

Risk factors and outcome of urinary tract infections by extended spectrum beta lactamase producing microorganisms in children

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Abstract

Objectives: To describe the outcome and risk factors for Urinary Tract Infection (UTI) caused by Extended Spectrum Beta Lactamase (ESBL) producing microorganisms, in children aged 2 months to 15 years, at a tertiary care centre in South India over a period of 1 year.

Method: During the study period, there were 352 children with UTI, of which 100 had ESBL UTI and they were included in the study. These 100 children were analysed for risk factors of UTI, nature of treatment, duration of hospital stay and response to treatment and these were recorded in the preformed proforma. Urine routine, urine culture and sensitivity, ultrasonogram, micturating cystourethrogram and dimercapto-succinic acid (DMSA) scan were done for all patients. If colony count was $\geq 10^5$ colony forming units (CFUs) /ml on clean catch sample or urobag sample or any number in catheterized or suprapubic sample with significant ESBL strain growth on urine culture were recorded along with sensitivity pattern. Follow up was done for 3 months.

Results: Age and sex distribution of ESBL UTI were 20 (37%) boys and 13 (28.2) girls in the age group 2 months to 2 years, 15 (27.7%) boys and 15 (32.6%) girls in the age group 2 to 5 years, 12 (22.2%) boys and 5 (10.8%) girls in the age group 5 to 10 years and 7 (11.9%) boys and 13 (28.2%) girls in the age group 10 to 15 years. Common risk factors for ESBL UTI in our study were recent antibiotic use within the last 3 months (55%),

previous UTI (40%), underlying renal problems (31%), recent hospitalization within the last 3 months (26%), antibiotic prophylaxis (24%), recent catheterization within the last 3 months (18%) and comorbidities (8%). Seventy patients were followed up after treatment for a period of 3 months. Among them 14 (20%) had another episode of UTI.

Conclusions: ESBL UTI was common in the age group 2 months to 2 years and was more common in males. Fever was the most common presentation. Underlying renal problems, recent antibiotic use, recent hospitalization, recent catheterization, previous UTI and antibiotic prophylaxis were found to be significant risk factors for ESBL UTI. Higher rates of pyelonephritis, voiding dysfunction, renal abnormalities and VUR were detected in ultrasonogram of patients with ESBL UTI. VUR was more common in patients with ESBL UTI. Renal scarring was more frequent in patients with ESBL UTI. Recurrence of UTI was more likely in patients with ESBL UTI.

(Key words: UTI, ESBL, Risk factor, Recurrence)

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Introduction

Urinary tract infection (UTI) is one of the predominant causes of febrile illness in children with demanding antimicrobial therapy and it is also a common nosocomial infection^{1,2}. Overall, 8% of females and 2% of males, experience at least one incident of UTI by seven years of age, and recurrence occurs in up to 30% during a year¹. In infancy, UTI has a male to female ratio of 3-5:1. Beyond infancy, male to female ratio is 1:10³. Worldwide prevalence of Extended Spectrum Beta Lactamase (ESBL) infections has been steadily increasing with predominantly *Escherichia coli* and *Klebsiella* uropathogens and they were described as a pandemic in most regions¹. ESBLs were first described in 1983⁴. Beta lactamases produced by bacteria protect against lethal effects of penicillins, cephalosporins and monobactams on their cell wall synthesis. ESBLs have now become widespread all over the world⁴. UTI due to ESBL range from uncomplicated infection to life-threatening sepsis. Furthermore, therapy of ESBL UTI is more difficult as these strains are increasingly resistant to other non-Beta lactam antibiotics, thus

promoting increased usage of expensive broad spectrum antibiotics like carbapenems⁵.

Infancy, delay in starting treatment, recurrences and vesico-ureteric reflux (VUR) are risk factors for renal scarring^{6,7,8}. South India ESBL UTI was reported in 40% of the population and among this *Escherichia coli* and *Klebsiella* were 46.3% and 25%, respectively⁷. Preventing the spread of ESBL-producing Enterobacteriaceae in the community and healthcare settings is a significant global challenge with the increasing trend of antimicrobial resistance, which is even more significant in the sub-Saharan African region. Furthermore, high levels of antimicrobial resistance related to ESBL producing Enterobacteriaceae complicate individual patient care, increasing the mortality and morbidity associated with common infectious diseases in children like UTI⁹. ESBL infections in children are associated with longer hospital stays, frequent complications, and increased mortality at higher than adult rates in certain regions⁶. Infancy, children on uroprophylaxis, recent antibiotic usage, recurrent urinary tract infections (UTI), urinary tract anomalies, non-renal comorbidities and male gender should guide antibiotic therapy pending culture results in ESBL UTI children^{6,7,8}. Fastidious hygiene, patient isolation, cohorting, dedicated staff and alternating antibiotic regimen policies were all employed to control outbreaks of ESBL infection with varying degrees of success. The drug with preserved efficacy for ESBL producers and non-ESBL producers is nitrofurantoin⁶.

National and international programmes dedicated to the health of children worldwide need to consider the emerging threat of ESBL-producing bacteria in both resource-rich and resource-challenged countries, and research efforts should focus on the molecular characterization of ESBL types as well as additional controlled studies assessing risk factors and outcomes in children¹⁰. Many studies have been carried out in various centres globally to assess the risk factors of infections associated with ESBL producing strains in adults. However, studies in this regard on Indian children, especially from the South are limited. Hence this study was undertaken.

Objectives

To describe the outcome and risk factors for UTI caused by ESBL producing microorganisms in children aged 2 months to 15 years.

Method

A prospective observational study was carried out in Rich Hospitals, Nellore, Andhra Pradesh, a tertiary care centre in South India, over a period of 1 year.

Inclusion criteria: Children aged 2 months to 15 years with significant ESBL strain growth on urine culture and sensitivity ($>10^5$ CFUs/ml) on clean catch sample or any colony count on suprapubic aspiration / catheterized sample.

Exclusion criteria: ESBL positivity on urine culture and sensitivity without clinical manifestations of UTI (asymptomatic bacteriuria).

The study population consisted of 100 consecutive children admitted to the hospital due to community-acquired UTI (ESBL UTI). Child's history, clinical examination and risk factors for UTI were recorded in the proforma. Urine routine and urine culture and sensitivity were done for all patients. If the colony count was $\geq 10^5$ CFUs /ml on clean catch sample or urobag sample or any number in catheterized or suprapubic sample then the organism and sensitivity pattern was recorded. Of the total 352 children, in 326 midstream urine or catheter sample was collected and in 26 children urine specimens were collected with urine collecting bag due to unavoidable circumstances, out of which 9 were reported with ESBL UTI; these ESBL UTI positive children again underwent catheterised urine sample culture for confirmation; the other 17 children were reported as non-ESBL UTI.

Urine cultures were repeated when contamination was suspected, e.g., mixed growth of two or more pathogens, or growth of organisms that normally constitute the peri-urethral flora (lactobacilli in healthy girls and enterococci in infants and toddlers). The culture was also repeated in situations where UTI was strongly suspected but colony counts were equivocal as per microbiologist's suggestion.

Contamination by peri-urethral and preputial organisms was minimized by washing the genitalia with soap and water. Antiseptic washes and forced preputial retraction were not advised. The specimen was directly collected in a sterile glass or plastic bottle. In infants, urine samples were preferably obtained by urethral catheterization. Prompt plating of the urine specimen was done within one hour of collection and if delay was anticipated, the sample was stored in a refrigerator.

Ultrasonogram, micturating cystourethrogram (MCU) and dimercapto-succinic acid (DMSA) scan were done as per Indian Academy of Pediatrics (IAP)/American Academy of Pediatrics (AAP) Guidelines¹¹. Positive findings of ultrasonogram, Kidney Ureters Bladder (KUB) like pyelonephritis, cystitis, faecal loading, renal abnormalities, post-void significant residual urine volume and VUR were noted. Grade 1 to grade 5 VUR or any

anatomical abnormality in bladder and urethra were considered as abnormal MCU in patients who underwent MCU. Renal scarring or inflammation either unilateral or bilateral was considered as abnormal DMSA in patients who underwent DMSA. Nature of treatment, duration of hospital stay and response to treatment were recorded in case of in-patients. In case of outpatients, duration and response to treatment was recorded. Follow up was done for 3 months. Follow up details (UTI recurrence, uroprophylaxis) were recorded.

Ethical issues: Approval for the study was obtained from the Institutional Ethics Committee of Rich Hospitals, Nellore, Andhra Pradesh, India (No. RICH/RES/2020/048). Written Informed consent was obtained from the parents of the children included in the study.

Statistical analysis: Data were entered in MS-Excel spreadsheet, validated and analysed using SPSS version 11. Incidence was calculated from

data. Chi square test and Fischer t test were used to analyse variables.

Results

During the study period, there were 352 children with UTI, of whom 100 had ESBL UTI and were enrolled into the study group. Hence total percentage of ESBL UTI was $100/352 \times 100 = 28.4\%$. The study flow chart is shown in Figure 1.

Table 1 shows the age and sex distribution of ESBL.

Table 2 shows the clinical features of ESBL UTI.

Table 3 shows the risk factors of ESBL.

Table 4 shows the investigations used in the study.

Table 5 is the logistic regression analysis of risk factors for UTI.

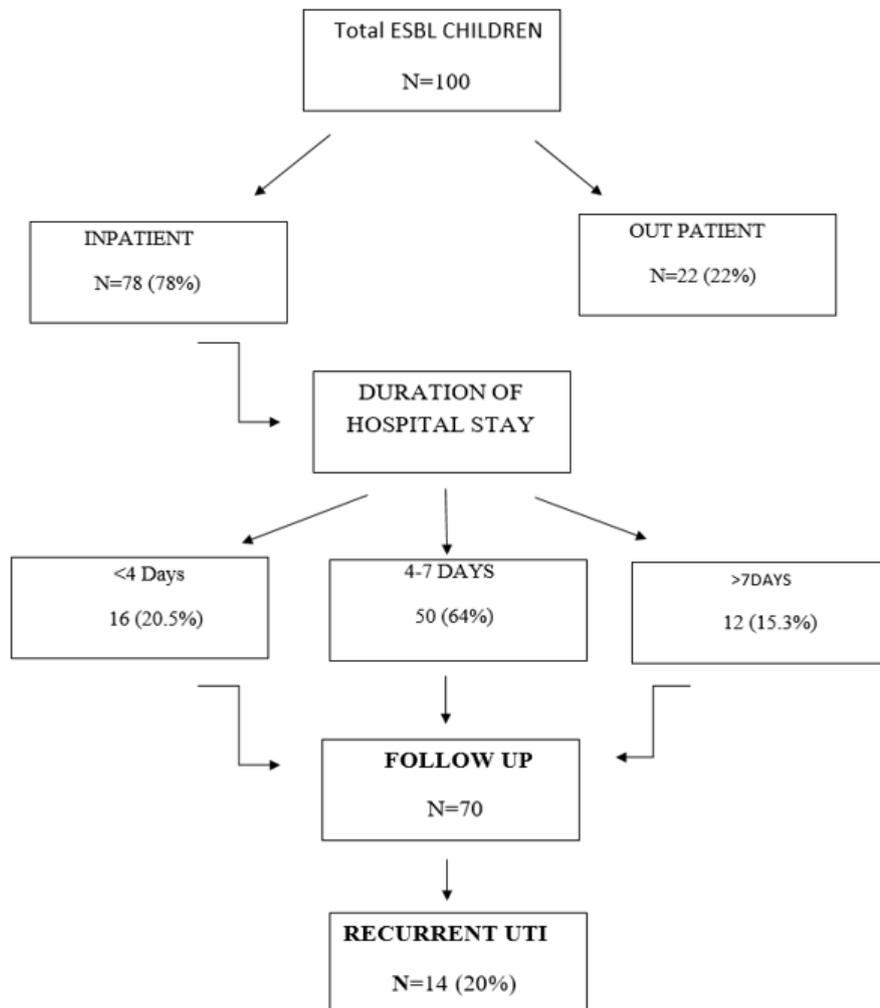


Figure 1: Study flowchart

Table 1: Age and sex distribution of Extended Spectrum Beta Lactamase (ESBL)

Age group	ESBL (n=100) n (%)	Non ESBL (n=252) n (%)	Odds ratio	p-value
2 months - < 2 years	33 (33)	45 (17.9)	1.97	0.01*
2 years - < 5 years	30 (30)	70 (27.8)	1.22	0.4
5 years - < 10 years	17 (17)	82 (32.5)	0.46	0.04
10 years - 15 years	20 (20)	55 (21.8)	0.8	0.76
Sex				
Male	54 (54)	139 (55.2)	0.95	0.84
Female	46 (46)	113 (44.8)		

Table 2: Symptomatology of patients with ESBL UTI (n=100)

Symptom	n (%)
Fever	78 (78)
Urinary frequency	37 (37)
Dysuria	25 (25)
Poor feeding	07 (07)
Vomiting	15 (15)
Loose stools	06 (06)
Pain in abdomen	26 (26)
Chills and rigors	17 (17)
Enuresis	19 (19)

Table 3: Risk factors of Extended Spectrum Beta Lactamase (ESBL)

Risk factor	ESBL (n=100) n (%)	Non ESBL (n=252) n (%)	Odds ratio	p-value
Renal problems	31 (31)	21 (8.3)	4.942	0.000*
Recent antibiotic use	55 (55)	38 (15.1)	6.883	0.000*
Recent hospitalisation	26 (26)	21 (8.3)	3.865	0.000*
Previous urinary tract infection	40 (40)	30 (11.9)	4.933	0.000*
Recent catheterisation	18 (18)	06 (2.4)	3.238	0.001*
Neurological abnormality	04 (04)	07 (2.8)	1.458	0.515
Constipation	12 (12)	37 (14.7)	0.792	0.512
Comorbidities	08 (08)	01 (0.4)	21.826	0.000*

Table 4: Investigations used in the study

Investigation	ESBL Number (%)	
<i>Ultrasonography</i> (n=100)	Pyelonephritis	36 (36.0)
	Cystitis	34 (34.0)
	Post void significant residual bladder volume	10 (10.0)
	Faecal loading	08 (08.0)
	Renal abnormality	12 (12.0)
	Vesico ureteric reflux (VUR)	10 (10.0)
<i>Micturating cystourethrogram</i> (n=27)	Grade 1-5 VUR / abnormality in bladder and urethra	15 (55.5)
<i>Dimercaptosuccinic acid scan</i> (n=42)	Renal parenchymal inflammation and renal scarring (unilateral/bilateral)	32 (76.1)
<i>Urine culture</i> (n=100)	Escherichia coli	81 (81.0)
	Klebsiella	16 (16.0)
	Enterobacter	02 (03.0)

Table 5: Logistic regression analysis of risk factors for urinary tract infection

Complication	B	SE	t score	df	p	95% CI	
						Lower	Upper
Known renal problems	0.796	0.033	23.972	1	0.000*	0.731	0.861
Recent hospitalization	0.723	0.065	11.058	1	0.000*	0.594	0.852
Recent catheterization	0.457	0.099	4.631	1	0.000*	0.263	0.652
Recent antibiotic use	0.211	0.066	3.205	1	0.001*	0.082	0.341
Previous urinary tract infection	0.145	0.063	2.302	1	0.022*	0.021	0.268
Neurological abnormality	-0.037	0.089	-0.416	1	0.678	-0.212	0.138
Constipation	-0.131	0.079	-1.651	1	0.100	-0.287	0.025
Comorbidities	0.678	0.065	10.436	1	0.000*	0.550	0.805

B: Coefficient for constant, SE: Standard error, df: degrees of freedom for Wald Chi square test, CI: confidence interval

Discussion

This prospective hospital-based observational study of ESBL UTI in children between 2 months to 15 years, enrolled a total of 100 children as per pre-defined inclusion criteria. The incidence of ESBL UTI in children varies worldwide and ranges from 10.4%-45.1%¹²⁻¹⁸, whereas in this study it was 28.4%. This was less than the incidence reported from Aligarh, India by Mohammed A, *et al*¹² and Delhi, India by Kaur N, *et al*¹³ which were 45.1% and 42% respectively. Children between 2 months to 2 years had higher rates of ESBL UTI (33%) than other age groups and this age group had statistically significant higher rates of ESBL UTI [Table 1]. This was similar to the study by Kizilca O, *et al*⁵ where age less than one year had higher rates of ESBL UTI. On analysis of ESBL UTI, we found that 78% of children presented with fever, similar to the study by Topalogulu R, *et al*¹⁹ who found that fever was most common presenting symptom in patients with ESBL UTI (40.6%) [Table 2].

The most common risk factor for ESBL UTI in this study was recent antibiotic use within the last 3 months which was seen in 55% children [Table 3]. Other risk factors for ESBL UTI in this study in descending order were previous UTI (40%), underlying renal problems (31%), hospitalization within the last 3 months (26%), antibiotic prophylaxis (24%), catheterization within the last 3 months (18%) and co-morbidities (8%). Our findings were comparable to previous studies by Topalogulu R, *et al*¹⁹, *et al*²⁰ and Dayan N, *et al*²⁰. In the study by Topalogulu R, *et al*¹⁹, the most common risk factor for ESBL UTI was recent antibiotic use within the last 3 months (79%) followed by renal problems (63.9%), previous UTI (54.8%) and recent hospitalization within the last 3 months (47%). In the study by Dayan N, *et al*²⁰, 40% of children with previous UTI, 32% of children with underlying renal problems and 32% of children on antibiotic prophylaxis had ESBL UTI. Fan N, *et al*²¹ demonstrated that risk factors for ESBL UTI were similar to our study except for previous UTI, which

was not found as a risk factor. Constipation and underlying neurological disease were found as risk factors for ESBL UTI in our study, whereas Fan N, *et al*²¹ found neurological disease to be a significant risk factor for ESBL UTI.

In patients with ESBL UTI, ultrasonogram showed pyelonephritis in 36%, cystitis in 34%, renal abnormalities in 12%, VUR in 10% and post void significant residual urine volume in 10% [Table 4], whereas the study by Dayan N, *et al*²⁰ found cystitis in 24% and pyelonephritis in 76% of patients with ESBL UTI. In our study 15/27 (55.5%) of children with ESBL UTI had abnormal MCU, which was comparable to studies by Topalogulu R, *et al*¹⁹ and Dotis J, *et al*⁴ which reported VUR in 19.4% and 41% respectively. In our study DMSA scans were required in 42% patients with ESBL UTI and an abnormality was detected in 76.1% of them. Similarly, DMSA scan abnormality was found in 23% of patients with ESBL UTI with higher rates of renal scarring in the study by Dotis J, *et al*⁴. In our study, the most common organism isolated in ESBL UTI patients was *Escherichia coli* (81%) followed by *Klebsiella* (16%). This was comparable to the study by Hanna-Wakim RH, *et al*¹⁷ where *Escherichia coli* was isolated in 79.4% of patients and *Klebsiella* in 7.9% of patients with ESBL UTI.

In our study when binary logistic regression analysis was done for risk factors between cases and controls as non ESBL UTI, underlying renal problems, antibiotic use within last 3 months, hospitalization within the last 3 months, catheterization within the last 3 months and previous UTI were found to be independent risk factors causing ESBL UTI [Table 5]. In our study, 20%, 64% and 15.3% of patients with ESBL UTI required hospital stay of less than 4 days, 4 to 7 days and more than 7 days respectively [Figure 1]. Dayan N, *et al*²⁰ and Fan N, *et al*²¹ demonstrated no significant difference in duration of hospital stay in patients with ESBL UTI and in patients with non ESBL UTI. Dotis J, *et al*⁴ and Topalogulu R, *et al*¹⁹

demonstrated that patients with ESBL UTI required longer duration of hospital stay than with non ESBL UTI. In our study, out of 100 ESBL patients, 70 patients were followed up after treatment for a period of 3 months. Among this 14 (20%) had another episode of UTI [Figure 1]. Fan N, *et al*²¹ found no statistical difference in recurrent UTI among patients with ESBL UTI and non ESBL UTI,

There were some limitations. As this is a single centre study conducted at a tertiary care hospital, the demography and socio-economic distribution may be biased. There are probably a few hospital acquired infections in the current study sample despite strict adherence to the study methodology. Even though the urine culture samples were plated at the earliest and in cases of suspicious results they were repeated, there is still a chance of minimal contamination. Therefore a community based multi-centric study is suggested to confirm the findings of this study and reduce the limitations.

Conclusions

ESBL UTI was common in the age group 2 months to 2 years and was more common in males. Fever was the most common presentation. Underlying renal problems, recent antibiotic use, recent hospitalization, recent catheterization, previous UTI and antibiotic prophylaxis were found to be significant risk factors for ESBL UTI. Higher rates of pyelonephritis, voiding dysfunction, renal abnormalities and VUR were detected in ultrasonogram of patients with ESBL UTI. VUR was more common in patients with ESBL UTI. Renal scarring was more frequent in patients with ESBL UTI. Recurrence of UTI was more likely in patients with ESBL UTI.

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