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Review Article

Occurrence of nosocomial multi-drug resistant *Klebsiella pneumoniae* in India: A systemic review and meta-analysis

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ABSTRACT

Introduction: The continuous rising of hospital acquired Multi Drug resistant *Klebsiella pneumoniae* creates an alarming condition in public health worldwide. Objective of this study is to identify quantitative analysis of hospital acquired Multi-Drug resistant *Klebsiella pneumoniae* in India.
Materials and Methods: Data were collected from Pub Med and Google scholar specific study of India to identify prevalence of Multi-drug resistant nosocomial *Klebsiella pneumoniae* starting from 2011 to 2023. Literature review were collected and analysed through Preferred reporting Items for Systematic Reviews and meta-analysis (PRISMA) guideline and SPSS- 25 software used for Data analysis. Meta-analysis report reveals that prevalence of multi-drug resistant *klebsiella pneumoniae* among hospital acquired is 34.37 % and pooled prevalence rate of hospital acquired multi drug resistant *klebsiella pneumoniae* infection found at 2 % (97.5 % CI, 2.5) with p-value is 0.01. Genotypic analysis reveals bla$_{SHV}$ gene identified most among the studied samples.
Conclusion: Prevalence of ESBL, MDR *Klebsiella pneumoniae* associated with nosocomial infections estimated and correlated with mortality and death ratio as well as antibiotic susceptibility tests pattern was analysed in India which shows continuous rising number of MDR and ESBL *Klebsiella pneumoniae* especially hospital acquired infection. A finding of this study is indicating alarming situation of public health and it should control through interdisciplinary one health approach.

1. Introduction

The rapidly rise of Multi-Drug resistant *Klebsiella* pneumoniae infections specifically associated to hospital-acquired infections, are one of the major concern in the clinical settings.[1] Understanding the prevalence of nosocomial multi-drug resistant *Klebsiella pneumoniae* is essential for developing effective infection control strategies (Figure 1). As per report of Mohd Asri et al.[2] the global pooled prevalence of hospital acquired multi drug resistant *klebsiella pneumoniae* infection was 32%. It is awkward situation for immunocompromised and patients who are suffering from major surgeries and organ transplantations. Due to highly capsule producer strain, infection of *Klebsiella pneumoniae* increases hospital stays with risk of morbidity and mortality rate. *Klebsiella pneumoniae* is the most leading opportunistic pathogen associated with multi-drug resistance where it resist to last line antibiotics such as Carbapenem, Colistin and Tigecycline.[3]

Over use and mis-use of β-lactam antibiotics, β-lactamase enzymes are because of wide spread mobilized enzyme around plasmid. By introducing β-lactamase antibiotics, TEM-1 and SHV-1 enzymes are arise which led to Extended spectrum β-lactamase antibiotics cefotaxime

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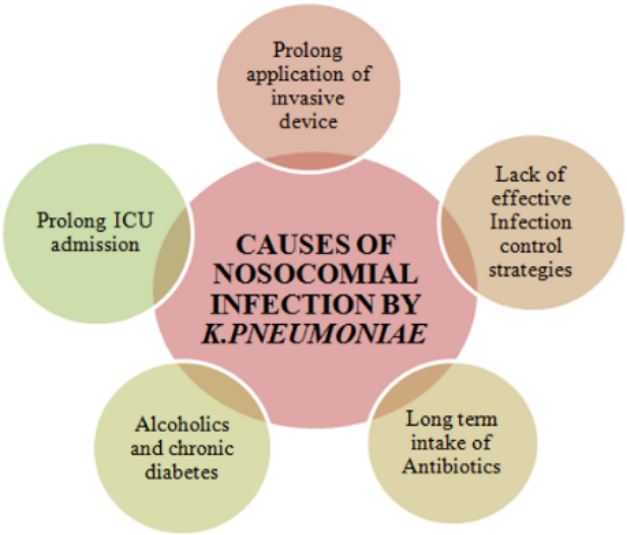


Figure 1: Factors influencing for nosocomial infection by *Klebsiella pneumoniae*

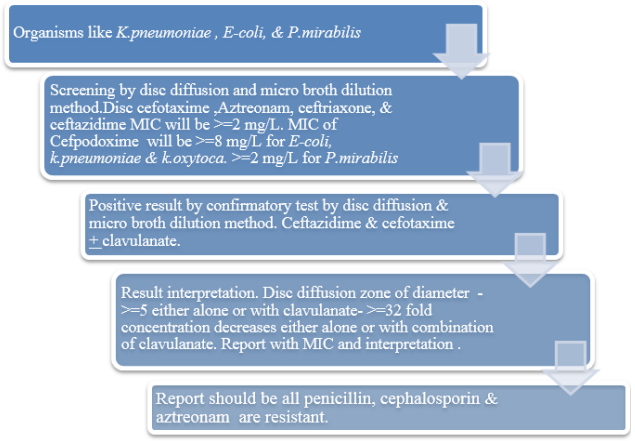


Figure 2: Screening and confirmatory test procedure of ESBL as per CLSI Guideline.

and ceftazidime that unfold to new β-lactamase that can hydrolyse the both new available antibiotics. ESBL are endemic enzyme belongs to serine β-lactamase and is widely seen in Enterobacterales & *Ps. aeruginosa*. All new β-lactamase variants are originated from TEM-1 and SHV-1 enzymes. So the rise of ESBL producing gram negative bacteria is found in both community and hospital settings. To overcome from ESBL producers, Carbapenems class of antibiotics became empirical antimicrobial therapy in majority of health care settings. This transformation of antimicrobial therapy gradual results into increase the report of carbapenem resistance. For better outcome there is necessary to evaluate data of prevalence rate of ESBL producing strains, their detection methods and other therapeutic options.[4]

TEM and SHV are predominant ESBL families. TEM types -3 ESBL are more prevalent in France and rare in USA. TEM type -26 are isolated from all over globally.[5] While SHV type β-lactamase first originated from chromosome of *K.pneumoniae* and also it is most commonly found in clinical isolate *K.pneumoniae*. ESBL variant, SHV- type 5 and SHV- type 12 are most commonly observed globally out of 228 SHV variant.[6] blaTEM and blaSHV are most commonly observed virulence gene among blaOXA, qnrB1, oqxA, sul2 and dfrA12.

A Nosocomial infection occurs during the time of health treatment receiving from 48 hours of hospitalization. It is usually absent at the time of hospital admission. It appear during implant of invasive devices, long term stay & ambulatory. It is transmitted from patient to all health care workers of settings.[7]

This study represents a systematic review with meta-analysis of relevant literature to deliver a descriptive overview of the occurrence of multi drug resistant nosocomial *Klebsiella pneumoniae*.

2. Materials and Methods

A systematic and meta-analysis review was initiated by identification through searching several electronic based data containing Pub Med and Google scholar. Articles published from 2011 to 2023. Occurrence of Nosocomial Multi Drug resistant *Klebsiella pneumoniae* in India was considered for inclusion. The search terms used included "nosocomial infections," "*Klebsiella pneumoniae*," "Multi-drug resistant," and “prevalence in India." Total 35 articles screened and out of them 10 articles were covering global prevalence while 7 articles found duplicate so it excluded from study. After screening titles, abstracts, and full texts, relevant studies were included for data extraction 11 articles were finalized. All Articles were analysed through Preferred reporting Items for Systematic Reviews and meta-analysis (PRISMA) guideline & SPSS- 25 software used for Data analysis (Figure 3).

2.1. Exclusion criteria

Beta-lactams containing six classes of antibiotics are penicillins, β-lactamase/penicillins inhibitors, cephalosporins, cephalosporins-β-lactamase inhibitor, Monobactams & carbapenems. Here trimethoprim, chloramphenicol, fosfomycin, rifampin, and nitrofurantoin etc classes of antibiotics were not included as the study only focused nosocomial MDR *K. pneumoniae* occurrence cases.

3. Results & Discussion

The systematic review yielded a total of 11 studies from various geographic regions of India. A meta-analysis

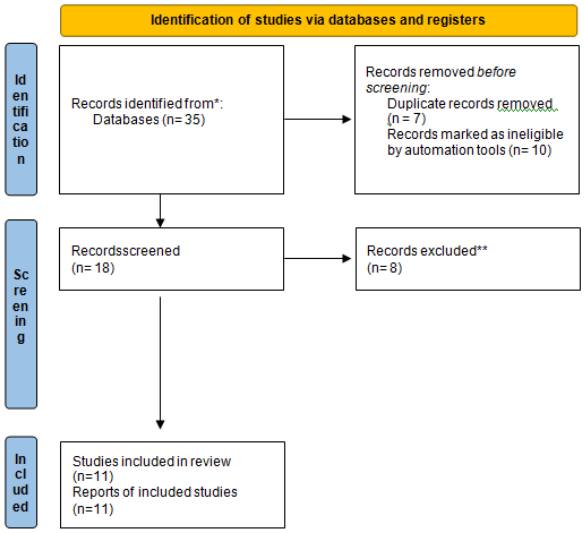


Figure 3: PRISMA frame work

was carried out to estimate the overall occurrences of nosocomial multi-drug resistant *Klebsiella pneumoniae*.

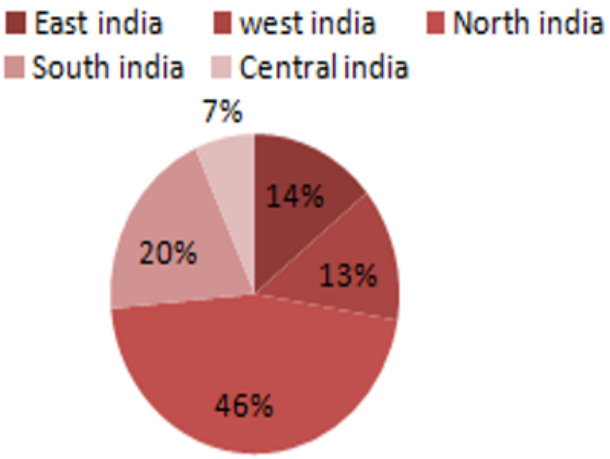


Figure 4: Geographic distribution of nosocomial associated multi-drug resistant *K. pneumoniae* in India

11 studies included total 7265 patients and from them 2497 patient were identified as Multi drug resistant *Klebsiella pneumoniae* infection while 2330 patient recorded as ESBL producer strains. Patient's infection type and their antibiotic sensitivity pattern were analysed. There was 82.76%, 78.6%, 268.32% and 39.80% prevalence from East, West, North, south and Central India respectively (Figure 4).

Meta-analysis report reveals that prevalence of multi-drug resistant *Klebsiella pneumoniae* among hospital acquired is 34.37 % and pooled prevalence rate of nosocomial associated multi drug resistant *k.pneumoniae* infections found 2 % (97.5 % CI, 2.5) with 0.01 p-values (Figure 5).

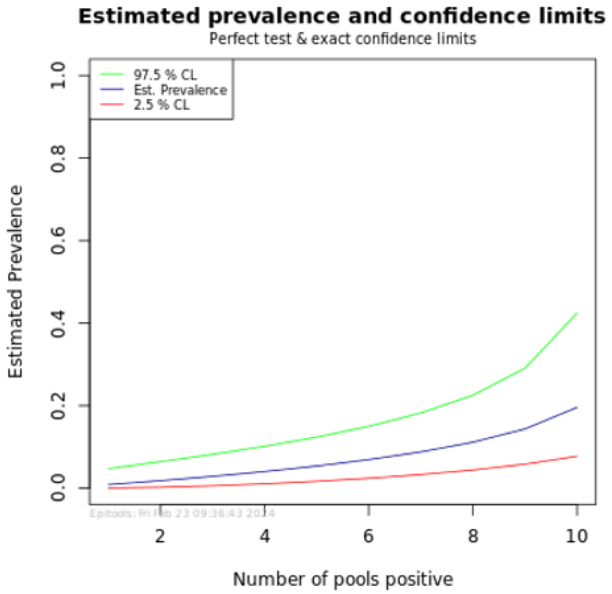


Figure 5: The pooled prevalence rate of nosocomial associated multi drug resistant *k. pneumoniae* infection

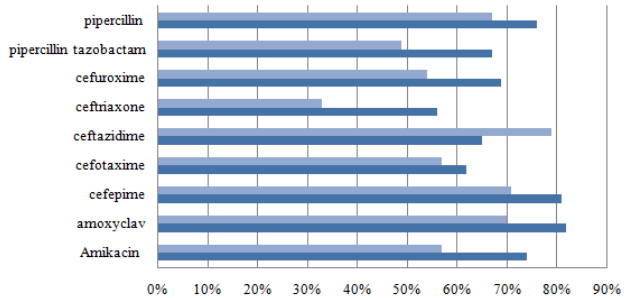
Since the collected data is not uniform according to methodology to characterized ESBL *Klebsiella pneumoniae*, each unique study discussed separately.

In East India study of Das and Dasgupta et al. (2015) carried out prospective observational study to identify risk factors & rate of infection associated with nosocomial and found that 11.98% infection rate associated and from them 0.71% patient get infected from pneumoniae by *Klebsiella pneumoniae* infection including mortality and morbidity. [7]

While Chandramouli Bhattacharya et al. (2019) studied 78 patients of cirrhosis and out of them 18 infected with *Klebsiella pneumoniae*. 15 patients were Multi Drug resistant *Klebsiella pneumoniae*, among them 13 patients infected with Urinary tract infection followed by pneumonia. 27.7 % community acquired, 52.9% health care associated and 19.3% were nosocomial infection include mortality and morbidity rate. [8]

Figure 6 reveals that contribution of antibiotics resistant rates which involves drastic shift of Amikacin from community acquired (57%) to health care associated (74%). cephalosporins and cephalosporins inhibitors like Amikacin, were shown changing trends of their resistant patterns. So it is alarming situation for public health care setting especially immunocompromised and ICUs patients. There are antibiotic resistant Genes (ARGs) also contribute to transmit infection from patient to health care workers. Shakti Rath et al. (2014) studied rate of nosocomial and health care associated for three years and found that occurrence of multi drug resistant *k.pneumoniae* was 74 %

(200 isolates) out of 270 positive samples. [4,9]



	Amikacin	amoxyclav	cefepime	cefotaxime	ceftazidime	ceftriaxone	cefuroxime	pipercillin tazobactam	pipercillin
Community acquired	57%	70%	71%	57%	79%	33%	54%	49%	67%
Health care associated	74%	82%	81%	62%	65%	56%	69%	67%	76%

Figure 6: Characterization of Antibiotic Susceptibility testing of community acquired and health care associated infection. [9]

In report of Abhishek Sharma et al. (2023) found that there was significantly rise of antibiotic resistant from 7.5% to 21.4% from 2018 to 2022.while patient who are in ventilator, their antibiotic resistant trend increase from 62.5% to 71% in 2022 [10](Figure 8).

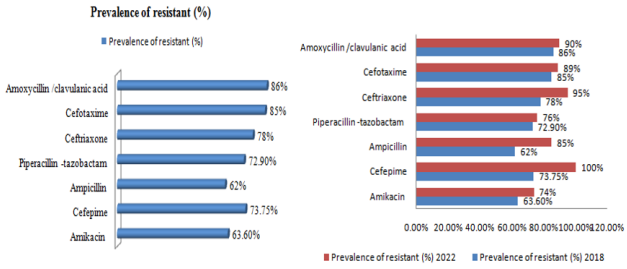


Figure 7: Antibiotic resistance profile among nosocomial multi-drug resistant *K.pneumoniae* infection.

Archana sikarwar et al. (2011) found that highly resistant *k. Pneumoniae* ESBL and SHV, TEM strains associated with nosocomial infections. Their rapidly rise of infection leads to increase morbidity and mortality (Figure 8). [11]

Nosocomial infections are foremost cause of prolong stays of patient in hospital with high mortality associated with it. Study reveals that prevalence of multi-drug resistant *Klebsiella pneumoniae* among hospital acquired is 34.37 % while pooled prevalence is 2%. It was found that high mortality rate also associated with it. [8] We report the occurrence of nosocomial multi-drug resistant *Klebsiella pneumoniae* in India (Table 1).

The high occurrence of nosocomial multi-drug resistant *K. pneumoniae* globally is a cause for concern. The factors contributing to the spread of this MDRO include inadequate infection control practices, excessive and inappropriate antibiotic use, and the frequent transfer of

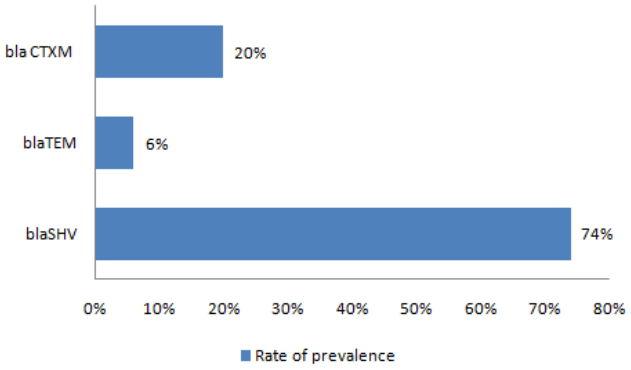


Figure 8: Prevalence of ESBL gene

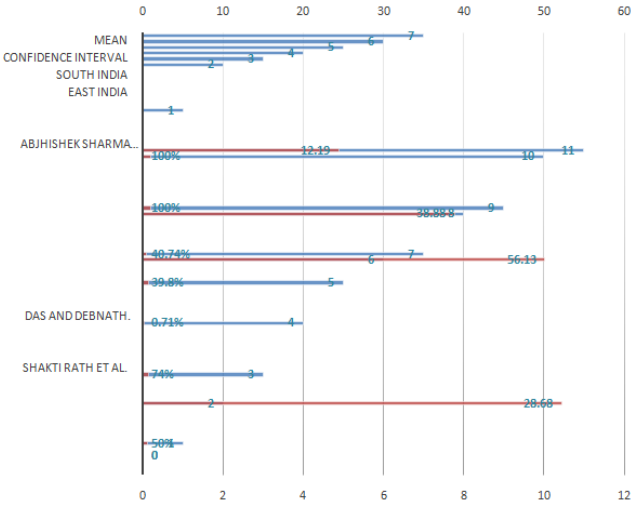


Figure 9: Forest plot of occurrence of nosocomial ESBL & Multi Drug resistant *K. Pneumoniae* (Table 1).

patients between healthcare facilities. The variability in prevalence among regions can be attributed to differences in healthcare systems, antibiotic prescribing practices, and local epidemiology.

In India, due to high population and poor sanitation practices contribute to the rapid transmission of antibiotic Resistant Genes (ARGs). To understand this issue, A NICU outbreak report of India, 2023 where total 6 out of 7 neonates infected with blood stream infection of *Klebsiella pneumoniae* and they all were resistant to carbapenems & Colistin antibiotics. Their genomic analysis of clinical samples found that 3 different sequence of isolates namely ST-101, ST-11 and ST-16. Their environmental analysis report reveals that *k.pneumoniae* ST-101 isolated from incubator water sample which contains ESBL genes bla$_{CTX-M}$, Carbapenem gene bla$_{NDM-5}$, bla $_{OXA-232}$ genes. No mcr gene for Colistin detected. So infection control strategies should apply to prevent spread of highly infectious genes of multi-drug resistant

Table 1: Clinical presentation of *Klebsiella pneumoniae* isolates.

S.No.	Author	Year of Publication	Site of study	Type of specimen	Age of participant	Infection site	Infection source	Sample no.	Total MDR & ESBL *K.pneumoniae*	MDR & ESBL *K.pneumoniae* %
1	Archana sikarwar et al.[11]	2011	West India	Respiratory, urinary tract infection and pus	All age group	Different	HAI	3296	1648	50
2	B.L.Chaudhary, Shailja Srivastava et al.[1]	2014	West India	Blood, pus, urine, ET, Sputum	All age group	Different	HAI	122	35/67	28.68
3	Shakti rath et al.[9]	2014	south East India	Urine, stool and rectal swabs	All age group	Different	HAI, CAI	270	200	74
4	Das and Debnath.	2015	East India	Blood, body fluid, urine, sputum, ET, TT, BAL, pus, wound swab	All age group	ICU	HAI	697	5	0.71
5	Vaibhavi subhedar et al.[12]	2016	Central India	Blood, sputum, pus, endotracheal secretions, urine, fluids	All age group	ICU	HAI	500	199	39.8
6	Nitin gupta et al.[7]	2018	North India	Brocho-alveolar lavage (BAL),) and endotracheal aspirates	All age group	Lungs ,nosocomial pneumonia for ICU stay	HAI	269	151	56.13
7	Kalaivani Ramakrishnan et al.[13]	2019	South India	Blood, body fluid, urine, sputum, ET, TT, BAL, pus, wound swab	All age group	ICU	HAI	562	229	40.74
8	Chandramouli bhattacharya et al.[8]	2019	East India	Liver cirrhosis	All age group	ICU	HAI	78	64	82.05
9	Tuhina Banerjee et al.[14]	2021	North India	Blood , sepsis	All age group	ICU	HAI	9	9	100
10	Ashutosh Pathak et al.[3]	2023	North India	Blood , sepsis	Neonate	ICU	HAI	5	5	100
11	Abhishek Sharma et al.[10]	2023	North India	Endotracheal aspirate	All age group	mechanically ventilated ICU patients	HAI	82	10	12.19

*HAI- Hospital Acquired Infection, CAI- Community Acquired Infection

organisms to the community.[3] There is high prevalence of occurrence of ventilator associated pneumonia in intubated patient after 48 hours of patient admission in ICU. So Infectious Disease Society of America (IDSA) recommends to preparing of antibiogram for optimal selection of antibiotics. As per IDSA, A good regimen should work maximum 95% of patients like use of anti-pseudomonal as a empirical therapy. It should include piperacillin –tazobactam, carbapenems and cefoperazone salbactam. Second anti-pseudomonal regimen should include either aminoglycosides or fluoroquinolones. There is necessity to develop antibiogram to formulate regimen for empirical therapy to overcome and treat hospital acquired infection. To apply IDSA guideline, Nitin gupta et al., 2018 carried out prospective study on search of best effective regimen among nosocomial pneumonia patients and found that *Ps.aeruginosa* was most common isolate organism and effective regimen was cefoperazone-salbactam alone as well with combination of Amikacin.[7,15–19]

Moreover, the widespread utilization of broad-spectrum antibiotics in this Indian health care practices promotes the natural selection and evolution of multi-drug resistant *K.pneumoniae*. On other side, notifiable results from comprehensive Infection control programs, Implement of antibiotic stewardship, and efficient surveillance systems are possible strategies to prevent Antibiotic Resistance regionally and globally.

Limitations of the included studies should be acknowledged. There was heterogeneity in the methodology used to define nosocomial infections and multi-drug resistance, making direct comparisons between studies challenging. Additionally, publication bias may be present as studies reporting higher prevalence rates are more likely to be published.

4. Conclusion

Nosocomial associated multi-drug resistant *K. pneumoniae* is a significant healthcare burden worldwide. Efforts to control and prevent the spread of this MDRO should focus on improving infection control practices, implementing effective antibiotic stewardship programs, and guide enhancing surveillance systems. Understanding the geographical variation in prevalence can targeted interventions tailored to specific regions. Further research is required to address the Gaps in knowledge and to develop evidence-based strategies to mitigate the impact of this MDRO.

By analysing different geographic regions of India, meta-analysis reveals prevalence of multi-drug resistant *Klebsiella pneumoniae* among hospital acquired is 34.37% and pooled prevalence of multi drug resistant *k.pneumoniae* among hospital acquired was found at 2%. It can be considered as moderate level. By analysing their antibiotic resistance pattern shown that high resistant to β-lactamase inhibitors (86%). While some studied recorded genomic analysis which has shown that majority of resistant genes, blaSHV encoded for β-lactamase responsible for transmission of disease from patient to health care workers. So accurate infection control protocol required to implementing in health care settings and more community based data required to prevent antibiotic resistance specifically for virulent strain like *k.pneumoniae*.

5. Source of Funding

None.

6. Conflict of Interest

None.

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