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ORIGINAL ARTICLE

Risk factors in community-acquired urinary tract infections caused by ESBL-producing bacteria in children

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Abstract In this study, risk factors were investigated in children with community-acquired urinary tract infections (UTI) caused by extended-spectrum beta-lactamases (ESBL)-producing *E. coli* or *Klebsiella* spp. One hundred and fifty-five patients were diagnosed with ESBL-positive UTI (case group) in the outpatient clinics of Hacettepe University Children's Hospital between 1 January 2004 and 31 December 2006. A control group, 155 out of 4,105 children, was matched by age and sex among children with ESBL-negative UTI. A total of 310 patients' files were evaluated retrospectively. As regards the symptoms of UTI, no statistical differences were seen between the two groups. Although the most frequently isolated microorganism was *E. coli* in both groups, *Klebsiella* spp. was found to be more frequent in those diagnosed with ESBL(+) UTI ($p<0.001$). Having an underlying disease and hospitalization, infections, and use of antibiotics within the last 3 months were found to be potential risk factors ($p<0.001$). With conditional logistic regression analysis, having an underlying disease and hospitalization within the last 3 months were identified as independent risk factors for ESBL(+) UTI. In conclusion, the recognition of risk factors for UTI, caused by ESBL(+) bacteria in children, may aid in the identification of high-risk cases and may enable proper management of these patients.

Keywords Extended-spectrum beta-lactamases (ESBL)-producing bacteria · Urinary tract infection · Community-acquired infection · Risk factors · Children

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Introduction

Extended-spectrum beta-lactamases (ESBL) are plasmid-mediated enzymes that cause resistance to various types of the newer β-lactam antibiotics, including the expanded-spectrum cephalosporins and monobactams [1–4]. Initially reported in the mid-1980s in Europe, ESBL-producing *E. coli* and *Klebsiella pneumoniae* were first reported in Turkey in 1992 and are now widespread all over the world [1, 4, 5]. Treatment failures and mortality are increasingly being reported in patients who are infected with ESBL-producing *E. coli* or *Klebsiella* and treated with cephalosporins [6–12].

Several case-control studies in adults reported the risk factors of colonization or infection with ESBL-positive microorganisms for the hospitalized patients as severity of illness, presence of an intravascular or urinary catheter, gastrointestinal (GI) tubes, abdominal surgery, GI colonization, prior use of antibiotics (including cephalosporins), nursing home stay, length of stay in hospital or intensive care unit [8, 10, 13]. The risk factors for the community-

acquired infections caused by ESBL-producing microorganisms, which were described in two recent publications, are previous hospital admission, previous use of cephalosporins, penicillins or fluoroquinolones, recurrent urinary tract infections (UTIs), diabetes mellitus, age over 60 years, male sex, and genitourinary pathologies [14, 15].

Few studies examining the risk factors for infections due to ESBL-producing *E. coli* or *K. pneumoniae* in children have focused on infections in the hospital [12, 16]. The risk factors and the measures to be taken in UTIs caused by ESBL-producing microorganisms in children and the treatment for these infections are not clear. The aim of this study was to investigate the risk factors in children who were seen at the clinics of a university hospital with community-acquired UTIs caused by ESBL(+) *E. coli* or *Klebsiella* spp.

Materials and methods

In this case-control study, 4,105 children, diagnosed with UTI, were seen at the clinics of Children's Hospital of Hacettepe University Faculty of Medicine between 1 January 2004 and 31 December 2006 were investigated. The case group consisted of 155 patients diagnosed with UTI due to ESBL(+) organisms (ESBL(+) UTI). Cases and controls were matched by age and sex in a 1:1 ratio. A total of 310 patient records were examined retrospectively. The necessary permission for the retrospective study was obtained from the hospital administration. Patients with ESBL(+) *E. coli* or *Klebsiella* spp. growth $\geq 10^5$ CFU/ml urine cultures were included in the study. WHO age classification criteria (0–11 months, 12–59 months, 60+ months) was used for grouping ages [17]. In addition to the potential risk factors, symptoms (fever, vomiting, dysuria, abdominal pain, restlessness, loss of appetite, failure to thrive, and voiding dysfunction) and radiological findings were evaluated.

The percentages of urine specimen-obtaining methods for urine culture, sterile urine bags, midstream clean catch urine, indwelling urinary catheter, and supra pubic aspiration were 60, 31, 8, and 1 respectively in ESBL(+) UTIs and 56, 38, 5, and 1 respectively in ESBL(−) UTIs. Urine cultures were evaluated for the growth of ESBL(+) *E. coli* and *Klebsiella* spp. in the Clinical Microbiology Laboratory of the study hospital. Cultures and identification of the isolates were performed following standard methods. Contaminated specimens were discarded from the study. Antimicrobial susceptibilities against various antibiotics were determined with the disk diffusion method following Clinical Laboratory Standards Institute (CLSI) guidelines [18]. The following antimicrobial agents were tested: amoxicillin-clavulanate, cefprozil, cephalothin, cefazolin, cefuroxime, cefixime, ceftriaxone, cefotaxime, ceftazidime, cefepime, ciprofloxacin, amikacin, imipenem, trimetoprim-sulfamethoxazole (TMP-SMX), and nitrofurantoin (BBL, Becton, Dickinson and Company, Sparks, MD, USA).

Identification of ESBLs

Extended-spectrum beta-lactamase production in *E. coli* and *Klebsiella* spp. was investigated with phenotypic disk diffusion tests following the CLSI guidelines. Both ceftazidime (30 μg), ceftazidime-clavulanic acid (30/10 μg), and cefotaxime (30 μg), cefotaxime-clavulanic acid (30/10 μg) disks (BBL) were employed for confirmation of ESBL production. A ≥5-mm increase in the zone diameter of ceftazidime-clavulanic acid or cefotaxime-clavulanic acid versus their zone when tested alone was accepted as the indication of ESBL production [18].

Statistical evaluation

The data were analyzed by using SPSS 10.0 program. The statistical significance was evaluated by using χ^2 and Fisher's exact χ^2 tests for bivariate analysis and the risk factors were evaluated by backward conditional logistic regression analysis [19].

Results

In the study period, out of 4,105 children diagnosed with UTI, 155 patients had ESBL(+) UTIs (3.8%) and 3,950 had ESBL-negative UTIs (96.2%). Distribution of ESBL(+) UTIs was 3.6% in 2004, 3.9% in 2005, and 4.2% in 2006 with a slight trend toward insignificant increase (p=0.776).

The age and sex distribution of the patients with ESBL (+) UTI are shown in Table 1. While there was a male predominance up to 1 year of age, after 1 year of age ESBL (+) UTI, was found predominantly in girls, as is seen in UTIs in general. Median age of the patients was 20 months (range 0–192 months); the median age for the boys was 6.5 months and for the girls 54 months.

Table 1 The age and sex distribution of the patients with extended-spectrum beta-lactamase (ESBL)-positive urinary tract infection (UTI)

Age (months)	Male		Female		Total	
	n	%	*n*	%	*n*	%
0–11	45	71.4	18	28.6	63	40.6
12–59	16	40.0	24	60.0	40	25.8
60, +	11	21.5	41	78.8	52	33.6
Total	72	46.5	83	53.5	155	100.0

The percentages of urine specimen-obtaining methods for urine culture were matching in both groups.

Regarding the signs and symptoms (fever, vomiting, dysuria, abdominal pain, restlessness, loss of appetite, failure to thrive, voiding dysfunction, primary and secondary enuresis), there was no statistically significant difference between the groups (Table 2). Patients with asymptomatic bacteriuria are excluded.

According to the ultrasound findings, renal and collecting system abnormalities, nephrocalcinosis/-lithiasis were more frequent in ESBL(+) patients (52.2%; $p=0.006$). High degree (4–5º) unilateral and/or bilateral vesicoureteral reflux (VUR) was frequent in ESBL(+) patients (71.7%) compared with ESBL(−) (68.0%; $p=0.018$).

The most frequent isolate was *E. coli* for both case and control groups; however, *Klebsiella* spp. were more frequent among ESBL(+) UTI compared with ESBL(−) UTI ($p<0.001$; Table 3).

Risk factors

Since the cases were matched one-by-one according to age and sex and the data were limited to the patients' records, four main risk factors were evaluated as follows: underlying disease, hospitalization in the last 3 months, use of antibiotics in the last 3 months, infection in the last 3 months including UTI. All the differences observed in the risk factors were found to be statistically significant in the ESBL(+) group ($p<0.001$; Table 4).

Renal and nonrenal causes of underlying diseases and statistical comparison were seen in Table 5. When the underlying diseases were evaluated among themselves, anatomical abnormalities and functional abnormalities, septicemia, and systemic diseases were significantly higher in ESBL(+) patients except duplex systems and recurrent urinary tract infections without renal abnormalities (Tables 4, 5).

Regarding the history of infections in the past 3 months, UTIs were significantly more frequent among ESBL(+) patients ($p<0.001$; Table 4). When the antibiotics used within 3 months were evaluated among themselves, the use of third and fourth generation cephalosporins alone, use of other antibiotics (fluoroquinolone, carbapenems, and aminoglycosides) alone, suppression treatment with TMP/SMX or nitrofurantoin, and various combinations of these antibiotics, were found to be significantly higher in ESBL(+) patients. Detailed analysis of history of hospitalization within the last 3 months showed that being hospitalized for any reason given in Table 4 was found to be significantly higher in ESBL(+) patients ($p<0.01$). According to backward stepwise conditional logistic regression analysis, having renal abnormalities (OR=4.8) or septicemia/systemic diseases (OR=16.8), hospitalization within the last 3 months due to renal problems (OR=3.2) or other identified causes (prematurity, indirect hyperbiluribinemia, systemic infections, non-urinary system operations; OR=3.2) were found to be independent risk factors for developing an ESBL(+) UTI (Table 6).

Discussion

Extended-spectrum beta-lactamases have been increasingly reported from all parts of the world since their first description in 1983. They were originally reported more frequently in *Klebsiella pneumoniae* causing hospital infections; however, in recent years their prevalence has increased in *E. coli* causing community-acquired infections, most of which are UTIs [4, 15, 20–22]. Risk factors in UTIs due to ESBL-producing bacteria have been studied in community and hospital isolates [6, 14, 15, 23–25]. However, most of these studies have been performed in the adult population and are rare in children [26, 27].

This case-control study is one of the very first studies among children evaluating the risk factors in community-acquired ESBL(+) UTIs with the aim of contributing to the diagnosis and management of these children. Within the

Table 2 Signs and symptoms of children with ESBL(+) and ESBL(−) UTI

Signs and symptoms	ESBL(+) (N=155)		ESBL(−) (N=155)		p
	n	%	n	%	
Fever	63	40.6	50	32.3	0.125
Vomiting	52	33.5	52	33.5	1.000
Dysuria	29	18.7	39	25.2	0.170
Abdominal pain	31	20	35	22.6	0.579
Enuresis and voiding dysfunction	40	25.8	29	18.7	0.133
Restless	47	30.3	41	26.5	0.450
Low appetite	27	17.4	33	21.3	0.388
Failure to thrive	8	5.2	12	7.7	0.355

Table 3 Distribution of *E. coli* and *Klebsiella* spp. in ESBL(+) and ESBL(−) UTI

Microorganisms	ESBL(+) (*N*=155)		ESBL(−) (*N*=155)	
	n	%	*n*	%
E. coli	100	64.5	132	85.2
Klebsiella spp.	55	35.5	23	14.8

χ^2=17.5, df=1, p<0.001

study period (1 January 2004 and 31 December 2006), among 4,105 children diagnosed with UTI, 155 (3.8%) had ESBL(+) UTIs.

In both cases and controls, *E. coli* was the leading isolated microorganism; however, among the cases, *Klebsiella* spp. was more than two times as frequent compared with the controls (35.5%, p<0.001). Other studies report similar findings [14, 27–30]. These findings may suggest that if the isolated microorganism is *Klebsiella* spp. in UTI, production of ESBL may more frequently be expected. This result may be useful in deciding on empirical therapy for UTI until the production of ESBL has been verified.

Several authors have reported age over 60 years to be an associated or independent risk factor for having community-acquired infections with ESBL-producing microorganisms in adults [14, 15, 21]. Male sex has also been found to be an associated or independent risk factor in some studies [14, 30, 31] while others have not shown any association [15, 21]. In the present study, however, since age and sex were considered to be potential confounders and controlled, these variables were excluded from the association and risk analysis.

Table 4 Bivariate analysis of the potential risk factors in ESBL(+) UTI

Risk factors	ESBL(+) (*N*=155) Percentage	ESBL(−) (*N*=155) Percentage	*p*
Underlying diseases			
Any	94.2	69.7	0.001
Renal abnormalities[a]	63.9	48.4	0.001
Recurrent UTI (no renal abnormalities)	12.3	17.4	0.004
Septicemia	9.0	1.3	0.001
Systemic diseases[b]	9.0	2.6	0.001
History of infection (last 3 months)			
Any	66.5	43.9	0.001
UTI	54.8	33.5	0.001
Others[c]	11.6	10.3	0.098
Use of antibiotics (last 3 months)			
Any	79.0	52.2	0.001
2nd generation cephalosporin	5.8	5.2	0.065
3rd–4th generation cephalosporin	14.9	11.0	0.002
Penicillin	8.4	11.6	0.221
Other antibiotics[d]	7.1	0.6	0.001
Combinations[e]	23.4	7.7	0.001
Suppression (TMP-SMX/nitrofurantoin)	19.5	16.1	0.003
History of hospitalization (last 3 months)			
Any	47.7	18.7	0.001
Renal causes[f]	27.7	7.7	0.001
Other causes[g]	20	11	0.001

TMP-SMX trimetoprim/sulfametoxazole

[a] Anatomical and functional renal abnormalities±VUR, nephrolithiasis/nephrocalcinosis, multiple congenital abnormalities

[b] Sepsis, metabolic disease, and malignancies

[c] Pneumoniae, sepsis or upper respiratory tract infection

[d] Quinolones, carbapenems, aminoglycoside

[e] Combination of 2nd/3rd/4th generation cephalosporins, penicillin, quinolones, carbapenems, aminoglycoside

[f] UTI and genitourinary system operations

[g] Prematurity, indirect hyperbilirubinemia, systemic infections, other operations

Table 5 Underlying diseases in patients with ESBL(+) and ESBL(−) UTI

Underlying diseases	ESBL(+) (*N*=155)		ESBL(−) (*N*=155)		*p*
	n	%	*n*	%	
No underlying disease	9	5.8	47	30.3	
VUR	30	19.4	28	18.1	0.001
Urinary abnormalities	37	23.9	19	12.3	0.001
HN/HUN	15	9.7	8	5.2	0.001
UPJO/UVJO	5	3.2	1	0.6	0.002
Duplex systems	4	2.6	5	3.2	0.070
Multiple congenital anomalies	13	8.4	5	3.2	0.001
Nephrolithiasis/-calcinosis	5	3.2	4	2.6	0.002
Functional abnormalities	27	17.4	24	15.5	0.001
Neurogenic bladder	18	11.6	11	7.1	0.001
Voiding dysfunction	9	5.8	13	8.4	0.041
Recurrent UTIs (without known renal anomaly)	19	12.3	27	17.4	0.004
Others	28	18.1	10	6.5	0.001
Sepsis	14	9.0	2	2.6	0.001
Systemic diseases (metabolic, hematological–oncological diseases)	14	9.0	4	1.3	0.001

HN hydronephrosis, *HUN* hydroureteronephrosis, *UPJO* ureteropelvic junction obstruction, *UVJO* ureterovesical junction obstruction

Underlying diseases as risk factors in community-acquired ESBL(+) UTIs have been evaluated in several studies in adults. While diseases such as diabetes, cardiovascular, gastrointestinal, genitourinary diseases, recurrent UTI, urolithiasis, urethral catheter, previous urological operations malignancies were found to be associated with ESBL(+) UTIs, only diabetes and previous urological operations were reported to be independent risk factors [14, 15, 21, 30, 31]. Four main risk factors were analyzed in the study: underlying disease, hospitalization in the last 3 months, use of antibiotics in the last 3 months, and infection in the last 3 months including UTIs.

Table 6 Logistic regression analysis of the risk factors

Risk factor	Odds ratio	95% CI		*p*
		Lower	Upper	
Underlying disease				
Renal abnormalities[a]	4.8	2.0	11.5	0.001
Septicemia/systemic diseases[b]	16.8	5.1	55.8	0.001
Hospitalization in last 3 months				
Renal causes[c]	3.2	1.5	6.7	0.002
Other causes[d]	3.2	1.3	7.6	0.009

[a] Anatomical and functional renal abnormalities±VUR, nephrolithiasis/nephrocalcinosis

[b] Sepsis, metabolic disease, and malignancies

[c] UTI and genitourinary system operations

[d] Prematurity, indirect hyperbilirubinemia, systemic infections, other operations

In our study, while several underlying diseases were shown to be potential risk factors by bivariate analysis (Table 4), renal abnormalities, sepsis, and systemic diseases were found to be independent risk factors according to multivariate analysis (Table 6). Regarding the history of infections including UTI, pneumonia, sepsis, upper respiratory tract infection in the past 3 months, UTIs were significantly more frequent among ESBL(+) patients ($p<0.001$), but it was not an independent risk factor according to multivariate analysis (Table 6).

In terms of the use of antibiotics as risk factors for the development of ESBL(+) UTIs, the results of several studies are diverse. While Calbo et al. [15] indicated previous second generation cephalosporin use to be strongly associated with UTIs in adults with community-onset ESBL-producing bacteria, they did not find any relation between exposure to other antimicrobials and ESBL-producing *E. coli* UTI [15]. Colodner and colleagues [14] indicated previous use of penicillin, second- and third-generation cephalosporins and quinolones as independent risk factors. Yılmaz et al. [30] reported cephalosporins and quinolones to be independent risk factors in their study and Ena et al. [21] reported only quinolones to be independent risk factors. In our study, use of penicillin, second and third generation cephalosporins and other antibiotics (quinolones, carbapenems, aminoglycosides), the combination of any of these and the suppression treatment (TMP/SMX, nitrofurantoin) were potential risk factors in bivariate analysis; however, none of them was an

independent risk factor according to multivariate analysis with logistic regression. Although exposure to antibiotics is frequent in our population, we could not show any antibiotic to be an independent risk factor. This may be explained by the high number of combination treatments (n=41) in these patients compared with single treatments. In previous studies, it is not clear whether use of combination treatment has been taken into consideration when the use of antibiotics was evaluated [14, 21]. Previous hospitalization in the last 3 months due to renal problems such as UTIs and genitourinary system operations or other causes such as prematurity, indirect hyperbilirubinemia, systemic infections, and operations of other systems was found to be an independent risk factor according to multivariate analysis with logistic regression, similar to other studies [14, 15, 21, 30].

This study indicates that having an underlying disease and hospitalization, infections, use of antibiotics within the last 3 months are potential risk factors (p <0.001). With logistic regression analysis, having an underlying disease (renal abnormalities, OR=4.8; septicemia-–systemic disease, OR=16.8) and hospitalization within the last 3 months (due to renal problems, OR=3.2; other causes, OR=3.2) were identified to be independent risk factors for ESBL(+) UTI. We recommended that these findings should be supported by more comprehensive studies.

In conclusion, the recognition of risk factors for UTI, caused by ESBL(+) bacteria in children, may aid in the identification of high-risk cases and may enable proper management of these patients. Although further studies are needed regarding empirical therapy in these children, cephalosporins should be used cautiously; furthermore, response to treatment must be followed closely.

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