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Clinical and laboratory differences between extended-spectrum β-lactamase-positive and extended-spectrum β-lactamase-negative bacteria in febrile urinary tract infection in pediatrics

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ABSTRACT

Introduction: The prevalence of urinary tract infections (UTIs) due to extended-spectrum beta-lactamase (ESBL)-producing bacteria is rising, which needs more potent antibiotics, such as carbapenems.

Objectives: To evaluate the clinical and laboratory differences between ESBL-positive and ESBL-negative bacteria in febrile UTI in children between one month to seven years to indicate prognostic parameters for ESBL$^+$ UTI and to suggest appropriate antibiotic treatment.

Patients and Methods: This cross-sectional study investigated 282 patients diagnosed with the first febrile UTI. The participants were assigned to ESBL-positive and ESBL-negative UTI groups. The groups were compared based on their clinical and laboratory characteristics and outcomes; the infant group was assessed separately (with the onset age of <3 months).

Results: The ESBL UTI was detected in 10.2% of the cases with a history of more frequent hospitalization ($P=0.002$), longer hospitalization ($P=0.04$), higher recurrence rate ($P=0.003$), and more red blood cell count in urine analysis findings ($P=0.02$). In the antimicrobial susceptibility assay, the ESBL-positive UTI group indicated resistance to third-generation cephalosporins; nevertheless, 93.1% of the cases responded clinically. The infant group showed 13% of the patients with ESBL-positive UTI that was correlated with a history of longer pre-onset hospital stay ($P=0.001$), elevated C-reactive protein (CRP) concentration ($P=0.002$), and elevated recurrence rate ($P=0.03$), compared to the older group.

Conclusion: The ESBL UTI should be further considered due to the resulted recurrence rate. The antimicrobial sensitivity assay indicated resistance to third-generation cephalosporins; however, these drugs are applied as the first choice due to the high response rate. Aminoglycosides are applicable as second choice drugs prior to initiating the use of carbapenems, if third-generation cephalosporins did not indicate bactericidal impacts on ESBL UTI.

Implication for health policy/practice/research/medical education:
In a cross-sectional study on 282 children, we evaluated the clinical and laboratory significance of extended-spectrum β-lactamase (ESBL) urinary tract infection (UTI) in children who were diagnosed with their first febrile infection. Patients were divided into ESBL$^+$ and ESBL$^-$ groups. ESBL$^+$ occurred in 10.2% of patients who had more frequent previous hospitalization, duration of hospitalization and higher recurrence rate. The antimicrobial susceptibility test demonstrated resistance to third-generation cephalosporins among ESBL-positive UTI. ESBL$^+$ UTI requires more attention because of its high recurrence rate and antibiotic resistance.

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Original

Introduction

Urinary tract infection (UTI) is a bacterial infection commonly observed in pediatrics (1). The severity of UTI manifestations and potential short- and long-term consequences are various based on the UTI site (i.e., lower/upper urinary tract or renal parenchyma) (2,3). Acute pyelonephritis (APN) causes renal scarring, resulting in long-term complications, such as hypertension, chronic renal injury, and end-stage kidney disease (4). In addition, renal scarring is possible due to the improper treatment of febrile UTI caused by APN and chronic renal injury. Therefore, appropriate antibiotic treatment is crucial to prevent these clinical complications.

Extended-spectrum beta-lactamase (ESBL)-producing bacteria can degrade the β-lactam ring in the majority of cephalosporins and penicillins (5). Furthermore, genes encoding resistance to different antimicrobial drugs, such as aminoglycosides and fluoroquinolones, can be observed near the genes encoding ESBL on bacterial plasmids, by which they confer multidrug resistance models (6). *Escherichia coli* species use different resistance strategies, such as producing ESBL (7). Antibiotic agents belonging to the carbapenem family have been the first-line treatment for ESBL-producing bacteria; however, there has been debate on maintaining or changing experimental antibiotics against carbapenems for the treatment of UTI caused by ESBL-producing bacteria.

The ESBL-producing bacteria were initially observed in Germany in 1983 (8). Their existence in UTI among children is rising (7,9). The complications of UTI caused by these bacteria have been controversial. According to the study by Fan et al, UTI caused by ESBL-producing bacteria can prolong hospitalization length, increase medical expenses, and reduce the rate of clinical outcomes (9). Nonetheless, Han et al announced that the infection with ESBL-producing bacteria causes no remarkable variations in the defervescence rate, eradication of bacteria from the urine, vesicoureteral reflux, APN, or length of fever (10).

Objectives

The current study evaluated the clinical and laboratory differences between ESBL-positive and ESBL-negative bacteria in febrile UTI among children within the age range of one month to seven years to assess the risk factors for ESBL and UTI and suggest proper antibiotic therapy.

Patients and Methods

Study design

This cross-sectional study investigated 282 patients diagnosed with the first febrile UTI at Amir-Kabir children hospital in Arak, Iran, from September 2016 to December 2019. Eligible cases meeting the American Academy of Pediatrics (AAP) guideline were enrolled in this study. The cases with no fever or with recurrent UTI were not included. Figure 1 displays a flow diagram of the studied patients. The participants were assigned to the ESBL$^+$ UTI

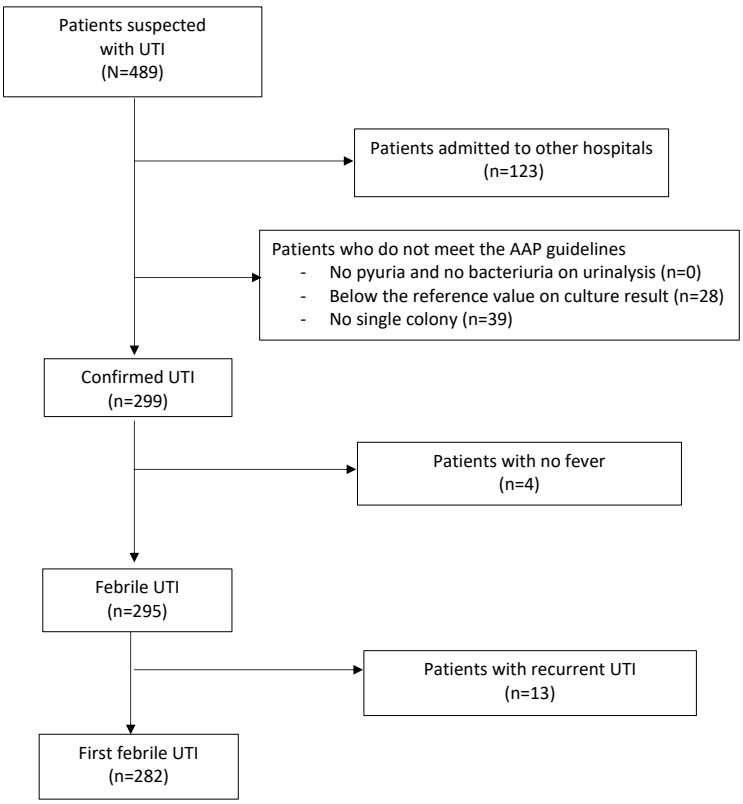

Figure 1. Flow diagram summarizing the patient selection process.

and ESBL⁻ UTI groups.

The urine samples were collected through urinary bladder catheter (n = 174), urine bag (n = 103), and mid-stream method (n = 5) in older cases. The diagnosis of UTI was made according to the instructions of the AAP, based on the results of pyuria or bacteriuria in urine assessment (white blood cell [WBC] counts over 10-20/HPF) and a positive urine culture finding when indicated a bacterial colony, including over 50 000 CFU/mL using a clean-catch and mid-stream technique or over 100 000 CFU/mL by the urine bag sampling.

Antimicrobial susceptibility testing (AST) was performed through the standard disc diffusion technique according to the recommendation of the Clinical and Laboratory Standards Institute (CLSI). The ESBL phenotypic confirmatory testing was also conducted using cefotaxime for all the samples through the disc diffusion technique on Mueller-Hinton agar plates.

Repeated urine assessments and urine cultures were conducted 18 to 36 hours when the first experimental antibiotic was administrated. The intravenous administration of cefotaxime as experimental antibiotics was performed in all cases. The antibiotic clinical impact was assessed using defervescence and negative culture findings when antibiotics were administrated. Antibiotics were not modified based on the antibiogram after the observation of clinical improvement and negative urine culture, and the treatment was continued with intravenous administration for 14 days.

The clinical and laboratory characteristics and outcomes of both groups were compared for the determination of risk factors for ESBL⁺ UTI. Additionally, the ESBL⁺ UTI group was evaluated regarding AST, causative organisms, and antibiotic reactions. The infants under three months of age were separately assessed.

Data analysis

All the analyses were performed by SPSS software (version 20). Moreover, the results were presented as mean ± standard deviation (for continuous variables) and percentage (for categorical variables). Fisher's exact test was employed for the comparison of categorical variables. The Mann-Whitney U test was used for continuous variables. A *P* value of less than 0.05 was considered statistically significant.

Results

Subjects' characteristics

The majority of the patients were male (63.1%) with an average age of 30 months. In addition, 18.4% of the subjects had a history of hospitalization. The rate of UTI caused by ESBL-producing bacteria was 10.2% (Table 1).

Table 1. Demographics of the patients

Total number of patients	282
Gender ratio (male/female)	1.71
Age (months)	30.0 ± 10.0
Weight (kg)	17.5 ± 1.4
Previous hospitalization	53 (18.7%)
Duration of hospitalization (days)	3.9 ± 1.2
Sepsis[a]	17 (6.02%)
Urine culture	ESBL⁻ 253 (89.7%), ESBL⁺ 29 (10.2%)

Data are presented as mean ± standard deviation or number (%).
[a] Patients with bacteria in the blood culture and the same bacteria in the urine culture.

Comparison of ESBL⁺ UTI and ESBL⁻ UTI groups

Tables 2 and 3 show the comparison of ESBL⁺ UTI and ESBL⁻ UTI groups. The patients with ESBL⁺ UTI showed a higher frequency of hospitalization (31%; $P = 0.002$), compared to the cases with ESBL⁻ UTI (16%). In addition, the average duration of hospitalization in the ESBL⁺ UTI group (4.8 days) was longer than that reported for the ESBL⁻ UTI group (3.15 days; $P = 0.04$). The average time to defervescence after antibiotics use was observed to be 1.35 ± 0.7 days (1.8 ± 0.62 in the ESBL⁺ UTI and 0.9 ± 0.82 in ESBL⁻ UTI groups; $P = 0.61$). There was no significant difference regarding age, gender, or prevalence of hydronephrosis on antenatal ultrasound between both groups.

Furthermore, the ESBL⁺ UTI group was reported with a short fever duration. There was no significant difference in blood laboratory markers, such as erythrocyte sedimentation rate, WBC count, and C-reactive protein (CRP), indicating infection severity. In addition, both groups were observed with no significant differences regarding the findings of β2-microglobulin reflecting tubular inflammation during the early stage of UTI. The image studies of hydronephrosis, vesicoureteral reflux, and renal scarring showed no significant differences between the two groups. In the urinary analysis findings (Table 3), the mean red blood cell (RBC) count in patients with ESBL⁺ UTI (10.42 ± 15.4) was higher than that of those with ESBL⁻ UTI (5.56 ± 10.5; $P = 0.02$). However, no significant differences were noticed in other urinary findings, such as pH, WBC count, bacteria, ketone, glucose, and protein quantity, between both groups.

The UTI recurrence rate was higher in the ESBL⁺ UTI group (41.3%; $P = 0.003$), compared to that reported for the ESBL⁻ UTI group (16.6%). In the ESBL⁺ UTI group, 12 out of 29 (41.3%) cases recurred, and 7 out of 12 (58.3%) patients had the same ESBL-producing bacteria.

Causative agents and treatment response of UTI

Table 4 tabulates the causative agents of UTI and antibiotic responses. *E. coli* (87.7%), *Klebsiella* (3.9%), *Enterobacter* (3.5%), *Proteus mirabilis* (1.1%), and *Citrobacter* spp. (1.1%), were the most important causative agents in the

Table 2. Comparison of ESBL⁻ and ESBL⁺ UTI groups

	ESBL⁻ (n = 253)	ESBL⁺ (n = 29)	*P* value
Patient characteristics			
Gender(male/female)	1.69	1.9	0.41
Age (months)	31.4 ± 7.32	29.3 ± 1.54	0.2
Previous hospitalization[a]	42/253 (16%)	11/29 (31%)	0.002
Hydronephrosis on antenatal sonography	6/253 (3%)	2/29 (6%)	0.12
Duration of hospitalization (days)	3.15 ± 1.1	4.8 ± 1.05	0.04
Duration of fever (days)	2.71 ± 1.14	2.66 ± 1.3	0.81
Duration of fever after antibiotics (days)	1.12 ± 0.82	1.04 ± 0.51	0.67
Gastrointestinal symptom	39/253 (15%)	3/29 (10%)	0.55
Blood laboratory findings			
Hemoglobin (g/dL)	13.3	14.1	0.67
Platelet count (×10³/µL)	398 ± 105	403 ± 99	0.33
WBC (×10³/µL)	14750 ± 4980	14557 ± 5170	0.21
MPV (fL)	6.6 ± 0.4	6.3 ± 0.3	0.7
ESR (mm/h)	35.6 ± 21.4	34.3 ± 20.2	0.32
CRP (mg/L)	39.6 ± 28.3	41.5 ± 25.4	0.50
BUN (mg/dL)	7.3 ± 2.4	7.9 ± 2.9	0.91
Cr (mg/dL)	0.24 ± 0.28	0.25 ± 0.45	0.87
β2-microglobulin (mg/L)	0.58 ± 0.78	1.48 ± 0.22	0.54
Radiologic findings and outcomes			
Abnormal sonographic findings	181/253 (71.5%)	21/29 (72.4%)	0.89
Hydronephrosis	32/145 (22%)	6/18 (33.3%)	0.65
DMSA abnormality	91/212 (42.9%)	11/26 (42.3%)	0.8
VUR	42/141 (29.7%)	6/19 (31.5%)	0.91
High-grade VUR (IV, V)	15/39 (38.4%)	2/5 (40%)	0.77
Sepsis	16 (6.3%)	2 (6.8%)	0.12
Surgery[b]	8 (3.1%)	1 (3.4%)	0.83
Recurrence of UTI[c]	42 (16.6%)	12 (41.3%)	0.003

Data are presented as mean± SD or number (%).
Abbreviations: WBC, white blood cell; MPV, mean platelet volume; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BUN, blood urea nitrogen; Cr, creatinine; DMSA, dimercaptosuccinic acid; VUR, vesicoureteral reflux; UTI, urinary tract infection.
[a] Previous hospitalization excluded patients who were hospitalized without use of antibiotics. It indicates previous hospitalization with antibiotic treatment due to infection, and re-admission due to UTI occurred at least 2 weeks after the previous hospitalization.
[b]Surgery included ureteroneocystostomy, deflux injection, and detrusorhaphy.
[c] The date of recurrence ranged from 35 to 293 days.

ESBL⁻ UTI group; however, *E. coli* was dominant in the ESBL⁺ UTI group (100%). All the cases were given third-generation cephalosporins parenterally. The response to antibiotics was assessed using urine culture findings 18 to 36 hours following the first antibiotic administration. The cases with ESBL⁻ bacteria and 27 of 29 (93.1%) cases with ESBL⁺ bacteria had negative culture findings following antibiotic injection. Two cases with no response to empirical antibiotics received carbapenem and had negative culture findings.

Table 5 shows AST in cases infected with ESBL-producing bacteria resistant and susceptible to the carbapenem family. Furthermore, amikacin (100%) and gentamicin (82%) were observed with increased vulnerability and low average minimum inhibitory concentration (MIC).

Comparison of ESBL⁺ UTI and ESBL⁻ UTI (<3 months; 90 patients)

In the infant group, ESBL⁺ UTI occurred in 11 (12.2%) patients. The ESBL⁺ UTI and ESBL⁻ UTI groups (including cases of <3 months of age) were compared in this study. In the early years, the ESBL⁺ UTI group was detected with a more frequent history of hospitalization (63.6%; $P=0.001$), compared to the ESBL⁻ UTI group (12.6%). Moreover, the ESBL⁺ UTI group showed a higher hydronephrosis rate detected by antenatal ultrasound (27.2%; $P=0.032$), compared to the ESBL⁻ UTI group (2.5%) (Table 6). The ESBL⁺ UTI group had higher CRP levels in the early years (<3 months) ($P=0.002$). The recurrence rate of the ESBL⁺ UTI group was higher (63.6%; $P=0.03$) than that reported for the ESBL⁻ UTI group (24%). No significant difference was noticed in urinary indicators, such as RBC and WBC counts, bacteria, ketone, glucose, and protein quantity, between the two groups.

Discussion

The ESBL-producing organisms commonly appear in hospitals; however, they can be observed in communities, with an increasing prevalence (1,9,11). Therefore, recognizing the risk factors to develop ESBL-producing

Table 3. Comparison of ESBL⁻ and ESBL⁺ UTI groups in urinary analysis findings

		ESBL⁻ (n=253)	ESBL⁺ (n=29)	*P* value
Urinary analysis findings				
Urine Specific Gravity, mean ± SD		1.01 ± 0.06	1.01 ± 0.07	0.06
pH, mean ± SD		5.95 ± 0.85	6.06 ± 0.98	0.45
WBC, mean ± SD		34.82 ± 18.32	33 ± 18.37	0.54
RBC, mean ± SD		5.56 ± 10.5	10.42 ± 15.4	0.02
EP, mean ± SD		1.69 ± 1.75	1.9 ± 2.69	0.56
Bacteria, No. (%)	Negative	10 (3.9)	1 (3.4)	0.44
	Rare	15 (5.9)	3 (1.3)	
	Few	49 (19.3)	5 (17.2)	
	Moderate	71 (28)	7 (24.1)	
	Many	101 (39.9)	11 (37.9)	
	Heavy	7 (2.7)	2 (6.8)	
Glucose, No. (%)	Negative	228 (90.1)	27 (93.1)	0.2
	+1	10 (3.9)	1 (3.4)	
	+2	3 (1.1)	0 (0)	
	+3	12 (4.7)	1 (3.4)	
Ketones, No. (%)	Negative	230 (90.9)	26 (89.6)	0.1
	+1	9 (3.5)	1 (3.4)	
	+2	14 (5.5)	2 (6.8)	
Protein, No. (%)	Negative	211 (83.3)	24 (82.7)	0.57
	+1	23 (9.0)	3 (10.3)	
	+2	17 (6.7)	2 (6.8)	
	+3	2 (0.7)	0 (0)	
	+4	0 (0)	0 (0)	
Bilirubin, N (%)	Negative	251 (99.2)	29 (100)	0.43
	Positive	2 (0.7)	0 (0)	
Urobilinogen, No. (%)	Negative	253 (100)	29 (100)	0.11
Nitrite, No. (%)	Negative	161 (63.6)	20 (68.9)	0.16
	+1	82 (32.4)	9 (31.0)	
	+2	10 (3.9)	1 (3.4)	
Mucus,No. (%)	Negative	236 (93.2)	26 (89.56)	0.56
	Light	13 (5.13)	2 (6.8)	
	Moderate	4 (1.5)	0 (0)	
	Heavy	0 (0)	1 (3.4)	

Abbreviations: WBC, white blood cell; SD, standard deviation; RBC, red blood cell; n, number; EP, epithelial cell.

Table 4. Causative organisms of UTI and results of treatment

Organisms	ESBL⁻ (n=253)		ESBL⁺ (n=29)
	E. coli	222 (87.7%)	*E. coli* 29 (100%)
	K. pneumoniae	10 (3.9%)	
	P. mirabilis	3 (1.1%)	
	Enterobacter spp.	9 (3.5%)	
	Citrobacter spp.	3 (1.1%)	
	Others	6 (2.3%)	
Antibiotic response to first antibiotics	228/228 (100%)		27/29 (93.1%)[a]

[a] Two patients did not respond to third-generation cephalosporin and required carbapenem.

organisms is of great importance. Studies have widely investigated the prognostic factors, severity, and therapy of ESBL⁺ UTI for pediatrics (1,9,10,12). According to the study by Fan et al, UTI caused by EBSL-producing bacteria can prolong hospitalization, increase medical expenses, and reduce the rate of clinical and microbiologic outcomes (9). The ESBL⁺ UTI significantly increased the length of hospitalization than ESBL⁻ UTI.

In a study conducted by Dotis et al, patients with ESBL⁺ UTI were observed with unusual results on 99mTc dimercaptosuccinic acid (DMSA) scans and hospitalized longer, compared to cases with ESBL⁻ UTI (12). The ESBL⁺ UTI was linked to unusual findings on voiding cystourethrogram (1). According to the study by Han et al, ESBL and non-ESBL groups showed no remarkable difference in the defervescence rate, APN, eradication of

Table 5. Antibiotic susceptibility test results for ESBL bacteria (n=29)

Antibiotics	Sensitivity	Resistant	Mean MIC
Amikacin	29/29 (100%)	0/29 (0%)	2.22
Gentamicin	24/29 (82%)	5/29 (17%)	1.15
Ampicillin	0/29 (0%)	29/29 (100%)	
Ampicillin/Sulbactam	7/29 (24%)	22/29 (75%)	11.44
Aztreonam	13/29 (44%)	16/29 (55%)	1.06
Cefazolin	0/29 (0%)	29/29 (100%)	
Cefoxitin	29/29 (100%)	0/29 (0%)	6.54
Cefotaxime	0/29 (0%)	29/29 (100%)	
Ceftazidime	17/29 (58%)	12/29 (41%)	1.54
Cefepime	17/29 (58%)	13/29 (44%)	1.32
Piperacillin/Tazobactam	29/29 (100%)	0/29 (0%)	5.61
Ertapenem	29/29 (100%)	0/29 (0%)	0.24
Meropenem	29/29 (100%)	0/29 (0%)	
Levofloxacin	15/29 (51%)	14/29 (48%)	0.42
Co-trimoxazole	18/29 (62%)	11/29 (37%)	15
Tigecycline	29/29 (100%)	0/29 (0%)	0.65

Table 6. Comparison between $ESBL^-$ and $ESBL^+$ UTI groups (age below three months, 90 patients)

	$ESBL^-$ (n = 79)	$ESBL^+$ (n = 11)	*P* value
Patient characteristics			
Gender (male/female)	2.81	2.9	0.43
Admission history	10/79 (12.6%)	7/11 (63.6%)	0.001
Hydronephrosis on antenatal sonography	2/79 (2.5%)	3/11 (27.2%)	0.032
Duration of hospitalization (days)	3.92 ± 1.5	4.13 ± 1.54	0.4
Duration of fever (days)	2.53 ± 1.2	2.88 ± 1.31	0.12
Duration of fever after antibiotics (days)	1.04 ± 0.50	1.11 ± 1.4	0.53
Gastrointestinal symptom	7/79 (8.8%)	1/11 (9%)	0.99
Blood laboratory findings			
Hemoglobin (g/dL)	10.3	10.1	0.42
Platelet count ($\times10^3/\mu L$)	434 ± 112	456 ± 117	0.9
WBC ($\times10^3/\mu L$)	12,980 ± 5670	13100 ± 4561	0.8
MPV (fL)	7.5 ± 0.5	7.4 ± 0.3	0.6
ESR (mm/h)	26.5 ± 15.6	28.5 ± 17.9	0.09
CRP (mg/L)	30.3 ± 17.3	49.4 ± 20.8	0.002
BUN (mg/dL)	7.9 ± 1.5	8.1 ± 3.1	0.97
Cr (mg/dL)	0.21 ± 0.02	0.22 ± 0.14	0.35
β2-microglobulin (mg/L)	0.69 ± 1.55	3.43 ± 2.1	0.38
Radiologic findings and outcomes			
Abnormal sonographic findings	56/79 (70.8%)	7/11 (63.6%)	0.5
Hydronephrosis	11/58 (18.9%)	1/7 (14.2%)	0.63
DMSA abnormality	21/70 (30%)	3/9 (33.3%)	0.43
VUR	16/42 (38%)	4/9 (44.4%)	0.81
High-grade VUR (IV, V)	4/12 (33.3%)	2/5 (40%)	0.88
Sepsis	9/79 (11.3%)	2/11 (18.1%)	0.1
Surgery	3/79 (3.7%)	1/11 (9%)	0.72
Recurrence of UTI[a]	19/79 (24%)	7/11 (63.6%)	0.03

Data are presented as mean ± SD or number (%).

Abbreviations: WBC, white blood cell; MPV, mean platelet volume; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BUN, blood urea nitrogen; Cr, creatinine; DMSA, dimercaptosuccinic acid; VUR, vesicoureteral reflux; UTI, urinary tract infection.

[a] The date of recurrence ranged from 35 to 247 days.

bacteria from the urine, and vesicoureteral reflux (10).

There was no difference in microbiologic responses, renal scarring on DMSA scan and vesicoureteral reflux on voiding cystourethrogram between the ESBL$^+$ UTI and ESBL$^-$ UTI groups. Nonetheless, ESBL$^+$ UTI showed a significant association with a higher UTI recurrence rate. Due to UTI recurrence, patients affected by ESBL$^+$ UTI need more attention through follow-up. In addition, more investigations are required if cases with ESBL$^+$ UTI are possibly repeatedly faced with the same ESBL$^+$ bacteria since 73% of recurred cases in the ESBL$^+$ UTI group showed infection with the same ESBL$^+$ bacteria.

The ESBL$^+$ UTI more frequently occurs in cases with a history of antibiotic administration (1,7). According to the study of Kizilca et al, the use of prophylactic antibiotics for a longtime is a great risk factor to be infected with ESBL-producing bacteria (13). A history of hospitalization and using antibiotics could increase the rate of ESBL$^+$ UTI. Therefore, the administration of antibiotics for UTI prophylaxis is a risk factor for ESBL bacterial infection.

This study also assessed ESBL effects on UTI in infants (under three months of age). These cases have possibly weaker immune systems showing different clinical features in ESBL$^+$ UTI. The CRP assessment indicated a significant difference in the infants under three months of age ($P = 0.002$). It is essential to perform further studies using a larger sample size to confirm the necessity of complete control of ESBL$^+$ UTI in this group.

The ESBL-producing bacteria are rare pathogens causing UTI in pediatrics; however, they have an increasing prevalence (7,9). The third-generation cephalosporins are currently the most common candidates for the UTI empirical treatment of children (4,14). The ESBL-producing bacteria are resistant to these drugs in vitro (15). However, the ESBL-producing bacteria response to antibiotics is better, compared to their in vitro susceptibility (16,17).

The response to third-generation cephalosporins was observed in 27 out of 29 cases (93.1%) with ESBL-producing bacterial infection. Consequently, they continued the use of similar antibiotics within 14 days, indicating that the in vitro resistance of these bacteria to this drug noted by standard techniques could not effectively predict their in vivo susceptibility. The disagreement between in vitro and in vivo sensitivity has not yet been understood. Hoo et al reported that the antibiotic response could be influenced by different factors, such as bacterial resistance mutation, immune function, and medication use (18).

According to Gentry et al, the majority of cephalosporins can be excreted mainly through the kidneys, and after even using a small dose, urinary concentrations are higher than 1000 mg/L (19). Accordingly, antibiotics are more concentrated in urine; however, blood concentration is considered for susceptibility testing (4). As a result, the administration of third-generation cephalosporins may be useful for ESBL-producing bacteria in UTI and is continued when the cases are observed with improved symptoms.

In general, carbapenems are used to treat infections caused by ESBL-producing strains (20,21). However, due to the excessive use of carbapenems, the resistance issue should be considered (22,23). Aminoglycoside antibiotics are possible alternatives to carbapenems due to their high susceptibility and low average MIC. Amikacin was noticed to be sensitive to ESBL-producing bacteria.

In this study, 17 out of 29 (58%) ESBL isolates were susceptible to ceftazidime and cefepime, and 29 out of 29 (100%) isolates were susceptible to cefoxitin (Table 5). In the studied hospital, ESBL phenotypic confirmatory assay was conducted using cefotaxime through the disc diffusion technique. Susceptibility and therapy response to cefotaxime, cefoxitin, ceftazidime, and cefepime in ESBL vary according to the ESBL$^+$ bacteria subtypes. For instance, CTX-M beta-lactamases, as ESBLs, are highly resistant to cefotaxime, compared to others, such as ceftazidime, ceftriaxone, and cefepime (24).

In addition, cefotaxime was observed with a favorable response to treatment, compared to ceftazidime for TEM-6 and TEM-12, because their ESBLs possess a weak hydrolytic effect on extended-spectrum cephalosporins (25). The subtypes of ESBL were not detected because they have a retrospective nature. Nonetheless, the identification of dominant subtypes of ESBL is effective for the determination of proper antibiotics. Therefore, it is required to carry out further studies in this regard.

Conclusion

The ESBL$^+$ UTI should be highly considered due to its high recurrence rate. The infants under three months of age with a history of hospitalization were observed with more severe infections and higher recurrence rates; consequently, antibiotics should be cautiously selected. Third-generation cephalosporins were observed with resistance in AST; however, they may be utilized as the first-line experimental antibiotics due to higher clinical response frequency. Regarding ESBL$^+$ UTI resistance to third-generation cephalosporins, aminoglycoside can be considered the second antibiotic choice prior to carbapenems.

Study limitations

The current study has several limitations. The urine culture technique included a urine bag assessment increasing the likelihood of contamination. It seems essential to perform a prospective, large-scale, and longitudinal study to investigate the clinical features of ESBL$^+$ UTI based on patient age, course of the disease, and treatment response, the results of which may provide a proper therapeutic guideline to manage ESBL$^+$ UTI.

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Authors' contribution

SN, MK and PY were the principal investigators of the study. DH, and MSh were included in preparing the concept and design. MSh and MK revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study was carried out based on the Declaration of Helsinki. The Ethics Committee of Arak University of Medical Sciences approved this study (Ethical code#IR.ARAKMU.REC.1396.199). The study subjects signed the written informed consent before the study. The current study was extracted from the MD thesis of Somaie Nejabat at Arak University of Medical Sciences (Thesis #2857). Moreover, ethical issues (including plagiarism, data fabrication, double publication) also were completely observed by the authors.

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