Japanese man working in India, diagnosed with poor-grade subarachnoid hemorrhage and underwent emergency surgery consisting of clipping of a ruptured brain aneurysm, partial removal of the overlying skull and tracheostomy.	CSF culture	NDM-1-producing *K. pneumoniae* producing a metallo-b-lactamase.

Nayak et al., 2022	A 48 year old T2DM man with myalgia for 10 days with fever and jaundice, developed a liver abscess.	Blood and CSF culture	Hypermucoviscous and positive string test hypervirulent *Klebsiella pneumoniae*.

Diverse clinical presentation of *K. pneumoniae* infections

The reviewed case reports on *K. pneumoniae* infections from India displayed various diseases ranging from respiratory and urinary tract infections to systemic diseases, such as sepsis, liver abscess, and endophthalmitis. Respiratory tract infections are the common presentations of the diseases caused by *K. pneumonia*, though a noticeable majority are hospital acquired infections (HI) or co-infections. According to Shankar et al. (2019) (15), a case of colistin-resistant infection due to K. *quasipneumoniae subsp. similipneumoniae* where the patient was a 41-year-old female who had a tracheostomy for traumatic brain injury had developed a secondary infection with colistin-resistant *K. quasipneumoniae subsp. similipneumoniae* harboring blaKPC-9 gene.

Another recent case published by Bhatia et al. in 2024 reported a rare coinfection of *K. pneumoniae* with Aspergillus in a 66-year-old male suffering from chronic obstructive pulmonary disease. The patient presented with breathlessness and intermittent episodes of hemoptysis, on investigation sputum and tracheal cultures were positive for coinfection of *K. pneumoniae* and Pulmonary aspergillosis (16).

Simner et al. 2018 (17) Presents a case wherein a 44-year-old male patient was admitted for fall related injuries and diagnosed later to develop pneumonia. Highly mucoid and XDR isolates of *K. pneumoniae* were isolated from the patient samples and hospital room environment which had a positive result in the string test. Whole genome sequencing revealed XDR *K. pneumoniae* belongs to ST147 and possessed two MDR plasmids IncR and IncFII, the blaOXA-181-bearing ColKP3 plasmid and chromosomal mutations conferring the XDR phenotype, while the hyperucoid *K. pneumoniae* belonged to ST23 and harboured an IncH1B virulence plasmid.

Chrystle et al. (2021) (18) present a case of a 63-year-old male with long-standing Type 2 Diabetes and chronic kidney disease diagnosed with a lung abscess and his bronchial lavage cultures positive for MDR *Klebsiella pneumoniae* producing New Delhi metallo-beta lactamase and class D oxacillinase. In this case, the patient presented with pneumonia was not initially responding to treatment, further revaluation to identify the causes for non-resolving pneumonia led to the identification of MDR *Klebsiella pneumoniae*, a rare organism as a causative agent for community-acquired pneumonia.

All these respiratory tract infections had a varied clinical presentation and were reported as HI or co-infection. The isolation of hyper viscous and MDR strains from both patients and the hospital room is a serious threat that needs immediate attention and intervention.

Besides this, Systemic infections comprising sepsis and liver abscesses were also reported. Gupta et al. (2016) reported a case of multidrug-resistant *Klebsiella pneumoniae* infection in a 20-year-old male who presented with sepsis. The report indicates that the patient had been undergoing treatment with second-generation cephalosporins and aminoglycosides for fever and cough for one month but was not responding to the treatment. His condition subsequently deteriorated into sepsis. Initially, the patient was treated with meropenem and teicoplanin, but there was no improvement. He was then empirically switched to colistin, which also did not yield any positive results. According to the susceptibility testing, the only effective antibiotic available for this case was Elores. The patient was then switched to Elores, and his laboratory parameters began to improve by day two, leading to a full recovery within ten days of starting Elores therapy (19).

Nayak et al. (2022) (20) presented a case of hypervirulent *K. pneumoniae* in the patient with a liver abscess where the patient was a 48-year-old male, a known diabetic but with poor compliance. He had consumed alcohol almost daily for the past 10 years with vitals stable. He was icteric with liver palpable 6 cm below the costal margin, drowsy, presented with myalgia for 10 days with fever and jaundice for 4 days, and altered sensorium for a day. The laboratory investigations on blood and abscess culture revealed the colonies were hypermucoviscous, as evidenced by a positive string test which suggested hypervirulent *Klebsiella*. Community-acquired pyogenic liver abscess due to *K. pneumoniae* is probably on the rise among Asian countries. Clinicians should be aware of the emerging hypervirulent strain of *K. pneumoniae* like this which can cause liver abscesses and spread in the hospital environment. This report necessitates the importance of early diagnosis to facilitate percutaneous drainage which are crucial step in the management of liver abscesses. Infections involving less common sites such as the eyes and central nervous system were also reported like an ESBL-producing *K. pneumoniae* that caused keratitis in a 16-year-old girl was reported by Dhiman et al.

(2023). *Klebsiella keratitis* was presented involving a 16-year-old girl, who exhibited a ring infiltrate in her right eye. Corneal scraping and blood cultures suggested the possibility of endogenous Klebsiella keratitis; however, the exact source of the primary infection was not identified. This rare case was treated with intravenous antibiotics, including gentamicin and piperacillin combined with tazobactam (21).

An endogenous case of endophthalmitis was developed in a 35-year-old man with pancreatitis as documented by Dogra et al. (2018). The patient had a pancreatic pseudocyst and developed bilateral endogenous endophthalmitis, 4 days after surgical drainage of the pseudocyst. Bacterial cultures of the pancreatic drain fluid and the vitreous tap showed the growth of *Klebsiella pneumoniae*. The cultured organism was resistant to all the tested antibiotics except colistin. This MDR *Klebsiella* infection was managed with both intravenous and intravitreal colistin (22).

CNS infections reported by Inamasu et al. (2016) (23) as meningitis due to NDM-1-producing *K. pneumoniae* in a 38-year-old Japanese man who was working in India. He was diagnosed with poor-grade subarachnoid hemorrhage and underwent emergency surgery consisting of clipping of a ruptured brain aneurysm, partial removal of the overlying skull and tracheostomy. The patient was earlier treated with colistin for MDR Acinetobacter and after surgery and tracheostomy patient developed aspiration pneumonia, and *K. pneumoniae* producing a metallo-b-lactamase was identified in body fluids. Based on the previous experience from MDR Acinetobacter baumannii meningitis in the same patient, colistin was administered in this case also because of its effectiveness against NDM-1-producing bacteria. In the report, the authors suggest that colistin should be administered via intrathecal or intraventricular routes in patients with CNS infections because of its poor penetration of the blood-brain barrier (23).

These cases exemplify the capacity of *K. pneumoniae* to cause invasive diseases that result in high morbidity and necessitate intensive care. Timely diagnosis and intervention by physicians were crucial in saving the patients' lives and reducing complications. Most cases involved strains that were previously resistant to multiple classes of antibiotics, including beta-lactams, aminoglycosides, and fluoroquinolones. The failure of standard antibiotics, such as carbapenems and colistin, seems to further complicate these cases.

Genetic Determinants

The most frequently reported genes in case reports are those that confer resistance to carbapenems, such as blaNDM-1, blaKPC-9, and blaOXA-48-like.

Simner et al. (2018) reported a hypermucoviscous strain co-harboring blaCTX-M-15, blaTEM-1, and blaOXA-181 that made treatment challenging. Other genes they reported include Aminoglycosides [aac(6′)Ib-cr, APH(3′′)Ib, APH(6)Id, rmtF], Rifampicin [arr-2], Chloramphenicol [cat, catII], Trimethoprim [dfrA12, dfrA14], and Fluoroquinolone [aac(6′)Ib-cr, qnrB1]. They also reported the chromosomally encoded blaSHV11, multi-drug efflux pump genes such as oqxA/oqxB, and fosfomycin resistance genes fosA5. The presence of multiple resistance mechanisms from a single isolate is an extraordinary situation that no other studies have reported and the authors assume that these gene expressions may be influenced by external antibiotic pressure and environmental factors. According to Simner et al. (2018), the improved resistance phenotypes result from plasmid fusion and mobilization of resistance elements under selective pressure (17). This is because the resistance genes are activated or overexpressed due to the regulatory elements, such as insertion sequences, including IS26 (17). In this case, twelve *K. pneumoniae* strains were isolated from both the patient and hospital room. This particular case was reported and conducted in the USA and the patient presented in this case returned to the US after 2 month visit in India, and it is argued that the patient got the infection while here in India.

Karad et al. (2020) (24) also reported a *K. pneumoniae* with blaTEM-1 genes from a tracheal aspirate culture. Similarly, Shankar et al. (2019) (16) also reported an isolate resistant to all the antimicrobials except tigecycline and the whole-genome sequencing revealed colistin-resistant *K. quasipneumoniae subsp. similipneumoniae* harbouring blaKPC-9 gene. Whereas Inamasu et al. (2016) (23) documented an NDM-1-gene harbouring *K. pneumoniae* producing a metallo-b-lactamase isolated from tracheal aspirate & respiratory catheter tip culture (23).

The co-occurrence of resistance and virulence genes in hypervirulent strains (e.g., those exhibiting hypermucoviscosity) poses a dual threat because this combination increases the pathogen’s ability to cause

severe infections while reducing treatment options. For instance, the co-presence of blaKPC-9 and hypermucoviscosity-associated factors in the report of Shankar et al. (2019) (16) highlights the clinical significance of these determinants and in addition to this, resistance to last-resort antibiotics like colistin, mediated by chromosomal mutations in mgrB, stresses the adaptability of *K. pneumoniae.*

Therapeutic Challenges and Options

The increasing prevalence of resistance to last-resort antibiotics such as colistin and carbapenems underscores the limitations of current therapeutic options. Cases reported by Gupta et al. (2016) and Dogra et al. (2018) point to the failure of conventional therapies, necessitating alternative approaches. Gupta et al. (2016) reported the MDR *K. pneumoniae* with resistance to carbapenems and colistin but sensitivity to Elores. Their report suggests Elores is an effective alternative against MDR *K. pneumonia* cases because Elores is an antibiotic adjuvant entity comprising ceftriaxone, sulbactam, and disodium edetate combination to address the challenges posed by MDR and XDR strains. While case studies and observational data support Elores's efficacy in terms of resistance coverage, effective biofilm penetration, lower nephrotoxicity and neurotoxicity, Elores may be more expensive than generic antibiotics, potentially limiting its accessibility to all (19).

Similarly, combination regimens involving ceftazidime/avibactam and aztreonam, as discussed by Shah et al. (2021) report, provide hope for managing MDR and XDR infections. This combination exploits the ability of avibactam to inhibit class A and C beta-lactamases while aztreonam remains stable against class B metallo-beta-lactamases (MBLs)(25). However, these therapies require further clinical validation and cost-effective implementation strategies.

The development of newer antibiotics and adjuvant therapies, such as meropenem/vaborbactam and imipenem/relebactam, has also generated optimism. These agents are specifically designed to target carbapenem-resistant Enterobacteriaceae (CRE). Meropenem/vaborbactam, for example, has shown high efficacy against *K. pneumoniae* harboring *blaKPC* but is less effective against MBL-producing strains. Similarly, imipenem/relebactam combines a beta-lactam with a beta-lactamase inhibitor to tackle resistant strains, though its role in Indian healthcare has yet to be extensively studied (31)(17).

Prevention and Future Directions

The reliance on traditional cultural methods for diagnosis which usually takes time for results, shows the need for rapid, precise diagnostic tools. In the MDR and XDR *K. pneumonia* systemic infections, the delayed diagnosis will halt the timely effective intervention and management, which is very crucial to save the life of a patient. Only a few case reports implemented the genotyping on isolated strains and techniques like whole-genome sequencing and molecular assays, that can be integrated into routine diagnostics to enable early detection and targeted therapy, which is practically not applicable in resource-constrained facilities (26).

Many case reports, including Gupta et al. (2016), highlighted the delayed identification of resistant strains due to reliance on traditional culture methods. This delay often resulted in inappropriate empirical treatments, worsening patient outcomes (19).

The widespread misuse of antibiotics in both healthcare and community settings is a significant driver of resistance. Antimicrobial stewardship programs must prioritise rational antibiotic use, particularly in high-risk environments such as ICUs and neonatal units (27,28,29), moreover, public awareness campaigns can help curb the misuse of antibiotics in the community. Studies such as Simner et al. (2018) suggested that resistant strains often persist in the hospital; environments, contributing to their dissemination within healthcare facilities. Routine environmental monitoring and proper disposal of hospital effluents could mitigate this risk (17). In most case reports, *K. pneumoniae* infections were identified as co-infections or HAIs. The patients were hospitalised for other reasons. Prolonged hospital stays, invasive procedures and mechanical ventilation were also common predisposing factors (30,31).

Such methods of hand hygiene, device sterilization, and environmental cleaning may prevent the spread, nevertheless, in addition to focusing merely on patient samples for screening, the role of the environmental reservoir in the propagation of resistance has been underexplored. Studies like Simner et al. (2018) (17), which focused also on hospital wastewater and environmental samples, provide insights into these mechanisms of resistance dissemination from the environment.

All these results invite our immediate notice to the fact that there is an urgent need to develop strategies and guidelines for disinfection and sterilization practices, regular training for healthcare workers on infection prevention strategies, periodic surveillance of hospital wastewater to identify potential reservoirs of resistant strains, public awareness about the risks of overusing antibiotics through targeted campaigns.

Conclusion

Klebsiella pneumoniae poses a significant threat to Indian healthcare due to its evolving resistance mechanisms and diverse clinical presentations. The reviewed case reports highlight the critical need for prevention and control measures for *K. pneumoniae* infections in Indian healthcare settings.

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