Urinary tract infections caused by extended-spectrum beta-lactamase-producing bacteria in children: a matched case-control study

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Extended-spectrum beta-lactamase (ESBL)-producing pathogens are emerging as a cause of urinary tract infections (UTI) worldwide. In this matched-case control study, clinical characteristics and associated risk factors for ESBL UTI were evaluated. In a total of 463 positive urine cultures, 48 (10.4%) (from 39 patients, 23 boys) were phenotypically ESBL-producing bacteria. The most frequently isolated microorganism was *Escherichia coli,* followed by Klebsiella spp. and *Enterobacter cloacae*. Children with ESBL UTI (n=39) were on prophylaxis more (21% vs. 6%, p=0.01), had higher rates of urinary tract anomalies (36% vs. 10%, p=0.0007), presented abnormal 99m Tc-dimercaptosuccinic acid (DMSA) findings (i.e. scars) (23% vs. 4%, p=0.001), and had longer hospitalization (9.8 vs. 7.4 days, p=0.004) compared to those with non-ESBL UTI (n=117). 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.

Key words: extended-spectrum beta-lactamase (ESBL), urinary tract infection, clinical characteristics, risk factors.

Urinary tract infections (UTIs) constitute a common clinical problem in pediatric hospitals. The increasing incidence of resistance of Gram-negative pathogens leads to serious difficulties concerning the treatment. In Gram-negative pathogens, beta-lactamase production remains the most important factor to induce beta-lactam resistance[1–3]. Organisms producing extended-spectrum beta-lactamases (ESBLs) are distributed worldwide, complicating further the treatment of UTIs due to these threatening pathogens[4,5].

Published data in children on the existence and magnitude of ESBL production in urinary pathogens in the local setting are limited[6–12]. This retrospective study was conducted to compare the clinical, laboratory, microbiological, and imaging findings of UTIs caused by ESBL-producing pathogens with that of UTIs caused by non-ESBL-producing pathogens in pediatric patients.

Material and Methods

A matched case-control study was performed in Hippokratio, a 976-bed tertiary-care general hospital. The necessary permission for the retrospective study was obtained from the hospital administration. In this study, carried out over a 36-month period between January 2008 and December 2011, files from children hospitalized with UTI due to ESBL-producing isolates were evaluated; age ≤14 years and urine culture positive for bacterial species were used as the inclusion criteria. Patients aged ≤18 years who were being followed for systematic diseases in our Pediatric Department and presented with an UTI due to ESBL were also included.

Patients with a positive urine culture for ESBL-producing isolates were defined as cases. Patients of the same gender and age, who were admitted in about the same period with the case patient and had a positive urine culture for non-ESBL-producing isolates, were defined as controls. Every case patient was matched with three control patients with priority to gender and age and then admission date.

For each patient included in the study, data

were recorded and organized as follows: a) clinical information, including age, gender, presenting symptoms, underlying disease, any history of infection or previous administration of antibiotics or hospitalization in the last three months, UTI antimicrobial prophylaxis, and length of hospital stay, b) laboratory findings, including white blood cells (WBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), c) microbiologic information, including species identification and susceptibility tests, and d) imaging data, including renal ultrasonography (US), voiding cystourethrography (VCUG), and 99m Tc-dimercaptosuccinic acid (DMSA) scan for renal parenchymal scarring.

Urine samples were obtained with suprapubic aspiration or bladder catheterization for children ≤3 years old and by clean midstream catch for older children, while positivity was interpreted according to standard criteria. Identification and susceptibility testing of microorganisms was

Table I. Clinical and Laboratory Characteristics of 156 Patients with Urinary Tract Infection

Variables	ESBL group (n=39)	Non-ESBL group (n=117)	OR (95% CI)	P
Demographic data				
Male gender (n, %)	23 (59)	65 (55.6)		0.85
Median age (month, range)	5 (0.3-187)	5.5 (0.2-180)		0.98
Pathogen (n, %)				
Escherichia coli	20 (51.3)	79 (67.5)	0.76 (0.55-1.06)	0.085
Klebsiella spp.	12 (30.8)	17 (14.5)	2.1 (1.11-4.03)	0.032
Enterobacter cloacae	4 (10.3)	2 (1.7)	6 (1.14-31.51)	0.035
Underlying disease (n, %)				
Any	16 (41)	31 (26.5)	1.55 (0.96-2.51)	0. 1
Renal abnormalities[a]	14 (35.9)	12 (10.3)	3.5 (1.77-6.91)	0.0007
Recurrent UTI (no renal abnormalities)	1 (2.6)	11 (9.4)	0.27 (0.04-2.05)	0.3
Presenting symptom (n, %)				
Fever	23 (59)	85 (72.6)	0.81 (0.61-1.08)	0.11
Other[b]	37 (94.9)	92 (78.6)	1.21 (1.07-1.36)	0.026
Presenting laboratory finding				
White blood cells [mean ± SE (cells/mm^3)]	11553 ± 4537	13932 ± 5739		0.045
C-reactive protein [mean ± SE (mg/dl)]	25.1 ± 17.9	48.1 ± 45.1		0.051
History of infection[c] (n, %)	14 (36)	40 (34.2)	1.05 (0.64-1.71)	0.85
Use of antibiotics[c] (n, %)				
Any	14 (36)	36 (30.8)	1.17 (0.71-1.92)	0.56
Prophylaxis (co-trimoxazole/nitrofurantoin)	8 (20.5)	7 (6)	3.42 (1.33-8.85)	0.013
History of hospitalization[c] (n, %)	17 (43.6)	36 (30.8)	1.42 (0.9-2.22)	0.17
Voiding cystourethrography finding (n, %)				
Any grade VUR	11 (28.2)	24 (20.5)	1.38 (0.74-2.54)	0.38
VUR grade ≥3	5 (12.8)	11 (9.4)	1.36 (0.51-3.68)	0.55
99Tc DMSA renal parenchymal scarring (n, %)	9 (23.1)	5 (4.2)	5.4 (1.93-15.15)	0.0013
Duration of hospitalization [mean ± SE (d)]	9.8 ± 6.3	7.4 ± 2.3		0.0038

[a] Anatomical and functional renal abnormalities with/without VUR, nephrolithiasis/nephrocalcinosis, multiple congenital abnormalities.
[b] "Other" symptoms include anorexia, flank pain, diarrhea, vomiting, abdominal pain, hematuria, and decreased food intake.
[c] During the past 3 months.
CI: Confidence interval. DMSA: 99m Tc-dimercaptosuccinic acid. OR: Odds ratio. UTI: Urinary tract infection. VUR: Vesicoureteral reflux.

performed by a VITEK 2 system (bioMérieux, Marcy l'Etoile, France). ESBL pathogens were also investigated with phenotypic disk diffusion tests following the Clinical and Laboratory Standards Institute (CLSI) guidelines for further confirmation[13].

Statistical Analysis

Comparisons between categorical variables were done using the statistical program GraphPad Instat (Graphpad Inc, San Diego, CA). Continuous data were expressed as mean ± standard deviation (SD) or median with ranges. Frequencies were expressed as percentages. Statistical evaluation of differences in proportions was performed by Fisher's exact test. A two-sided p value of <0.05 indicated significance. Odd ratios (OR) with 95% confidence intervals (95% CI) were calculated for each variable. Variables in which the 95% CI did not include 1.0 were maintained in the final analysis.

Results

During the study period, from among a total of 463 positive urine cultures, 48 (10.4%) (from 39 patients, 23 boys) were phenotypically ESBL-producing bacteria, with 66% of cases being younger than 12 months. It was found that 2 patients had 3 episodes and 4 patients had 2 episodes. Finally, a total of 39 patients and 117 controls were included in this study. Characteristics of the patients and laboratory data are described in Table I.

The most frequently isolated uropathogen was *Escherichia coli* in both groups. Klebsiella spp. and *Enterobacter cloacae* followed, and were found to be more prevalent in those diagnosed with UTI due to ESBL compared to non-ESBL ($p<0.05$, each). Additionally, *Citrobacter freundii* was isolated from both groups (1 each), and concerning exclusively the control group, other isolates were *Proteus mirabilis, Enterococcus faecium* and *Pseudomonas aeruginosa*.

Children with ESBL UTI were on antimicrobial prophylaxis more (21% vs. 6%, $p<0.05$), had higher rates of urinary tract anomalies (36% vs. 10%, $p<0.01$), presented abnormal DMSA findings (i.e. scars) (23% vs. 4%, $p<0.01$), and had longer hospitalization (9.8 vs. 7.4 days, $p<0.01$) compared to those with non-ESBL UTI. In addition, with the exception of fever, other presenting symptoms, including anorexia, flank pain, diarrhea, vomiting, abdominal pain, hematuria, and decreased food intake, were noticed to be more common in children with ESBL UTI (95% vs. 79%, $p<0.05$) than non-ESBL UTI. On the other hand, WBC count was lower in the ESBL UTI group ($11553\pm4537/mm^3$ vs. $13932\pm5739/mm^3$, $p<0.05$) compared to those with non-ESBL UTI.

The initial empiric treatment for UTIs, which was in most cases a 2nd generation cephalosporin or amoxicillin/clavulanate, was discontinued after antimicrobial susceptibility results showed phenotypically ESBL-producing bacteria. Then, an efficacious antimicrobial agent was given based on the susceptibility pattern of the isolated ESBL pathogens, which were found to be sensitive to imipenem (91.7%), amikacin (80.6%) and ciprofloxacin (75%).

Discussion

The increased prevalence of ESBL-producing bacteria constitutes an undeniable phenomenon. Worldwide, UTIs due to ESBL-producing bacteria are an important part of this problem[4,5]. This study aimed to evaluate the risk factors in ESBL UTIs, with the purpose of contributing to the early diagnosis and prompt management of these children and improving infection control locally.

In both cases and controls, *E. coli* was the leading isolated pathogen. Among the cases, Klebsiella spp. was more than two times and *E. cloacae* was more than six times as frequent compared with the controls. These findings may suggest that if the isolated microorganism of a UTI is Klebsiella spp. or *E. cloacae,* production of ESBL may be expected more frequently, as has also been reported in previous studies of Klebsiella spp.[10,11].

This study revealed that children with urinary tract anomalies and those receiving antimicrobial prophylaxis appear to be at higher risk for UTIs due to ESBL-producing pathogens. The same conclusions were also found in a previous study in which they were potential risk factors in bivariate analysis; however, multivariate analysis with logistic regression suggested that these findings should be supported by more comprehensive studies[10]. Furthermore, our study showed that children with UTIs due to ESBL-producing pathogens had an abnormal DMSA scan and longer duration of

hospitalization. Summarizing, abnormal DMSA scan, most commonly complicated with scars, may be the result of more severe UTIs due to ESBL-producing pathogens as compared to those with non-ESBL UTI. In addition, longer hospitalization can be explained easily by the delay in therapy due to the administration of an empirical treatment for non-ESBL-producing pathogens.

In the present study, children with ESBL UTI presented clinically most commonly with symptoms other than fever, including anorexia, flank pain, diarrhea, vomiting, abdominal pain, hematuria, and decreased food intake, as compared to children with non-ESBL UTI. Similar findings were reported in other studies[2,8,10,11]. On the other hand, the finding of lower mean WBC count in the ESBL UTI group as compared to those with non-ESBL UTI seems to be a paradox, probably explained by the limitations of the study.

Study limitations imposed by the data may affect the strength of conclusions drawn from it. Specifically, this study was retrospective, was conducted from a consecutive patient series rather than by random selection, and included a small number of cases due to the low prevalence of UTIs due to ESBL-producing pathogens.

In conclusion, treatment of UTIs is usually empirical while the results of urine culture are pending. Simultaneously, the growing resistance of pathogens to antimicrobial agents requires the need for periodic study of the pathogens isolated, their sensitivity, and the risk factors for UTI due to resistant pathogens such as ESBL. The results of this study may be useful in deciding empirical therapy for UTI until the production of ESBL has been verified.

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