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Prevalence of extended spectrum beta lactamase producing *Escherichia coli* and *Klebsiella pneumoniae* urinary isolates in a tertiary care hospital in Kathmandu, Nepal

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Abstract

Background: *Escherichia coli* and *Klebsiella pneumoniae* are the major bacterial pathogens being isolated and reported from mid stream urine (MSU) specimens, globally. These uropathogens are mostly implicated as the major extended spectrum beta-lactamase (ESBL) producers, severely limiting the therapeutic management in cases of urinary tract infections. Limited studies had been reported from Nepal investigating the ESBL producers among uropathogens. This study was designed to assess the prevalence of ESBL producing *E.coli* and *K. pneumoniae* in urinary isolates at a centrally located major tertiary care hospital in Kathmandu valley, Nepal.

Methods: Between September 2011 and May 2012, during the nine months period, 6308 MSU specimens were collected aseptically from the same number of clinically suspected patients of urinary tract infections. The samples were cultured on MacConkey agar and blood agar. The isolates with significant bacteriuria (10^5 CFU / ml) were identified based on standard laboratory procedures. Antimicrobial susceptibility tests were carried out using various antimicrobial discs alongwith ceftriaxone on *E.coli* and *K. pneumoniae* isolates by Kirby Bauer disc diffusion method as per the recommendations of CLSI. On initial screening with ceftriaxone (30 µg) disc showing resistance was then confirmed for ESBL production by phenotypic confirmatory disc diffusion test (PCDDT) using ceftazidime (30 µg) and ceftazidime + clavulanic acid (30 µg + 10µg) disc as per guidelines of CLSI (2011).

Results: Out of a total of 6308 MSU specimens investigated for significant bacteriuria, *E.coli* isolates were 444 (7.04%) and *K.pneumoniae* were 145 (2.3%) making a total of 589 (9.34%). Initial screening with ceftriaxone disc revealed 155 isolates of *E.coli* and 70 isolates of *K.pneumoniae* to be resistant. Further testing by PCDDT method showed 60/444 (=13.51%) of *E. coli* and 24/145 (=16.55%) of *K. pneumoniae* isolates to be confirmed ESBL producers. These ESBL – producer uropathogens showed high degree of resistance to ceftriaxone (100.0%), amoxicillin, fluoroquinolones and co-trimoxazole.

Conclusion: An emerging and moderately high prevalence of ESBL-producing *E. coli* and *K. pneumoniae* was observed and confirmed in the urinary isolates investigated. It is essential to have a regular and routine monitoring of ESBL producing clinical isolates in laboratory practice.

Keywords: Antimicrobial resistance, Extended spectrum beta lactamase (ESBL), *Escherichia coli*, *Klebsiella pneumoniae*, Mid stream urine (MSU), Prevalence, Urinary isolates

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Background

Antimicrobial resistance among bacterial strains is an emerging problem, worldwide. Urinary tract infections (UTIs) are one of the most common bacterial infections in humans both in the community and the hospital settings [1-3]. *Escherichia coli* and *Klebsiella pneumoniae* are the two pre-dominant pathogens commonly isolated in urine. These uropathogens have also developed resistance to commonly prescribed antimicrobial agents, This severely limits the treatment options of an effective therapy.

Primarily, these uropathogens exerts their antimicrobial resistance against beta-lactams by producing extended spectrum beta-lactamases (ESBLs) enzymes that confers bacterial resistance to all beta-lactams except carbapenems, cephamycins and clavulanic acid [4-6]. ESBLs are class A beta-lactamases, and are plasmid-mediated enzymes that hydrolyze oxyimino-cephalosporins and monobactams, with various genotypes such as SHV, TEM, CTX-M, VEB, PER, BEL-1, BES-1, TLA and IBC [7,8]. Further, plasmids carrying ESBLs are transferable from one bacterial strain to the next and between different bacterial species [8]. ESBLs are clinically significant and when detected, indicate the need for the use of appropriate antibacterial agents. The mortality rate in misdiagnosed patients with ESBLs producing UTIs have ranged from 42-100% [9-11]. Antibacterial choice is often complicated by multi-resistance. There is an increasing association between ESBL production and fluoroquinolone resistance [12,13] and aminoglycoside resistance [14]. Multi-drug resistance (MDR) among ESBL expressing strains is complex and is influenced by the location of resistance genes on integrons that possess promoters that drive the co-ordinated expression of downstream resistance cassettes [15]. Thus, multi-resistance has severely limited the treatment options for ESBLs producing strains of Enterobacteriaceae. More recently, the emergence of carbapenem resistance has been reported among ESBL producing organisms [8].

The prevalence of bacteria producing ESBLs varies world-wide, with reports from North America, Europe, South America, Africa and Asia [16-18]. There is ample evidence to suggest the spread of ESBL infections is higher in resource poor countries [19,20].

Limited number of studies had been reported in this regard from Nepal [21-23]. This study was thus designed to estimate the current prevalence and antimicrobial resistance patterns among ESBL producing urinary isolates of *E.coli* and *K.pneumoniae* in a centrally located tertiary care centre in Kathmandu valley, Nepal.

Methods

Setting

This investigation was carried out in the Department of Microbiology, Kathmandu Medical College Teaching

Hospital (affiliate Kathmandu University), a tertiary healthcare facility centrally located in the capital city of Kathmandu, Nepal. Ethical approval was not required to carry out this work as the bacterial isolates were collected as part of standard patient care investigation.

Specimens

Between 1st September 2011 and 31st May 2012, 6308 consecutive and non-duplicate mid-stream urine specimens were collected aseptically from clinically suspected patients of UTIs attending outpatient and inpatient departments (medicine, surgery, paediatrics and gynecology and obstetrics) of the hospital. Urine specimens were transported to the Department of Microbiology laboratory and processed immediately.

Inclusion criteria

Patients who did not have a course of antibiotics at least two weeks prior to selection in the study.

Identification of isolates

The urine sample was cultured on to MacConkey agar and blood agar plates and incubated at 37°C for 24 hours and the colonies identified based on morphology and gram negative bacilli isolated were characterized by performing gram's staining, motility and standard biochemical tests [24].

Anti-microbial susceptibility testing

E.coli and *K. pneumoniae* isolates were selected to determine their susceptibility patterns against the first line antimicrobial agents, by the disc diffusion method of Kirby- Bauer as described by Clinical Laboratory Standards Institute (CLSI) [25]. The antimicrobial agents used were: amikacin (30 µg), gentamicin (10 µg), ofloxacin (5 µg), norfloxacin (10 µg), nitrofurantoin (300 µg), amoxicillin (10 µg), nalidixic acid (30 µg), co-trimoxazole (1.25/23.75 µg) and ceftriaxone (30 µg).

Screening of ESBL producing strains of *E.coli* and *K.pneumoniae*

Strains showing zone of inhibition of ≤ 25 mm for ceftriaxone were selected for confirmation test of ESBL, according to guidelines of CLSI [25].

Phenotypic Confirmatory Disc Diffusion Test (PCDDT) for ESBL

The potential ESBL producing strains of *E.coli* and *K.pneumoniae* were confirmed for ESBL production by phenotypic test. Briefly, a lawn culture of the isolated bacteria on Mueller Hinton agar (MHA) was made and ceftazidime (30 µg) and the combination disc ceftazidime + clavulanic acid (30 µg + 10 µg) was placed with 25 mm apart. An increase of ≥ 5 mm in zone of inhibition for

ceftazidime + clavulanic acid compared to ceftazidime alone was confirmed as ESBL producing strains, as per recommendations of CLSI [25]. ESBL positive strains of *E.coli* and *K. pneumoniae* were selected to determine their susceptibility patterns against the second line of antimicrobial agent (imipenem –10 µg), by the disc diffusion method of Kirby- Bauer as described by the CLSI [25]. The antimicrobial agents disc were obtained from Hi-Media Laboratories Pvt. Ltd., Mumbai, India. *E.coli* ATCC 25922 (ESBL negative) and *K.pneumoniae* ATCC 700603 (ESBL positive) were used as controls throughout the study.

All data were analyzed using SPSS statistical software (SPSS Inc., Chicago, IL).

Results

Out of a total of 6308 mid-stream urine specimens screened for significant bacteriuria, a total of 444 (7.03%) and 145 (2.29%) isolates of *E.coli* and *K.pneumoniae* were confirmed, respectively. Initial screening of these isolates for ESBL production showed 155/ 444 of *E.coli* and 70/ 145 of *K.pneumoniae* strains to be ceftriaxone resistant. Confirmation test (PCDDT) revealed 60/444 (13.51%) of *E.coli* and 24/145 (16.55%) of *K.pneumoniae* isolates to be ESBL positive (Table 1). A high rate of non-ESBL mediated ceftriaxone resistance was observed i.e. (95/155 = 63.33%) for *E.coli* and (46/70 = 65.71%) for *K.pneumoniae* isolates.

The age varied from 7 months to 72 years and the sex ratio male:female was (1:2), of the patients from whom *E.coli* was isolated. The age range was 17 years to 70 years and the sex ratio male:female was (1:2.4) of the patients from whom *K.pneumoniae* was isolated. Clearly, the female group constituted the majority of the patients (Table 2).

A wide spectrum of resistance patterns to various antimicrobial agents was shown by the ESBL positive *E.coli* and *K.pneumoniae* strains. These *E.coli* strains showed a high degree of resistance (> 80%-95%) to ofloxacin, norfloxacin, co-trimoxazole, nalidixic acid and amoxicillin. The *E.coli* strains were much less resistant to gentamicin (23.33%), nitrofurantoin (11.66%) and least resistant to amikacin (6.66%).

K.pneumoniae isolates were maximally resistant (100%) to amoxicillin. A moderately high resistance of 66.66%, 58.33% and 45.83% were shown to nalidixic acid, co-trimoxazole and gentamicin, respectively by these

Table 2 Age groups and sex-wise details of patients with ESBL positive *E.coli* and ESBL positive *K.pneumoniae* isolates

Age group (years)	ESBL positive <i>E.coli</i>			ESBL positive <i>K.pneumoniae</i>		
	M	F	Total	M	F	Total
< 15	6	2	8	0	0	0
16-30	2	20	22	2	10	12
31-45	8	10	18	1	1	2
46-60	2	2	4	2	2	4
>60	6	2	8	4	2	6
Total	24	36	60	9	15	24

K. pneumoniae strains. Moderate resistance of 37.5% and 29.16% were shown toward the fluoroquinolone drugs norfloxacin and ofloxacin. Nitrofurantoin (20.83% resistance) and amikacin (12.5% resistance) were the most effective antimicrobial agents against ESBL producing *K.pneumoniae* isolates. All the *E.coli* and *K.pneumoniae* isolates were susceptible (100%) to the carbapenem, imipenem (Table 3).

A high multi-drug resistance (defined as resistant to ≥ 3 different classes of antimicrobial agents) of 91.66% and 87.5% respectively was observed among the ESBL producing strains of *E.coli* and *K.pneumoniae*. None of the strains of ESBL positive *E.coli* and *K.pneumoniae* were found to be sensitive to all the antimicrobial agents tested (Table 4).

Discussion

There is a paucity of documented literature on investigation of ESBLs producing uropathogens from Nepal [23]. To the best of our knowledge this is the first report from Nepal with an exclusive focus on investigating the current prevalence and antimicrobial susceptibility patterns among ESBL producing *E. coli* and *K. pneumoniae* – the predominant uropathogens, globally. The urine culture positivity rate was 9.32% (*E.coli* =7.03% and *K.pneumoniae* = 2.29%), which was low compared to that reported from South Africa (51%) [26]. Nicaragua (30%) [27] and India (39%) [28]. ESBL production was more prevalent in *K.pneumoniae* strains, as compared to that in *E.coli* strains, which agrees with findings reported in previous studies [13,29]. The occurrence of ESBLs among clinical isolates vary greatly worldwide and geographically and are rapidly

Table 1 ESBL pattern of *E.coli* and *Klebsiella pneumoniae* isolated from urine specimens

Bacterial sp. isolated	No. of isolates obtained / total bacterial specimens screened (%)	No. of screened and selected isolates for ESBL confirmatory test (ceftriaxone resistant)	No. of isolates confirmed by PCDDT / No. of isolates obtained (%)
<i>E.coli</i>	444/6308 (7.03)	155	60 /444 (13.51)
<i>K.pneumoniae</i>	145/6308 (2.29)	70	24 /145 (16.55)

Table 3 Antimicrobial resistance patterns of confirmed ESBL producing *E.coli* and *K.pneumoniae* isolates from urine specimens

Antibiotic	ESBL positive <i>E.coli</i> (n = 60) T/ R (%)	ESBL positive <i>K.pneumoniae</i> (n = 24) T/R (%)
Amikacin	60/04 (6.66)	24/3 (12.5)
Gentamicin	60/14 (23.33)	24/11 (45.83)
Ofloxacin	60/49 (81.66)	24/07 (29.16)
Norfloxacin	60/54 (90.0)	24/9 (37.5)
Nitrofurantoin	60/07 (11.66)	24/05 (20.83)
Amoxycillin	60/57 (95.0)	24/24 (100.0)
Nalidixic acid	60/57 (95.0)	24/16 (66.66)
Co-trimoxazole	60/51 (85.0)	24/14 (58.33)
Ceftriaxone	60/60 (100.0)	24/24 (100.0)
Ceftazidime	60/60 (100.0)	24/24 (100.0)
Imipenem	60/0 (0.0)	24/0 (0.0)

T = Total no. of isolates tested; R = No. of isolates resistant.

changing overtime. ESBL prevalence was 29.86% (*E.coli* = 13.51% and *K.pneumoniae* = 16.55%). It was low as compared to a study done in India [30], which reported nearly 40% of urinary isolates of *E.coli* and *K.pneumoniae* were ESBL positive. The highest isolation rate of ESBLs producing *K.pneumoniae* had been reported from the Latin America (54.4%), the western Pacific (24.6%) and Europe (22.6%). The frequency of ESBL producing *E.coli* in these areas was reported to be 8.5%, 7.8% and 5.3%, respectively [31]. Females showed a higher rate of isolation of ESBL producing *E.coli* (60%) and *K.pneumoniae* (62.5%), which parallels the findings as reported earlier [32,33]. This study revealed a higher occurrence of ESBL producing uropathogens in the adult age group of 16–45 years, which is similar to that reported in a study done in Pakistan [1].

The high rates for non – ESBL mediated ceftriaxone resistant *E.coli* (63.33%) and *K.pneumoniae* (65.71%) isolates may be due to their different mechanisms for resistance such as the production of ampC β lactamase, metallo-betalactamase, etc. [34]. This further limits the therapeutic options available to treat these infections.

Table 4 Antimicrobial resistance patterns among ESBL positive *E.coli* and ESBL positive *K.pneumoniae* urine isolates

ESBL positive <i>E.coli</i> isolates no. (%)	ESBL positive <i>K.pneumoniae</i> isolates no. (%)	Resistance to no. of classes of antibiotics tested
0	0	0
0	0	1
5 (8.34)	3 (12.5)	2
55(91.66)	21 (87.5)	≥3

The susceptibility patterns of the ESBL producing *E.coli* and *K. pneumoniae* varied widely with the class of antimicrobial agents used. All isolates were uniformly resistant (100%) to the third generation cephalosporin, ceftriaxone. All ESBL positive *K.pneumoniae* strains were resistant (100%) to amoxicillin, while resistance rate for ESBL positive *E.coli* was 95%. In a study reported from Madagascar [35], 80% of the *E.coli* isolates were resistant to amoxicillin. In our study *E.coli* showed a high resistance rate (85%) to co-trimoxazole where as the *K.pneumoniae* showed resistance rate (58.33%) to co-trimoxazole. A comparable resistance rate of 80% and 45% to co-trimoxazole was shown among ESBL producing *E.coli* and *K.pneumoniae* isolates in a study conducted in Iran [36]. A striking feature in this study was that the quinolones, ofloxacin, norfloxacin and nalidixic acid demonstrated a high resistance varying from > 80% to 95% among ESBL positive *E.coli*, while 29.16% to 66.66% of *K. pneumoniae* were resistant. This parallels with the findings of the studies done in Indore, India [37] and Bangladesh [38]. A lower resistance rates varying from 24% to 44% to norfloxacin had been reported in European countries [39]. This probably reflects a better management of these clinically significant infections in resource-rich countries.

Conversely, this study revealed resistance rates of 45.83% and 12.5% to the aminoglycosides, gentamicin and amikacin by ESBL positive *K.pneumoniae* strains. In comparison, *E.coli* shown a much low resistance rate - gentamicin (23.33%) and amikacin (6.66%). In contrast. *K. pneumoniae* showed resistance to gentamicin (69%) and amikacin (38%) while 59% and 33% resistance rates were shown by *E.coli* isolates in a study done in Indore, India [37]. A resistance rate of 46.7% to gentamicin was shown by *K.pneumoniae* isolates in a report from Karachi, Pakistan [40], which is similar to results in this study. This report supports that aminoglycosides have good activity against clinically important gram negative bacilli [41]. The resistance rates of ESBL positive *E.coli* and *K.pneumoniae* to nitrofurantoin were 11.66% and 20.83%, respectively. Parallel resistance rate (12%) by *E.coli* isolates was shown in a report from Indore, India [37].

A significant finding in this report was that aminoglycosides and nitrofurantoin proved to be the optimal drugs. This may be due to the restricted use of these drugs in our hospital setting and nitrofurantoin is usually reserved to be prescribed only in cases of UTIs since it is excreted and concentrated in urine. All ESBL positive *E.coli* and *K.pneumoniae* strains in this study were sensitive (100%) to imipenem. A very high MDR rates of 91.66% and 87.5% among ESBL positive *E.coli* and *K.pneumoniae* were obtained in this study. A comparable MDR rate of 83% among *E.coli* isolates was reported in a study done in Peshawar, Pakistan [1].

Nepal represents a unique geographical terrain with sparsely-populated areas mainly in hilly and mountainous regions, severely limited health-care resources and a low-income economy. And the health care facilities are concentrated in the capital city of Kathmandu and people come here for treatment, from far-flung areas of the country. These people may acquire pathogens and when they return to their native areas in villages, may act as carriers of drug resistant pathogens.

Multi-center studies involving major health-care facilities in other parts of the country are required to have a more clear picture of ESBL producing uropathogens. Further, molecular epidemiological studies of resistance genes among the uropathogens would provide us much needed details on bacterial clones circulating in this region.

Conclusion

This report documents the emergence and occurrence of ESBL producing *E.coli* and *K.pneumoniae* in urinary isolates in Nepal. A moderately high prevalence of ESBL producing *E.coli* and *K.pneumoniae* was observed and confirmed in the urinary isolates. A strict hospital infection control policies and a prudent anti-microbials use regimens are to be adopted by the physicians. It is essential and mandatory to have a regular and routine monitoring of ESBL producing clinical isolates in clinical laboratories.

Abbreviations

MSU: Mid stream urine; ESBL: Extended spectrum beta-lactamase; NCCLS: National committee on clinical laboratory standards; PCDDT: Phenotypic confirmatory disk diffusion test; CLSI: Clinical laboratory standards institute; UTIs: Urinary tract infections; MHA: Mueller Hinton Agar; MDR: Multi drug resistance.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AC did the interpretation, statistical analysis of data and drafted the manuscript. CDS has been involved in conception, design and acquisition of data. Both authors have read and approved the final manuscript.

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