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Multi-drug resistant and extended-spectrum β-lactamase producing *Klebsiella pneumoniae* from clinical samples

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Abstract

This study aimed to determine the MDR and ESBL producing *Klebsiella pneumoniae* from clinical samples. Laboratory based cross-sectional study was conducted from the samples obtained from the patients of Tribhuvan University Teaching Hospital. Antibiotic susceptibility test was performed and ESBL was detected through the combination disk method. Of the 377 *K. pneumoniae* isolates, 304 (80.6%) were MDR and 279 (74%) exhibited ESBL activity. Significant percentages of MDR were detected in blood (p=0.004) and urine (p=0.058) whereas ESBL in urine (p=0.026). Most ESBL-producing *K. pneumoniae* exhibited resistance to ß-lactams, quinolones, aminoglycosides and macrolids. This suggests for strict adherence to antimicrobial susceptibility results for the treatment and implementation of antibiotic stewardship programme.

Key words: *Klebsiella pneumoniae*, clinical samples, MDR, ESBL, antibiotic susceptibility

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Introduction

Klebsiella pneumoniae is a frequent opportunistic pathogen responsible for severe infections in hospitalized individuals, particularly immunocompromised patients [1]. Antibiotic resistant bacteria are difficult to manage in elderly, immunosuppressed or underdeveloped immunity patients [2]. Antibiotic resistant *K. pneumoniae* infections can disseminate beyond healthcare settings through contaminated wastewater streams [3]. In 2019, it ranked as the second leading cause of mortality worldwide and the primary cause of bloodstream infection–associated death in Southeast Asia [4].

Transmission of *Klebsiella* in hospitals is influenced by colonization of the patient's gastrointestinal tract, hand contamination among healthcare workers, the use of invasive medical devices, respiratory care equipment, urinary catheterization, and prior antibiotic exposure [5]. The frequent administration of broad-spectrum antibiotics in hospital settings has accelerated gastrointestinal carriage of *Klebsiella* species and contributed to the expansion of MDR strains capable of producing extended-spectrum β-lactamases (ESBL) and carbapenemase-producing *K. pneumoniae* (CRKP) [6]. ESBLs hydrolyze penicillins and cephalosporins—including β-lactam/β-lactamase inhibitor combinations such as sulbactam and clavulanic acid—and monobactams like aztreonam [7]. The first report of ESBL-producing *K. pneumoniae* originated from Germany in 1983, after which global resistance to cephalosporins progressively increased [8]. In Nepal, the prevalence of ESBL-producing *K. pneumoniae* has been documented at 23% [9]. ESBL-producing *K. pneumoniae* frequently demonstrates reduced susceptibility to several routinely used antimicrobial agents [10 11, 12, 13]. It is important to monitor the resistance trends of ESBL *K. pneumoniae* for suggesting the appropriate antibiotics for management. Due to limited coverage of the hospitals by AMR surveillance systems, the surveillance data on AMR have limitations and often shortage for tracking MDR and ESBL-producing *K. pneumoniae*. Further, trends in resistance patterns are poorly understood. It is essential to generate updated data on MDR and ESBL producing *K. pneumoniae* for rationale clinical practice based on local antibiogram for antibiotic stewardship programme. In addition, we analyzed ESBL producing *K. pneumoniae* based on different clinical samples which could provide insights into prevalence by infection site, and also could provide guidance on rationale antibiotic treatment of the infections. Therefore, this study was conducted to assess the status of ESBL-producing *K. pneumoniae* from various clinical specimens obtained from a referral hospital in Kathmandu.

Materials and Methods

Study design and sample collection

This was cross-sectional descriptive study conducted in the microbiology laboratory of Tribhuvan University Teaching Hospital, Kathmandu. Clinical specimens were obtained from the patients over the period from April 2021 to April 2024. In the hospital laboratory, preliminary

isolation and identification were performed, additional processing and analysis were carried out in Central Department of Microbiology, Tribhuvan University.

Sample size and sampling

Purposive sampling was conducted with objective of collecting consecutive *K. pneumoniae* from clinical specimens. A total of 377 *K. pneumoniae* isolates were collected. Inadequate, improperly labeled and duplicate specimens from the same patient were excluded.

Processing of samples and identification of K. pneumoniae

All specimens were inoculated onto MacConkey agar. The isolated pink mucoid colonies were subculture on nutrient agar. Identification of *K. pneumoniae* was accomplished through evaluation of colony characteristics, Gram staining results, and standard biochemical assays. For quality control of tests *Escherichia coli* ATCC 25922 was used.

Antimicrobial susceptibility test

Antimicrobial susceptibility testing (AST) was performed by Kirby–Bauer disc diffusion technique following Clinical Laboratory Standards Institute (CLSI,2020) guidelines (**Figure 1**). The antimicrobial discs applied in this study included of different classes in clinical practice and CLSI relevance. Interpretation of the susceptibility results followed the criteria outlined by the CLSI [14]. An isolate was classified as MDR when it exhibited resistance to three or more distinct classes of antimicrobial agents [15]. *K. pneumoniae* ATCC 700603 was employed for quality control in each lot of the test [14].

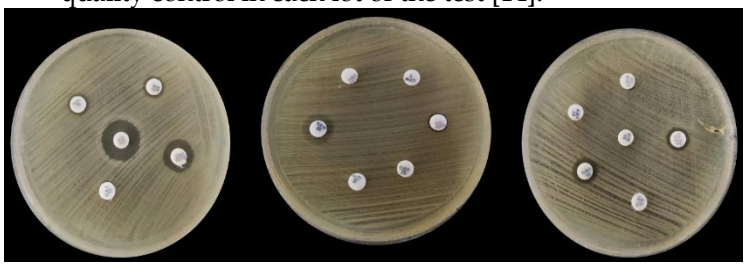

Figure 1. Antibiotic Susceptibility Pattern of *K. pneumonie* GEN- Gentamicin, AMC - Amoxyclav, CFM - Cefixime, PTZ - Piperacillin-tazobactam COT - Cotrimoxazole, CIP - Ciprofloxacin, LE - Levofloxacin, CAZ - Ceftazidime, CX- Cefoxitin, AMX - Amoxicillin, IPM - Imipenem, MRP - Meropenem, CPM - Cefepime, CFS - Cefoperazone Sulbactam, A/S - Ampicillin Sulbactam CAC – Ceftazidime with Clavulanic acid

Screening of ESBL producing isolates

Screening of ESBL producers was done using ceftazidime (30 µg) and cefotaxime (30 µg) discs. Strains demonstrating a zone of inhibition ≤22 mm for ceftazidime and/or ≤27 mm for cefotaxime were potential ESBL producers (CLSI, 2020) [14].

Combination disc test for confirmation of ESBL producers

Isolates that screened positive were further confirmed using the combination disc test (CDT) (**Figure 2**). A lawn culture of each organism was prepared, and discs of ceftazidime (30 µg) and ceftazidime with clavulanic acid (30/10 µg), as well as cefotaxime (30 µg) and cefotaxime with clavulanic acid (30/10 µg) were kept on the agar plate with a center-to-center distance of 25 mm. Plates were incubated at 37°C for 24 hours. An increase of ≥5 mm zone of inhibition around ceftazidime/clavulanic acid or cefotaxime/clavulanic acid compared to the respective cephalosporin alone confirmed ESBL producer [14]. *K. pneumoniae* ATCC 700603 (ESBL positive) and *E. coli* ATCC 25922 (ESBL negative) served as quality control strains in each test [14].

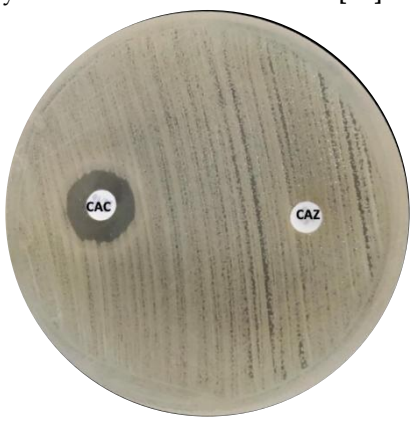

Figure 2. ESBL Test CAZ – Ceftazidime CAC – Ceftazidime and Clavulanic acid

Ethical consideration

Approval for this study was granted by Tribhuvan University Teaching Hospital. Prior to the collection of samples and associated data, informed consent was obtained in written from all participants. Additionally, ethical approval was provided from the Nepal Health Research Council (Regd. No.: 293-2020).

Statistical analysis

Data were analyzed using SPSS version 25.0. Results were expressed as percentages. Associations of antibiotic resistance rates and ESBL production, associations of sample wise MDR and ESBL proportions were determined using the Chi-square test assuming p-value less than 5% as significant.

Results

A total of 377 *K. pneumoniae* isolates were identified in this study, including 120 (31.8%) from urine, 122 (32.4%) from sputum, 53 (14.1%) from pus, 37 (9.8%) from blood, 24 (6.4%) from body fluids, and 21 (5.5%) from swab specimens. (**Table 1**).

Table 1. Sample wise comparison of MDR *K. pneumoniae* (n=377)

Sample	Total isolates		MDR		Non-MDR		p-value
	N	%	N	%	N	%	
Urine	120	31.8	90	75.0	30	25.0	0.058
Pus	53	14.1	41	77.4	12	22.6	0.515
Blood	37	9.8	37	100	0	0.0	0.004
Sputum	122	32.4	100	82.0	22	18.0	0.651
Swab	21	5.5	17	81.0	4	19.0	0.970
Body fluids	24	6.4	19	79.2	5	20.8	0.852
Total	377	100	304	80.6	73	19.3	0.002

Table 2. ESBL-producing *K. pneumoniae* across different clinical specimens (n=377)

Clinical samples	ESBL positive (%)	ESBL negative (%)	p-value
Urine	80 (66.7)	40 (33.3)	0.026
Pus	40 (75.5)	13 (24.5)	0.793
Blood	32 (86.5)	5 (13.5)	0.068
Sputum	96 (78.7)	26 (21.3)	0.152
Swab	13 (61.9)	8 (38.1)	0.193
Body fluids	18 (75.0)	6 (25.0)	0.909
Total	279 (74.0)	98 (26.0)	0.094

All the isolates obtained from blood samples are found to be MDR *K. pneumoniae* 37 (100%) followed by sputum samples 100 (82%). The least MDR were obtained from urine samples 90 (75%). Significant association was found between MDR and isolates from urine (p=0.058) and blood (p=0.004) whereas no significant association was found between MDR and pus (p=0.515), sputum (p=0.651), swab (p=0.970) and body fluids (p=0.852).

ESBL producers among *K. pneumoniae*

Among 377 *K.pneumoniae,* 279 (74%) were found to be ESBL producer (**Figure 3**).

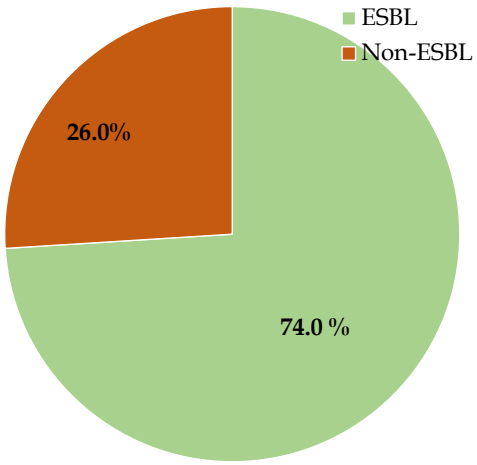

Figure 3. ESBL producers among *K. pneumoniae* (n=377)

Distribution of ESBL among different clinical samples

Over 50% of *K. pneumoniae* were ESBL producers. The highest proportion of ESBL-producers was observed in blood samples 32 (86.5%), followed by sputum samples 96 (78.7%), whereas swab samples 13 (61.9%) showed the relatively lowest prevalence. The prevalence of ESBL-positive was significantly associated with urine as compared to other specimen types (p = 0.026) (**Table 2**).

Antibiotic susceptibility of ESBL and non-ESBL *K. pneumoniae*

Majority of ESBL producer isolates were resistant to amoxicillin 278 (100%), amoxyclav 264 (94.6%), ciprofloxacin 246 (88.2%) and cotrimoxazole 237 (84.9%). Among ESBL not-producing isolates, 98 (100%) were resistant to amoxycilin, 36 (36.7%) to amoxyclav, 35 (35.7%) to ciprofloxacin and 32 (32.7%) to cotrimoxazole. Among the antibiotics tested, there were no significant associations of amoxicillin (p=0.438) with ESBL producing *K. pneumoniae* (**Table 3**).

Discussion

This study demonstrates that a substantial proportion of *K. pneumoniae* isolates exhibited multidrug resistance (MDR) indicating that only few antibiotics remain for the treatment of *K. pneumoniae* infections. Reports from previous studies from Nepal have documented MDR *K. pneumoniae* within a wide range, from 21% to 89%, highlighting a concerning public health issue [16, 17, 18]. Many patients infected with MDR strains receive suboptimal treatment, often due to the use of empirical therapy without adequate screening of antimicrobial susceptibility [16, 19]. Furthermore, antimicrobial resistance is disseminated among bacterial populations through horizontal gene transfer mechanisms, facilitating the rapid spread of resistance genes [20, 21]. Weak implementation of antibiotic stewardship programs, insufficient infection prevention practices, and poor hygiene standards within healthcare settings further intensify the development and spread of drug-resistant organisms [19, 22, 23, 24]. Therefore, containment of drug resistant bacteria through antibiotic stewardship program is essential in hospitals.

In this study, 74% of *K. pneumoniae* were ESBL producers. Similar results have been reported for ESBL since last few years in Nepal [12, 24, 25, 26]. This high rate of ESBL producers could be attributed to the selection pressure of use of cephalosporins and carbapenems and further spread of ESBL strains.

Table 3. Antibiotic susceptibility status of ESBL producer and ESBL non-producer *K. pneumoniae*

Antibiotics	ESBL producers Number (%)			ESBL non-producers Number (%)			p-value
	S	I	R	S	I	R	
Gentamicin	69(24.7)	7(2.5)	203(72.8)	76(77.6)	2(2.0)	20(20.4)	< 0.001
Amikacin	70(25.1)	12(4.3)	197(70.6)	77(78.6)	4(4.1)	17(17.3)	< 0.001
Ciprofloxacin	24(8.6)	9(3.2)	246 (88.2)	57(58.2)	6(6.1)	35(35.7)	< 0.001
Levofloxacin	44(15.8)	9(3.2)	226 (81.0)	69(70.4)	6(6.1)	23(23.5)	< 0.001
Imipenem	94(33.7)	13(4.7)	172(61.6)	81(82.7)	3(3.1)	14(14.3)	< 0.001
Meropenem	85(30.5)	6(2.2)	188(67.4)	79(80.6)	2(2.0)	17(17.3)	< 0.001
Amoxyclav	9(3.2)	6(2.2)	264(94.6)	55(56.1)	7(7.1)	36(36.7)	< 0.001
Ampicillin Sulbactam	34(12.2)	11(3.9)	234(83.9)	75(76.5)	3(3.1)	20(20.4)	< 0.001
Aztreonam	48(17.2)	8(2.9)	223(79.9)	80(81.6)	2(2.0)	16(16.3)	< 0.001
Chloramphenicol	102(36.6)	37(13.3)	140(50.2)	69(70.4)	9(9.2)	18(18.4)	< 0.001
Tigecycline	186(66.7)	54(19.4)	39(14.0)	81(82.7)	9(9.2)	8(8.2)	0.011
Doxycycline	135(48.4)	36(12.9)	108(38.7)	80(81.6)	3(3.1)	15(15.3)	< 0.001
Piperacillin Tazobactam	68(24.8)	8(2.9)	203(72.8)	76(77.6)	1(1.0)	21(21.4)	< 0.001
Cefoperazone/ Sulbactam	63(22.6)	19(6.8)	196(70.3)	79(80.6)	1(1.0)	18(18.4)	< 0.001
Cotrimoxazole	38(13.6)	4(1.4)	237(84.9)	64(65.3)	2(2.0)	32(32.7)	< 0.001
Cefoxitin	75(26.9)	3(1.1)	201(72.0)	78(79.6)	1(1.0)	19(19.4)	< 0.001
Nitofurantoin	15(10.9)	14(10.2)	108(78.8)	15(29.4)	14(27.5)	22(43.1)	< 0.001
Amoxycillin	-	-	279(100.0)	-	-	98(100.0)	0.438

Foot note: S- Sensitive, I- Intermediate, R- Resistant

Majority of specimens processed in the hospital were sputum, urine, pus and blood. There were significantly higher rates of MDR isolates in blood and sputum samples, as compared to other samples. Although *K. pneumoniae* is predominant pathogen in respiratory and urinary tract infections, higher detection of ESBL-producing strains was observed in blood, sputum, and swab samples. All the isolates of blood samples were found to be MDR ESBL producer, a pattern consistent with findings reported by Schulte et al. (2020) [13]. This may be due to bacteremia by primary MDR bacteria. Increasing resistance to ESBL *K. pneumoniae* were also reported in other studies [27, 28, 29, 30]. The high incidence of blood infections due to MDR and ESBL-producing isolates can exert a considerable effect on healthcare costs and mortality rate [12,13].

ESBL producing *K. pneumoniae* were resistant to amoxyclav, fluroquinolone, ampicillin sulbactam and cotrimoxazole than ESBL non-producing isolates. Similar results have been reported from most of the other studies [9, 10, 12, 16, 20]. The coexistence of diverse resistance mechanisms is often associated with resistance to many antibiotics by the bacterial isolates along with various pre disposing factors like weak and debilated people, severe comorbidities, elder patient, prolonged hospitalization [29]. Therefore, treatment of *K. pneumoniae* infections should be supported by antibiotic susceptibility test results from the laboratory.

This study has some limitations such as it was confined to collect bacterial isolates from a single hospital, ESBL producers were confirmed only by phenotypic methods. We did not have other risk factors including demographic data and clinical history of the patients to link with resistance profile of bacteria. Molecular work focusing on ESBL genes profiling at multi-hospitals isolates could provide more insights on resistance to ß-lactam antibiotics.

Conclusion

Relatively high frequency of MDR and ESBL producing *K. pneumoniae* suggests the emergence of antibiotic resistant *K. pneumoniae* as a potential health threat. Most MDR *K. pneumoniae* isolates were obtained from blood, sputum and swab samples. All the blood isolates were found to be ESBL producer. Only few common antibiotics are effective against ESBL *K. pneumoniae* isolates. The considerable burden of ESBL-producing *K. pneumoniae* suggests for implementation of antibiotic stewardship programme in the hospitals, strict adherence to

antimicrobial susceptibility results for the treatment and robust infection-control practices to prevent these bacteria. Molecular profiling of ESBL genes could provide detail insights on MDR and ESBL producing *K. pneumoniae*.

Author's Contributions

Shova Shrestha: Laboratory work, Clinical and Experimental studies, Manuscript writing and Editing; Prof. Dr. Prakash Ghimire: Supervision, Manuscript editing & Review; Dr. Hari Prasad Kattel: Technical guidance for laboratory work, Data acquisition, manuscript editing; Assoc. Prof. Dr. Megha Raj Banjara: Data analysis, Supervision, Manuscript editing and Review.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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