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Clinical Patterns and Seasonal Distribution of Urinary Tract Infection Caused by Extended-spectrum Beta-lactamase-producing Bacteria in Children

Çocuklarda Genişlemiş Spektrumlu Beta-laktamaz Üreten Bakterilerin Neden Olduğu İdrar Yolu İnfeksiyonlarının Klinik Paterni ve Mevsimsel Dağılımı

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ABSTRACT

Introduction: *Extended-spectrum β-lactamase-producing Escherichia coli or Klebsiella pneumoniae infections in the pediatric age group are mostly nosocomial infections. This study aimed to investigate the clinical pattern of extended-spectrum β-lactamase positive urinary tract infection and its seasonal distribution.*

Materials and Methods: *We retrospectively reviewed the medical records of pediatric patients with extended-spectrum β-lactamases-positive UTI, who were followed-up in our clinic between June 2015 and June 2020.*

Results: *One hundred-and-ten patients with ESBL-positive UTI and 231 with non-ESBL UTI were enrolled in this study. The rate of male sex in the ESBL group was significantly lower than that in the non-ESBL group (10.9% vs 27.2%, p= 0.001). The patients with ESBL were older than those in the non-ESBL group (81.3 ± 49.0 months vs 56.0 ± 47.2 months, p= 0.001). E. coli was the most isolated bacteria in both groups (68% and 70.5%, respectively). The rate of Klebsiella isolation in urine culture was significantly greater in the ESBL group than in the non-ESBL group (p= 0.04). The seasonal distribution of ESBL-positive patients was as follows: spring (18/16.4%), summer (25/22.7%), autumn (25/22.7%), and winter (42/38.2%).*

Conclusion: *There is a substantially high rate of antibiotic resistance among patients with urinary tract infection in developing countries like Turkey. Moreover, we should be aware of the risk of ESBL-positive UTIs, especially in winter.*

Key Words: *Extended-spectrum β-lactamase; Urinary tract infection; Pediatric; Season*

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ÖZ

Çocuklarda Genişlemiş Spektrumlu Beta-laktamaz Üreten Bakterilerin Neden Olduğu İdrar Yolu İnfeksiyonlarının Klinik Paterni ve Mevsimsel Dağılımı

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Giriş: *Çocukluk yaş grubunda, genişlemiş spektrumlu β-laktamaz (GSBL) üreten Escherichia coli veya Klebsiella pneumoniae kaynaklı infeksiyonlar genelde hastane kaynaklıdır. Bu çalışmada GSBL (+) bakterilerle gelişen idrar yolu infeksiyonların klinik paterni ve mevsimsel dağılımını araştırmayı amaçladık.*

Materyal ve Metod: *Haziran 2015 - Haziran 2020 tarihleri arasında kliniğimizde izlenen genişlemiş spektrumlu β-laktamaz pozitif bakterilerle gelişen idrar yolu infeksiyonu tanılı pediatrik hastaların tıbbi kayıtlarını geriye dönük olarak inceledik.*

Bulgular: *Bu çalışmaya, GSBL (+) bakterilerle gelişen idrar yolu infeksiyonu olan 110 hasta ve GSBL negatif bakterilerle gelişen idrar yolu infeksiyonu olan 231 hasta dahil oldu. GSBL (+) grubundaki erkek cinsiyet oranı, GSBL (-) grupla karşılaştırıldığında anlamlı olarak daha düşüktü (%10.9'a karşı %27.2, p= 0.001). GSBL (+) hastalar, GSBL (-) olanlara göre daha yaşlıydı (81.3 ± 49.0 ay vs 560 ± 47.2 ay, p= 0.001). E. coli her iki grupta da en çok izole edilen bakteriydi (GSBL (+): %68, GSBL (-): %70.5). İdrar kültüründe Klebsiella izolasyon oranı GSBL (+) grubunda, GSBL (-) grubuna göre anlamlı olarak daha yüksekti (p= 0.04). GSBL (+) infeksiyonların, mevsimsel dağılımı şu şekildeydi: ilkbahar (18/%16.4), yaz (25/%22.7), sonbahar (25/%22.7) ve kış (42/%38.2).*

Sonuç: *Türkiye gibi gelişmekte olan ülkelerde, idrar yolu infeksiyonu olan hastalar arasında oldukça yüksek oranda antibiyotik direnci vardır. Özellikle antibiyotik kullanımın arttığı kış aylarında GSBL (+) idrar yolu infeksiyonların farkında olunmalıdır.*

Anahtar Kelimeler: *Genişlemiş spektrumlu β-laktamaz; idrar yolu infeksiyonu; Pediatrik; Mevsim*

INTRODUCTION

Due to the frequent use of antibiotics, resistant strains are emerging. Pathogens that cause urinary tract infections (UTI) have different resistance mechanisms, one of which is by producing extended-spectrum β-lactamases (ESBL). ESBL are plasmid-mediated enzymes that degrade the β-lactam ring of most penicillins and expanded spectrum cephalosporins, thereby causing resistance[1,2]. The identification of risk factors for antimicrobial resistance may improve the empirical treatment of UTI. Nowadays, ESBL producers causing UTIs are not only encountered in hospital settings but they are widely spread in the community[3-5]. This is a principal mechanism of the spread of antibiotic resistance because of the horizontal transfer of the genetic material coding for antibiotic resistance via conjugation between two different bacteria[6]. Physicians should consider regional antibiotic resistance while determining empirical therapy until they obtain culture results, or they have no culture tests. Among the recognized risk factors for pediatric infections by ESBL-producing *E. coli* or K. pneumonia are vesicoureteral reflux, hospitalizations in the last 3 months, UTI prophylaxis, previous UTI, recent antibiotic use, and high UTI recurrence rate[7-12]. This study aimed to investigate the clinical pattern of ESBL positive urinary tract infection and its seasonal distribution.

MATERIALS and METHODS

We retrospectively reviewed the medical records of pediatric patients with ESBL-positive UTI and control group with ESBL-negative UTI, who were followed-up in between June 2015 and June 2020 at Kırıkkale University Hospital. Exclusion criteria included the presence of neurological lesions, anatomical abnormalities of the lower urinary tract, and antibiotic usage at the time of urine culture test. All urine samples were collected by midstream clean catch, catheterization, or urine bags. Significant growth was

defined as ≥50.000 colony-forming units (CFU)/mL, and pyuria was defined as >10 WBC/mm^3 in the urine sample[13]. Antimicrobial susceptibility testing was performed on the cultures using the Vitek-2 automated system. In addition to demographic findings, prevalence and patterns of antibiotic resistance of the uropathogens were recorded on a standard form. Children with clinical upper UTIs were hospitalized and treated with parenteral antibiotics for 7 to 14 days. Children with lower UTI were managed on an outpatient basis[14]. The following information was obtained from the patients' medical histories: (1) voiding dysfunction; (2) first or recurrent UTI; (3) antibiotic prophylaxis. Some patients were investigated further to identify underlying abnormalities that may predispose to urinary tract infection, as recommended by the NICE (National Institute for Health and Care Excellence) guidance for pediatric patients with UTI[15]; such as voiding cystourethrogram (VCUG), dimercaptosuccinic acid scan (DMSA).

Extended-spectrum β-lactamase detection and confirmation was made by BD Phoenix automated identification and susceptibility testing system.

The ethics committee approval of the study was obtained from Kırıkkale University Non-invasive Research Ethics Committee (Date: 26.08.2020, No: 2020.07.04) All study procedures were performed in accordance with the Helsinki declaration, and patient data were collected and processed per legal requirements.

Statistical Analysis

Study data were analyzed by SPSS (Statistical Package for Social Science) 16.0 software package. The results are shown as mean ± SD unless stated otherwise. Mann Whitney-U test and Chi-square test were used to assess differences between the two groups. Logistic regression was used to determine the risk factors for ESBL-producing bacteria. The level of statistical significance was set at $p< 0.05$.

RESULTS

One hundred and ten patients with ESBL-positive UTI and 231 with non-ESBL UTI were enrolled in this study. The rate of male sex in the ESBL group was significantly lower than that in the non-ESBL group (10.9% vs 27.2%, p= 0.001). The patients with ESBL were older than those in the non-ESBL group (81.3 ± 49.0 months vs 56.0 ± 47.2 months, p= 0.001). Significantly more patients had a history of recurrent UTI in the non-ESBL group (38.4% vs 22.9%, p= 0.012). The seasonal distribution of ESBL-positive patients was as follows: spring (18/16.4%), summer (25/22.7%), autumn (25/22.7%), and winter (42/38.2%).

As for the UTI symptoms in the study groups, abdominal pain, back pain, fever, vomiting, and enuresis were more frequent in the ESBL group. The incidence of vesicoureteral reflux (VUR) was higher in the ESBL group (15.4% vs 10.6%, p= 0.04). The rate of nitrite positivity was significantly higher in the non-ESBL group (22.3% vs 15.2%, p= 0.011). *E. coli* was the most isolated bacteria in both groups (68% and 70.5%, respectively). The rate of *Klebsiella* isolation in urine culture was significantly greater in the ESBL group than in the non-ESBL group (p= 0.04) (Table 1).

Regression analysis revealed that older age and female sex were risk factors for ESBL UTI (OR=1.011, 95% CI 1.006-1.016; p> 0.001, and OR= 3.062, 95% CI 1.574-5.959; P< 0.001, respectively). However, having a history of UTI and presence of VUR were not risk factors for ESBL (OR= 0.642, 95% CI 0.329-1.253; p= 0.642, and OR= 0.999, 95% CI 0.533-1.872; p= 0.998, respectively)

DISCUSSION

This study aimed to assess the clinical characteristics, seasonal distribution, and possible risk factors for ESBL UTI in the pediatric age group. Previous studies have shown that the use of antibiotics in the last 3 months, previous hospitalization in the last 3 months, a history of recurrent UTI, and the presence of renal anomalies are risk factors for ESBL infection[10,16]. In the present cohort, there was a female predominance with a proportion of girls of 89.1 %, which is significantly higher compared with other studies[17]. Hence, we found a significantly lower proportion of males and a lower rate of history of infection in the ESBL group. While some previous studies have identified male sex as a risk

Table 1. Comparison of ESBL-positive and non-ESBL-positive groups with respect to clinical data and laboratory results

	ESBL n= 110	Non-ESBL n= 231	p
Sex (female) n (%)	98 (89.1)	168 (72.8)	0.001
Mean age (months)*	81.3 ± 49.0	56.0 ± 47.2	0.001
History of urinary tract infection n (%)	78 (22.9)	131 (38.4)	0.012
Fever n (%)	72 (21.1)	33 (9.7)	0.001
Vomiting n (%)	24 (7.0)	21 (6.2)	0.001
Abdominal pain n (%)	61 (17.9)	45 (13.2)	0.001
Back pain n (%)	45 (13.2)	10 (2.9)	0.001
Enuresis n (%)	32 (9.4)	23 (6.8)	0.001
VUR n (%)	17 (15.4)	36 (10.6)	0.04
Urine nitrite positivity (%)	52 (15.2)	76 (22.3)	0.011
Neurogenic bladder n (%)	9 (2.7)	0	
CRP (mg/L)*	57.8 ± 7.3	37.8 ± 8.2	0.032
Leucocyte (/mm³)*	13500 ± 5900	11200 ± 4300	0.342
Serum creatinine (mg/dL)*	0.53 ± 0.04	0.58 ± 0.9	0.892
Urine culture			
E. coli n (%)	75 (68)	163 (70.5)	0.812
Klebsiella n (%)	32 (29)	38 (16.5)	0.04
Proteus n (%)	2 (1.8)	15 (6.5)	
Pseudomonas n (%)	1 (0.9)	5 (2.2)	
Others n (%)	-	10 (4.3)	

ESBL: Extended-spectrum Beta-lactamase, VUR: Vesicoureteral reflux. CRP: C-reactive protein.
*Mean ± SD.

factor for ESBL-positive UTI[18,19], some others have reported the opposite[20]. Urinary tract infection is more common in girls (1-3%) than boys (1%) as a result of factors related to their urinary anatomy such as short urethra among others[21]. There is also a common irrational antibiotic use in our country. An irrational antibiotic use for every infection leads to an increased rate of ESBL UTI. This affects both the general population and specifically girls, rendering female sex a risk factor[22,23].

Escherichia coli was the predominant pathogen in both the ESBL and non-ESBL groups, with *Klebsiella* being the second most commonly detected microorganism. The prevalence of ESBL producing *K. pneumoniae* have risen substantially in several countries[24,25]. Besides, parent medication practice, which is high in our country, could have accounted for this higher prevalence. The rate of *Klebsiella* infection (29%) was significantly greater in the ESBL group than in the non-ESBL group. Topaloglu et al. have reported an even higher rate (35.5%)[10]. Previous studies have already shown that *Klebsiella* UTI is a significant risk factor for ESBL UTI[17].

Although former studies have suggested the opposite, there was a significant difference in the clinical presentation of ESBL-UTI and non-ESBL UTIs[10,17]. Although ESBL is not a virulence factor, this can be attributed to a limitation in the availability of oral therapy in these patients as well as a delay in initiating appropriate antimicrobial therapy while waiting for urine culture results.

We found that ESBL-positive UTI was mostly seen in winter. However, Yolbas et al.[26] have found that UTIs were mostly seen in summer (35.3%). They have also found that UTI was less common in spring (23.3%), agreeing with our results. We suggest that the increased incidence of ESBL-positive UTI in winter is caused by an

increased rate of antibiotic use in winter because of upper airway infections.

The rate of VUR was higher in the ESBL group as previous studies have also suggested[9,10]. This was probably caused by prophylactic antibiotic use in patients with VUR.

The present study has a number of potential limitations. Firstly, because of its retrospective nature and reliance on medical records, some of the investigated data were not available for all patients. Secondly, this study was conducted in a single tertiary referral hospital and may thus not be generalized to the general population.

In conclusion, the recognition of risk factors for pediatric UTIs caused by ESBL (+) bacteria may aid in the identification of high-risk cases and enable proper management of these patients. There is a substantially high rate of antibiotic resistance among patients with UTI in developing countries like Turkey. Moreover, we should be aware of the risk of ESBL-positive UTIs, especially in winter.

ETHICS COMMITTEE APPROVAL

The approval for this study was obtained from Kırıkkale University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (Decision no: 2020.07.04 Date: 26.08.2020).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: All of authors

Analysis/Interpretation: ST, AA, SG, YK

Data Acquisition: All of authors

Writing: ST, AA, YK, SG

Revision and Correction: ST, YK, SG

Final Approval: All of authors

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