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Retrospective Study

Antibiogram of Extended-spectrum Beta-lactamase (ESBL) and Non-ESBL Producers in Urinary Tract Infections in Children: A Six-year Retrospective Study

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Abstract

Objective: Urinary tract infection (UTI) is a common infection in children, due to the increased prevalence of antibiotic-resistant, extended-spectrum beta-lactamase (ESBL) and non-ESBL producers. Analyzing antibiotic sensitivity data and monitoring the changes in the susceptibility profiles is crucial for accurate diagnosis and treatment. This study aimed to retrospective analyze *in vitro* susceptibility profiles of gram-negative bacteria isolated in urine samples in a single institution.

Methods: Antibiotic sensitivity data were collected retrospectively from 1372 patients, aged 0-19 years, who were suffering from UTI. Data was analyzed for the prevalence of ESBL and non-ESBL producers. Wilcoxon Rank Sum Test, Chi-square test and odds ratios were used to compare the mean age, find the association and relative odds of having infection. Cochran-Armitage test was used to analyze the trend of antibiotic susceptibility test (AST) pattern. p- value of <0.05 was considered as statistically significant.

Results: A significant difference in the mean age and association between sex and ESBL and non-ESBL UTIs were noted ($p < 0.05$). Out of 1417 bacterial isolates from 1372 urine samples, *E. coli* (84.12%), followed by *K. pneumoniae* (12.63%) were the most predominant. Imipenem, meropenem, and ertapenem along with amikacin and netilmicin were highly effective against the ESBL producers; however, an increased resistance towards imipenem and meropenem was noted against non-ESBL producers ($p < 0.001$).

Conclusion: Carbapenems were effective against ESBL producers, along with amikacin and netilmicin. A declining AST pattern was observed for majority of antibiotics, except gentamicin against non-ESBL producers, suggesting the need for the practice of antibiotic stewardship.

Keywords: Antimicrobial Stewardship; Carbapenems; Child; *Escherichia coli*

Introduction

Bacterial pathogens, such as *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*), are frequently identified causative agents of urinary tract infection (UTI) and are significantly associated with morbidity and mortality in pediatric patients [1,2]. It has been reported that nearly 2.6-3.4% children are affected by

UTI in the United States and out of which 2% are boys and 8% are girls throughout their childhood [3]. UTI incidences among Indian pediatric population ranges from 9.46-20.74% [4,5]. Antibiotics are routinely used to eradicate these bacteria; however, exploitation of these antibiotics has led to an increased bacterial resistance, which has become a major concern, across the world.[2] The increased prevalence of extended-spectrum beta-lactamase (ESBL) producers has made the management of gram-negative infections more challenging in the last few years with additional challenges of ineffectiveness of common antibiotics, such as ampicillin and amoxicillin along with cephalosporins to cure ESBL infections [6-8].

A range of antibiotics and their combinations, such as piperacillin-tazobactam, and cefoperazone-sulbactam, are used to combat UTI, caused by either ESBL or non-ESBL producers [9,10]. Hence, critical evaluation of the bacterial UTI along with monitoring their antibiotic susceptibility test (AST) trend is important for providing proper patient care through appropriate antibiotic treatment to treat the infection successfully, thereby improving patient's quality of life, and reducing morbidity and mortality.

Many researchers have analyzed the changing trend of bacterial infections and their respective antimicrobial susceptibility profiles in different clinical conditions, including UTI [7,11,12]. Therefore, a retrospective trend analysis can provide valuable information regarding the current resistance pattern of bacteria causing UTI. It can also be helpful to choose the best possible range of antibiotics or their combinations for devising improved treatment plans in pediatric patients [11,12].

Hence, the primary aim of this study was to retrospective analyze *in vitro* susceptibility profiles of gram-negative bacteria isolated in urine samples in a single institution. The study also assessed the varying degree of effectiveness of drugs for each strain of bacteria by utilizing the effective data analysis strategy in 2013-18 period.

Materials and Methods

A retrospective study was carried out to analyze the AST pattern in suspected cases of UTI in pediatric patients from 2013-2018 at a tertiary care hospital in Bangalore, Karnataka, India. Patients aged 0-19 years with culture proven UTI were included in this study. Those patients with congenital abnormality of the urinary tract were excluded from this study.

Data with respect to demographics, culture, and sensitivity reports were collected from medical records of the 1372 patients by anonymizing the data. Hence, prior institutional ethical approval and signed consent form from the patients and parents or guardians were not required. The patients were grouped as per their age such as <1 month, 1 month - 1 year, 1 year - 10 years, >10 years. Urine samples showing single organism or mixed culture growth of two organisms were included in the present study. The patients were clinically diagnosed for fever or clinical symptoms of UTI (increased frequency, urgency, burning sensation, cloudy or strong-smelling urine, blood in urine etc.). Dipstick and urine microscopy was used as screening method for urine collection [13]. Clean-catch mid-stream urine samples were collected in a sterile container and examined without delay for culture and antibiotic sensitivity. Urine samples were cultured under aseptic conditions on MacConkey's agar and 5% sheep blood agar and organisms were identified with the help of Gram-staining and biochemical methods [14]. One culture per patient was considered. Double disc and Kirby-Bauer disk diffusion methods were used for screening and antibiotic sensitivity determination of ESBL and non-ESBL, as per Clinical and Laboratory Standard Institute (CLSI) guidelines [15,16].

To determine the AST patterns of ESBL-producing organisms, the different antibiotics tested were beta-lactams (ampicillin and aztreonam), beta-lactams/beta-lactamase inhibitors (amoxicillin-clavulanic acid and piperacillin-tazobactam), sulfonamides (trimethoprim-sulfamethoxazole), quinolones (norfloxacin), fluoroquinolones (ciprofloxacin and ofloxacin), nitrofuran (nitrofurantoin), aminoglycosides (gentamicin, amikacin, netilmicin and tobramycin), first generation cephalosporins (cephalexin), second generation cephalosporins (cefuroxime), third generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime and cefoperazone), fourth generation cephalosporins (cefepime), third generation cephalosporins/beta-lactamase inhibitors (cefoperazone-sulbactam) and carbapenem (imipenem, meropenem, ertapenem). However, polymyxin E (colistin, last-resort for multidrug-resistant Gram-negative infections) was additionally used along with the above-mentioned antibiotics to determine the AST patterns of non-ESBL producing organisms. The cultures exhibiting intermediate sensitivity value were excluded from further analysis. Determining AST patterns for other non-ESBL producers, such as *M. morganii, P. vulgaris, P. mirabilis*, and *C. koseri* was difficult due to fewer numbers of isolates; hence, they were not included for further analysis.

All the antibiotic discs were purchased from HiMedia Pvt. Ltd., India.

R v. 3.6.0 was used for data analysis and results were presented as frequency and percentage. However, percentage effectiveness of each antibiotic against each type of bacteria was calculated by dividing the sensitive isolates of each type of bacteria by the total number of isolates for a particular year. Wilcoxon Rank Sum Test and Chi-square tests were used to compare the mean age and association between ESBL and non-ESBL producers. The relative odds of occurrence of ESBL and non-ESBL infection among patients were calculated using odds ratios with 95% confidence interval (CI). Cochran-Armitage test was used to analyze trend for AST against the tested antibiotics. A p-value of <0.05 was considered as statistically significant.

Results

Total of 1417 bacteria were isolated from 1372 cases of UTI in pediatric patients. Age and sex distribution of the patients of ESBL and non-ESBL producers is presented in table 1. The patients' age varied from a few days to 19 years with female preponderance of 59.42%. The mean age of patients belonging to age group of 1 - 10 years was significantly different among patients suffering from ESBL and non-ESBL producing organism (3.89 ± 2.719 years vs. 4.38 ± 2.879 years; p = 0.014). There was a significant difference in the patients infected by ESBL and non-ESBL producing organisms (p = 0.0007) with respect to gender, with males getting1.44 times more prone to be infected with ESBL producer than females (95% CI: 1.16-1.8). The emergence trends of ESBL and non-ESBL producers from 2013-2018 showed a higher percentage of EC among both ESBL (46.15%) and non-ESBL producers (37.97%), followed by *K. pneumoniae* (ESBL producer: 4.94% and non-ESBL producer: 7.69%), as shown in table 2. Detailed distribution of microorganism is shown in Table 2 both for ESBL and non-ESBL.

The antibiotics sensitivity patterns for ESBL and non-ESBL producers are tabulated in tables 3 and 4, respectively. A statistically significant decrease in the antibiotic sensitivity among non-

Characteristics of Patients		ESBL	Non-ESBL	p-value
Age ¥	<1 month	21.9 ± 6.385	17.43 ± 9.541	0.318
	1 month - 1 year	6.05 ± 2.966	6.29 ± 3.027	0.467
	1 year - 10 years	3.89 ± 2.719	4.38 ± 2.879	0.014*
	>10 years	15.24 ± 2.566	15.27 ± 2.496	0.961
Sex £	Female	403 (55.13)	439 (63.99)	0.0007**
	Male	328 (44.87)	247 (36.01)	

Note: ESBL: Extended-Spectrum Beta Lactamase.

¥ Data was presented as mean ± Standards deviation and Wilcoxon Rank Sum Test was used for analysis.

£ Data was presented as frequency (%) and Chi-square test was used for analysis.

* and ** indicates statistically significant value of <0.05 and <0.01, respectively.

Table 1: Demographic distribution of patients with ESBL and Non-ESBL producers.

Pathogen Isolated	Number of organisms, (n = 1417)	
	ESBL n (%)	Non-ESBL n (%)
Escherichia coli	654 (46.15)	538 (37.97)
Klebsiella pneumoniae	70 (4.94)	109 (7.69)
Citrobacter koseri	0 (0)	2 (0.14)
Morganella morganii	0 (0)	2 (0.14)
Proteus mirabilis	5 (0.35)	24 (1.69)
Proteus vulgaris	1 (0.07)	2 (0.14)
Enterobacter cloacae	0 (0)	3 (0.21)
Enterobacter species	0 (0)	0 (0)
Klebsiella oxytoca	0 (0)	3 (0.21)
Klebsiella ozaenae	1 (0.07)	2 (0.14)
Total	731 (51.59)	686 (48.41)

Note: ESBL: Extended-Spectrum Beta Lactamase

Table 2: Prevalence of ESBL and Non-ESBL producers among pediatric population.

ESBL producers was noted against all tested antibiotics, except trimethoprim-sulfamethoxazole, ciprofloxacin, ofloxacin, and nitrofurantoin over the period of six years from 2013-2018 (p value: <0.05, Table 4). On the contrary, a statistically insignificant trend towards antibiotic sensitivity was noticed among ESBL producers from 2013-2018 (p value: >0.05).

Antibiotics	Number of Susceptible Isolates, (N = 731) n (%)						
	2013	2014	2015	2016	2017	2018	p- value
AM	0	0	0	0	0	0	—
A/C	19 (13.39)	33 (19.08)	16 (12.13)	27 (24.11)	25 (24.04)	14 (20.59)	0.96
CN	1 (0.71)	0	0	0	0	0	—
XM	1 (0.71)	1 (0.58)	0	0	0	1 (1.48)	—
T/S	45 (31.7)	67 (38.73)	42 (31.82)	33 (29.47)	40 (38.47)	28 (41.18)	0.8
NX	15 (10.57)	36 (20.81)	13 (9.85)	21 (18.75)	28 (26.93)	23 (33.83)	1.00
Cp	15 (10.57)	37 (21.39)	13 (9.85)	21 (18.75)	28 (26.93)	22 (32.36)	0.99
OF	21 (14.79)	49 (28.33)	20 (15.16)	26 (23.22)	32 (30.77)	26 (38.24)	0.99
NI	88 (61.98)	99 (57.23)	86 (65.16)	80 (71.43)	79 (75.97)	48 (70.59)	0.96
Gm	62 (43.67)	79 (45.67)	59 (44.7)	57 (50.9)	61 (58.66)	40 (58.83)	0.99
Ak	136 (95.78)	162 (93.65)	124 (93.94)	108 (96.43)	99 (95.2)	61 (89.71)	0.37
Nt	137 (96.48)	162 (93.65)	125 (94.7)	108 (96.43)	100 (96.16)	62 (91.18)	0.35
TM	38 (26.77)	78 (45.09)	55 (41.67)	63 (56.25)	61 (58.66)	36 (52.95)	1.00
XM (P)	1 (0.71)	0	1 (0.76)	0	0	1 (1.48)	—
C/C	1 (0.71)	0	0	0	0	0	—
TZ	1 (0.71)	0	0	0	0	0	—
CPZ	2 (1.41)	0	0	0	0	0	—
PM	4 (2.82)	3 (1.74)	0	0	0	0	—
P/T	113 (79.58)	127 (73.42)	96 (72.73)	93 (83.04)	87 (83.66)	50 (73.53)	0.87
C/S	135 (95.08)	166 (95.96)	116 (87.88)	106 (94.65)	99 (95.2)	64 (94.12)	0.20
IP	141 (99.3)	169 (97.69)	126 (95.46)	112 (100)	103 (99.04)	67 (98.53)	0.72
MP	141 (99.3)	169 (97.69)	126 (95.46)	112 (100)	103 (99.04)	67 (98.53)	0.71
Etp	115 (80.99)	124 (71.68)	106 (80.31)	108 (96.43)	96 (92.31)	63 (92.65)	0.23
AT	1 (0.71)	0	0	0	0	0	—

Note: A/C: Amoxicillin-clavulanic acid; Ak: Amikacin; AM: Ampicillin; AT: Aztreonam; C/C: Cefotaxime/Ceftriaxone; CN: Cephalexin; Cp: Ciprofloxacin; CPZ: Cefoperazone; C/S: Cefoperazone-Sulbactam; ESBL: extended-spectrum beta lactamase; Etp: Ertapenem; Gm: Gentamicin; IP: Imipenem; MP: Meropenem; NI: Nitrofurantoin; Nt: Netilmicin; NX: Norfloxacin; OF: Ofloxacin; PM: Cefepime; P/T: Piperacillin-tazobactam; TM: Tobramycin; T/S: Trimethoprim-sulfamethoxazole; TZ: Ceftazidime; XM: Cefuroxime.

'0' and '-' indicates resistant against antibiotic and values could not be determined, respectively. 'P' indicates parenteral.

Cochran-Armitage test was used to determine significant value.

Table 3: Antibiotic sensitivity pattern for ESBL producers from 2013-2018.

Antibiotics	Number of Susceptible Isolates, (N = 686) n (%)						
	2013	2014	2015	2016	2017	2018	P value
AM	30 (23.26)	32 (21.2)	32 (26.02)	25 (25.52)	19 (15.97)	9 (13.64)	0.03*
A/C	73 (56.59)	78 (51.66)	65 (52.85)	50 (51.03)	44 (36.98)	21 (31.82)	<0.001***
CN	65 (50.39)	85 (56.3)	64 (52.04)	44 (44.9)	32 (26.9)	0	—
XM	83 (64.35)	71 (47.02)	70 (56.92)	56 (57.15)	61 (51.27)	28 (42.43)	0.001**
T/S	76 (58.92)	86 (56.96)	74 (60.17)	62 (63.27)	67 (56.31)	32 (48.49)	0.3
NX	85 (65.9)	98 (64.91)	84 (68.3)	63 (64.29)	75 (63.03)	33 (50)	0.06
Cp	88 (68.22)	98 (64.91)	84 (68.3)	63 (64.29)	77 (64.71)	33 (50)	0.05
OF	88 (68.22)	101 (66.89)	83 (67.48)	70 (71.43)	79 (66.39)	39 (59.1)	0.13
NI	84 (65.12)	89 (58.95)	87 (70.74)	60 (61.23)	78 (65.55)	43 (65.16)	0.50
GM	111 (86.05)	128 (84.77)	109 (88.62)	88 (89.8)	96 (80.68)	45 (68.19)	0.003**
Ak	92 (71.32)	127 (84.11)	97 (78.87)	70 (71.43)	80 (67.23)	32 (48.49)	<0.001***
Nt	92 (71.32)	127 (84.11)	99 (80.49)	70 (71.43)	80 (67.23)	32 (48.49)	<0.001***
TM	80 (62.02)	111 (73.51)	88 (71.55)	66 (67.35)	72 (60.51)	25 (37.88)	0.002**
XM (P)	95 (73.65)	80 (52.99)	83 (67.48)	66 (67.35)	81 (68.07)	35 (53.04)	0.007**
C/C	83 (64.35)	108 (71.53)	77 (62.61)	58 (59.19)	72 (60.51)	17 (25.76)	<0.001***
TZ	83 (64.35)	108 (71.53)	77 (62.61)	59 (60.21)	71 (59.67)	17 (25.76)	<0.001***
CPZ	83 (64.35)	107 (70.87)	77 (62.61)	58 (59.19)	35 (29.42)	8 (12.13)	<0.001***
PM	83 (64.35)	110 (72.85)	78 (63.42)	59 (60.21)	73 (61.35)	18 (27.28)	<0.001***
P/T	86 (66.67)	108 (71.53)	80 (65.05)	59 (60.21)	75 (63.03)	20 (30.31)	<0.001***
C/S	88 (68.22)	120 (79.48)	87 (70.74)	63 (64.29)	79 (66.39)	23 (34.85)	<0.001***
IP	93 (72.1)	124 (82.12)	99 (80.49)	69 (70.41)	80 (67.23)	29 (43.94)	<0.001***
MP	93 (72.1)	124 (82.12)	98 (79.68)	69 (70.41)	81 (68.07)	30 (45.46)	<0.001***
Etp	82 (63.57)	77 (51)	67 (54.48)	62 (63.27)	76 (63.87)	27 (40.91)	<0.001***
AT	84 (65.12)	108 (71.53)	77 (62.61)	59 (60.21)	71 (59.67)	17 (25.76)	<0.001***
CT	3 (2.33)	13 (8.61)	9 (7.32)	5 (5.11)	11 (9.25)	0	—

Note: A/C: Amoxicillin—clavulanic acid; Ak: Amikacin; AM: Ampicillin; AT: Aztreonam; C/C: cefotaxime/ceftriaxone; Cp: Ciprofloxacin; CPZ: Cefoperazone; CN: Cephalexin; C/S: Cefoperazone-Sulbactam; CT: Colistin; ESBL: Extended-Spectrum Beta Lactamase; Etp: Ertapenem; Gm: Gentamicin; IP: Imipenem; MP: Meropenem; NI: Nitrofurantoin; NX: Norfloxacin; OF: Ofloxacin; PM: Cefepime; P/T: Piperacillin-tazobactam; TM: Tobramycin; T/S: Trimethoprim-sulfamethoxazole; TZ: Ceftazidime; XM: Cefuroxime.

'0' and ' —' denotes resistant against antibiotic and values could not be determined, respectively; 'P' indicates parenteral.

Cochran-Armitage test was used to determine significant value.

*, ** and *** indicate statistically significant values with p value <0.05, <0.01 and <0.001, respectively.

Table 4: Antibiotic sensitivity pattern for non-ESBL producers from 2013-2018.

Among the different antibiotics, amikacin, netilmicin, imipenem, and meropenem demonstrated higher bactericidal properties towards *E. coli* (ESBL producer) with antibiotic sensitivity of 93.22%-100%, followed by cefoperazone-sulbactam (94.92%-95.31%) and piperacillin-tazobactam (76.27%-83.96%). However, the antibiotic sensitivities against KP (ESBL producer) were

found to be 61.54%-98.11% (amikacin and netilmicin), 69.23%-100% (imipenem and meropenem), 46.15%-95.28% (cefoperazone-sulbactam) and 15.38%-83.96% (piperacillin-tazobactam). In case of non-ESBL producers, only gentamicin demonstrated higher bactericidal properties, reported in terms of bacterial sensitivity, and recorded to be 75%-90.27%, 66.67%-100% and 60%-100% for *E. coli*, *K. pneumoniae* and *P. mirabilis*, respectively (Supplementary data: Table S-1 and 2). In 2013, non-ESBL producers were resistant (53.33%-74.07% sensitivity) against certain antibiotics, namely imipenem and meropenem as compared to ESBL producers (99.22%). Furthermore, imipenem and meropenem sensitivity against ESBL producers was observed to be more (100 % *vs.* 86%) than non-ESBL producers in 2014. Similar observation was noticed in 2015 as well, in addition to an increase in the resistance of ESBL organisms against imipenem and meropenem (86% *vs.* 81% sensitivity). Furthermore, the trend was higher in 2016, demonstrating a reduced activity against both *E. coli* and *K. pneumoniae*, indicating an increase in resistance patterns amongst non-ESBL producers till 2018, except in 2017 (excluding *E. coli*, following the similar pattern of increasing resistance).

Organ-isms	Number of organisms susceptible to antibiotic n (%)																						
	AM	A/C	CN	XM	T/S	NX	Cp	OF	NI	Gm	Ak	Nt	TM	XM (P)	C/C	TZ	CPZ	PM	P/T	C/S	IP	MP	Etp	AT
2013																								
E. coli	0	17 (13.28)	1 (0.78)	1 (0.78)	42 (32.81)	15 (11.7)	15 (11.7)	15 (11.72)	86 (67.19)	56 (43.75)	127 (99.22)	127 (99.22)	36 (28.13)	1 (0.78)	1 (0.78)	1 (0.78)	1 (0.78)	3 (2.34)	104 (81.25)	122 (95.31)	127 (99.22)	127 (99.22)	103 (80.47)	1 (0.78)
K. pneu-moniae	0	1 (7.69)	0	0	3 (23.08)	0	0	6 (46.15)	2 15.38)	5 (38.46)	9 (69.23)	9 (69.23)	2 (15.38)	0	0	0	1 (7.69)	1 (7.69)	8 (61.54)	12 (92.31)	13 (100.0)	13 (100.0)	12 (92.31)	0
PM	0	1 (100.0)	0	0	0	—	0	—	0	1 (100.0)	0	1 (100.0)	0	0	0	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	—	0
2014																								
E. coli	0	30 (20.0)	—	1 (0.67)	56 (37.33)	25 (16.67)	26 (17.33)	34 (22.67)	97 (64.67)	66 (44.0)	147 (98.0)	147 (98.0)	65 (43.33)	0	0	0	0	2 (1.33)	116 (77.33)	148 (98.67)	150.0 (100.0)	150.0 (100.0)	109 (72.67)	0
K. pneu-moniae	0	2 (10.0)	—	0	11 (55.0)	10 (50.0)	10 (50.0)	14 (70.0)	1 (5.0)	12 (60.0)	14 (70.0)	13 (65.0)	12 (60.0)	0	0	0	0	1 (5.0)	8 (40.0)	15 (75.0)	16 (80.0)	16 (80.0)	12 (60.0)	0
PM	0	0	—	0	0	0	0	0	—	—	0	1 (50.0)	0	0	0	0	0	0	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	0
KOz	0	1 (100.0)	—	0	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	0	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0
2015																								
E. coli	0	16 (13.56)	0	0	38 (32.20)	11 (9.32)	11 (9.32)	16 (13.56)	85 (72.03)	55 (46.61)	115 (97.46)	116 (98.31)	52 (44.07)	1 (0.85)	0	0	0	0	93 (78.81)	109 (92.37)	116 (98.31)	116 (98.31)	97 (82.20)	0
K. pneu-moniae	0	0	0	0	3 (23.08)	2 (15.38)	2 (15.38)	4 (30.77)	1 (7.69)	3 (23.08)	8 (61.54)	8 (61.54)	2 (15.38)	0	0	0	0	0	2 (15.38)	6 (46.15)	9 (69.23)	9 (69.23)	8 (61.54)	0
PM	0	0	0	0	1 (100.0)	0	0	0	—	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	0	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0
2016																								
E. coli	0	27 (25.47)	0	0	33 (31.13)	21 (19.81)	21 (19.81)	22 (20.75)	80 (75.47)	55 (51.89)	104 (98.11)	104 (98.11)	61 (57.55)	0	0	0	0	0	89 (83.96)	101 (95.28)	106 (100.0)	106 (100.0)	102 (96.23)	0
K. pneu-moniae	0	0	0	0	0	0	0	4 (66.67)	0	2 (33.33)	4 (66.67)	4 (66.67)	2 (33.33)	0	0	0	0	0	4 (66.67)	5 (83.33)	6 (100.0)	6 (100.0)	6 (100.0)	0
2017																								
E. coli	0	25 (26.88)	0	0	38 (40.86)	24 (25.81)	24 (25.81)	26 (27.96)	78 (83.87)	59 (63.44)	90 (96.77)	91 (97.85)	59 (63.44)	0	0	0	0	0	78 (83.87)	89 (95.70)	93 (100.0)	93 (100.0)	88 (94.62)	0
K. pneu-moniae	0	0	0	0	2 (22.22)	2 (22.22)	2 (22.22)	4 (44.44)	1 (11.11)	1 (11.11)	8 (88.89)	8 (88.89)	1 (11.11)	0	0	0	0	0	7 (77.78)	8 (88.89)	8 (88.89)	8 (88.89)	7 (77.78)	0
PM	0	0	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	0	—	0	0	0	0	0	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	—	0
PV	0	0	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	0	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0
2018																								
E. coli	0	13 (22.03)	0	1 (1.69)	26 (44.07)	21 (35.59)	20 (33.90)	21 (35.59)	46 (77.97)	35 (59.32)	55 (93.22)	56 (94.92)	31 (52.54)	1 (1.69)	0	0	0	0	45 (76.27)	56 (94.92)	58 (98.31)	58 (98.31)	57 (96.61)	0
K. pneu-moniae	0	1 (11.11)	0	0	2 (22.22)	2 (22.22)	2 (22.22)	5 (55.56)	2 (22.22)	5 (55.56)	6 (66.67)	6 (66.67)	5 (55.56)	0	0	0	0	0	5 (55.56)	8 (88.89)	9 (100.0)	9 (100.0)	6 (66.67)	0

Note: AM: Ampicillin, A/C: Amoxicillin—clavulanic acid, CN: Cephalexin, XM: Cefuroxime, T/S: Trimethoprim—sulfamethoxazole, NX: Norfloxacin, Cp: Ciprofloxacin, OF: Ofloxacin, NI: Nitrofurantoin, Gm: Gentamicin, Ak: Amikacin, Nt: Netilmicin, TM: Tobramycin, C/C: Cefotaxime/Ceftriaxone, TZ: Ceftazidime, CPZ: Cefoperazone, PM: Cefepime, P/T: Piperacillin—tazobactam C/S: Cefoperazone+Sulbactam, IP: Imipenem, MP: Meropenem, Etp: Ertapenem, AT: Aztreonam.EC: *Escherichia coli*; KP: *Klebsiella pneumoniae*; PM: *Proteus mirabilis*; PV: *Proteus vulgaris*; KO: *Klebsiella oxytoca* and KOz: *Klebsiella ozaenae*

0, — and (P) indicates resistant, not tested and parenteral, respectively.

Table S-1: Emergence of EBSL producers from 2013-2018.

Organisms	Number of organisms susceptible to antibiotic n (%)																							
	AM	A/C	CN	XM	T/S	NX	Cp	OF	NI	Gm	Ak	Nt	TM	XM (P)	C/C	TZ	CPZ	PM	P/T	C/S	IP	MP	Etp	AT	CT
2013																									
E. coli	29 (26.85)	60 (55.56)	52 (48.15)	68 (62.96)	61 (56.48)	67 (62.04)	70 (64.81)	70 (64.81)	81 (75.0)	92 (85.19)	79 (73.15)	79 (73.15)	67 (62.04)	80 (74.07)	70 (64.81)	70 (64.81)	70 (64.81)	71 (65.74)	73 (67.59)	75 (69.44)	80 (74.07)	80 (74.07)	71 (65.74)	71 (65.74)	—
K. pneumoniae	0	9 (60.0)	8 (53.33)	10 (66.67)	11 (73.33)	12 (80.0)	12 (80.0)	12 (80.0)	1 (6.67)	13 (86.67)	8 (53.33)	8 (53.33)	8 (53.33)	10 (66.67)	8 (53.33)	8 (53.33)	8 (53.33)	8 (53.33)	8 (53.33)	8 (53.33)	8 (53.33)	8 (53.33)	8 (53.33)	8 (53.33)	3 (20.0)
CK	—	1 (50.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	1 (50.0)	1 (50.0)	1 (50.0)	2 (100.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	—
MM	—	0	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	—	1 (100.0)	—
PM	1 (50.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	0	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	1 (50.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	1 (50.0)	2 (100.0)	—
PV	—	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	—
2014																									
E. coli	31 (27.43)	67 (59.29)	64 (56.64)	56 (49.56)	64 (56.64)	74 (65.49)	74 (65.49)	74 (65.49)	85 (75.22)	102 (90.27)	99 (87.61)	99 (87.61)	89 (78.76)	64 (56.64)	83 (73.45)	83 (73.45)	83 (73.45)	85 (75.22)	82 (72.57)	94 (83.19)	98 (86.73)	98 (86.73)	59 (52.21)	83 (73.45)	5 (4.42)
K. pneumoniae	0	6 (22.22)	15 (55.56)	10 (37.04)	16 (59.26)	17 (62.96)	17 (62.96)	19 (70.37)	3 (11.11)	18 (66.67)	17 (62.96)	17 (62.96)	14 (51.85)	11 (40.74)	14 (51.85)	14 (51.85)	13 (48.15)	14 (51.85)	15 (55.56)	15 (55.56)	15 (55.56)	15 (55.56)	8 (29.63)	14 (51.85)	8 (29.6)
MM	—	0	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	0	0	1 (100.0)	1 (100.0)	0	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	—
PM	1 (20.0)	3 (60.0)	4 (80.0)	3 (60.0)	2 (40.0)	2 (40.0)	2 (40.0)	3 (60.0)	0	3 (60.0)	5 (100.0)	5 (100.0)	3 (60.0)	3 (60.0)	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	—
EnC	—	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	—	1 (100.0)	—
En. spp.	—	0	0	0	0	0	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	—
KO	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	—
KOz	0	1 (50.0)	1 (50.0)	1 (50.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	1 (50.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	1 (50.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	—
2015																									
E. coli	31 (31.31)	52 (52.53)	49 (49.49)	56 (56.57)	52 (52.53)	61 (61.62)	61 (61.62)	61 (61.62)	82 (82.83)	85 (85.86)	80 (80.81)	81 (81.82)	70 (70.71)	65 (65.66)	61 (61.62)	61 (61.62)	61 (61.62)	62 (62.63)	65 (65.66)	70 (70.71)	81 (81.82)	81 (81.82)	55 (55.56)	61 (61.62)	8 (8.08)
K. pneumoniae	0	10 (50.0)	12 (60.0)	11 (55.0)	19 (95.0)	19 (95.0)	19 (95.0)	19 (95.0)	5 (25.0)	20 (100.0)	15 (75.0)	16 (80.0)	16 (80.0)	15 (75.0)	15 (75.0)	15 (75.0)	15 (75.0)	15 (75.0)	14 (70.0)	16 (80.0)	16 (80.0)	15 (75.0)	11 (55.0)	15 (75.0)	1 (5.0)
PM	1 (50.0)	2 (100.0)	2 (100.0)	2 (100.0)	1 (50.0)	2 (100.0)	2 (100.0)	1 (50.0)	0	2 (100.0)	1 (50.0)	1 (50.0)	1 (50.0)	2 (100.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	—
EnC	0	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	0	0	0	0	0	0	1 (100.0)	1 (100.0)	0	0	—
KO	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	—	—	—	1 (100.0)	—	—	—	—	—	—	—	—	—	—	—
2016																									
EC	21 (27.63)	38 (50.0)	29 (38.16)	41 (53.95)	44 (57.89)	44 (57.89)	44 (57.89)	51 (67.11)	55 (72.37)	68 (89.47)	58 (76.32)	58 (76.32)	54 (71.05)	50.0 (65.79)	47 (61.84)	48 (63.16)	48 (63.16)	49 (64.47)	48 (63.16)	52 (68.42)	58 (76.32)	58 (76.32)	51 (67.11)	48 (63.16)	3 (3.95)
E. coli	0	8 (47.06)	11 (64.71)	11 (64.71)	13 (76.47)	14 (82.35)	14 (82.35)	14 (82.35)	5 (29.41)	15 (88.24)	10 (58.82)	10 (58.82)	10 (58.82)	12 (70.59)	9 (52.94)	9 (52.94)	9 (52.94)	8 (47.06)	9 (52.94)	9 (52.94)	9 (52.94)	9 (52.94)	9 (52.94)	9 (52.94)	2 (11.76)
PM	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	0	4 (100.0)	1 (25.0)	1 (25.0)	1 (25.0)	4 (100.0)	1 (25.0)	1 (25.0)	—	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	—
EnC	0	0	0	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	—
2017																									
EC	17 (18.89)	33 (36.67)	21 (23.33)	45 (50.0)	50 (55.56)	53 (58.89)	55 (61.11)	56 (62.22)	72 (80.0)	73 (81.11)	61 (67.78)	61 (67.78)	54 (60.0)	60 (66.67)	54 (60.0)	54 (60.0)	30 (33.33)	55 (61.11)	57 (63.33)	61 (67.78)	61 (67.78)	62 (68.89)	59 (65.56)	53 (58.89)	8 (8.89)
K. pneumoniae	—	3 (15.79)	3 (15.79)	7 (36.84)	11 (57.89)	13 (68.42)	13 (68.42)	13 (68.42)	5 (26.32)	13 (68.42)	12 (63.16)	12 (63.16)	11 (57.89)	11 (57.89)	11 (57.89)	10 (52.63)	1 (5.26)	11 (57.89)	11 (57.89)	11 (57.89)	12 (63.16)	12 (63.16)	12 (63.16)	11 (57.89)	3 (15.79)
PM	2 (22.22)	7 (77.78)	7 (77.78)	8 (88.89)	5 (55.56)	8 (88.89)	8 (88.89)	9 (100.0)	0	9 (100.0)	6 (66.67)	6 (66.67)	6 (66.67)	9 (100.0)	6 (66.67)	6 (66.67)	4 (44.44)	6 (66.67)	6 (66.67)	6 (66.67)	6 (66.67)	6 (66.67)	4 (44.44)	6 (66.67)	—
KO	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	—	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	—
2018																									
E. coli	9 (17.31)	16 (30.77)	—	22 (42.31)	27 (51.92)	27 (51.92)	27 (51.92)	30 (57.69)	41 (78.85)	39 (75.0)	29 (55.77)	29 (55.77)	23 (44.23)	29 (55.77)	15 (28.85)	15 (28.85)	8 (15.38)	16 (30.77)	18 (34.62)	21 (40.38)	27 (51.92)	28 (53.85)	25 (48.08)	15 (28.85)	—
K. pneumoniae	0	2 (18.18)	—	3 (27.27)	4 (36.36)	3 (27.27)	3 (27.27)	6 (54.56)	2 (18.18)	3 (27.27)	1 (9.09)	1 (9.09)	—	3 (27.27)	0	0	0	0	0	0	0	0	0	0	—
PM	—	2 (100.0)	—	2 (100.0)	1 (50.0)	2 (100.0)	2 (100.0)	2 (100.0)	0	2 (100.0)	1 (50.0)	1 (50.0)	1 (50.0)	2 (100.0)	1 (50.0)	1 (50.0)	—	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	—
PV	—	1 (100.0)	—	1 (100.0)	—	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	—	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	—

Note: AM: Ampicillin, A/C: Amoxicillin—clavulanic acid, CN: Cephalexin, XM: Cefuroxime, T/S: Trimethoprim—sulfamethoxazole, NX: Norfloxacin, Cp: Ciprofloxacin, OF: Ofloxacin, NI: Nitrofurantoin, Gm: Gentamicin, Ak: Amikacin, Nt: Netilmicin, TM: Tobramycin, TZ: Ceftazidime, CPZ: Cefoperazone, PM: Cefepime, P/T: Piperacillin—tazobactam, C/S: Cefoperazone+Sulbactam, IP: Imipenem, MP: Meropenem, Etp: Ertapenem, AT: Aztreonam and CT: Colistin

E. coli: *Escherichia coli*; *K. pneumoniae*: *Klebsiella pneumoniae*; CK: *Citrobacter koseri*; MM: *Morganella morganii*; PM: *Proteus mirabilis*; PV: *Proteus vulgaris*; EnC: *Enterobacter cloacae*; En. spp: *Enterobacter* species; KO: *Klebsiella oxytoca* and KOz: *Klebsiella ozaenae*

0, — and (P) indicates resistant, not tested and parenteral, respectively.

Table S-2: Emergence of non-EBSL producers from 2013-2018.

Discussion

In the present study, there was ESBL preponderance and *E. coli* and *K. pneumoniae* were mainly responsible for UTI. A higher prevalence of EC (84.12%) followed KP (12.63%) was found that were in concurrence with the reports of Bhatt., *et al*. and Tanko., *et al.* where they reported *E. coli* and *K. pneumoniae* prevalence of more than 85% among UTI cases [17,18], conducted in Nepal and Nigeria, respectively. A higher prevalence of *K. pneumoniae and Enterobacter* species among Ethiopian paediatric population and Nigerian population has been reported [12,19]. Variations in the results may be attributed to the demographics differences, such as age and the study region.

Patients suffering from non-ESBL UTI had a higher mean age than patients suffering from ESBL UTI and was in accordance with the finding of Balasubramanian., *et al*. [20] conducted in Tamil Nadu. They reported patients with non-ESBL infection had higher median than patients with ESBL infection. This study also observed a significant association between sex and ESBL and non-ESBL infection, which is in contrast to the findings reported by a previous study that male gender was at risk for ESBL infection [20]. However, the authors also noticed that there were higher incidences of UTI among females as compared to males (59.42% vs. 40.58%) during the six years of retrospective study, which in accordance with the results of Somashekara., *et al*. who highlighted a female dominance of 61.16% [20]. Higher incidences of UTI in females may be attributed to shorter urethra, which grants swift access of microorganisms to urinary bladder or poor hygiene [21,22].

Many researchers have documented that ESBL producers are resistant towards the amino-penicillin, beta-lactam, and cephalosporins category of antibiotics [23,24]. The study also observed a high resistance towards amino-penicillin, beta-lactam, and majority of cephalosporins during AST patterns analysis from 2013 to 2018 which is in concurrence with Jan., *et al*. findings [24]. They reported ESBL producers were nearly 100% resistant ampicillin and displayed a higher resistance towards third generation cephalosporins and aztreonam.

Among ESBL and non-ESBL producers, *E. coli* and *K. pneumoniae* were the major etiological agents for UTI among children, due to this, the study mainly focused on these two organisms. Insignificant changes in antibiotic susceptibility was noted in this study ($p > 0.05$). Aminoglycosides (amikacin and netilmicin) and carbapenems (imipenem, and meropenem), were highly effective in the case of ESBL producers. Cho., *et al.* highlighted the potential use of amikacin for treating non-severe UTI, caused by ESBL producers and these findings were in accordance with the results in the case of amikacin [25]. However, a higher resistance rate of >59% for aminoglycosides were reported previously for *E. coli* -ESBL infection which was not observed in the current study [26]. Imipenem and meropenem showed a sensitivity of nearly 100% and were found to be most effective drug in *E. coli* -ESBL infection. Similarly, 100% sensitivity towards imipenem was reported for ESBL by Poovendran., *et al.* [27] Interestingly *K. pneumoniae* showed lower sensitivity (61.54%-70.0%) among ESBL-producers from 2015 to 2018, except 2017 (88.89%) and a similar antibiotic susceptibility was maintained till 2016, followed by a declining trend till 2018. So, imipenem can be used as a preferred choice for UTI, caused by *E. coli* -ESBL producers [28,29].

A declining trend in the antibiotic sensitivity was noted for most of the antibiotics used in this study ($p < 0.05$). Highest susceptibility towards gentamicin (an aminoglycoside) was noted amongst non-ESBL producers *(E. coli* and *K. pneumoniae*) which were not observed in previous studies such as conducted by Poovendran., *et al*. [27] who reported a higher resistance towards aminoglycosides and non-effectiveness of gentamicin against both non-ESBL and ESBL producers. They also reported 100% sensitivity towards imipenem for non-ESBL producers and these findings were not in accordance with this study results. The emergence of antibiotic and multi-drug resistant bacteria is one of the primary concerns among physicians and poses a serious threat as also validated by Centers of Disease Control and Prevention reports, owing to the natural evolution of bacteria [29]. Hence, proper surveillance studies for assessing the AST patterns are regularly needed.

There are certain limitations to the present study due to its retrospective nature, where data was collected from medical records only. Furthermore, susceptibility trends of some of the strains could not be calculated due to fewer numbers of isolates. Moreover, the AST patterns of the pathogenic bacteria vary based on the geographical region. Thus, a multi-centric study of a larger sample size, with varied disease conditions and age groups can be further explored for generalization of the present study findings. In addition, data on antibiotic prescription prior the AST were not considered (i.e. children with a prescription in the previous 60 days might have been at higher risk of having a resistant bacteria), clini-

cal assessment, exclusion of patients with congenital malformation of the urinary tract were also limitations of the study.

Conclusion

The present study demonstrated that *E. coli* and *K. pneumoniae* were frequently responsible for ESBL and non-ESBL UTI in children. Carbapenems, namely imipenem, meropenem, and ertapenem, were very effective against ESBL producers along with amikacin and netilmicin (aminoglycosides). In the ESBL group, there was no evidence of any decreasing sensitivity trend for any of the antibiotics studied. But, among the non-ESBL producers, there was a decreasing trend in sensitivity of antibiotics, observed from 2013-2018, particularly in the year 2018 and especially against carbapenems (imipenem, meropenem, and ertapenem). This finding is cautionary and suggests an urgent need for the practice of antibiotic stewardship and to renew the quest for newer or novel combinations of antibiotics as a treatment option for UTI.

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