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Antibiotic Resistance Patterns in Pediatric Urinary Tract Infections: A Comparison Between 2013-2015 and 2019-2021

Çocukluk Çağı İdrar Yolu Enfeksiyonlarında Antibiyotik Direnç Paternleri: 2013-2015 ve 2019-2021 Arasında Bir Karşılaştırma

Esra Nagehan Akyol Önder[1]*, Pelin Ertan[1]

Manisa Celal Bayar University, Department of Pediatrics, Division of Pediatric Nephrology, Turkey.

e-mail: esra.nagehan.7@hotmail.com, pelinertan@hotmail.com
ORCID: 0000-0003-0321-2204
ORCID: 0000-0002-1882-5962

*Sorumlu Yazar / Corresponding Author: Esra Nagehan Akyol Önder
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Öz

Giriş ve Amaç: İdrar yolu enfeksiyonları (İYE) çocuklarda en sık görülen enfeksiyonlardan biridir. Bu çalışmanın amacı 2013-2015 ve 2019-2021 yılları arasında idrar kültürlerinin etiyoloji ve antibiyotik duyarlılık sonuçlarını değerlendirmek, karşılaştırmak ve yıllar içindeki lokal epidemiyolojik farkı ortaya koymaktır.
Gereç ve Yöntemler: Bu çalışmaya üreme olan 1000 idrar kültürü (2013-2015 ve 2019-2021 dönemleri için 500'er kültür) ve antibiyogram sonuçları dahil edildi.
Bulgular: Her iki yıl aralığında da idrar kültürlerinde en çok saptanan üropatojenler *E. coli* ve *Klebsiella* türleri olarak bulundu. *E. coli* ve *Klebsiella* türleri ampisilin, amoksisilin, trimetoprim-sulfametoksazol, sefuroksim ve seftriakson'a karşı yüksek direnç göstermiştir. *E. coli*'nin ampisilin, amoksisilin ve trimetoprim-sulfametoksazole direnç oranları sırasıyla %65, %46 ve %45 olarak bildirilmiş ve 2019-2021 yılları arasında anlamlı olarak artmıştır (sırasıyla p <0,001, p <0,001, p = 0,003). Bu iki çalışma döneminde *Klebsiella, Proteus* ve *Enterococcus* türlerinin antibiyotiklere direnç oranlarında anlamlı bir fark saptanmamıştır.
Sonuç: E. coli'ye karşı en sık kullanılan antibiyotikler olan ampisilin, amoksisilin, trimethoprim-sulfametaksazolün en yüksek direnç oranlarına sahip olduğu görüldü. İYE'lerde ampirik antibiyotik önerileri için yerel kılavuzları yeniden düzenlemek amacı ile antibiyotiklerin yerel duyarlılıklarını araştırmak önemlidir.

Anahtar kelimeler: Antibiyotik Tedavisi, Antimikrobial Direnç, Çocuk, İdrar Yolu Enfeksiyonu.

Abstract

Objective: Urinary tract infections (UTIs) are one of the most common infections in children. The aim of this study was to assess and compare the etiology and antibiotic susceptibility results of urine cultures obtained between 2013-2015 and 2019-2021 and evaluate local epidemiologic differences over years.
Materials and Methods: A total of 1,000 samples with positive urine cultures (500 cultures each for the 2013-2015 and 2019-2021 periods) and antibiogram results were included in this study.
Results: The most grown uropathogens were *Escherichia coli* and *Klebsiella* spp. in both two periods. *E. coli* and *Klebsiella* spp. showed high resistance to ampicillin, amoxicillin, trimethoprim-sulfamethoxazole, cefuroxime, and ceftriaxone. The resistance rates of *E. coli* to ampicillin, amoxicillin and trimethoprim-sulfamethoxazole were reported as 65%, 46%, and 45%, respectively and significantly increased in 2019-2021 compared to 2013-2015 ($p<0.001$, $p<0.001$, and $p=0.003$, respectively). There was no significant difference in the resistance rates of *Klebsiella, Proteus* and *Enterococcus* spp. to antibiotics during the two-study period.
Conclusion: It was observed that the most commonly used antibiotics, ampicillin, amoxicillin, trimethoprim-sulfamethoxazole, against *E. coli* had the highest resistance rates. It is important to confirm the local susceptibility patterns of antibiotics to revise local guidelines in terms of empirical antibiotic recommendations in UTIs.

Keywords: Antibiotic Therapy, Antimicrobial Resistance, Child, Urinary Tract Infections.

1. Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections in children [1]. In infants, UTIs are seen more frequently in boys (3.7%) than in girls (2%), but their incidence among girls increases after infancy [2], with 3-7% of girls and 2% of boys being infected with an UTI in their first seven years of life [3]. The frequency of recurrence within six to 12 months after the first UTI is 12-30% [3,4]. The most common pathogen is *Escherichia coli,* causing almost 80-90% of childhood UTIs [3]. This is followed by other Gram-negative bacteria, such as *Proteus* species (spp.), *Klebsiella* spp., *Enterobacter* spp., and *Pseudomonas aeruginosa* and Gram-positive pathogens, such as *Enterococcus* spp. [3-5]. Early diagnosis and appropriate treatment are essential to prevent the complications of UTIs, including renal scarring, hypertension, and renal dysfunction [6]. Symptomatic children with suspected UTIs should be treated with an empiric antibiotic while awaiting the results of urine culture [7]. Empiric antibiotic treatment should be based on local susceptibilities derived from local epidemiologic studies [8-10]. As a result of the inappropriate and widespread use of antibiotics in UTIs, antibiotic resistance has been increasing in recent years [11]. In order to increase treatment success and prevent antibiotic resistance, it is essential to continuously monitor local pathogen microorganisms causing UTIs and their antibiotic response pattern [9,11]. For this purpose, we assessed the demographic characteristics, UTI agents, and antibiotic resistance rates over two periods (2013-2015 and 2019-2021) in pediatric patients. We compared these two periods to evaluate local epidemiologic differences over years and change our preferences concerning the prescription of empiric antibiotics accordingly.

2. Materials and Methods

After obtaining approval from the local ethics committee, a total of 10,000 (4,620 in 2013-2015, 5,380 in 2019-2021) urine culture samples of patients who presented to our pediatric nephrology outpatient unit from September 2013 to 2015 and from September 2019 to 2021 were retrospectively analyzed, and 1,000 samples (500 for each period) with nitrite and leucocyte positive urine tests and positive urine cultures and antibiogram reports were included in the study. All the non-repetitive positive urine cultures were included in the sample regardless of the signs and laboratory findings of the patients. Patients with congenital anomalies of the urinary tract and nephrolithiasis were excluded. The samples were classified according to patient age and gender, uropathogen microorganisms, and antimicrobial susceptibility. Growth of >105 single colonies (CFU/mL) in urine culture was considered as positive. Antimicrobial susceptibility testing of the urine cultures was performed with the disk diffusion method in accordance with the National Committee for Clinical Laboratory Standards. The examined antibiotics were ampicillin, amoxicillin-clavulanic acid (AMC), trimethoprim-sulfamethoxazole (TMP-SMX), cefazolin, cefuroxime, ceftriaxone, cefepime, cefixime, ciprofloxacin, nitrofurantoin, gentamicin, imipenem, meropenem, ertapenem, vancomycin, piperacillin/tazobactam, tetracycline, and fosfomycin.

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) for Windows, version 26.0. The normality of the distribution of variables was assessed using a histogram and the Kolmogorov-Smirnov or Shapiro-Wilk test. Continuous variables were reported as median and interquartile range (IQR) values when not normally distributed. Categorical variables were reported as numbers and percentages, and compared with the chi-square test. A p value of <0.05 was accepted as statistically significant.

3. Results and Discussion

3.1 Results

Overall, 1,000 positive urine cultures were evaluated in 594 female and 406 male children with a median age of 6 years (minimum:0.2, maximum:18, IQR: 3-9 years,). Before the age of 1 year, the male/female ratio was 1.9. Over 1 year, the male/female ratio decreased to 0.6.

Over the entire study period, the most commonly grown uropathogen was *E. coli* (675/1,000, 67.5%), followed by *Klebsiella* spp. (152/1,000, 15.2%), *Proteus* (48/1,000, 4.8%), *Enterococcus* (54/1,000, 5.4%), *Pseudomonas* (26/1,000, 2.6%), *Staphylococcus* (26/1,000, 2.6%), *Morganella* (10/1,000, 1%), and *Streptococcus* spp. (9/1,000, 0.9%). *E. coli* was found to be the most common uropathogen for UTIs in all age groups of children (59% in 0-≤1 year, 59% in 1-≤5 years, 75% in 5-≤10 years, 73% in 10-18 years).

Table 1 presents the demographic data and distribution of uropathogens according to the evaluation period. There was no significant difference between the two periods in terms of age and gender (p = 0.5 and p = 0.9, respectively).

Figure 1 shows the age distribution of the culture samples detected to have UTIs according to the evaluation period.

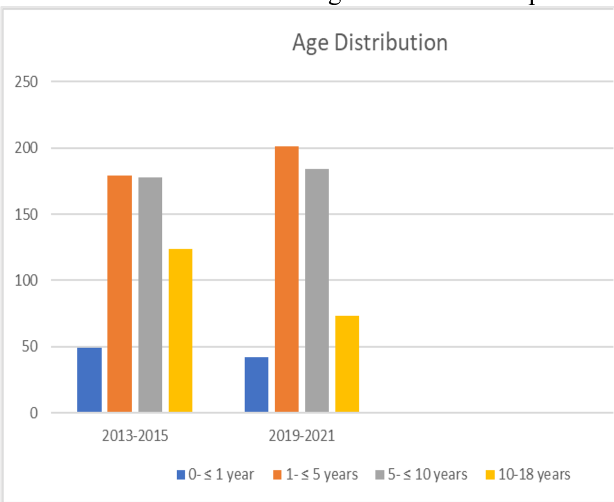

Figure 1. Age distribution of patients with urinary tract infections detected in culture samples

There was no significant difference between the two periods in relation to age groups (p = 0.2). Before the age of 1 years, the male/female ratio was 2.8 for 2013-2015 and 1.3 for 2019-2021 (p = 0.12). Over the age of 1 year, the male/female ratio decreased to 0.6 in both evaluation periods (p = 0.6).

The most detected uropathogens were *E. coli* and *Klebsiella* spp. in both periods. There was no significant difference between the two periods in relation to the rates of positivity for *E. coli* and *Klebsiella* spp. (p = 0.08 and p = 0.86, respectively). The rates of *Proteus* were significantly higher and *Enterococcus* spp. were significantly lower in the 2019-2021 period compared to 2013-2015 (p = 0.008 and p = 0.005, respectively) (Table 1).

Table 1. Demographic data and distribution of uropathogens according to the evaluation period

	2013-2015	2019-2021	*P* value
Age (min-max) (IQR)	6(0.2-18) (2.5-9)	6(0.3-16) (3-9)	0.5
Gender (Male/Female)	204/296	202/298	0.9
Uropathogen:			
Escherichia coli	325(65%)	350 (70%)	0.083
Klebsiella spp.	75 (15%)	77 (15.4%)	0.86
Proteus mirabilis	15 (3%)	33 (6.6%)	0.008
***Enterococcus* spp.**	37 (7.4%)	17 (3.4%)	0.005
***Pseudomonas* spp.**	13 (2.6%)	13 (2.6%)	0.98
***Staphylococcus* spp.**	22 (4.4%)	4 (0.8%)	-
***Streptococcus* spp.**	7 (1.4%)	2 (0.4%)	-
Morganella morganii	6 (0.8%)	4 (0.8%)	-

(min: minimum, max: maximum, IQR: interquartile range)

The antibiotic resistance pattern of the most seen uropathogens is presented in Table 2 by evaluation period. *E. coli* showed high resistance to ampicillin, AMC, TMP/SMX, cefuroxime, and ceftriaxone (59%, 33%, 32%, 28%, and 25%, respectively) while it remained susceptible to cefazolin, ciprofloxacin, meropenem, amikacin, and nitrofurantoin for the 2013-2015 period. The resistance rates of *E. coli* to ampicillin, AMC and TMP-SMX were reported as 65%, 46%, and 45%, respectively and significantly increased in 2019-2021 compared to 2013-2015 (p < 0.001, p < 0.001, p = 0.003, respectively).

Klebsiella spp. were found to be resistant to ampicillin, TMP/SMX, AMC, cefuroxime, and ceftriaxone at the rates of 88%, 39%, 27%, 27%, and 25%, respectively while it remained 100% susceptible to amikacin and meropenem for the 2013-2015 period. The resistance rates of *Klebsiella* spp. to ampicillin, AMC, and TMP-SMX were reported as 76%, 39%, and 25%, respectively for 2019-2021. There was no significant difference between the two evaluation periods in terms of the resistance rates of *Klebsiella* spp. to ampicillin and AMC (p = 0.9 and p = 0.165, respectively) while a significant decrease was observed in the resistance rate of *Klebsiella* to TMP-SMX (p = 0.043) from 2013-2015 to 2019-2021.

Proteus and *enterococcus* spp. were found to be resistant to ampicillin, TMP/SMX, and AMC in 2013-2015. There was no significant difference in the microorganism resistance rates of *Proteus* and *Enterococcus* spp. to antibiotics between the two evaluation periods (Table 2).

3.2 Discussion

UTIs are common in children and their diagnosis is based on the detection of causative uropathogens in urine culture [1,3]. In suspected cases, it is recommended to start early empirical antibiotic therapy until urine culture results are obtained in order to avoid complications related to UTIs [2,3,5]. Increased antibiotic resistance is one of the major problems in the treatment of UTIs [9,10]. Also, broad-spectrum antibiotics prescribed for non-bacterial infections or infections for which narrow-spectrum drugs are indicated and recommended increases drug resistance. Many children receive antibiotic prescriptions indicating an incorrect total daily dosage or fractioning or for a period of time significantly longer than needed [14]. Therefore, it is important to predict antibiotic resistance when prescribing empiric antibiotics.

In our retrospective study, the most common isolated uropathogens were *E. coli, Klebsiella* spp*., Proteus* spp. and *Enterococcus* spp., and female gender was predominant, which is in line with previous studies [8,13-16]. The antibiotic resistance rates of *E. coli* were previously reported as 44-89% for ampicillin, 43-61% for TMP-SMX, and 28-65% for AMC in studies conducted in Turkey [15,16]. This is consistent with the results of our study. Ahmed et al. detected a rising resistance for *E. coli* to AMC and TMP from 2002-2008 to 2009-2019 [17]. We also found that the resistance rates of *E. coli* to ampicillin, AMC, TMP-SMX, and cefazolin significantly increased in 2019-2021 compared to 2013-2015. These antibiotics are the most prescribed antibiotics in pediatric infections. Routine and improper use in various infectious disease along with easy availability of antibiotics is one of the reasons in antimicrobial resistance [17]. Therefore, these antibiotics should be carefully used in the empiric treatment of UTIs caused by *E. coli.* We also determined that *E. coli* had lower rates of resistance to amikacin, meropenem, and nitrofurantoin, as also reported by Samancı et al. [15] and

Ahmed et al. [17]. Oral antibiotics such as ampicillin, MC, TMP-SMX are prescribed more frequently than parenterally administered agents such as amikacin and meropenem, as they are more appropriate for their ease of use in children receiving empirical therapy for UTI. Therefore, while resistance to these orally administered antibiotics has increased over the years, resistance to parenteral agents may have decreased relatively.

In the current study, *Klebsiella* spp. were reported the second most common uropathogens detected in culture samples. The resistance rates of *Klebsiella* to ampicillin, AMC, TMP-SMX, cefuroxime, and nitrofurantoin were found to be high, similar to previous studies in the literature [15, 18]. In addition, we observed that *Klebsiella* had low rates of resistance to amikacin and meropenem, which is in agreement with the findings of Duicu et al. and İdil et al. [13, 19]. We found no significant increase in the antibiotic resistance rates of *Klebsiella* spp. from 2013-2015 to 2019-2021. There was even a significant decrease in the resistance of Klebsiella spp. to TMP-SMX in the 2019-2021 period. The increase in number of carbapenemase producing *Klebsiella* spp. in UTI can be responsible for the decrease in recent years. Therefore, TMP-SMX, which is also effective against these isolates, is regarded as an appropriate treatment option [20].

The antibiotic resistance rates of *Proteus* spp. to ampicillin (48.9%), TMP-SMX (44%), and nitrofurantoin (99.2%) were in agreement with those reported by Cag et al. [16]. We also similarly found that the antibiotics resistance rates of *Proteus* spp. increased from 2013-2015 to 2019-2021, but this increase was not statistically significant. However, these species were determined to be still susceptible to cefuroxime, ceftriaxone, amikacin, and meropenem.

Similar to Cag et al., we detected a high resistance rate of *Enterococcus* spp. to ampicillin. There was no significant difference in the microorganism resistance rates of *Enterococcus* spp. to antibiotics between 2013-2015 and 2019-2021.

The National Institute for Health and Care Excellence Clinical Guidance pathway (CG54) for UTIs in childhood recommends AMC and TMP-SMX as first-line therapy [8]. The Italian recommendations in febrile UTIs also indicate AMC as a first-line treatment in childhood febrile UTIs [21]. However, the rising resistance rates of these antibiotics in recent years calls into question the use of these antibiotics as empirical treatment. Accordingly, the European Society for Paediatric Urology (ESPU) and the European Association of Urology (EAU) also recommends a third-generation cephalosporin in uncomplicated pyelonephritis [22]. We use second or third generation cephalosporin in empirical treatment of UTI in our clinical practice.

The limitations of our study are retrospective nature dependent upon patient data from electronic health record. The analysis of positive urine cultures and antibiotic resistance patterns was performed without clinical correlations.

Table2. Antibiotic resistance pattern of the uropathogens by years

Antibiotic	**E. Coli**			**K.Pneumoni**			**Proteus mirabilis**			**Enterococcus**		
	2013-2015 (n = 325)	**2019-2021 (n = 350)**	***p* value**	**2013-2015 (n = 75)**	**2019-2021 (n = 77)**	***p* value**	**2013-2015 (n = 15)**	**2019-2021 (n = 33)**	***p* value**	**2013-2015 (n = 37)**	**2019-2021 (n = 17)**	***p* value**
Ampicillin	192 (59%)	229 (65%)	**<0.001**	66 (88%)	59 (76%)	0.9	4 (27%)	12 (36%)	0.34	15 (40%)	8 (47%)	0.5
AMC	108 (33%)	160 (46%)	**<0.001**	20 (27%)	30 (39%)	0.165	0	5 (15%)	-	1 (14%)	1 (5.9%)	1
TMP-SMX	103 (32%)	156 (45%)	**0.003**	29 (39%)	19 (25%)	**0.043**	2 (13%)	12 (36%)	0.178	5 (1.4%)	6 (35%)	0.2
Cefazolin	5 (1.5%)	12 (3.4%)	0.6	1 (1.3%)	5 (6%)	0.38	3 (20%)	3 (9%)	-	0	0	-
Cefuroxime	91 (28%)	96 (27%)	0.37	20 (27%)	23 (30%)	0.436	3 (20%)	2 (6%)	0.345	2 (5.4%)	3 (18%)	0.5
Ceftriaxone	81 (25%)	42 (12%)	0.85	19 (25%)	12 (16%)	0.3	0	0	-	1 (2.7%)	1 (5.9%)	-
Ciprofloxacin	30 (9.2%)	26 (7.4%)	0.7	7 (9.3%)	8 (10%)	0.26	0	1 (3%)	0.53	1 (2.7%)	1 (5.9%)	0.6
Fosfomycin	3 (0.9%)	0	-	8 (11%)	1 (1.3%)	0.7	1 (6.7%)	1(3%)	1	0	0	-
Gentamicin	43 (13%)	53 (15%)	0.73	12 (2.7%)	10 (13%)	0.49	0	3 (9%)	-	1 (2.7%)	2 (12%)	0.1
Meropenem	2 (0.6%)	0	-	-	-	-	0	1 (3%)	-	-	-	-
Nitrofurantoin	19 (5.8%)	21(6%)	0.42	11 (15%)	18 (23%)	**0.007**	7 (47%)	22 (67%)	0.173	0	0	-

(AMC: amoxicillin clavulanic acid, TMP-SMX: trimethoprim-sulfamethoxazole)

4. Conclusion

Antibiotic resistance is rising due to the misuse or overuse of antibiotics worldwide. In order to prevent antibiotic resistance, the most appropriate narrow-spectrum antibiotic should be selected considering its susceptibility pattern. According to the results of the current study, ampicillin, AMC, and TMP-SMX should be preferred in empiric treatment if urine culture is already available. It is essential to determine the local resistance of uropathogens to antibiotics to establish local guidelines in empiric therapy for UTIs.

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