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ORIGINAL ARTICLE

Pediatric-specific Antimicrobial Resistance Patterns of Urinary Tract Infections: A Single-Centre Experience from Turkey

Çocukluk çağı üriner sistem enfeksiyonlarında antibiyotik duyarlılığının araştırılması: tek merkezli çalışma

Yasar Kandur[1], Sevinc Ozden[2], Bahar Buyukkaragoz[3]

[1] Division of Pediatric Nephrology, Necip Fazıl City Hospital, Kahramanmaras, Turkey
[2] Department of Microbiology, Necip Fazıl City Hospital, Kahramanmaras, Turkey
[3] Department of Pediatrics, Division of Pediatric Nephrology, Kecioren Training and Research Hospital, Ankara, Turkey
Corresponding author: Yasar Kandur, Division of Pediatric Nephrology, Necip Fazıl City Hospital, Kahramanmaras, Turkey
e-mail: yaskan30@yahoo.com

Abstract

Objectives: Antimicrobial resistance of the causative microorganisms of pediatric urinary tract infection (UTI) is a growing problem. The aim of this study is to determine the changing pattern of antibiotic susceptibility in UTIs in an outpatient setting.

Methods: We retrospectively reviewed the medical records of pediatric patients with UTI who were followed-up in our center between January-2014 and May-2015.

Results: One hundred and seventy-one patients (M/F= 53/118; mean age 56 ± 47.2 months) with UTI were enrolled in this study. A total of 231 urinary pathogens were isolated from UTI episodes. The most common causative agent was Escherichia coli (E. coli) (70.6%) followed by Klebsiella spp. (16.5%), Proteus spp. (6.5%). One point eight percent of E. coli isolates were resistant to amikacin, 17.8% to gentamicin, 60.7% to TMP-SMX, 66,9% to ampicillin, 52.1% to cefixime, 46% to ceftriaxone, 54.6% to cefuroxime and 4.9% to nitrofurantoin.

Conclusions: TMP-SMX and nitrofurantoin are poor empirical choices for pediatric patients due high resistance rates and gastrointestinal side effects, respectively. Second and third -generation cephalosporins (cefixime) may not be considered as appropriate empiric antibiotic alternatives anymore given their high resistance rates in the next few years. Physicians who work in the primary health care should be encouraged for the selection of more appropriate antibiotics.

Key words: Urinary tract infection, antimicrobial resistance, cefixime

Özet

Amaç: Çocukluk çağında üriner sistem enfeksiyonu tedavisinde antimikrobiyal direnç son yıllarda büyüyen bir sorun olarak karşımıza çıkmaktadır. Bu araştırmamızda, merkezimizde poliklinik şartlarında tanı almış çocuklarda saptanan üriner sistem enfeksiyonuna yol açan etkenlerin dağılımını ve antibiyotik duyarlılıklarını araştırmayı amaçladık.

Yöntemler: Ocak- 2014 ve Mayıs - 2015 tarihleri arasında merkezimizde takip edilen üriner sistem enfeksiyonu tanısı alan çocuk hastaların tıbbi kayıtları retrospektif olarak incelendi.

Bulgular: Yüz yetmiş bir hastada (E/K = 53/118 ; ortalama yaş 56 ± 47.2 ay), 231 patojen izole edilmiştir. En sık izole edilen etkenler Escherichia coli (E. coli) (%70,6), Klebsiella spp (%16,5) , Proteus spp. (%6,5) olarak bulundu. Patojenlerin antibiyotik duyarlılıkları değerlendirildiğinde E.coli etkenine karşı amikasin direnci %1,8, gentamisin %17,8, trimetoprim–sulfometoksazol %60,7, ampisillin %66,9, sefiksim %52,1, seftriakson 46% , sefuroksim %54,6 ve nitrofurantoin direnci: %4,9 olarak bulundu.

Sonuç: Trimetoprim–sulfometoksazol'e karşı var olan yüksek direnç oranları ve nitrofurantoinin sık karşılaşılan gastrointestinal yan etkileri nedeniyle, üriner sistem enfeksiyonun ampirik tedavisinde bu antibiyotikler zayıf tercihler olarak karşımıza çıkmaktadır. Bunun yanısıra ikinci ve üçüncü kuşak sefalosporinlere özellikle de sefiksime karşı çalışmamızda da gösterildiği gibi son yıllarda gelişen yüksek direnç oranları nedeniyle, ampirik tedavi alternatifi olarak etkinliklerini kaybetme riski taşımaktadır. Bu nedenle sefalosporinlerin sık tercih edildiği birinci basamak sağlık hizmetlerinde görev yapan hekimlerin üriner sistem enfeksiyonu ampirik antibiyotik seçiminde daha dikkatli olmaları gerektiği sonucuna varılmıştır.

Anahtar kelimeler: Üriner sistem enfeksiyonu, Antimikrobiyal direnç, Sefiksim.

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INTRODUCTION

Urinary tract infection is common and an important cause of morbidity in children; it is acquired by an estimated 1% of boys and 3–5% of girls [1]. Approximately 2% out of the whole pediatric population under 10 years of age experiences at least one episode of UTI [2]. Early treatment reduces the rate of morbidity resulting from UTI, therefore antibiotic treatment is usually started empirically, before urine culture results are available. Ineffective empirical antibiotic therapy may contribute to increased morbidity [3]. On the other hand, antibiotic resistance has become an increasingly relevant clinical challenge in many countries. Moreover, there are considerable geographic variations in bacterial patterns and resistance properties depending on local antimicrobial prescription practices. Hereby, various centers consider the results of urine culture previously obtained from their microbiology laboratory in selecting empirical antibiotic treatment for UTI [4-6]. Therapy is based on information determined from the antimicrobial resistance pattern of the urinary pathogens. A previous study indicates that the most commonly used antibiotics for pediatric UTIs are TMP/SMX and broad-spectrum agents, especially third generation cephalosporins [7]. If UTIs are not treated by appropriate antibiotics, they may be transformed into chronic UTIs and may lead to formation of scar tissues in the kidneys, hypertension, and chronic renal failure. In this study, the current resistance patterns of urinary isolates to commonly used antimicrobials were determined in order to evaluate the options for empirical antibiotic therapy for UTI in pediatric patients.

METHODS

We retrospectively reviewed the medical records of pediatric patients with UTI who were followed-up in our center which is located in the south-east region of Turkey between January-2014 and May-2015. Study 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, catheterisation, or urine bags. These samples were processed on blood agar and EMB agar (Eosine Metilen Blue) with a standard loop and were incubated at 37ºC overnight. Significant growth was evaluated as ≥105 colony-forming units (CFU)/mL of midstream urine and bag urine samples, and ≥102 CFU/mL of a catheter specimen. Antimicrobial susceptibility testing was performed by the disk diffusion method on cultures with significant bacteriuria using a panel of antimicrobial agents depending on the causative organism. Interpretation was based on the National Committee for Clinical Laboratory Standards criteria [8]. All antimicrobial susceptibility tests of isolated and identified strains were performed manuel according to recommendations of the Clinical and Laboratory Standards Institute (CLSI) identification system against amikacin, amoxicillin/clavulanate, ampicillin, cefotaxime, ceftazidime, ceftriaxone, cefuroxime sodium, gentamicin, imipenem, meropenem, nitrofurantoin, piperacillin, piperacillin/tazobactam, tobramycin, TMP-SMX, and vancomycin. Cases showing pyuria and significant bacterial growth on culture were included in the study. In addition to demographic findings, prevalence and patterns of antibiotic resistance of the uropathogens were registered on a standard form. A clinical diagnosis of upper UTI was made on the basis of the presence of systemic symptoms such as fever (≥38.5º C), vomiting, flank/back pain and elevated acute phase reactants such as C-reactive protein (>2 mg/dL) and erythrocyte sedimentation rate (>20 mm/h). Children with clinical upper UTIs were hospitalized and treated with parenteral antibiotics for 10 days. Children with lower UTI were managed on an outpatient basis [9]. 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 guidance for pediatric patients with UTI [10]. In addition, subjects were divided into three age groups to analyze resistance to antibiotics in different ages: Group 1 <12 months; Group 2 between 13 and 60 months; and Group 3 >60 months.

Statistical Analysis

Data were analyzed by SPSS (Statistical Package for Social Science) 16.0 software package. Statistical analyses was performed with Chi-square test and Mann Whitney –U test. The level of significance was set at $p<0.05$.

RESULTS

One hundred and seventy-one patients (M/F= 53/118) with UTIs were enrolled in this study. Mean age was 56 ± 47.2 months (age range: 1 to 168 months). A total of 231 urinary pathogens were isolated from episodes of UTI. Sixty point six percent of the episodes presented with lower UTIs while 39.4% had upper UTI sign and symptoms. The most common causative agent was E. coli (70.6%) followed by Klebsiella spp. (16.5%), Proteus spp. (6.5%), and others (6.4%). Of E. coli strains, 3% (n= 5) were found positive for extended-spectrum beta-lactamases (ESBL), while this rate was 0% for Klebsiella spp. strains. All of the patients (n=5) with ESBL positive strain had a history of recurrent urinary tract infection and they were receiving antibiotic prophylaxis .

Thirty-six patients (15.6%) had vesicoureteral reflux, 11 (4.8%) had ureteropelvic junction obstruction, and 11 (4.8%) had nephrolithiasis. Table 1 shows the rates of resistance to selected antibiotics. One point eight percent of E. coli isolates were resistant to amikacin, 60.7% to TMP-SMX, 52.1% to cefixime, 46% to ceftriaxone, 4.9% to nitrofurantoin. None of the Klebsiella spp. isolates were resistant to amikacin, whereas 57.9% were resistant to TMP-SMX, 57.9% to cefixime, 55.2% to ceftriaxone and 21% to nitrofurantoin.Thirty-five percent (n=57) of cases had a history of recurrent UTIs and all of them were receiving antibiotic prophylaxis. According to the age of the patients, the number of collected isolates were as follows: Thirty-four point six percent were obtained from patients in Group 1, %28.1 from patients in Group 2, and 37.2% from patients in Group 3. There was no difference with respect to gender for mean antibiotic resistances to E.Coli (Table 2).

Table 1. Antimicrobial resistance rates of urinary tract isolates

Antibiotic	*E. coli* (n=163) (%)	*Klebsiella spp* (n=38) (%)	*Proteus spp.* (n=15) (%)
Amikacin	1.8	0	0
Gentamicin	17.8	23.7	26.6
Cefixime	52.1	57.9	20
Ceftriaxone	46	55.2	7.1
Cefuroxime	54.6	68.4	20
TMP-SMX	60.7	57.9	66.6
Nitrofurantoin	4.9	21	80
Ampicillin	66.9	86.8	46.6

Analysis of the results in terms of patient gender indicated that although E. coli is the predominant isolated pathogen in both sexes, it occurred significantly more frequently in girls (83% in girls compared to 17% in boys; $p < 0.05$); in contrast, the prevalences of UTI by Klebsiella spp, Proteus, and Pseudomonas aeruginosa were slightly higher in boys than in girls; M/F = 20/18, 8/7, and 3/2 respectively (Figure 1).

As for the UTI symptoms in different age groups, abdominal pain was the most frequent clinical finding in Group II (33.8%) and III (26.7%). On the other side, fever was the most frequent symptom in the infancy group (26.9%). A high percentage of rates were the "cause of routine examination urinary culture" performed due the presence of a urologic abnormality (VUR, ureteropelvic junction obstruction, etc.) (Table 3).

Table 2. Gender-based comparison of antibiotic resistance to E.coli

Antibiotic	Female (n=135)	Male (n=28)	P
Amikacin	2/1,4	1/3,5	>0,05
Gentamicin	26/19,2	3/10,7	>0,05
Cefixime	71/52,5	14/50	>0,05
Ceftriaxone	62/46	13/46,4	>0,05
Cefuroxime	74/54,8	15/53,5	>0,05
TMP-SMX	85/63	14/50	>0,05
Nitrofurantoin	5/3,7	3/10,7	>0,05
Ampicillin	91/67,4	18/64,2	>0,05

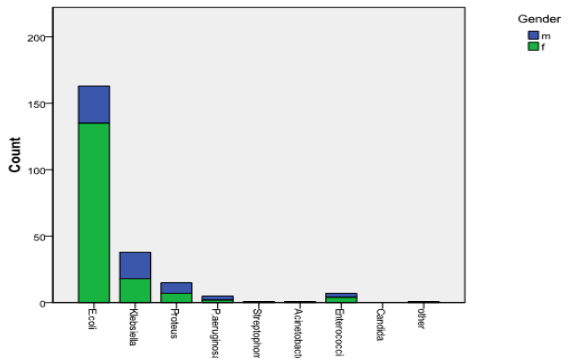

Figure 1: Gender-based frequencies of bacteria isolated from urine samples

Table 3. Age-based frequency of the UTI symptoms

Symptomps	Group I (n=78) (%)	Group II (n=65) (%)	Group III (n=86) (%)
Fever	26.9	13.8	3.5
Vomiting	12.8	12.3	3.5
Abdominal pain	0	33.8	26.7
Dysuria	0	3	9.3
Irritability	16.6	4.6	0
Urgency	0	4.6	22.3
Routine exam	33.3	21.5	20.9
Foul smell of urine	6.4	1.5	0

In patients with antibiotic resistance to E. coli, the number of collected isolates were as follows: thirty-eight (23%) were obtained from patients in Group I, 48 (30%) from patients in Group II, and 77 (47%) from patients in Group III. Although the number of resistance to amikacin and nitrofurantoin were very low for statistical evaluation, there were nonsignificant differences in resistance rates for other antibiotics (Table 4). Moreover, amikacin was a favourable antibiotic for all groups since the low levels of resistance in Group 1; and none of the isolates were found to be resistant to amikacin in Group II and III. In Group III, nitrofurantoin had the lowest resistance rate (1.3%).

Table 4. Antibiotic resistance to E.coli in different age groups

Antibiotic	Group I (n=38) n (%)	Group II (n=48) n (%)	Group III (n=77) n (%)	P
Amikacin	3 (7.9)	0 (0.0)	0 (0.0)	
Gentamicin	9 (23.7)	7 (14.5)	13 (16.8)	p>0.05
Cefixime	21 (55.2)	26 (54.1)	38 (49.3)	p>0.05
Ceftriaxone	20 (52.6)	24 (50)	31 (40.2)	p>0.05
Cefuroxime	20 (52.6)	28 (58.3)	41 (53.2)	p>0.05
TMP-SMX	23 (60.5)	33 (68.7)	43 (55.8)	p>0.05
Nitrofurantoin	4 (10.5)	3 (6.2)	1(1.3)	
Ampicillin	25(65.7)	32 (66.6)	52 (67.5)	p>0.05

DISCUSSION

Recent studies have shown that E. coli is still the most common pediatric uropathogen, accounting for 71-87% of cases, followed by Klebsiella pneumoniae (9.1-10%) [11-13]. Our study revealed similar results; E. Coli was responsible for 70.6% of all infections.

Similar to our results, a study showed that abdominal pain was the most common symptom in UTI in those over two years of age, while irritability, diarrhea, and vomiting were predominant in children under two years of age [14]. However, in our study fever was the most frequent clinical finding in infants.

Vesicoureteral reflux is the most important risk factor for UTI. It is found in 25–40% of children during evaluation of a first episode of UTI [15,16]. In our study 36 patients (15.6%) were diagnosed with VUR during the follow-up period. It was shown that in children with their first febrile UTI one of the best predictive marker for the presence of VUR is DMSA renal scan [17]. A DMSA scan is recommended in children younger than 3 years with atypical or recurrent urinary tract infections. The aim is to detect renal parenchymal defects or scarring, which occur in about 5% of children as a result

of infection. The NICE guidance recommends that micturating cystourethrography is indicated in all babies less than 6 months old with atypical or recurrent infection, and it should be considered in those with typical infection but an abnormal follow-up ultrasound scan [10]. A trend has recently emerged not to prescribe cystography when the DMSA scan is normal. So that we perform DMSA to patients younger than 3 years with atypical or recurrent urinary tract infections. Therefore, we found a lower prevalance of VUR.

Antimicrobial resistance represents an increasing global concern and is one of the major cause of failure in treatment of infectious diseases that results in increased morbidity and economic cost. Understanding antibiotic resistance patterns offers a chance for effective empirical antibiotic selection and decrease treatment failure. Effective empirical antibiotic therapy may contribute not only to decreased morbidity, but also to decreased costs due to prolonged antibiotic treatment, recurrent office or emergency room visits and hospital admissions [3,18-19]. There are limited data regarding the antibiotic resistance patterns of pediatric UTIs in the outpatient setting.

A previous study indicated that the most commonly used antibiotics for pediatric UTIs are TMP/SMX and broad-spectrum agents, especially third generation cephalosporins [20]. In a study performed between 2007-2009 in Italy, the antibiotic resistance of E. coli was found out to be highest for TMP-SMX (inpatients: 22%, outpatients: 15%), while the rate of resistance was below 1% for ceftazidime, ceftriaxone, nitrofurantoin and gentamycine [21]. Savas et al. [22] found the following rates of antibiotic resistance against E. Coli in the community-acquired UTIs: ampicillin (7%), gentamicin (17%), amikacin (10%), cefuroxime (18%), ceftriaxone (13%), ceftazidime (13%), TMP-SMX (59%), and against Klebsiella spp. ampicillin (79%), gentamicin (20%), amikacin (19%), cefuroxime (42%), ceftriaxone (35%), ceftazidime (25%), TMP-SMX (48%). A comparison of these two studies with our results showed that the resistance rates of E.coli and Klebsiella spp. to cephaloporins were higher in our study. The resistance rates to TMP-SMX have been reported to be as high as 40% in other countries [5,6,23], as was the case in our study. TMP/SMX should not be used empirically if local resistance rates of uropathogens exceed 20%. Trimethoprim is contraindicated in premature infants and newborns. There is also limited use for infants under six weeks due to the lack of adequate experience [7].

Besides, there is sufficient evidence demonstrating that the trend of E. coli resistance to cephalosporins is increasing, as in our study, possibly linked to higher use of TMP-SMX and cephalosporins (second and third generation) either by the individual and/or by the population. Moreover, a recent study reported that children receiving prophylactic antibiotics had a high rate of resistance to third-generation cephalosporins [24]. Thus, it seems rational to make any effort to reduce the widespread use of cephalosporins. Because of this trend, this class of antibiotics should be used with caution, particularly if no microbiological documentation is available.

On the other hand, amikacin resistance was found to be low in our study. In a study [25], E. coli showed 2.5–8 times higher antibiotic resistance than gentamicin compared to amikacin. In another study [26], it was found that amikacin was a more suitable aminoglycoside for treatment of children with UTI in the first year of life, whereas gentamicin may be adequate in children aged >1 year (9% resistance rate). In our study, amikacin was a more suitable antibiotic than gentamicin in all age groups. In our opinion, however, amikacin should not be the initial drug preferred over gentamicin since otherwise there is a risk of development of high resistance to amikacin in the future.

The low levels of resistance to nitrofurantoin make this drug a reasonable alternative in UTI

[27]. Our results support the inclusion of nitrofurantoin in the empirical treatment of lower UTI in older children. Because of the danger of haemolytic anaemia, nitrofurantoin is contraindicated for young infants until the third month of age [28].

However, it was shown that nitrofurantoin should not be used in the treatment of upper urinary tract infection because adequate tissue concentrations of the drug may not be achieved within the renal parenchyma despite its excellent urinary excretion [29,30].

In light of these findings, more effective antibiotics such as amikacin, ertapenem, imipenem, meropenem and nitrofurantoin should be used for empirical antibiotic treatment of E. coli strains in our country because of high antibiotic resistance of E. coli strains' against several antibiotics including ampicillin, TMP-SMX, ceftriaxone, and cefuroxime. Similarly, more effective antibiotics, for example amikacin, ertapenem, imipenem, meropenem or nitrofurantoin should be used for empirical antibiotic treatment of UTIs caused by Klebsiella spp. strains owing to the high antibiotic resistance of this species against ampicillin, TMP-SMX, ceftriaxone, and cefuroxime.

Most often, the bacterial strains producing ESBLs are Klebsiella spp and E. coli [31]. ESBL-producing strains are resistant to beta-lactam antibiotics, including third-generation cephalosporins such as ceftriaxone and ceftazidime. These strains cause to limited therapeutic options and increased risk of treatment failure. Previous use of antibiotics and recurrent urinary tract infections are known risk factor for ESBL-producing bacteria [32]. Our cases with ESBL positive strain shared these risk factors.

We suggest that empirical antibiotic selection should be based on the knowledge of the local prevalence of bacterial organisms and antibiotic sensitivities, because resistance patterns may vary in different regions. We found that second and third -generation cephalosporins especially cefixime may not be appropriate empiric antibiotic alternative within the next years anymore given their high resistance rates. This caused by the irrational use of these antibiotics especially in our region. So, we suggest that alternative new oral antibiotic forms for the empiric treatment of UTIs are required. We believe that physicians who work in the primary health care should be encouraged for the selection of more appropriate antibiotics. Finally, regional studies about UTIs should be repeated more frequently.

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