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Antimicrobial Resistance of Breakthrough-Urinary Tract Infections in Children under Antimicrobial Prophylaxis

Toshihito NOMURA[1,2], Ken HISATA[1], Yudai TOYAMA[1], Keita SAKAGUCHI[1], Naru IGARASHI[1], Akihiro NAKAO[1], Nobuaki MATSUNAGA[1], Mitsutaka KOMATSU[1], Kaoru OBINATA[1] and Toshiaki SHIMIZU[1]

1) Department of Pediatrics and Adolescent Medicine, Juntendo University
2) Department of Virology, Graduate School of Biomedical & Health Sciences, Hiroshima University

ABSTRACT

Antimicrobial prophylaxis using cefaclor or trimethoprim-sulfamethoxazole (co-trimoxazole) is recommended for children with vesicoureteral reflex (VUR) to prevent recurrent urinary tract infection (UTI). This retrospective study was performed by reviewing the data of children ≥5 years of age treated for recurrent UTI in six hospitals from 2010 to 2015. The criteria for UTI diagnosis is fever (≥38°C) and positive results in urine culture (>10^4 colony-forming units/ml in midstream or withdrawn urine specimens). In total, 41 children were reviewed, and 31 children had recurrent UTI without antimicrobial prophylaxis and 10 had breakthrough (BT)-UTI treated with prophylaxis using cefaclor or co-trimoxazole. In the cases of BT-UTI treated with prophylaxis, 5 children received cefaclor and 5 received co-trimoxazole. We collected data on pathogens, antimicrobial resistance, and antimicrobial agents chosen for the empirical treatment of recurrent UTI. We also evaluated the validity of empirical therapy for recurrent UTI in this study. Various pathogens were found in children who received prophylaxis with cefaclor. The rate of empirical antimicrobial agents that were inappropriate based on antimicrobial susceptibility tests was higher in children who received prophylaxis with cefaclor (60.0%) than in those who received no prophylaxis (25.9%) or prophylaxis with co-trimoxazole (20.0%). Prophylaxis with cefaclor was found to be a risk factor for inappropriate empirical treatment in BT-UTI cases. The results suggest that the choice of empirical antimicrobial agents in BT-UTI cases should be carefully considered before treatment with prophylaxis. To encourage the adequate use of antimicrobial agents, we recommend prophylaxis with co-trimoxazole to prevent recurrent UTI.

Key words: *Prophylaxis, breakthrough-urinary tract infection*

Vesicoureteral reflex (VUR) is a common urologic anomaly, with a prevalence rate of 1%–2% in children[11], and it increases the risk of recurrent urinary tract infection (UTI). Antimicrobial prophylaxis is recommended for children with VUR to prevent recurrent UTI. Cefaclor or trimethoprim-sulfamethoxazole (co-trimoxazole) is mainly selected in Japan[3,12]. One advantage of antimicrobial prophylaxis is that it reduces the risk of recurrent UTI[2,9,10]; however, antimicrobial prophylaxis may be a risk factor for inducing resistant bacteria. In particular, cephalosporin prophylaxis was reported to be a risk factor for resistant bacteria in breakthrough UTI (BT-UTI). The amount of extended-spectrum ß-lactamase (ESBL)-producing organisms was reported to be higher in children receiving cephalosporin[1,4,5]. Antimicrobial agents used for prophylaxis and the treatment of UTI are selected by the attending physician. We collected data on pathogens, antimicrobial resistant patterns, and antimicrobial agents chosen for empirical treatment of recurrent UTI. We hypothesized that the rates of pathogen resistance and inappropriate treatment with empirical antimicrobial agents, determined based on antimicrobial susceptibility tests, were higher with prophylaxis for VUR treatment. We investigated the difference in the antimicrobial resistant rate for ESBL-producing bacteria in children who received prophylaxis and in those who received no prophylaxis. We also evaluated the validity of empirical therapy for recurrent UTI in this study. Furthermore, we investigated the relationship of prophylaxis with inappropriate treatment.

MATERIALS AND METHODS

This retrospective study was performed in six hospitals in Japan: Juntendo University Urayasu Hospital, Juntendo University Nerima Hospital, Sanikukai Hospital, Tokyo Rinkai Hospital, Toshima Hospital, and Koshigaya Municipal Hospital. We reviewed data from April 2010 to March 2015 for

children up to 5 years of age treated for recurrent UTI and requiring hospitalization. The criteria for UTI diagnosis is fever (≥38°C) and positive results in urine culture (>10^4 colony-forming units/ml in midstream or withdrawn urine specimens). Recurrent UTI was defined as contracting UTI, recovering completely, then contracting UTI again, while BT-UTI was defined as contracting recurrent UTI after receiving antimicrobial agents for prophylaxis. 719 children out of a total of 782 hospitalized cases with a diagnosis of UTI, were considered. 52 cases were recurrent UTI, and 2 cases were excluded because of the detection of multiple bacteria in the urine culture. Another case was excluded because the culture result showed less than 10^3 colony-forming units/ml. Additionally, 6 cases that received multiple antimicrobial agents for prophylaxis were excluded. A case that required surgery for VUR before recurrent UTI was also excluded. Another case wherein the patient was administered ampicillin for prophylaxis was excluded. For analyses, we retrospectively reviewed the data for 38 children (41 cases).

Each attending physician chose the antimicrobial agent for prophylaxis and treatment of recurrent UTI. In total, 31 cases had recurrent UTI treated without prophylaxis, whereas 10 had recurrent BT-UTI treated with antimicrobial prophylaxis using cefaclor or co-trimoxazole. Among the BT-UTI cases, 5 received trimethoprim-sulfamethoxazole (co-trimoxazole) and 5 received cefaclor (Figure 1).

The Micro Scan system panel of antibiotics was used for susceptibility testing in each hospital (Beckman Coulter). The minimum inhibitory concentration for the antimicrobial agents was assessed by microdilution according to the Clinical and Laboratory Standards Institute guidelines (M100-S19~S24). Intermediate results were considered to indicate resistance. *Enterococcus faecalis* was found to be resistant to all cephalosporins while *Pseudomonas aeruginosa* was found to be resistant to antimicrobials such as cefazolin and ceftriaxone. Inappropriate treatment was defined as cases in which the empirical antimicrobial agent used was inappropriately based on the results of an antimicrobial susceptibility test. The Fisher exact test, the Kruskal-Wallis test and Man Whitney U test were used for comparing the subject's backgrounds. We analyzed the other tables by the Fisher's exact test. We considered that the p value of <0.05 was statistically significant, and two-side tests were used. Fisher's test was carried out using BellCurve for Excel (Social Survey Research Information Co., Ltd.). The Kruskal-Wallis test was carried out using Excel2016 (Microsoft Corporation).

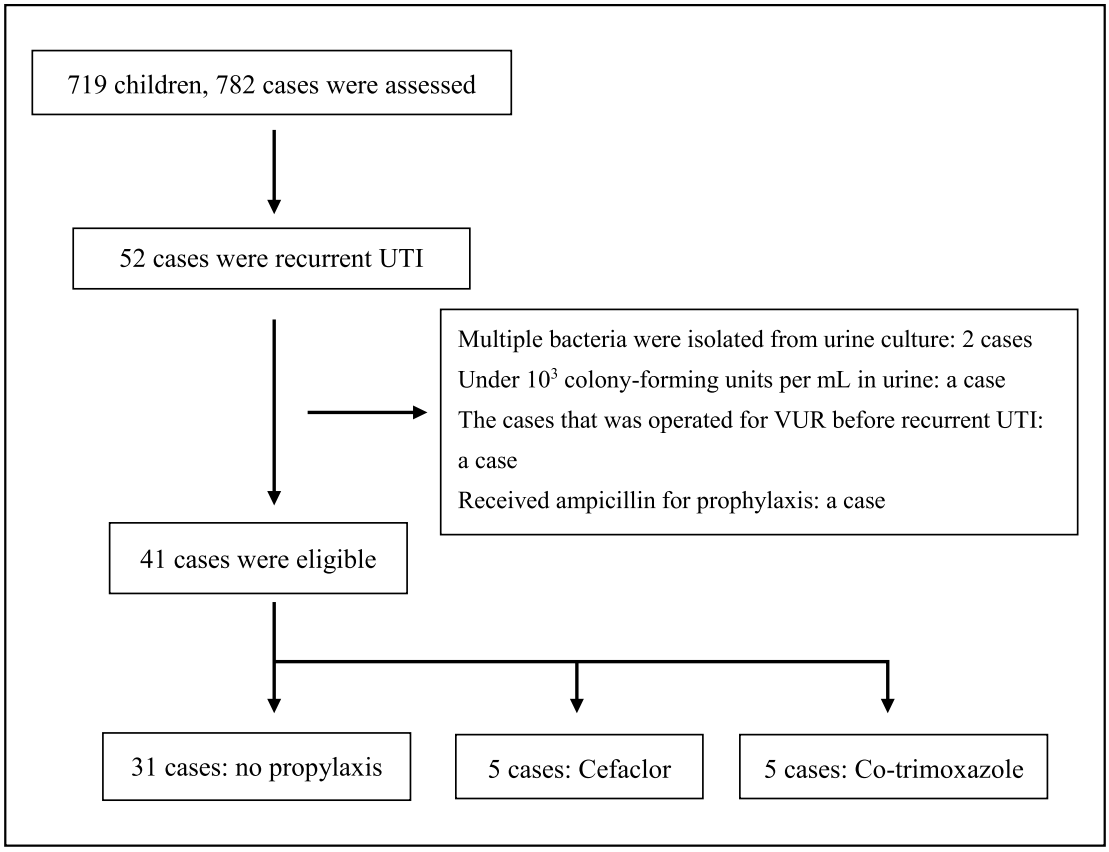

Figure. Children whose data were reviewed in this study

RESULTS

Table 1 shows the median age, gender, and VUR grade for each group. We defined high-grade VUR as grades III, IV, or V on one or both sides. The proportion of children with high-grade VUR was higher in the group that received co-trimoxazole than in the group that received no prophylaxis (p = 0.0365). We investigated median age and rate of high-grade VUR children receiveing co-trimoxazole. All of the children with high-grade VUR received co-trimoxazole, 60% of children received cefaclor, and 38.5% of children did not receive prophylaxis.

Table 2 shows the etiology of the UTI pathogen in each group. *Escherichia coli* and *E. faecalis* were the most common pathogens. Additionally, 71.0% children who did not receive prophylaxis had recurrent UTI due to *E. coli*. Furthermore, in this group, the most common pathogen, with the exception of two isolates *(Enterobacter cloacae* and *Haemophilus influenzae),* were *E. coli* or *E. faecalis* (93.6%). However, only 20.0% of children who received antimicrobial prophylaxis had recurrent UTI due to *E. coli*. The proportion of children with *E. coli* was lower in the group that received cefaclor than in the group that received no prophylaxis (71.0% vs 0%, p = 0.0053). Also, 40% of children who received co-trimoxazole had recurrent BT-UTI due to *E. coli*. A wide variety of pathogens was detected in the children who received prophylaxis, and this was particularly notable in children who received cefaclor.

Table 3 shows the antimicrobial agents used for empirical treatment. While 92.5% of children who did not receive prophylaxis were treated with cephalosporin, only 70.0% of children who received prophylaxis were treated with cephalosporin. The third generation of cephalosporin and carbapenem were mainly selected for empirical treatment in children who received cefaclor. Ampicillin and first or second-generation cephalosporin were mainly selected for empirical therapy in children who received co-trimoxazole or no prophylaxis.

Table 4 shows the antimicrobial susceptibility of co-trimoxazole and cefotaxime, isolates of ESBL-producing bacterium, and inappropriate treatment rates, defined as the rate when the empirical antimicrobial agent selected was inappropriate based on an antimicrobial susceptibility test. Co-trimoxazole-resistant pathogens were isolated in 10 cases of UTI. Of these, 4 cases were of children who received prophylaxis, 4 were of children who received co-trimoxazole, and 2 were of children who received cefaclor. Ceftriaxone-resistant pathogens were

Table 1. Demographic and Clinical Features of Children

	No prophylaxis	Cefaclor	p value	Co-trimoxazole	p value
Total, n	31	5		5	
Age, mo					
Median	6.0	6.5		11.4	0.12[a]
Interquartile	0.1–53.7	1.6–21.3		7.2–13.6	
Gender, n (%)					
Male	22 (71.0)	5 (100.0)	0.30	3(60.0)	0.63
Female	9 (29.0)	0 (0)		2 (40.0)	
Duration of prophylactic treatment, mo					
Median	0	3.1		7.9	< 0.05[b]
Interquartile	0	0.7–4.4		3.2–8.0	
VUR grade, n (%)					
0– II	16 (61.5)	2 (40.0)		0 (0.0)	
III–V	10 (38.5)	3 (60.0)	0.63	4 (100)	< 0.05
No date	5	0		1	

Fisher's test was used for comparing with no prophylaxis data.
[a] Kruskal-Wallis test was used for comparing age among three group.
[b] Man whitney U test was used for comparing duration of prophylactic treatment with co-trimoxazole data.

found in 13 cases of UTI. Of these, 8 cases were of children who did not receive prophylaxis, 4 were of those who received cefaclor, and 1 case was of a child who received co-trimoxazole. The ceftriaxone-resistant rate in children who received prophylaxis was higher than that of those who did not receive prophylaxis (50.0% vs 29.6%) and was significantly higher in children who received cefaclor (80.0%, p = 0.053). The co-trimoxazole-resistant rate in children who received co-trimoxazole was particularly high (80.0%, p = 0.0086).

ESBL-producing bacteria were isolated from 3 cases of UTI. Of these, 2 were of children who did not receive prophylaxis and one was of a child who received cefaclor. There were no ESBL-producing bacteria in children who received co-trimoxazole.

The inappropriate treatment rate for children with prophylaxis was higher than for those who

Table 2. Pathogens of UTIs

	n (%)				
	No prophylaxis	Cefaclor	p value	Co-trimoxazole	p value
Total	31	5		5	
Escherichia coli	22 (71.0)	0	< 0.05	2 (40.0)	0.31
Enterococcus faecalis	7 (22.6)	0	0.56	0	0.56
Enterobacter cloacae	1 (3.2)	1 (20.0)	0.26	1 (20.0)	0.26
Hemophilus infuenzae	1 (3.2)	0	1.0	0	1.0
Klebsiella pneumoniae	0	1 (20.0)	0.26	2 (40.0)	< 0.05
Pseudomonas aeruginosa	0	1 (20.0)	0.14	0	1.0
Enterobacter aerogenes	0	1 (20.0)	0.14	0	1.0
Serratia marcescens	0	1 (20.0)	0.14	0	1.0

Fisher's test was used for comparing with no prophylaxis data.

Table 3. Empirical antimicrobial agents for recurrent UTI

	n (%)				
	No prophylaxis	Cefaclor	p value	Co-trimoxazole	p value
Total	27	5		5	
Ampicillin	2 (7.4)	0	1.0	1 (20.0)	0.41
Cefazolin	8 (29.6)	0	0.30	2 (40.0)	0.64
Cefotiam	2 (7.4)	0	1.0	0	1.0
Cefmetazole	6(22.2)	1 (20.0)	1.0	1 (20.0)	1.0
Cefotaxime	8 (29.6)	2 (40.0)	0.64	0	0.30
Ceftazidime	1 (3.7)	0	0.84	1 (20.0)	0.29
Meropenem	1 (3.7)	1 (20.0)	0.29	0	0.84
Tazobactam/ Piperacillin	0 (0.0)	1 (20.0)	0.16	0	1.0
No date	4	0		0	

Fisher's test was used for comparing with no prophylaxis data.

Table 4. Frequency of Resistance to Antibiotics

	n (%)				
	No prophylaxis	Cefaclor	p value	Co-trimoxazole	p value
Total	27	5		5	
Ceftriaxone-resistant bacterium	8 (29.6)	4 (80.0)	0.053	1 (20.0)	1.0
Co-trimoxazole-resistant bacterium	4 (14.8)	2 (40.0)	0.23	4 (80.0)	< 0.05
ESBL-producing	2 (7.4)	1 (20.0)	0.41	0	1.0
Resistant rate for empiric antimicrobial agents	7 (25.9)	3 (60.0)	0.30	1 (20.0)	1.0

Fisher's test was used for comparing with no prophylaxis data.

did not receive prophylaxis (40.0% vs 25.9%). The inappropriate treatment rate for children who received cefaclor was the worst among the three groups (60.0%).

DISCUSSION

Cephalosporin was most frequently selected as the empirical antimicrobial agent in recurrent UTI cases. The third generation of cephalosporin was mainly selected for children who received cefaclor whereas the first or second generation was mainly selected for children who received co-trimoxazole or no prophylaxis. For BT-UTI cases, we speculated that each attending physician selected a broad-spectrum agent for empirical treatment because the number of resistant pathogens is higher in BT-UTI with prophylaxis. This tendency was observed among children who received cefaclor more often than in those who received co-trimoxazole. Past studies reported that resistant bacteria are higher when BT-UTI is treated with prophylaxis. Prophylaxis with cephalosporin was reported to have the highest risk of inducing resistant bacteria, including ESBL-producing bacteria. In this study, we compared children who received co-trimoxazole with those who received cefaclor and found similar results. Increasing ESBL-producing bacteria have been reported[7,8]. Even in the Japanese pediatric field, ESBL-producing bacteria have been detected and are considered an important problem[6]. A normal neonate that was an ESBL-producing bacteria carrier was reported recently[13]. The risk factor of increasing resistant bacterium should be disseminated to prevent the spread of infection. Various pathogens were found in children with BT-UTI who received cefaclor, and most of these bacteria were resistant to a large number of antimicrobial agents. In contrast, most pathogens observed in children who received co-trimoxazole were resistant to co-trimoxazole, but had no resistance to cephalosporin. Cephalosporin-resistant pathogens, including ESBL-producing bacteria, should be considered when children receive cefaclor as prophylaxis for recurrent BT-UTI.

We compared the inappropriate treatment rate for children who received antimicrobial prophylaxis with that for children who did not receive prophylaxis. The inappropriate treatment rate was higher in the former group and was highest in the children who received cefaclor. However, these children received broad-spectrum antimicrobial agents for empirical treatment.

We confirmed that the rate of *E. coli* was lower in children who received cefaclor than in those who received no prophylaxis. This is similar to past reports. We could not confirm that children who received cefaclor had higher rates of ceftriaxone-resistance and inappropriate treatment than those who received no prophylaxis. However, the ceftriaxone-resistance and inappropriate treatment in children who received cefaclor were the worst among the three groups. There was a wide variety of pathogens in children who received cefaclor, particularly. We presume that the wide variety of pathogens played a role in the ceftriaxone-resistance and the inappropriate treatment rate. We did not evaluate many BT-UTI cases; therefore, we could not confirm the rates. In future, we aspire to investigate more BT-UTI cases to confirm the relationship between prophylaxis and inappropriate treatment.

CONCLUSION

The tendency for children who received co-trimoxazole and for those who received no prophylaxis

was observed to be the same in this study. However, in children who received cefaclor, the inappropriate treatment rate was the worst among the three groups along with the presence of a wide variety of pathogens. Nevertheless, these children received broad-spectrum antimicrobial agents for empirical treatment. Prophylaxis with cefaclor seems to be a risk factor for inappropriate empiric treatment in BT-UTI cases. The results of this study suggest that the choice of empirical antimicrobial agent in BT-UTI cases should be considered carefully. To facilitate adequate antimicrobial agent usage, we recommend prophylaxis with co-trimoxazole to prevent recurrent UTI.

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