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Original Article

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Antibiotic Resistance in Pyelonephritis Episode in Children with Recurrent Urinary Tract Infections

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ABSTRACT

Objective: Bacterial resistance is a major problem in recurrent urinary tract infections. These infections are seen commonly in children with urinary tract anomalies. In this study, we aimed to determine the bacterial resistance patterns of antibiotics in pyelonephritis.
Methods: One hundred two patients were reviewed with recurrent UTI during a pyelonephritis episode retrospectively. The patients were using some antibiotics at different times as prophylaxis. Routine biochemical parameters and ultrasonographic results were also evaluated.
Results: Escherichia coli was detected as the main bacterial pathogen. Bacterial isolates were significantly found more resistant to trimethoprim-sulfamethoxazole in children with the risk factor. On the other hand, the causative microorganisms were significantly found more resistant to some antibiotics in patients under prophylaxis.
Conclusion: Frequent use of antibiotics due to recurrent infections might be a factor in the development of antibiotic resistance in children. However, drug selection should be made by considering antibiotic resistance rates.
Keywords: Antibiotic resistance, children, pyelonephritis, urinary tract infection

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INTRODUCTION

Urinary tract infections (UTIs) are very common in children. The risk factors of UTI are bacterial intestinal flora changes, immature immune system, and urinary tract anomalies.[1] Urinary tract anomalies are also the cause of recurrent UTIs. , The first sign of urinary tract anomaly is UTI in 30% of children.[2] The disease recurrence rate is 30% in a 6-12 months period after the first UTI.[3] Long-term morbidities such as hypertension, toxemia during pregnancy, the development of chronic kidney disease, and the need for kidney transplantation can be prevented by early diagnosis and treatment of recurrent UTI.[4] However febrile recurrent UTI is the cause of permanent kidney damage in 10-40% of cases.[5] Permanent kidney damage can be detected by Technetium-99m-dimerkaptosüksinikasit (DMSA) scintigraphy and ultrasound. They are the most common and the easiest methods.[6]

Although there is no controlled study to support the use of prophylaxis, a prophylactic antibiotic is used commonly in children with risk factors.[7] But, the increasing rate of antibiotic resistance with recurrent UTI is a serious health problem in these populations.[8,9] On the other hand, the studies showed that it is necessary to start empirical antibiotics in the first 72 h to prevent renal damage in pyelonephritis attacks.[10] Empirical antibiotic selection is made according to the antibiotic resistance of the bacteria.[11] It is recommended to use first or second-generation cephalosporins, trimethoprim-sulfamethoxazole (TMP-SMX), or amoxicillin/clavulanic acid as a first-line empiric treatment for pyelonephritis.[12]

The objective of this study was to determine urinary pathogens and frequency of risk factors and assess the resistance patterns of bacterial isolates to commonly used antibiotics during a pyelonephritis episode in children with recurrent UTI. Thus, the most frequent isolated microorganisms in the urine culture, the relationship between antimicrobial sensitivity and urinary tract anomalies will be determined, and empirical antibiotic treatment will be selected for recurrent UTI.

METHODS

We retrospectively reviewed the 102 patients with recurrent UTI during pyelonephritis episode who were admitted to Pediatric Nephrology Clinic, in 18 months period. The children aged 1-17 years old. This study was approved by the Ethics Committee of Duzce University School of Medicine (Approval Date: February 15, 2021 – No. 2021/19). Informed consent was obtained from all the participants. The patients were using TMP-SMX, nitrofurantoin, and cefixime at different times as prophylaxis. One hundred two urine isolates were obtained. Urine samples were collected by urinary catheter in non-toilet trained children and by mid-stream urine method after cleaning the perineum with soap or antiseptic liquid in the other children. All urine samples were submitted to the clinical microbiology laboratory for testing. Patients with pyuria in urine microscopy and significant growth in urine culture were included in the study. Multiple insignificant bacteria growth or below the standard quantity of colony-forming units/milliliter (CFU) or contamination in the urine culture were accepted as exclusion criteria. A single bacterial strain of 10^5 CFU/mL in the midstream sample and 10^3 CFU/mL in the sample obtained by catheter were defined as UTI. The standardized disk agar diffusion method or BD PhonEx automated systems were used for the identification of bacteria and antibiotic susceptibility testing. Leukocytosis and high C-reactive protein (CRP) levels, fever (>38°C), and at least one of the following symptoms/signs: dysuria, urgency, hematuria, suprapubic tenderness, costovertebral area tenderness to percussion were evaluated as pyelonephritis. There was no patient with a lower UTI. In addition, ultrasound results of all patients were scanned, and the presence of urinary anomalies and renal scarring was accepted as risk factors (RF). Urinary anomalies are determined as nephrolithiasis, vesicoureteral reflux (VUR), posterior urethral valve (PUV), hydronephrosis, neurogenic bladder, megaureter, duplex system, ureteropelvic junction (UPJ) obstruction, ectopic kidney, anorectal malformations, renal agenesis, and extrophia vesicale in our patients.

Statistical Analysis

In summarizing the data, continuous variables were given as mean ± standard deviation or median (min-max) depending on the distribution type, and categorical variables were given as frequency and percentage. Independent samples *t*-test or Mann–Whitney *U* test was used for comparison of the groups, depending on the distribution of the data. The relationships between categorical variables were examined by Pearson Chi-Square or Fisher's exact test, depending on the expected value rule. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) and, the significance level was considered as 0.05.

RESULTS

The mean age of the patients was 6.9 (1-17) years. Eighty-two children with UTI were female and 20 were male. Fifty-eight cases (56.8%) had urinary tract anomalies (Table 1). Escherichia coli (E. coli) (73.5%), Klebsiella pneumoniae (8.8%), and Enterococcus spp (7.8%) were detected as the main bacterial pathogens in all patients. The antibiotic resistance rates were shown at Table 2. There was no statistically significant difference between antibiotic resistance and urinary tract anomalies ($P > .05$). On the other hand, the obtained pathogens were also similar in patients with and without urinary anomaly (2.2 ±1.9 vs. 1.6 ±1.5, respectively, $P > .05$). Bacterial isolates were significantly found more resistant to trimethoprim-sulfamethoxazole with RF than without RF (48.4% vs. 31.8%, $P < .05$, respectively). Thirty-eight patients (37.2%) had pyelonephritis episodes while receiving antibiotic prophylaxis. The sort of causative pathogens was not different between with or without receiving prophylactic antibiotic treatment in the patients. The causative microorganisms were significantly found more resistant to some antibiotics in patients with under prophylaxis than without prophylaxis (Table 3).

DISCUSSION

Because of the increasing frequency of recurrent UTI in children with urinary tract anomalies, antibiotic usage appears to be increasing over time. In order to prevent permanent kidney

Table 1. The Risk Factors of the Patients

	Female	Male	*P*
Age (years)	7.7 ± 4.2	3.8 ± 3.9	<.05
Urinary tract anomalies, *n* (%)	>.05		
Nephrolitiasis	5 (6)	3 (15)	
Hydronephrosis	3 (7)	2 (10)	
VUR	13 (15.9)	2(10)	
PUV	0 (0)	3(15)	
Neurogenic bladder	7 (8.5)	6(30)	
Duplex system	1 (1.2)	0 (0)	
Anorectal malformation	1 (1.2)	1 (5)	
Hypoplastic kidney	4 (4.9)	1(5)	
UPJ obstruction	2 (2.4)	0 (0)	
Ectopic kidney	2 (2.4)	0 (0)	
Extrophia vesicale	2 (2.4)	0 (0)	

VUR: vesicoureteral reflux, PUV: posterior urethral valve, UPJ: ureteropelvic junction

Table 2. The Distribution of Antibiotic Resistance Rate According to Urinary Tract Anomaly

Antibiotic	Resistance Rate (%)		
	Urinary Tract Anomaly		
	Yes	No	*P*
Trimethoprim-Sulfamethoxazole (TMP-SMX)	40.8	42.2	NS
Ampicillin	28.9	28.1	NS
Ceftriaxone	23.2	21.7	NS
Co-Amoxiclav	17.9	16.9	NS
Ciprofloxacin	14.3	13.1	NS
Gentamycin	12.5	11.4	NS
Nitrofurantoin	7.2	6.6	NS
Ertapenem	2.4	2.2	NS
Piperacillin - Tazobactam	11.9	11.5	NS
Meropenem	3.9	3.8	NS
Gentamycin	12.0	11.7	NS

damage, empirical antibiotics were used in the early period in these patients. Unfortunately, empirical antibiotics decreased the success rates of UTI treatment due to antibiotic resistance.

In the present study, antibiotic resistance was evaluated in patients with urinary tract anomalies. TMP-SMX resistance was higher in the prophylaxis group. Similarly, in a study, TMP-SMX resistance was more common in the prophylaxis group than in the placebo group. The researchers found that the rate of TMP-SMX resistant microorganisms was 76% in children with VUR.[13] Eremenko et al. showed that TMP-SMX resistance was 16.9% in all UTIs. No significant resistance was also found in the first UTI attack, recurrent UTI, and febrile UTI attack for TMP-SMX. On the other hand, they found that resistance rates of Amoxicillin/Clavulanate were significantly higher in the recurrent UTI group compared to the first episode UTI group.[10] We found that TMP-SMX, Co-Amoxiclav, Ampicillin, Ceftriaxone, and Piperacillin-Tazobactam resistances were significantly higher in the prophylactic antibiotic-receiving group. Frequent use of antibiotics due to recurrent infections might be a factor in the development of antibiotic resistance in these children. In addition, compared to other studies, the higher rate of resistance may be related to the high local antibiotic resistance in our hospital.

Table 3. The Distribution of Antibiotic Resistance Rate in Patients with or without Prophylactic Antibiotic Usage

Prophylactic Antibiotic	Yes	No	*P*
Antibiotic resistance (%)			
TMP-SMX	60.5	29.7	<.01
Ampicillin	39.5	21.9	<.05
Ceftriaxone	34.2	15.6	<.05
Co-amoxiclav	31.6	9.4	<.01
Piperacillin-Tazobactam	21.1	6.3	<.01

Albaramki et al. found no significant differences between renal anomalies and antibiotic resistance. However, they notified that previous hospitalization, use of multiple antibiotics, and renal anomalies are risk factors for antibiotic resistance.[14] In our study, UTIs were detected most commonly in girls with VUR and in boys with neurogenic bladder, but we could not find a relationship between antibiotic resistance and urinary tract anomaly. Although urinary tract anomaly is considered as a risk factor, long-term and multiple antibiotic use should be seen as a more important factor in the development of resistance. However, since the patients previously had applied to other centers, the duration of prophylaxis and used antibiotics could not be evaluated in our study.

This study showed similar results with the studies in the literature stating that UTIs were found more commonly in girls than boys. However, no gender difference was found in terms of antibiotic resistance. Similarly, Stein et al. reported that antibiotic prophylaxis should be planned regardless of gender.[15]

Anvari et al. noticed that E.coli was the most prevalent microorganism in urine. They found positive urine culture for E.coli as 62.3% in patients.[16] Similar to this study, E. coli was the most common pathogen for recurrent UTI, but it was found to be highly resistant to antibiotics (TMP-SMX, Ampicillin, Cephtriaxone, etc.) which are the first choice in the treatment of E.coli in our study. Therefore, we think that empiric antibiotics should be based on local resistance patterns instead of recommended antibiotics as the first choice in empirical treatment until the result of the urine culture is available.

Although quinolone was not used for the treatment of our patients, we detected quinolone resistance as 13.7%. This condition suggested that the microorganisms have already been encountered with quinolone previously or this resistance could be related to bacterial transformation. Therefore, some bacteria might be resistant to antibiotics even if they have not been used before.

Nicolle et al.[17] reported that antibiotic resistance rates increased with inappropriate use of antibiotics in asymptomatic bacteriuria. The high rate of antibiotic resistance in our patient group might be related to the inappropriate treatment of asymptomatic bacteriuria in children with urinary anomalies. Because of the risk of permanent renal damage, this might cause unnecessary treatment in these patients. On the other hand, microorganisms also could be colonized in the damaged area and gain resistance to repeated antibiotic treatment in recurrent UTI.

Although Ertapenem resistance was low in our study, we think that this drug should be given according to the culture antibiogram result in complicated and recurrent UTIs. In addition, the use of this drug is not practical due to the need for hospitalization. Other agents with a low rate of resistance, such as Meropenem, also should not be the first choice for similar reasons. We think that oral treatment options such as Nitrofurantoin, which has lower resistance rates, would be a more accurate approach until the culture antibiogram result. In our study, we found a higher rate of resistance to TMP-SMX as in other studies. Therefore, we believe that it is inappropriate for empirical treatment although it is used frequently.

The risk of renal scar is significantly higher in patients with recurrent UTI and associated with urinary tract anomalies such as VUR and neurogenic bladder.[18,19] VUR should be considered in children with recurrent UTIs. Yilmaz et al. reported that CRP levels and the presence of renal scarring were significantly found higher in patients with VUR. They also showed that VUR and recurrent UTIs were significantly higher in patients with renal scars.[20] However, no significant pathology was observed in our patients. Therefore, the effect of permanent renal damage could not be evaluated.

CONCLUSION

Recurrent UTIs are one of the main factors that affect renal prognosis. These patients should be treated with appropriate drugs to increase the renal survival. For this purpose, drug selection should be made by considering antibiotic resistance rates. However, larger studies are needed to determine the local antibiotic resistance of common uropathogens.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of Duzce University School of Medicine (Approval Date: February 15, 2021 – No. 2021/19).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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