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Risk factors for trimethoprim-sulfamethoxazole-resistance of E. Coli in children with urinary tract infection

Erhan Karaaslan[1], Resul Yilmaz[1], Mustafa Ozcetin[2]

[1] Department of Pediatrics, School of Medicine, Gaziosmanpasa University Tokat, Turkey,
[2] Department of Pediatrics, School of Medicine, Karaelmas University, Zonguldak, Turkey.

Abstract

Background: Urinary tract infections are common in children and E.Coli is the most common organism causing UTI. TMP-SMX is a frequently prescribed agent for UTI, but resistance level for this antimicrobial is gradually rising.

Methods: The aim of this study was to evaluate risk factors for development of trimethoprim-sulfamethoxazole resistance of E.Coli in children with urinary tract infection with respect to age, gender, recent antimicrobial exposure and hospitalization. Between January 1, 2005, and December 31, 2010, a total of 397 isolates positive for E.Coli were evaluated retrospectively. We examined the relationships between trimethoprim-sulfamethoxazole resistance in E.Coli isolates and gender, age, recent antibiotic exposure, amoxicillin-clavulanate exposure and hospitalization. Univariate and multivariate logistic regression tests were applied for these variables.

Results: The mean age of the patients was 68.33±44.78 months. Of the 397 isolates, 50.6 % were resistant to TMP-SMX. Univariate analysis indicated that subjects who had received antibiotics in the previous 2 months were about 1.65 times more likely to have isolates resistant to TMP-SMX. Multivariate analyses indicated that subjects who had received antimicrobials were about 1.87 times more likely to have isolates resistant to TMP-SMX. Compared with children who had no hospital admissions in the previous 6 months, were more likely to have resistant isolates. Children under 4 years of age were more likely to have resistant isolates. Among specific antibiotic exposure, amoxicillin-clavulanate was found the main determinant of risk factor for TMP-SMX resistance.

Conclusion: In conclusions, recent antibiotic exposure, particularly amoxicillin-clavulanate, is a strong risk factor for the development trimethoprim-sulfamethoxazole-resistance of E.Coli in children with urinary tract infection, which limits the use of first-line antibiotics for UTI's in children.

Keywords: Urinary tract infection, Escherichia coli, trimethoprim–sulfamethoxazole resistance, children.

Introduction

Urinary tract infections are common clinical problem that affects 7 % of febrile children [1]. Young children with UTI are more prone to develop renal damage, and delayed treatment adds additional risks [2]; therefore, it is necessary to initiate treatment for UTIs before urine culture results are available [3]. However, a major concern is the identification of patients infected with a resistant microorganism in UTIs, because inappropriate empiric antibiotic treatment may cause high rates of treatment failures.

Previous studies in children have identified a variety of risk factors for antimicrobial resistance, such as contact with family members colonized with resistant bacteria [4], hospitalization [5], and antibiotic exposure [6]. The risk factors of Escherichia Coli antibiotic resistance in adults have been extensively studied and explained [6], but evidence for this causal relationship in community settings is limited in children.

The goal of this study study is to determine the risk factors for TMP-SMX resistance of Escherichia Coli isolated UTI in non-hospitalized children and to explore the relationships between age, gender, antibiotic exposure and hospitalization history.

Methods

This study is a retrospective study conducted between January 2005 and December 2010. We retrieved hospital electronic medical record (EMR) system using International Classification of Disease, Ninth Revision Codes. The EMR contains a patient's visit history, demographic information, laboratory data and medical history. The EMR was searched for children between 1 month and 15 years with a principal diagnosis of urinary tract infection and pyelonephritis.

All children had one of urinary symptoms such as dysuria, unexplained acute febrile fever, discomfort, or refusal to feed. The urine was collected thorough clean-catch method in children > 2 years or bag-collection method in children < 2 years. A UTI was defined as 100 000 colony forming units (CFU) of a single microorganism. Microbiological analysis was performed by standard methods on cultures with bacteriuria using a panel of antimicrobial agents depending on the causative agent. Intermediate results were considered resistant results.

All E.Coli positive isolates whether UTI was complicated or uncomplicated were included to the study. The children who had isolates resistant to trimethoprim- sulfamethoxazole were considered as cases, and children who had TMP-SMX-sensitive isolates were considered as controls. Patients with malignancy, diabetes, immunodeficiency, central nervous system malformations, or genitourinary malformation and age < 1 month were excluded from the study. If the patients have been receiving prophylactic antibiotics, only antibiotic used during breakthrough UTIs were included.

Cases were defined as exposed to an antibiotic agent, which is defined as a risk factor if they were dispensed any antibiotics within 60 days of submission of the urine sample. An antimicrobial exposure was considered non-exposed, if the sample was obtained between 0 and 7 days of a urine culture. Information about antibiotic consumption before the diagnosis of UTI was obtained from patients' electronic charts, by questioning patients or their families. Hospitalization for any reason within 180 days before urine sampling date was defined as a risk factor. The patients were assembled into two groups according to their age, 1 month - 4 years, and 4-15 years, and age below 4 years was defined as a risk factor.

Data were analyzed by SPSS (version 20, Chicago, USA). The association between antimicrobial resistance and variables were first tested by using univariate logistic regression analysis. Subsequently, multivariate logistic regression analysis was performed to assess the association between antimicrobial resistance and the other factors. The terms included for regression analysis are age, gender, and antibiotic exposure within 60 days of UTI, and hospitalization within 180 days of UTI. OR's, 95% CI's, and p values are presented for variables.

Results

A total of 391 E.Coli isolates was obtained over the study period from 297 patients. The mean age of cases was 68.33 ± 44.78 months. Three hundred thirty eight (86.4 %) patients were female with the mean age 75.93 ± 42.60 months, 53 (13.6 %) were male with the mean age 19.87 ± 22.47 months. The mean age of females was significantly higher than males (mean 75.93 ± 42.60 versus 19.87 ± 22.47 months, $p < 0.001$). The number of patients aged 1 month to 4 years was 133 (34.0 %); the number of patients with age > 4 years was 258 (66.0 %). The number of patients hospitalized within 180 days of UTI was 28 (7.2 %). The patients characteristics is shown in table 1.

When all resistant isolates were examined as a proportion of the total number of isolates, the highest rates of resistance were found for amoxicillin (67.8 %), piperacillin (54.7 %), trimetho-

Table 1. Patient characteristics

Variable	n	%
Gender		
Female	338	86.4
Male	53	13.6
Age		
1 mo.- ≤ 4 years	133	34.0
> 4 years	258	66.0
Hospitalization		
No	363	92.8
Yes	28	7.2
Antibiotic Exposure		
No	303	77.5
Yes	88	22.5

prim-sulfamethoxazole (50.6 %), amoxicillin-clavulanic acid (48.3 %), cefazolin (23.5 %), ceftriaxone (17.1 %), and the least rates resistance were found for meropenem (0.0 %), imipenem (0.5 %), amikacin (2.0 %), cefoperazone - sulbactam (3.6 %) and gentamicin (9.7 %) in E.Coli isolates. The rates of resistance to different antibiotics tested are reported in table 2.

Eighty- eight (22.5 %) patients received an antibiotic within 60 days of UTI for infections. The most commonly prescribed antibiotic was amoxicillin-clavulanic acid (7.9 %), prescription rates of cephalosporin' s were as follows: cefixime, 3.3 %; cefaclor 1.3 %; cefuroxime, 2.6%; ceftriaxone, 0.8 %; cefdinir, 1.0 %; prescription rates of macrolides were 2.0 %, TMP-SMX prescription rate is 0.5 %. The prescription rates of amikacin and gentamicin are 0.5 %, 0.8 % respectively. Three hundred three (77.5 %) patients were not received any antibiotics. The rates of antibiotic prescriptions are reported in table 3.

Children who had received antibiotic treatment within 60 days of UTI were more likely to have resistant isolates than children who had not received antibiotic treatment ($p < 0.04$ OR: 1.65 (95% (CI): 1.01-2.67)). The patients between 1 month- 4 years of age were more likely to have resistant bacteria ($p < 0.02$, OR: 1.63 (95% (CI): 1.06 - 2.49)). The other risk factor assessed was hospitalization within 180 days of UTI ($p < 0.02$, OR: 2.59 (95% (CI): 1.11 − 6.05). Univariate analysis showed that gender was not a risk factor for the development of TMP-SMX resistance ($p= 0.22$, OR: 1.44 (95% (CI): 0.80-2.59). The results of univariate analysis are shown in table 4.

In multivariate logistic regression analysis, the association between antibiotic exposure and TMP-SMX resistance was ($p= 0.01$ OR: 1.87, (95% (CI): 1.12 − 3.12)). The other association was age between 1 mo. - 4 years ($p < 0.02$, OR: 1.76, (95 % (CI): 1.08 − 2.88). However, gender ($p = 0.83$, OR: 1.07 (95% (CI): 0.55 − 2.07), hospitalization ($p= 0.09$, OR: 2.81 (95% (CI): 0.88 − 4.95) were not associated with TMP-SMX resistance in multivariate logistic regression analysis. The results of multivariate analysis are shown in table 4.

The associations between antibiotic exposure and TMP-SMX resistance are shown in table 5. Amoxicillin-clavunate prescription is significantly associated with TMP-SMX resistance, OR: 3.03 (95 % (CI): 1.32 − 6.97, $p= 0.009$. It was found that exposure of cefixime, cefuroxime were not associated with TMP-SMX resistance. Due to small numbers, other antimicrobials used were not studied.

Table 2. Rates of resistance to different antibiotics tested against E. coli strains isolated from urinary tract infections

	Resistant (%)	Susceptible (%)
Amoxicillin	67.8	32.2
Amoxicillin-clavulanic acid	48.3	51.7
Trimethoprim-sulfamethoxazole	50.6	49.4
Amikacin	2.0	98.0
Gentamicin	9.7	90.3
Cefazoline	23.5	76.5
Cefotaxime	17.1	82.9
Cefepime	16.1	83.9
Cephoxitine	7.4	92.6
Cephoperazone-sulbactam	3.6	96.4
Ciprofloxacin	13.0	87.0
Levofloxacine	10.0	90.0
Imipenem	0.5	99.5
Meropenem	0.0	100
Piperacilin	54.7	45.3
Piperacine-Tazobactam	19.2	80.8

Table 3. Prescription rates of antibiotics

	n	%
None	303	77.5
Amoxicillin-Clavulanic acid	31	7.9
Ampicillin	7	1.8
Cefixime	13	3.3
Cefaclor	5	1.3
Cefuroxime	10	2.6
Macrolide	8	2.0
Trimethoprim-Sulfamethoxazole	2	0.5
Ceftriaxone	3	0.8
Cefdinir	4	1.0
Amikacin	2	0.5
Gentamicin	3	0.8
Total	391	100.0

Table 4. Results of logistic regression analyses

	Univariate analysis		Multivariate Analysis	
Variable	OR (CI 95 %)	p	(OR (CI 95%))	p
Age				
>4 years	1		1	
1 mo-4 years	1.63 (1.06-2.49)	0.02*	1.76 (1.08- 2.88)	0.02*
Gender				
Female	1		1	
Male	1.44 (0.80- 2.59)	0.22	1.07(0.55-2.07)	0.83
Hospitalization				
No	1		1	
Yes	2.59 (1.11-6.05)	0.02*	2.08 (0.88-4.95)	0.09
Antibiotic Exposure				
No	1		1	
Yes	1.65(1.01-2.67)	0.04*	1.87 (1.12-3.12)	0.01*

** Statistically significant*

Table 5. Prior antibiotic prescriptions and risk of trimethoprim-resistant E. coli UTIs

Antimicrobial Consumed	Category	R/S**	OR	95 % CI	p
Amoxicillin-clavulanate					
	no	175/185	1		
	yes	23/8	3.03	1.32-6.97	0.009*
Cefixime					
	no	191/187	1		
	yes	7/6	1.14	0.37-3.46	0.81
Cefuroxime					
	No	195/186	1		
	Yes	3/7	0.40	0.10-1.60	0.20

** Statistically significant; **R: resistant, S: Susceptible*

Discussion

This study showed that a high number of E.Coli were resistant to first line antibiotics, trimethoprim-sulfamethoxazole, ampicillin and amoxicillin-clavunate, but resistances to carbapenems and amino-glycosides were found low. We found that infections with TMP-SMX resistant E.Coli were associated with prescriptions of amoxicillin-clavunate in the previous 2-month of UTI. Gender was not associated with resistance while younger age was found to be a risk factor for the development of resistance. Children below 4 years of age had high range of resistant E.Coli. Hospitalization history within 6 mo. of UTI appears to be an independent risk factor for the development of resistance.

Trimethoprim-sulfamethoxazole (TMP-SMX) is one the most common prescribed antimicrobial for childhood UTIs [7], but the prevalence of resistance E.Coli is progressively increasing [8]. Since early 1990s, in some European Countries, TMP-SMX resistance rate was reported about 10 %, but within 10 years period, it increased to 17% [9]. In a prospective study in Turkey TMP-SMX resistance of E.Coli was found about 60% [10]. Our study demonstrated that resistance level to TMP-SMX was 50.6 %. Although not every patient infected with a resistant microorganism fail treatment, it was shown that patients with in vitro resistant isolates to TMP-SMX had high rates of treatment failures [11]. Our results suggest that the use of TMP-SMX as a single agent for the empirical treatment of UTIs do not cover E.Coli.

In adults a wide range of antibiotic selection is applicable for UTIs; however, there is a restricted choice of first-line antimicrobials in UTIs due to resistant organism in children. A combination of empirical ampicillin and amino-glycosides was suggested for UTIs in children [12]. Other authors suggested amoxicillin-clavunate or cefuroxime [13], or cefixime [14] for empirical treatment of

community acquired UTIs. Our result suggests that resistance rates for amino-glycosides are relatively low; therefore, amino-glycosides can be used for empirical treatment of UTIs.

Although antibiotics have been effective in control of infectious diseases, extensive prescription and use of antibiotics caused the development and spread of antimicrobial resistance [15]. The univariate analysis of this study demonstrates that antibiotic exposure within 60 days of a UTI is strongly associated with TMP-SMX resistance among pediatric outpatients. In adult patients an association between excessive and/or inappropriate antibiotic use and resistance in UTI has been demonstrated [16]. In children, prolonged use of antibiotics such as for antibiotic prophylaxis was also associated with increased risk of resistant infections [17]. Policies against use of antimicrobials prescription have been successful; however, three are still high rates of antimicrobial prescription rates [18]. Our study showed that prescription rates of antibiotics were 22.5 % in children. In pediatric age group, acute bacterial infections, such as acute otitis media, sinusitis is common and antibiotics are generally prescribed [19]. However, guidelines and studies suggest limited use of antibiotics for these clinical conditions and short course of antibiotics for more severe infections, such as lower respiratory infections [20]. Therefore, it is necessary to restrict antimicrobial use to combat antimicrobial resistance.

Trimethoprim-sulfamethoxazole is considered an indicator first line agent that resistance to TMP-SMX was associated with resistance to other, pharmacologically unrelated agents, such as amoxicillin and first-generation cephalosporin's [21]. Thus, the main risk factors associated with TMP resistance would be associated with other agents. Our result showed that recent use of amoxicillin-clavunate increases the risk of TMP-SMX resistance development about 3 times more (OR: 3.03, $p<0.009$). It has been showed that use of amoxicillin-clavunate resulted in a high rate of ampicillin and sulfamethoxazole resistance, and is postulated that a partial cross-resistance mechanism played a role for the development of resistance [22]. The correlations between amoxicillin-clavunate use and TMP-SMX resistance suggested a linked resistance to both antibiotics. Transports of a linked resistance to these antibiotics via transmissible plasmids have been documented in fecal E.Coli [23]. The results of present study suggest that the same mechanism is involved in urinary E.Coli infections.

Although infections with resistant enterobacteriaceae in children have been reported more common in males [24], our study showed that resistant rates regarding to sex was insignificant. This study demonstrated that antibiotic resistance was more common in younger age. The odds for resistant rates in children below 4 years age was 1.643 (1.06- 2.49). Studies have shown that the resistance rates of E.Coli to TMP-SMX were found higher in younger infants [25, 26]. This high rate of resistance was attributed that younger aged children had a dysfunctional elimination of urine [27] that might lead to recurrent UTI, which in turn may increase probability of frequent antibiotic prescription, and that the younger age groups have high rates of respiratory tract infections [28], this may provide the rationale used by some physicians to prescribe multiple and prolonged courses of antibiotics in this age group. Another possible explanation is that the development of antimicrobial resistance in younger children was associated with diapering because resistant colonization of E.Coli was found to be high in diapered children; this was attributed to higher prevalence of fecal colonization with multi-resistance E.Coli [21].

It is well known that hospitalization is a major risk factor for the development of antimicrobial resistance [29]. We found that admission to hospital within 6 mo. of UTI increases the risk of resistance assessed by univariate analysis. However, in multivariate testing hospitalization did not contribute the development of resistance. This suggests that hospitalization is independent risk factor, and suggest spread of resistance within closed settings.

We have some limitations. We studied health children without major problems; our results are not applicable to hospitalized children with complex problems or those cared in intensive care unit. Another limitation is that data on antimicrobial drug exposure were limited to information from outside our institution and limited to parenteral reporting; therefore, we could not be able to define dose-response relationships for antimicrobial-re-

sistant infections, because mathematical models indicate when a critical level of drug consumption is reached, the prevalence of resistant bacteria will rise to significant levels as antibiotic exposure increases, and any antimicrobial drug reduces colonization with susceptible bacteria this in turn leads to an increased the probability of colonization by resistant bacteria [30].

Conclusions

Recent antibiotic exposure is a strong risk factor for the development of antimicrobial resistance for E.Coli UTIs in children. The data in this study allow some general conclusions to be made. First-line antibiotics such as amoxicillin and TMP-SMX should no longer be considered first-line agents in the treatment of most pediatric UTIs. Our results suggest that inappropriate use of antimicrobials should be limited in order to reduce the development of antimicrobial resistance.

Further prospective studies are required to search the similar data to evaluate this relationship in children. Frequent surveillance is necessary to observe antimicrobial resistance patterns. We suggest that the policies for the choice of antibiotic regimes for uncomplicated UTI in children should be reviewed every 2-3 years.

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Corresponding Author
Erhan Karaaslan,
Department of Pediatrics, School of Medicine,
Gaziosmanpasa University Tokat,
Turkey,
E-mail: drekaraaslan@gmail.com