Antibiotic resistance in children with complicated urinary tract infection

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ABSTRACT

Objective: To determine the resistance of antibiotics for complicated urinary tract infection (UTI), including urinary tract anomaly (UTA), for empirical antibiotic therapy of complicated UTI.

Methods: Four hundred and twenty urine isolates were obtained from 113 patients with recurrent UTI, who used prophylactic antibiotics between February 1999 and November 2004 in the Eskisehir Osmangazi University, Eskisehir, Turkey.

Results: Reflux was found to be the most important predisposing factor for recurrent UTI (31.9%). Renal scar was detected more in patients with UTA than without UTA (59.2% versus 12.4%, $p<0.05$). Gram-negative organisms were dominant in patients with and without UTA (91.5% and 79.2%). *Enterococci* and *Candida* spp. were more prevalent in children with UTA than without UTA ($p<0.001$). Isolates were significantly more resistant to ampicillin, trimethoprim-sulfamethoxazole, amikacin, co-amoxiclav, ticarcillin-clavulanate, and piperacillin-tazobactam in patients with UTA than without UTA. We found low resistance to ciprofloxacin and nitrofurantoin in UTI with and without UTA. *Enterococci* spp. was highly resistance to ampicillin and amikacin in patients with UTA.

Conclusion: Aztreonam, meropenem, and ciprofloxacin seemed to be the best choice for treatment of UTI with UTA due to *Escherichia coli* and *Klebsiella* spp. Nitrofurantoin and nalidixic acid may be first choice antibiotics for prophylaxis in UTI with and without UTA. The UTI with UTA caused by *Enterococci* spp. might not benefit from a combination of amikacin and ampicillin, it could be treated with glycopeptides.

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Urinary tract infection (UTI) is one of the most common diseases in children. At least 8% of girls and 2% of boys will have a UTI in childhood.[1] Most urinary tract infections are uncomplicated and respond readily to treatment. However, 30-40% of these patients also have another episode within 2 years, particularly in girls. Also, recurrent infections may be complicated. Treatment for recurrences or complicated UTI is difficult and serious adverse sequels may be seen. Early diagnosis and prompt antimicrobial treatment for recurrent or complicated UTI are required to minimize renal scarring and progressive kidney damage in children. Therefore, The American Academy of Pediatrics recommends that young children with culture proved UTI should be treated with parenteral or oral antibiotics, depending on the clinical status.[2] To ensure appropriate treatment, knowledge of the organisms causing the UTI, and their antibiotic susceptibility are mandatory. However, there is growing concern regarding the resistance of urinary pathogens to antibiotics because of the increasing number of therapeutic failures after empiric treatments. Resistance patterns of bacterial pathogens in pediatric UTI show large interregional variability, and rates of bacterial resistance are changing due to different antibiotic treatments. In some regions of the world, microorganisms have become resistant to many antibiotics.[3,4] Data are limited on the specific patterns of resistance and risk factors associated with resistant bacteria isolated from children. There is a need to reconsider treatment recommendations in the face of local resistance patterns, as well as the need to make better use of drugs. In this paper, the resistance of urinary pathogens to antibiotics in children with recurrent or complicated UTI and treatment options were investigated.

Methods. The study sample included 113 children with recurrent UTI, who had been treated in either inpatient or outpatient clinics of the Medical Faculty of Eskisehir Osmangazi University

Hospital, Eskisehir, Turkey, between February 1999 and November 2004. The study was approved by the Research Ethics Committee of Eskisehir Osmangazi Medical Faculty, Eskisehir Osmangazi University. Informed consent was obtained from the parents or guardians for patients and controls. Patients with recurrent UTI were separated into 2 groups: patients with renal anomaly in Group 1, and patients without renal anomaly in Group 2. All these children received antimicrobial prophylaxis against UTI including trimethoprim-sulfamethoxazole (TMP-SMX), cephaclor, and nitrofurantoin. Also, recent hospitalization history within 4 weeks, age, gender, area of residence, and the number of recurrent infections was recorded. Newborns were excluded from this study. Urinary tract infection was defined as the growth of a single pathogen of $>10^5$, 10^4 and 1 colony forming units/ml by properly collected urine specimens (bag collected specimens, transurethral catheterization and suprapubic aspiration) in children with urinary symptoms including fever, chills, flank pain, costovertebral angle tenderness, dysuria, frequency and urgency and pyuria defined of ≥10 leukocyte/high power field. In patients with systemic symptoms and who had elevated acute phase reactants, abnormal technetium Tc 99m dimercaptosuccinic acid (DMSA) findings were accepted as upper UTI. Antimicrobial susceptibility of the isolates was tested by the disc diffusion method on cultures with significant bacteriuria and funguria using a panel of antimicrobial agents depending on the causative organism. All interpretation followed the National Committee for Clinical Laboratory Standards criteria.[5,6] Recurrent urinary tract infection was defined as a single further infection by a new organism.[1] The UTI occurring in the presence of catheterization, functional, or anatomical abnormalities of the urinary tract, host with altered defenses, chronic renal failure, renal transplantation, and those receiving peritoneal and hemodialysis were defined as complicated UTI.[7] A sonogram, DMSA, voiding cystourethrogram was performed in all cases. Diethylene triamine penta-acetic acid (DTPA) was performed in children with the obstructive anomaly. The DMSA was routinely used at the time of the diagnosis of UTI in our clinic. It was also used for the follow-up of patients with renal scars after 6 infection-free months. A photon deficient area was defined as a focal or diffused area of reduced uptake of the radionuclide with preservation of the normal reniform outline. Thus, old renal scar ratios were calculated in follow-up (after 6 infection-free months) DMSA in all patients and renal scars were defined as persistent changes in the same location (focal decreased uptake associated with contraction and loss of volume in the involved cortex).

All data were analyzed with the Statistical Package for Social Sciences for Windows, version 10 (SPSS Inc., Chicago, IL, USA). Statistical analysis was performed with χ^2 test and Student's t-tests. Risk factors for UTI were calculated by multivariate logistic regression analysis including age, gender, hospitalization, and anatomic malformations. For statistical significance, the p value was <0.05.

Results. One hundred thirteen children (48 boys and 65 girls) with recurrent UTI were enrolled. Mean age was 7.2 ± 4.5 years (range 1-18 years) and 22 (19.4%) children were under 2 years. A total of 420 isolate were obtained from 113 children. Sixty-seven (59.2%) patients had some form of UTA (**Table 1**). Renal scar was seen using the DMSA scintigraphy in 67 (59.2%) patients with UTA and in 14 (12.4%) patients without UTA. Renal scars development in patients with vesicoureteral reflux (VUR) was 65.7% and 34.3% in those without VUR (p<0.05). All the patients with renal scar were accepted as upper UTI according to DMSA

Table 1 - Urinary tract anomalies (UTA) in patients with recurrent urinary tract infection.

Anomaly	All patients n (%)		With UTA (%)
Vesicoureteral reflux	36	(31.9)	(53.7)
Neurogenic bladder	11	(9.7)	(16.4)
Renal hypoplasia	7	(6.2)	(10.4)
Ureteropelvic junction obstruction	6	(5.3)	(9)
Cystic disease of kidney	5	(4.5)	(7.4)
Renal agenesia	2	(1.8)	(3)

Table 2 - Urinary tract anomalies and urine culture results.

Microorganisms	Presence of renal anomaly (N=310)		No renal anomaly (N=110)		*P*-value
	n	%	n	%	
Escherichia coli	148	(47.8)	77	(70.2)	<0.001
Klebsiella spp.	62	(20)	20	(18.3)	>0.05
Enterococci spp.	43	(13.9)	2	(1.7)	<0.001
CNS	9	(2.9)	3	(2.7)	>0.05
Candida spp.	30	(9.7)	1	(0.9)	<0.001
Acinetobacter spp.	6	(1.9)	3	(2.7)	>0.05
MRSA	0	(0)	0	(0)	>0.05
S. maltophilia	6	(1.9)	2	(1.7)	>0.05
Proteus spp	0	(0)	1	(0.9)	>0.05
Pseudomonas spp.	6	(1.9)	1	(0.9)	>0.05

CNS - coagulase negative staphylococcus
MRSA - methicillin resistant staphylococcus
S. maltophilia - stenotrophomonas maltophilia

scintigraphy (n=81; 71.6%). *Escherichia coli (E. coli)* was determined to be a predominant microorganism in children with recurrent UTI in the present study. The ratio of *E. coli* decreased in children with UTA than without UTA (47.6% versus 70.2%, $p<0.001$). *Enterococci* and *Candida spp.* were more prevalent in urine isolates of children with UTA (13.9/1.7%, $p<0.001$ and 9.7/0.9%, $p<0.001$). However, the same was not true of *Klebsiella spp*, which was determined to be equal in number in both of the study groups ($p>0.05$) (**Table 2**). However, causative microorganism rates did not show variation according to the infection area. Total antibiotic resistance ratios for ampicillin, TMP-SMX, amikacin, co-amoxiclav, ticarcillin-clavulanate, piperacillin and aztreonam were more common in patients with UTA compared to those patients without renal anomaly (**Table 3**). Vancomycin resistant *Enterococci* spp., *Staphylococci* spp., and liposomal amphotericin B resistant *Candida* spp. were not isolated from either group. *E. coli* and *Klebsiella* spp. resistance ratios of amikacin, ampicillin, ticarcillin-clavulanate, piperacillin, aztreonam, and co-amoxiclav were more common in patients with UTA compared to those without UTA (**Table 4**). In contrast to the *E. coli*, the resistance of TMP-SMX was higher in patients

Table 3 - Rates of total antibiotic resistances from all isolates (%).

Antibiotics	With renal anomaly	No renal anomaly	*P*-value	Renal scar without renal anomaly	No renal anomaly	*P*-value
Amikacin	66	19.6	0.001	50	19.6	0.008
Ampicillin	96	68.6	0.01	83.3	68.6	0.04
TMP-SMX	82	66	0.029	66.6	66	>0.05
Cefotaxime	39.5	27	>0.05	18.1	27	>0.05
Ciprofloxacin	2.3	1.3	>0.05	2.1	1.3	>0.05
Meropenem	1.7	2.1	>0.05	0	2.1	>0.05
Ticarcillin/Clavulanate	58	17.6	0.001	8	17.6	>0.05
Aztreonam	26.5	1	0.001	16.6	1	0.004
Piperacillin	58.8	16.6	0.001	18.1	16.6	>0.05
Co-amoxiclav	67	35.4	0.05	41.6	35.4	>0.05
Nitrofurantoin	14.3	1.9	0.01	17.4	2.8	0.01

TMP-SMX - trimethoprim sulphamethoxazole

Table 4 - Antibiotic resistances of *Escherichia coli (E. coli)*, *Klebsiella* spp., and *Enterococcus* spp.

Antibiotics	*E. coli* (%)		*P*-value	*Klebsiella* spp. (%)		*P*-value	*Enterococci* spp. (%)		*P*-value
	Anomaly present	No anomaly		Anomaly present	No anomaly		Anomaly present	No anomaly	
Amikacin	53.5	11.4	0.001	75	44.4	0.001	75	0	0.008
Ampicillin	96.4	68.5	0.01	100	66.6	0.001	100	0	0.008
TMP-SMX	78.5	67.6	>0.05	83.3	46.6	<0.05	100	0	0.008
Cefotaxime	48.1	17.1	0.01	75	55.5	0.05	-----	------	------
Ciprofloxacin	3.8	1.1	>0.05	0	0	>0.05	4.5	0	>0.05
Meropenem	1.6	2	>0.05	1.8	1.40	>0.05	-----	-----	------
Ticarcillin/ Clavulanate	53.5	11.4	0.001	58.3	33.3	0.001	37.5	0	>0.05
Aztreonam	14.2	2.8	0.001	36.3	11.1	0.001	-----	------	------
Piperacillin	59.2	11.4	0.001	58.3	33.3	0.001	-----	------	-------
Co-amoxiclav	82.1	25.7	0.001	83.3	36.6	0.001	62.5	0	>0.05
Nitrofurantoin	10.3	2.2	<0.05	25.5	10.4	<0.05	19.7	4.3	<0.05

TMP-SMX - trimethoprim-sulphamethoxazole

with UTA for *Klebsiella* spp. isolates. *Enterococci* spp. isolates were more resistant to amikacin, ampicillin, and TMP-SMX in the patients with UTA (**Table 4**). Using the multivariate logistic regression, we established anatomic malformations (OR 7.52; 95% CI: 2.46-22.98; $p<0.001$), age <2 year (OR 3.87; 95% CI: 0.98-5.23; $p=0.03$), the number of recurrent infections (OR 3.7; 95% CI: 0.95-5.1; $p=0.04$), female gender (OR 2.84; 95% CI: 1.30-6.190; $p=0.01$), and recent hospitalization (OR 2.69; 95% CI: 1.02-7.11; $p=0.045$) as independent risk factors for a positive urine culture.

Discussion. The UTI has a tendency to reoccur in children and its importance, as a cause of renal insufficiency is known. There are multiple risk factors for the UTI in pediatric patients, including age, gender, periurethral or colonization factors, native immunity, genitourinary abnormalities, and genetic, and iatrogenic factors.[8] Patients with recurrent UTI who have such risk factors, such as VUR, are at increased risk of pyelonephritis and subsequent risk of renal scarring with progressive renal disease in adulthood.[9] The incidence of VUR is 1-3% in the pediatric age, and 20-75% of these children have UTI.[2,10] Its prevalence in the present study was found to be in agreement with similar studies (**Table 1**). We also found that VUR, neurogenic bladder and unilateral renal hypoplasia were the most common anatomic malformations in the patients with recurrent UTI. We determined that presence of anatomic malformations could be an important group of risk factors for the development of UTI in children. Other independent risk factors were age under 2 years, the number of recurrent infections, female gender and recent hospitalization for a positive urine culture. In addition, it has been claimed that renal scarring could be related to anatomic malformations.[11] We observed that renal scar was seen in 65.7% of the patients with VUR, while it was 34.3% in those without VUR ($p<0.05$). We also found a high rate of renal scar in patients who had different anomalies from VUR (47.3%). So, we suggest that the risk factors, especially anatomic malformations, should be determined at early phases and treated accordingly.

There are only a small number of studies that have investigated pathogens responsibly for complicated UTI in children.[12] Prais et al[13] isolated *E. coli* in 86%, *Klebsiella* spp. in 6% and other pathogens in 8% from general population with UTI. However, Ladhani et al[14] found that *E. coli* was 40.3% in patients with renal problems and 63% in patients without renal anomalies. Although some studies reported increasing rate of infections with *Enterococci* spp. in hospitalized patients, this could not be determined for patients with UTA.[14,15]

In our study, the isolated pathogens were as follows: *E. coli, Klebsiella, Enterococci,* and *Candida* spp. The number of *E. coli* was low in patients with UTA, while the numbers of *Enterococci and Candida* spp. were found to be high. However, the number of *Klebsiella* spp. was equal in both of the study groups (**Table 2**). Misuse or use of broad-spectrum antibiotics and hospitalization may explain the high frequency of *Enterococci* and *Candida* spp. related UTI infections and the need for tighter control policies.

One of the important factors in the successful treatment of UTI is to determine the resistance profile of uropathogens. So, the different antibiotic resistance ratios have been reported from different countries. In a study performed on hospitalized febrile infants by Adjei et al,[16] 100% of the pathogens isolated from urine cultures were only sensitive to cefuroxime axetil in Africa. Haller et al[17] reported their resistance ratio of *E. coli* to ampicillin (50%), piperacillin (40%), and TMP-SMX (30%). Ladhani et al[14] found that their antibiotic resistance ratio of *E. coli* to different antibiotics with and without renal anomalies were as follows; ampicillin 51/51.9%, co-amoxiclav 3.6/10.6%, TMP-SMX 27.6/50.4%, ciprofloxacin 0/8%. In our study, the highest resistance was seen with ampicillin, TMP-SMX, amikacin, cephotaxim, and co-amoxiclav (**Table 3**). We do not propose the use of ampicillin, TMP-SMX, amikacin, cephotaxim, and co-amoxiclav as a single agent for empirical treatment of a complicated UTI with UTA since they would not cover most urinary pathogens in our country. According to our findings (**Tables 3 & 4**), we found low resistance to meropenem and ciprofloxacin in patients with UTA. Therefore, we propose meropenem or ciprofloxacin for the treatment of complicated UTI with UTA. Although, we did not examine resistance to nalidixic acid in our study, low resistance to ciprofloxacin was shown that fluoroquinolones including nalidixic acid seemed to be useful prophylactic agents in complicated UTI with UTA. In addition, there was low resistance to nitrofurantoin in both UTI with UTA and UTI without UTA. Therefore, nitrofurantoin seemed to be another useful prophylactic agent. Increasing resistance rates to TMP-SMX may be explained by the history of recent hospitalization and recent use of antibiotics, particularly TMP-SMX, for treatment purposes or prophylaxis.

Our study determined that recent hospitalization was an independent risk factor for UTI, and most of the pathogens obtained from the urine of our patients with both UTA and without UTA were resistant to TMP-SMX. For instance, resistance of *E. coli* isolates to TMP-SMX was high in both groups and could not be deemed of statistical difference regarding the 2 study groups (**Table 4**). Also, we think that frequent use of beta lactam antibiotics for empirical purposes in our clinic might have resulted in a wide spectrum of betalactamase in some of our patients (**Tables 3 & 4**). We found low levels of resistance of *Klebsiella* spp. to ciprofloxacin, meropenem, and aztreonam, which we think could

be due to limited usage of these 3 antibiotics in our clinic. Total resistance ratios of amikacin, ampicillin, co-amoxiclav, and TMP-SMX were found high also in our patients with renal scar without renal anomaly. This led us to assume that if a patient has developed renal scars, the UTI could be attributed to pathogens highly resistant to antibiotics, although development of renal scars does not pose a risk factor for resistant pathogens.

Enterococci spp. can develop resistance to aminoglycosides by decreasing entrance of aminoglycoside into cell and forming genes producing aminoglycoside-modifying enzymes.[17] In our study, *Enterococci* spp. developed high resistance to aminoglycosides and ampicillin. Therefore, we concluded that a combination of aminoglycosides and ampicillin might not be sufficient for the treatment of UTI with UTA. Based on our findings, we suggest that the UTI due to *Enterococci* spp. in patients with UTA could be treated with glicopeptide antibiotics. However, vancomycin-resistant *Enterococci* spp. related UTI might be an important problem. Frequency of vancomycin-resistant *Enterococci* spp. that causes UTI is known to be 6-7%; however, there are regional differences to be considered. For example, this ratio is under 0.01% in Japan, while it is more than 10% in Korea.[18] In our study, no vancomycin-resistant *Enterococci* spp. was seen. Although we did not examine mechanisms of antibiotic resistance, we still attributed high resistance to co-amoxiclav and ticarcillin-clavulanate in the present study to extended spectrum beta lactamase (ESBL). In fact, Henquell et al[19] reported that *E. coli* isolates could produce inhibitor-resistant TEM (IRT) beta-lactamase; therefore, these isolates may be highly resistant to co-amoxiclav. In fact, resistance to co-amoxiclav is on the increase across the world, and it has been reported to reach 35% or more.[20] Our study determined this rate to be 56% in patients with UTA. Further studies are required on antibiotic resistance mechanism including ESBL production in UTI with UTA.

In conclusion, the present study suggests that renal anomalies, scar development, and resistance profiles to antibiotics should be carefully determined in patients with complicated UTI. We also suggest that ampicillin, TMP-SMX, amikacin, co-amoxiclav, ticarcillin-clavulanate, and piperacillin-tazobactam, and co-amoxiclav could be avoided for the treatment and prophylaxis of UTI with UTA and renal scar. Therefore, we propose meropenem or ciprofloxacin for the treatment of complicated UTI with UTA. Also, nitrofurantoin and nalidixic acid may be the first choice antibiotics for prophylaxis in UTI with and without UTA. Another suggestion would be that a combination of aminoglycosides and ampicillin may not be sufficient for the treatment of UTI with UTA on its own, and so the UTI attributable to *Enterococci* spp. in the UTA patients could be treated with glycopeptides.

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