의학석사 학위논문

재발성 요로 감염증에 이환된 소아에서 동정균의 항생제 감수성 변화 양상과 신기능의 변화 분석

Changes in the antibiotics susceptibility patterns and renal function in pediatric patients with recurrent urinary tract infections

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Abstract

Changes in the antibiotics susceptibility patterns and renal function in pediatric patients with recurrent urinary tract infections

Objectives We aimed to evaluate the antibiotic usage and emergence of antibiotic resistance in pediatric patients with recurrent episodes of urinary tract infection (UTI), changes in estimated glomerular filtration rate (eGFR), and factors associated with the change in eGFR.

Material Patients who were admitted more than three times due to febrile UTI between January 2004 and September 2019 were included in this study. Data on the clinical and laboratory findings at each UTI episode were collected and statistically analyzed. eGFR% was calculated as (eGFR/lower limit of normal eGFR according to the patient's age)×100 (%). An eGFR% below 100 was considered low. △eGFR%(n^{th}/$(n+\alpha)^{th}$) was calculated as {[eGFR%($(n+\alpha)^{th}$ UTI)−eGFR%(n^{th} UTI)]/eGFR%(n^{th} UTI))}×100(%).

Results Over 47 patients experienced more than three episodes of UTI. The proportion of *Enterobacter* species significantly decreased as recurrent episodes occurred (p=0.004). The proportion of extended-spectrum β-lactamase (ESBL)-producing species and overall resistance rate to cefotaxime, cefepime, and ciprofloxacin increased as UTI recurred (p=0.056, p=0.037, p=0.045, and p=0.041, respectively). The use of cefotaxime, ampicillin-sulbactam, or trimethoprim-sulfamethoxazole (TMP-SMX) prior to UTI recurrence was significantly associated with increased resistance to these antibiotics (p=0.001, p=0.035, and p=0.010 respectively). The cut-off values for the duration of previous antibiotic use that contributed to the emergence of resistance were 21.5 days

for cefotaxime and 31.0 days for TMP-SMX (p=0.016, and p=0.014, respectively). The cut-off values for the antibiotic-free period to observe resistance were 16.5–23.5 days for cefotaxime (p=0.022) and 27.0 days for TMP-SMX (p<0.001). The eGFR% at each UTI episode (first to third) was significantly associated with the eGFR% at previous UTI episodes. ΔeGFR% showed significant a negative correlation with the baseline eGFR% between 1st and 2nd, 2nd and 3rd, 1st and 3rd UTI episodes, respectively (p<0.001). A negative correlation was also observed between ΔeGFR% at each UTI episode (1st to 3rd) and eGFR% at the last follow-up (p<0.001). Only the C-reactive protein (CRP) level at each admission showed a consistent negative correlation with eGFR% at each UTI episode (1st to 3rd) and a negative correlation with ΔeGFR% between 1st and 2nd, 2nd and 3rd, 1st and 3rd UTI episodes, respectively ($p<0.05$).

Conclusion With the recurrence of UTI, resistance to third-generation cephalosporins and emergence of ESBL-producing pathogens increased significantly, changes in antibiotic susceptibility were dynamically influenced by previous exposure to particular antibiotics, and eGFR decreased significantly when eGFR declined during the previous UTI episodes or when the CRP level was higher at the time of admission. However, restoration of normal renal function at follow-up was more remarkable when renal function deteriorated further upon admission.

Key words: Recurrent urinary tract infection, Antibiotics resistance, eGFR%, Renal function

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Introduction

Urinary tract infection (UTI) is one of the most common types of bacterial infections that occurs during infancy and early childhood, with a cumulative incidence of 3%–7% for girls and 1%–2% for boys age below six years.[1)] Although these infections are generally treatable, the increasing rate of resistance to first-line antibiotics indicates the importance of the proper selection of antibiotics, especially in patients with recurrent UTIs. Moreover, concerns regarding long-term morbidities such as permanent renal damage after renal scarring or hypertension are growing and increasingly being recognized.

Patients with acquired reflux nephropathy associated with recurrent UTIs were once reported to have the worst prognosis and progress to end-stage renal disease; hence, preventive approaches for recurrent UTIs have been evaluated.[2-4)] Along with this context, the risk factors for recurrent UTIs such as vesicoureteral reflux (VUR), bladder bowel dysfunction (BBD), innate immunity defects, and urogenital anomalies were emphasized and assessed.[3)]

Literature reviews of prospective studies focused on the stratification of these risk factors associated with UTI recurrence or renal scar formation, which showed that high-grade VUR was consistently associated with renal scar formation after febrile UTI, and reported inconsistent results with regard to race, sex, age, BBD, and antimicrobial prophylaxis.[1,2,5-7)] These results emphasized the active management of VUR and other accompanied urologic anomalies as well as BBD using both medical and surgical interventions to prevent the recurrence of UTIs. In clinical practice, antibiotic prophylaxis is still widely used in spite of the ongoing dispute on its effectiveness and unsettled standardized regimen. Moreover, no study has evaluated the impact of antibiotic prophylaxis on the pattern of antibiotic resistance or change in renal function when at-risk patients experience UTI recurrence.

Based on this context, we aimed to evaluate the actual change in renal function during and after each episode of recurrent UTI and assess the factors associated with deterioration in renal

function, as well as observe the antibiotic resistance pattern of the causative microorganisms during multiple recurrent UTIs.

Materials and methods

We reviewed the data of patients who were admitted to Asan Medical Center Children's Hospital more than three times due to recurrent febrile UTI between January 2005 and September 2019. Immunocompromised patients at the time of UTI recurrence were excluded. UTI was clinically diagnosed when the patient showed the following symptoms: a temperature of more than 38.0℃, leukocytosis, increased C-reactive protein (CRP) with pyuria (white blood cell (WBC) count: >5 cells/mm in the urine), and positive culture test (>10^5 colony-forming units (CFU)/ml of a single urinary tract pathogen) of urine samples obtained from urine bags or via the mid-stream clean catch technique. Catheterized urine with more than 10^4 CFU/ml of a single pathogen was also an indication of UTI, although catheterization was only adopted in patients who underwent vesicostomy or were unable to void. Urine samples were processed on blood agar and MacConkey medium following a standard loop technique (using a calibrated wire loop with inoculation of 0.001 ml of the specimen) and were incubated at 37℃ overnight. Bruker MALDI Biotyper (Bruker Daltonik, Bremen, Germany) matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) system with a user-supplemented database and an on-plate formic acid-based preparation method was used for identifying the bacterial species when growth was detected. Antimicrobial susceptibility testing was performed using the MicroScan AutoSCAN system (Beckman Coulter, Seoul, Korea); results were analyzed and interpreted according to the recommended clinical breakpoints indicated in the clinical and laboratory standard institutes (CLSI) guidelines at each urine culture test.[8, 9] Cultures that showed Candidal growth were excluded from this analysis. Cefotaxime was used as a first-line antibiotic agent in patients

suspected with UTI without history of resistant pathogen-derived infection, and treatment was switched to other oral third-generation cephalosporins at the time of discharge after the resolution of fever and symptoms. Ampicillin-sulbactam or ampicillin-clavulanate was used as the first-line antibiotic agent in patients suspected with gram-positive uropathogen, while ceftazidime was used in patients with UTI recurrence whose previous urine culture test showed the presence of *Pseudomonas* species. Clinical response to antibiotics was defined as resolution of fever and urinary symptoms and negative results of follow-up urine culture two days after initial treatment. For patients who did not show clinical response to initial antibiotic treatment, second-line antibiotics such as piperacillin-tazobactam and carbapenems were used to eradicate extended-spectrum β-lactamase (ESBL)-producing uropathogens or other resistant pathogens; if initial urine culture results were available, changes in antibiotic treatment were based on the sensitivity profile of the proven pathogen.

The estimated glomerular filtration rate (eGFR) was calculated using the Schwartz equation. For comparison, we also recalculated the percentage of eGFR (eGFR%) based on the lower limit of normal eGFR according to the patient's age. The lower limits of normal eGFR (ml/min/1.73 m^2) according to the patient's age were as follows: 30 below two weeks, 49 between two weeks and eight weeks, 72 between eight weeks and two years of age, and 90 after two years of age.[10)]

$$\text{eGFR (ml/min/1.73m}^2\text{)} = 0.413 \times \frac{\text{patient's height (cm)}}{\text{serum creatinine (mg/dL)}}$$

$$\text{eGFR\%} = \frac{\text{eGFR}}{\text{lower limit of normal eGFR according to the patient's age}} \times 100 \ (\%)$$

All statistical analyses were performed using SPSS® for Windows, version 21.0. The incidence of antibiotic resistance was determined according to the number of UTI episodes and was compared with that before antibiotic exposure using the chi-square test. Clinical variables were compared with eGFR%, and the emergence of resistance after antibiotic exposure was

analyzed using the Mann-Whitney *U test*. The Fischer's exact test was used to compare the incidence of infection with ESBL-producing organisms, evaluation results of antibiotic resistance distribution, change in antibiotic resistance stratified based on exposure status, and change in eGFR% at each UTI episode. The receiver operating characteristic curve was used to calculate the cut-off values for the duration of previous antibiotic exposure in relation to resistance. Linear by linear association test was used to analyze the response rate to certain antibiotics at each UTI episode. Finally, Spearman's correlation analysis was used to evaluate the association between eGFR% and clinical variables. A p-value of <0.05 was considered significant.

Result

A total of 47 patients had more than three recurrent episodes of UTI during the study period. The median ages were four months (range, 1–18) at 1st UTI episode, seven months (range, 1–23) at 2nd UTI episode, and eleven months (range 3-41) at 3rd UTI episode. 53.2% (25/47) of the patients were male. All patients had at least three episodes of UTI, 16 had four episodes, 11 patients had five episodes, 7 patients had six episodes, and 3 had seven and eight episodes, respectively. Overall 181 UTIs occurred from these 47 patients. Less than half of the cases (43.6 %, 79/181) occurred during the first half of the study period; from January 2005 to May 2012 (data not shown). The median age at the last follow-up was 63 months (range, 6–168 months) with a median follow-up period of 60 months (range, 1–162 months) after the 1st UTI episode. A total of 36 (76.6%) patients had VUR. Over 13 (27.7%) patients had an isolated VUR, while the remaining patients had concomitant complex urogenital anomalies with VUR including hydronephrosis, cloacal deformities, duplex urinary system, posterior urethral valve (PUV), dysplastic kidney, and bladder lesions (**Table 1)**. Apart from urologic anomalies, 19 (40.4%) patients had other systemic comorbidities including major cardiac anomalies, gastrointestinal tract anomalies, neurologic disease, and prematurity (**Table 2**). Use of anti-reflux interventions including surgery and endoscopic injection treatment after

UTI recurrence either decreased the relapse rate or prevented the occurrence of UTI relapse in patients with isolated VUR, VUR with hydroureteronephrosis, PUVs, or duplex kidneys. However, patients with other underlying anomalies that were not completely corrected such as persistent cloaca and BBD experienced recurrent UTIs even after undergoing anti-reflux surgery and/or partial correction of the anomalies (**Supplementary Table 1**).

Table 1. Presence of VUR and underlying urogenital anomalies in patients with UTI

Accompanying urogenital anomalies (n, %)	Bilateral VUR	Right VUR	Left VUR	No VUR
Isolated VUR (n=13, 27.6%)	7 (53.8 %)	5 (38.5%)	1 (7.7%)	-
Hydronephrosis with or without UPJO, hydroureteronephrosis (n=14, 29.8%)	8[a] (57.1%)	1 (7.1%)	2 (14.3%)	3[b] (21.4%)
Cloacal deformities (n=7, 14.9%)	2[c] (28.6%)	2[d] (28.6%)	0 (0.0%)	3[e] (42.9%)
Duplex kidney (n=5, 10.6%)	3[f] (60.0%)	0 (0.0%)	1 (20.0%)	1 (20.0%)
PUV, UVJO with dysplastic kidneys, with or without ureter abnormalities (n=4, 8.5%)	3 (75.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)
Utricle cyst (n=1, 2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100%)
Urachal remnant (n=1, 2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100%)
Corrrected bladder exstrophy (n=1, 2.1%)	1 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
No underlying urogenital anomalies and no VUR (n=1, 2.1%)	-	-	-	-
Total (n=47)	24 (51.1%)	8 (19.1%)	4 (8.5%)	10 (21.3%)

VUR, vesicoureteral reflux; n, number; pts, patients; UPJO, ureteropelvic junctional obstruction; PUV, posterior urethral valve; UVJO, uretero-vesical junctional obstruction

[a]Two patients with rectovesical fistula, one patient with left UPJO, and three patients with concomitant hydroureter
[b]One patient with both UPJO, one patient with left UPJO, and another patient with hydroureteronephrosis
[c]One patient with right duplex kidney and duplex ureter
[d]One patient with left renal agenesis and another patient with right duplex kidney and concurrent recto-vesical fistula
[e]One patient with rectovesical fistula
[f]One patient with rectovesical fistula

Table 2. Other accompanying systemic diseases in recurrent UTI patients

Systemic disease	Number (%)	Disease
Major cardiac anomaly	9 (19.1)	Complex congenital heart disease, DCMP, CHARGE syndrome, Edward syndrome
Gastrointestinal anomaly	8 (17.0)	VACTERL association (high-type imperforate anus)
Prematurity	4 (8.5)	GA 28-34 weeks*
Neurologic anomaly	2 (4.3)	Stickler syndrome
No other systemic involvement	28 (59.6)	-

*Three of the premature patients had other systemic anomalies, and one patient with VACTERL association had structural cardiac disease (VSD)

DCMP, dilated cardiomyopathy; CHARGE, coloboma, heart defects, atresia of choanae, growth retardation/genital abnormalities, and ear abnormalities; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, limb abnormalities

Supplementary Table 1. Time sequence of UTI occurrence and corrective intervention among patients with urologic anomalies and the presence of BBD

Urologic anomaly	Presence of VUR(n), BBD (n)	Surgical intervention and recurrence of UTI
Isolated VUR	Both VUR (7)	Five out of seven patients underwent anti-reflux surgery without UTI recurrence.
	Right VUR (5)	Three out of five patients underwent anti-reflux surgery, of whom one patient experienced one episode of UTI.
	Left VUR (1)	None of the patients underwent anti-reflux intervention.
	BBD (**0**)	-
Hydronephrosis with/without UPJO or hydroureter	Both VUR (8)	Six out of eight patients with anti-reflux surgery after experiencing three episodes of UTI, of whom one had three episodes of UTI after surgery
	Right VUR (1)	One patient with right hydroureteronephrosis with nonfunctioning kidney had eight episodes of UTI, and recurrence finally stopped after undergoing right nephrectomy.
	No VUR (3)	Two patients with UPJO underwent pyeloplasty, of whom one had three episodes of UTI after undergoing pyeloplasty.
	BBD (**2**)	Two patients with both VUR had high-type imperforate anus with rectovesical fistula: both of them experienced chronic constipation after final correction of the anus, while one had overactive bladder dysfunction.
Cloacal deformities	Both VUR (2)	All patients had recurrent UTI with persistent cloaca; no anti-reflux surgery was performed due to low-grade reflux
	Right VUR (2)	All patients underwent anti-reflux surgery; one patient underwent surgery after six episodes of UTI, without recurrence; the other patient with persistent cloaca had three episodes of UTI after re-implantation, and three more episodes of UTI recurrence after intravesical re-implantation.
	No VUR (3)	All patients had recurrent UTI with persistent cloaca.
	BBD (**7**)	All patients with persistent cloaca had chronic constipation, two had vesicostomy, and one required CIC due to acontractile bladder.
Duplex system	Both VUR (3)	Two out of three patients underwent anti-reflux surgery after three episodes of UTI, and one had one more episode of UTI recurrence after surgery.
	Left VUR (1)	One patient had ureterocele puncture without anti-reflux surgery and had two more episodes of UTI recurrence.
	No VUR (1)	One patient had ureteroneocystostomy after two episodes of UTI and experienced two more episodes of UTI.
	BBD (**1**)	One patient with a high-type imperforate anus had chronic constipation after anal correction.
PUVs, UVJO with dysplastic kidneys, ureter abnormalities	Both VUR (3)	All patients had urethrotomy and bilateral anti-reflux surgery; only one patient had no recurrence after surgery, while the other two patients had three or four episodes of UTI.
	Right VUR (1)	One patient had undergone two urethrotomies, but experienced two more episodes of UTIs; hence, anti-reflux surgery was not performed.
	BBD (**4**)	All patients had bladder dysfunction, overactivity, acontractility, and decreased compliance.

UTI, urinary tract infection; BBD, bladder bowel dysfunction; VUR, vesicoureteral reflux; n, number; UPJO, uretero-pelvic junctional obstruction; CIC, clean intermittent catheterization; PUV, posterior urethral valve; UVJO, ureterovesical junctional obstruction

The different types of bacteria that caused all episodes of UTIs are presented in **Table 3**. *Escherichia coli* (*E. coli*) was the most common pathogen throughout all episodes of UTIs followed by *Klebsiella pneumoniae*, *Enterobacter* species, *Pseudomonas aeruginosa*, *Citrobacter freundii,* and *Enterococci*. The proportion of *Enterobacter* species significantly decreased after the 3rd episode of UTI, and none of the recurrent episodes were caused by *Enterobacter* species (p=0.004). The prevalence of antibiotic resistance according to the number of UTI episodes is shown in **Table 4**. The proportion of ESBL-producing species increased as the number of UTI recurrence increased (p=0.056); the overall rates of resistance to cefotaxime, cefepime, and ciprofloxacin also increased (41.1%, 26.0%, and 21.5%, respectively) as the number of UTI recurrence increased (p=0.037, p=0.045, and p=0.041, respectively). Although the proportion of ESBL-producing uropathogens showed a tendency to increase in all episodes of UTI recurrence, a few patients infected with ESBL-producing organisms showed disappearance of ESBL at subsequent periods of UTI recurrence as shown in the analysis of the 2nd and 3rd episodes of UTI recurrence (**Supplementary Table 2**).

Table 3. Prevalence of causative bacteria according to the number of UTI episode

No. of UTI	1st	2nd	3rd	4th	5th	6th	7th	8th	Total	*p*-value*
No. of patients	47	47	47	16	11	7	3	3		
E.coli	**40.4%**	**34.0%**	**42.6%**	**43.8%**	**45.5%**	**71.4%**	**66.7%**	**100.0%**	**42.5%**	**0.101**
Klebsiella	**17.0%**	**40.4%**	**21.3%**	**37.5%**	**18.2%**	**14.3%**	**33.3%**	**0.0%**	**26.0%**	**0.955**
K.pneumonia	14.9%	27.7%	21.3%	31.3%	18.2%	14.3%	33.3%	0.0%	21.5%	0.587
K.aerogenes	0.0%	10.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.8%	0.051
K.oxitoca	2.1%	2.1%	0.0%	6.3%	0.0%	0.0%	0.0%	0.0%	1.7%	0.753
Enterobacter	**14.9%**	**12.8%**	**6.4%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**8.8%**	0.004
E.cloacae	10.6%	8.5%	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%	5.5%	0.009
E.aerogenes	4.3%	4.3%	4.3%	0.0%	0.0%	0.0%	0.0%	0.0%	3.3%	0.250
Pseudomonas/ Stenotrophomonas	**8.5%**	**10.6%**	**14.9%**	**18.8%**	**9.1%**	**0.0%**	**0.0%**	**0.0%**	**11.0%**	**0.724**
P.aeruginosa	8.5%	10.6%	12.8%	12.5%	9.1%	0.0%	0.0%	0.0%	9.9%	0.926
S.maltophilia	0.0%	0.0%	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.6%	0.323
C.freundii	**8.5%**	**10.6%**	**6.4%**	**0.0%**	**18.2%**	**14.3%**	**0.0%**	**0.0%**	**8.3%**	**0.743**
Enterococcus	**8.5%**	**4.3%**	**6.4%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**5.0%**	**0.105**
E.faecalis	8.5%	2.1%	6.4%	0.0%	0.0%	0.0%	0.0%	0.0%	4.4%	0.136
E.faecium	0.0%	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.6%	0.332
P.mirabilis	**2.1%**	**0.0%**	**4.3%**	**0.0%**	**9.1%**	**0.0%**	**0.0%**	**0.0%**	**2.2%**	**0.572**
A.baumanii	**0.0%**	**0.0%**	**0.0%**	**6.3%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.6%**	**0.315**
M.morganii	**0.0%**	**0.0%**	**2.1%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.6%**	**0.323**
S.marcescens	**0.0%**	**0.0%**	**0.0%**	**6.3%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.6%**	**0.315**
S.aureus	**2.1%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.6%**	**0.314**
S.agalactiae	**0.0%**	**0.0%**	**2.1%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.6%**	**0.323**
Gram-negative	89.4%	95.7%	91.5%	100.0%	100.0%	100.0%	100.0%	100.0%	93.9%	0.085
Gram-positive	10.6%	4.3%	8.5%	0.0%	0.0%	0.0%	0.0%	0.0%	6.1%	

* Linear by linear association, UTI: urinary tract infection

Table 4. Prevalence of antibiotic resistance according to the number of UTI episodes (excluding gram-positive bacteria, Pseudomonas and Stenotrophomonas)

No. of UTI	Test (%)	1st (%)	2nd (%)	3rd (%)	4th (%)	5th (%)	6th (%)	7th (%)	8th (%)	Total %	*p*-value*
Total No. of patients		47	47	47	16	11	7	2	2		
Penicillins											
Ampicillin	89.9	88.1	97.6	88.1	100.0	90.0	100.0	100.0	100.0	92.5	0.686
Piperacillin	46.4	50.0	58.3	50.0	83.3	40.0	50.0	-	-	54.2	0.598
β-lactamase inhibitors											
Amoxicillin/clavulanate	25.1	33.3	36.4	33.3	20.0	0.0	0.0	-	-	28.9	0.105
Ticarcillin/clavulanate	63.1	23.1	31.0	18.8	30.0	16.7	0.0	0.0	0.0	22.1	0.058
Ampicillin/sulbactam	86.0	53.8	67.5	71.8	53.3	50.0	42.9	100.0	0.0	61.0	0.392
Piperacillin/tazobactam	93.9	7.0	13.6	6.8	13.3	0.0	0.0	0.0	0.0	8.3	0.253
Cephalosporins											
First-generation											
Cefazolin	85.5	51.3	60.0	66.7	71.4	60.0	57.1	100.0	100.0	61.4	0.164
Cephalothin	25.1	50.0	58.3	77.8	40.0	50.0	100.0	-	-	57.8	0.915
Second-generation											
Cefoxitin	64.8	25.0	28.6	25.0	8.3	22.2	28.6	0.0	0.0	23.3	0.277
Cefuroxime	84.9	38.5	48.7	51.3	50.0	50.0	42.9	100.0	100.0	48.0	0.676
Cefotetan	20.7	18.2	45.5	25.0	0.0	0.0	-	-	-	27.0	0.761
Third-generation											
Cefotaxime	93.9	28.6	43.2	45.5	37.5	45.5	42.9	100.0	100.0	41.1	0.037
Ceftrixone	55.9	31.0	40.0	57.7	25.0	16.7	0.0	-	-	39.0	0.981
Ceftazidime	95.0	27.9	35.9	36.4	37.5	36.4	28.6	100.0	50.0	34.7	0.265
Fourth-generation											
Cefepime	94.4	18.6	22.7	27.3	37.5	27.3	28.6	100.0	50.0	26.0	0.045
Monobactam											
Aztreonam	95.0	27.9	33.3	38.6	37.5	27.3	14.3	100.0	100.0	61.9	0.672
Carbapenems											
Imipenem	94.4	2.3	0.0	2.3	0.0	0.0	0.0	0.0	0.0	1.2	0.895
Meropenem	76.0	3.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.7	-
Ertapenem	64.2	0.0	3.6	3.7	0.0	0.0	0.0	0.0	0.0	1.7	0.721
ESBL (+)	94.4	31.1	44.4	39.5	40.0	50.0	42.9	100.0	100.0	40.8	0.056
Sulfonamides											
TMP/SMX	86.6	51.3	69.2	67.5	68.8	60.0	14.3	100.0	100.0	61.9	0.672
Aminoglycosides											
Gentamicin	95.0	31.8	25.0	22.7	31.3	36.4	28.6	0.0	50.0	27.6	0.759
Tobramycin	93.9	27.9	20.5	22.7	25.0	27.3	16.7	50.0	50.0	24.4	0.899
Amikacin	94.4	2.4	6.7	4.5	6.3	0.0	0.0	0.0	0.0	4.1	0.572
Quinolones											
Nalidixic acid	27.9	60.0	75.0	75.0	60.0	100.0	75.0	100.0	100.0	74.0	0.497
Ciprofloxacin	98.9	12.8	19.6	19.6	31.3	45.5	28.6	50.0	50.0	21.5	0.041
Levofloxacin	97.2	13.3	17.8	10.9	18.8	27.3	28.6	50.0	50.0	16.7	0.201
Protein synthesis inhibitors											
Tetracycline	69.3	48.4	40.0	60.0	71.4	55.6	50.0	50.0	50.0	52.4	0.289
Tigecycline	26.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
Others											
Nitrofurantoin	30.2	0.0	7.1	9.1	20.0	25.0	0.0	0.0	-	7.4	0.173
Colistin	33.0	0.0	14.3	0.0	0.0	0.0	0.0	0.0	0.0	3.4	0.317

* Linear by linear association,

UTI, urinary tract infection; ESBL, expanded-spectrum beta-lactamase; TMP/SMX, trimethoprim/sulfamethoxazole

Supplementary Table 2. Changes in ESBL positivity according to the number of UTI episodes

ESBL	1st UTI	2nd UTI	Previous UTI		3rd UTI	Previous UTI	
Negative	30 (69.8%)	25 (58.1%)	Negative	19 (76.0%)	25 (59.5%)	Negative	18 (72.0%)
			positive	6 (24.0%)		Positive	7 (28.0%)
Positive	13 (30.2%)	18 (41.9%)	Negative	11 (61.1%)	17 (40.5%)	Negative	6 (35.3%)
			Positive	7 (38.9%)		Positive	11 (64.7%)
Fisher's exact test (one-sided)			*p*-value	0.237		*p*-value	0.020

An overall significant decrease was observed in the usage of cefotaxime and ampicillin-sulbactam at each episode of UTI ($p<0.001$), while a significant increase was observed in the use of piperacillin-tazobactam and carbapenems ($p=0.001$, $p=0.001$) as the number of UTI episodes increased (**Table 5**). The rate of clinical response to cefotaxime and ampicillin-sulbactam for ESBL-producing organisms was inconsistent, but more than 60% of the patients showed a clinical response to these first-line β-lactam antibiotics from the 1st to the 5th episode of UTI. Switching to second-line antibiotics occurred more frequently than expected considering the actual response rate to first-line antibiotics at each episode of UTI. The presence of previous exposure to antibiotics before each UTI episode within 6 months, irrespective of the purpose (prophylaxis or treatment of other infection), was analyzed (**Table 6)** for the impact on antibiotics resistance at the time of UTI. The use of cefotaxime or ampicillin-sulbactam prior to the 1st episode of UTI was significantly associated with increased resistance to each antibiotic ($p=0.001$, $p=0.035$ respectively). Prior use of trimethoprim-sulfamethoxazole (TMP-SMX) before the 2nd and 3rd episodes of UTI led to a significant increase in the rate of resistance to TMP-SMX at the 2nd and 3rd episodes of UTI ($p=0.010$), but decreased the resistance rate to cefotaxime at the 2nd episode of UTI ($p=0.004$). Further analysis regarding the duration of previous exposure to certain antibiotics and the emergence of resistance to that antibiotic revealed the duration cut-off values of 21.5 days for cefotaxime ($p=0.016$) and 31.0 days for TMP-SMX ($p=0.014$) were required to develop resistance. The cut-off values for the interval of the antibiotic-free period in order to observe resistance were 16.5–23.5 days for cefotaxime ($p=0.022$) and 27.0 days for TMP-SMX ($p<0.001$). Exposure to TMP-SMX within 91.5 days was associated with decreased emergence of ESBL-producing species ($p=0.021$) (**Table 7**).

Table 5. Antibiotic choice according to the number of UTI episodes

No. of UTI	1st (%)	2nd (%)	3rd (%)	4th (%)	5th (%)	6th (%)	7th (%)	8th (%)	Total (%)	*p*-value*
No. of Pt.	47	47	47	16	11	7	3	3		
Initial antibiotics at admission										
1st-line antibiotics†	91.5	80.9	70.2	62.5	63.6	57.1	0.0	0.0	74.6	<0.001
TZP	0.0	12.8	10.6	12.5	18.2	28.6	66.7	66.7	11.6	0.001
Carbapenem	2.1	6.4	19.1	25.0	18.2	14.3	33.3	33.3	12.2	0.001
Others (1)	6.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.7	0.065
Response** rate										
Total	89.4	85.1	70.2	87.5	90.9	100.0	100.0	100.0	83.8	0.727
1st-line antibiotics to ESBL	92.9	72.2	63.6	75.0	100.0	-	-	-	77.1	0.285
Change of antibiotics	19.1	31.9	34.0	37.5	36.4	14.3	0.0	50.0	29.1	0.414
TZP	22.2	26.0	37.5	33.3	75.0	100.0	-	100.0	36.5	0.016
Carbapenem	11.1	40.0	25.0	33.3	0.0	0.0	-	0.0	25.0	0.468
Ceftazidime	33.3	13.3	18.8	0.0	0.0	0.0	-	0.0	15.4	0.091
Others (2)	33.3	20.0	25.0	16.7	25.0	0.0	-	0.0	23.1	0.426

*Linear by linear association, UTI: urinary tract infection, Pt.: patients, TZP: piperacilline-tazobactam

†1st-line antibiotics: cefotaxime, ceftazidime, ampicillin-sulbactam (TZP, cefepime, and carbapenem excluded)

Others (1): amikacin, cefepime, and vancomycin

**Response: subside of febrile symptom and culture conversion to no growth

Others (2): amikacin, cefotaxime, cefepime, ampicillin-sulbactam, ciprofloxacin

Table 6. Association between previous use of antibiotics and antibiotic resistance

UTI No.	Previous use*	Resistance	Test%	Previous use		*p*-value**
				Yes	No	
1st	TMP-SMX	TMP-SMX	52.0	5 (71.4%)	15 (46.9%)	0.225
		AMC	20.0	0 (0.0%)	5 (38.5%)	0.429
		SAM	52.0	3 (50.0%)	18 (54.5%)	0.590
		Cefotaxime	56.0	3 (50.0%)	9 (25.0%)	0.216
		Ceftriaxone	38.7	2 (50.0%)	7 (28.0%)	0.364
	AMC/SAM	AMC	20.0	2 (66.7%)	3 (25.0%)	0.242
		SAM	52.0	5 (100%)	16 (47.1%)	0.035
	Cefotaxime	Cefotaxime	56.0	5 (100%)	7 (18.9%)	0.001
		Ceftriaxone	38.7	4 (100%)	5 (20.0%)	0.005
2nd	Amikacin	Amikacin	60.0	0 (0.0%)	3 (7.0%)	0.870
	TMP-SMX	TMP-SMX	52.0	14 (93.3%)	13 (54.2%)	0.010
		AMC	14.7	0 (0.0%)	4 (66.7%)	0.045
		SAM	53.3	9 (60.0%)	18 (72.0%)	0.329
		Cefotaxime	58.7	2 (13.3%)	14 (58.6%)	0.004
		Ceftriaxone	40.0	3 (25.0%)	9 (50.0%)	0.162
	AMC/SAM	AMC	14.7	1 (100%)	3 (30.0%)	0.364
		SAM	53.3	3 (100%)	24 (64.9%)	0.296
	Cefotaxime	Cefotaxime	58.7	18 (43.9%)	1 (33.3%)	0.604
		Ceftriaxone	40.0	11 (40.7%)	1 (33.3%)	0.653
3rd	Amikacin	Amikacin	58.7	0 (0.0%)	2 (2.8%)	0.910
	TMP-SMX	TMP-SMX	53.3	10 (100.0%)	17 (56.7%)	0.010
		AMC	12.0	0 (0.0%)	3 (37.5%)	0.667
		SAM	52.0	7 (70.0%)	21 (72.4%)	0.591
		Cefotaxime	58.7	3 (27.3%)	17 (51.5%)	0.147
		Ceftriaxone	34.7	1 (20.0%)	14 (66.7%)	0.082
		Cefepime	58.7	2 (18.2%)	10 (30.3%)	0.359
		Ciprofloxcin	61.3	3 (27.3%)	6 (17.1%)	0.841
		Meropenem	45.3	0 (0.0%)	0 (0.0%)	-

* Antibiotics used before the present UTI (since last UTI when the number of previous UTI was more than once)

** Fisher's exact test (one-way)

UTI,urinary tract infection; TMP-SMX, trimethoprime-sulfamethoxazole;
AMC, amoxicillin-clavulanic acid; SAM, ampicillin-sulbactam

Table 7. Clinical correlations between previous exposure to antibiotics and antibiotic susceptibility in children with recurrent urinary tract infection

	Previous use	Cefotaxime		ESBL	
		Susceptible	Resistant	Negative	Positive
3rd-generation cephalosporine	No	14 (87.5%)	2 (12.5%)	13 (81.3%)	3 (18.8%)
	Yes	78 (55.7%)	62 (44.3%)	74 (53.6%)	64 (46.4%)
	p-value*	0.011		0.029	
	Duration	44.7±59.4	60.6±59.2	45.6±60.7	57.7±58.7
	(days)	26.0 (0.0–324.0)	36.0 (0.0–235.0)	26.0 (0.0–324.0)	35.0 (0.0–235.0)
	p-value**	0.016		0.059	
	AUC	0.613 (p=0.016)		0.589 (p=0.059)	
	Cut-off	21.5 days (sens 78.1%, spec 44.6%)		21.5 days (sens 74.6%, spec 43.7%)	
	Interval	84.4±125.2	72.6±118.3	86.6±128.0	71.4±116.8
	(days)	44.5 (0.0–780.0)	16.0 (0.0–431.0)	44.5 (0.0–780.0)	16.0 (0.0–431.0)
	p-value**	0.022		0.022	
	AUC	0.612 (p=0.022)		0.613 (p=0.022)	
	Cut-off	16.5 days (sens 75.6%, spec 51.6%)		23.5 days (sens 71.6%, spec 56.3%)	
Trimethoprim-sulfamethoxazole	No	36 (58.1%)	26 (41.9%)	33 (53.2%)	29 (46.8%)
	Yes	56 (59.6%)	38 (40.4%)	54 (58.7%)	38 (41.3%)
	p-value*	0.491		0.306	
	Duration	71.7±103.9	65.7±86.6	73.4±105.9	63.8±85.7
	(days)	20.5 (0.0–575.0)	35.5 (0.0–395.0)	22.0 (0.0–575.0)	30.0 (0.0–395.0)
	p-value**	0.948		0.684	
	Interval	126.8±252.2	161.9±211.1	120.4±254.4	162.7±211.3
	(days)	15.5 (0.0–1230.0)	95.5 (0.0–790.0)	5.0 (0.0–1230.0)	95.5 (0.0–790.0)
	p-value**	0.037		0.017	
	AUC	0.624 (p=0.043)		0.642 (p=0.021)	
	Cut off	91.5 days (sens 52.6%, spec 71.4%)		91.5 days (sens 52.6%, spec 74.1%)	

		Trimethoprim-sulfamethoxazole		
		Susceptible	Resistant	
	No	31 (50.8%)	30 (49.2%)	
	Yes	29 (30.9%)	65 (69.1%)	
	p-value*	0.010		
	Duration	60.1±114.8	75.7±84.1	AUC 0.618 (p=0.014)
	(days)	0.0 (0.0–575)	62.0 (0.0–339.0)	Cut-off 31.0 days
	p-value**	0.011		(sens 57.9%, spec 66.7%)
	Interval	285.38±311.8	76.6±157.0	AUC 0.791 (p<0.001)
	(days)	188.0 (0.0–1230)	0.0 (0.0–1045.0)	Cut off 27.0 days
	p-value**	<0.001		(sens 93.1%, spec 60.0%)

* Fisher's exact test (one-way), ** Mann-Whitney's *U* test

Duration: administration period of each antibiotics before UTI

Interval: The interval between the last administration of each antibiotic and UTI

ESBL, expanded-spectrum β lactamase; AUC, area under the curve; sens, sensitivity; spec, specificity

The overall eGFR% (median [minimum, maximum][11]) at each admission were 89.2% [12.8, 205.2] at 1st UTI episode, 89.8% [13.4, 259.1] at 2nd UTI episode, 96.7% [24.2, 207.8] at 3rd UTI episode, and persistently higher than 90.0% at later episodes of UTIs. The percentage of low eGFR% was 61.7 % at 1st UTI episode, 55.3% at 2nd episode, 55.3% at 3rd episode, and 23.4% at the last follow-up, not showing as a significant tendency with increasing episodes of UTIs (**Table 8**). In subgroup analysis, the eGFR% of the patients at 1st UTI episode who have at least one morphologically and functionally normal kidney (Group 1) was 98.2±35.5% (87.2%, 46.3–167.4%), while that of the patients with both kidneys having either defects on 99mTc-dimercaptosuccinic acid (DMSA) scan, dysplasia or any urologic anomaly that can cause renal damage (Group 2) was 74.9±35.0% (88.3, 12.8–117.6%) (*p=0.456* on Mann-Whitney's *U* test, data not shown). The prevalence of decreased renal function in Group 1 was 62.1% (18/29), while that in Group 2 was 85.7% (6/7) at 1st UTI (*p=0.235*, one-sided Fisher's exact test).

Table 8. Changes in eGFR% in children according to the number of UTI episodes

No. of UTI		1st	2nd	3rd	4th	5th	6th	7th	8th	*p*-value
Total No. of Pt.		47	47	47	16	11	7	3	3	
eGFR%	Mean±SD	95.8±36.7	98.0±35.7	102.8±32.8	98.0±29.5	124.5±101.8	103.4±14.4	109.9±30.4	114.4±30.0	
	Median	89.2%	89.8%	96.7%	91.7%	98.3%	100.3%	96.5%	112.0%	0.702
	[Min, Max]	[12.8, 205.2]	[13.4, 259.1]	[24.2, 207.8]	[60.8, 174.4]	[70.6, 424.5]	[89.3, 131.3]	[88.4, 144.7]	[85.7, 145.4]	
Prevalence of low eGFR%		61.7%	55.3%	55.3%	68.8%	63.6%	42.9%	66.7%	33.3%	0.745

A low eGFR% at 1st UTI episode was related to persistently low eGFR% at 2nd UTI episode, while normal eGFR% at 1st UTI episode was related to a higher possibility of normal eGFR% at 2nd UTI episode (p=0.018) (**Table 9**.) Correlation analysis revealed a significant positive correlation between eGFR% indices from consecutive UTI episodes (1st to 3rd). ΔeGFR% showed a significant negative correlation with the baseline eGFR% between 1st and 2nd, 2nd and 3rd, and 1st and 3rd UTI episodes, respectively (p<0.001). A negative correlation was also shown between ΔeGFR% at each UTI episode (1st to 3rd) and eGFR% at the last follow-up (p<0.001) (**Table 10).**

Table 9. Changes in the proportion of low eGFR % among 1st and 3rd UTI episodes

eGFR%	1st UTI	2nd UTI	Previous UTI		3rd UTI	Previous UTI		Last f/u	Previous UTI	
Normal (%)	18 (38.3)	21 (44.7)	Normal	12 (57.1)	21 (44.7)	Normal	11 (52.4)	36 (76.6)	Normal	15 (41.7)
			Low	9 (42.9)		Low	10 (47.6)		Low	21 (58.3)
Low (%)	29 (61.7)	26 (55.3)	Normal	6 (23.1)	26 (55.3)	Normal	10 (38.5)	11 (23.4)	Normal	6 (54.5)
			Low	20 (76.9)		Low	16 (61.5)		Low	5 (45.5)
Fisher's exact test (one-sided)			*p*-value	0.018		*p-value*	0.255		*p*-value	0.341

Table 10. Correlations between paired eGFR% of two time points from each UTI, and correlations between eGFR% and △eGFR%

	r	*p*-value*
eGFR % at 1st vs 2nd UTI	0.386	0.004
eGFR % at 2nd vs 3rd UTI	0.406	0.002
eGFR % at 1st vs 3rd UTI	0.292	0.023
eGFR % at 1st UTI vs last f/u	0.16	0.141
eGFR % at 2nd UTI vs last fu	0.07	0.321
eGFR % at 3rd UTI vs last fu	-0.069	0.322
eGFR % at 1st UTI vs ΔeGFR % (1st UTI/2nd UTI)	-0.592	<0.001
eGFR % at 2nd UTI vs ΔeGFR % (2nd UTI/3rd UTI)	-0.597	<0.001
eGFR % at 1st UTI vs ΔeGFR % (1st UTI/3rd UTI)	-0.734	<0.001
eGFR % at 1st UTI vs ΔeGFR % (1st UTI/Last f/u)	-0.592	<0.001
eGFR % at 2nd UTI vs ΔeGFR % (2nd UTI/Last f/u)	-0.524	<0.001
eGFR % at 3rd UTI vs ΔeGFR % (3rd UTI/Last f/u)	-0.617	<0.001
eGFR % at Last UTI vs ΔeGFR % (Last UTI/Last f/u)	-0.456	0.001

eGFR: estimated glomerular filtration rate, UTI: urinary tract infection, ΔeGFR: changes in eGFR during given periods, f/u: follow-up

*Fisher's exact test: one-sided

Variables indicating clinical course were analyzed to evaluate the correlation between eGFR% at each UTI episode. Only CRP level at each admission showed a consistent negative correlation with eGFR% at each UTI episode (1st to 3rd), and a negative correlation with ΔeGFR% between 1st and 2nd, 2nd and 3rd, and 1st and 3rd UTI episodes, respectively (p<0.05). Fever duration before and after treatment, peak body temperature, WBC, percentage of neutrophils, hemoglobin level, platelet count, liver enzymes, and sodium/potassium level at admission showed inconsistent correlation with eGFR%. Indices from urinalysis also showed inconsistent correlation with eGFR% at each UTI episode (**Tables 11 and 12).**

Table 11. Correlations between clinical findings and eGFR% in children with recurrent UTIs

Clinical findings		eGFR%*	eGFR%**	eGFR%**	△eGFR%**	△eGFR%**	△eGFR%**
		at 1st UTI	at 2nd UTI	at 3rd UTI	1st/2nd	2nd/3rd	1st/3rd
Fever duration	r	0.330	0.027	-0.079	0.066	-0.187	-0.032
(total)	*p*-value	0.414	0.431	0.307	0.336	0.115	0.419
Fever duration	r	-0.103	0.089	-0.051	0.053	-0.170	-0.168
(pre-treatment)	*p*-value	0.248	0.283	0.373	0.367	0.138	0.141
Fever duration	r	0.107	-0.040	-0.052	0.032	-0.810	0.073
(post-antibiotics)	*p*-value	0.248	0.398	0.370	0.419	<0.001	0.321
Peak body temperature (℃)	r	-0.006	-0.241	0.049	-0.272	-0.030	-0.086
	p-value	0.485	0.057	0.376	0.037	0.424	0.291
UTI interval	r		-0.019	-0.161	0.073	-0.159	-0.217
(days)	*p*-value		0.451	0.143	0.314	0.145	0.074

Table 12. Correlations between laboratory findings and eGFR% in children with recurrent UTIs

Laboratory Findings		eGFR%* at 1st UTI	eGFR%** at 2nd UTI	eGFR%** at 3rd UTI	△eGFR%** 1st/2nd	△eGFR%** 2nd/3rd	△eGFR%** 1st/3rd
WBC	r	-0.288	-0.020	-0.133	-0.022	-0.103	-0.086
(/uL)	*p*-value	0.025	0.450	0.198	0.444	0.256	0.292
Neutrophil (%)	r	0.161	-0.073	-0.415	-0.097	-0.441	-0.390
	p-value	0.143	0.318	0.003	0.266	0.002	0.005
Hemoglobin	r	0.239	-0.028	-0.054	-0.032	-0.083	-0.095
(g/dL)	*p*-value	0.053	0.428	0.365	0.418	0.298	0.272
Platelet	r	0.148	0.188	0.232	0.107	0.253	0.123
($x10^3$/uL)	*p*-value	0.161	0.111	0.067	0.244	0.051	0.217
AST	r	-0.161	0.060	-0.108	0.240	-0.112	0.112
(IU/L)	*p*-value	0.140	0.348	0.245	0.058	0.238	0.238
ALT	r	0.053	0.074	-0.093	0.265	-0.096	0.120
(IU/L)	*p*-value	0.364	0.317	0.277	0.041	0.271	0.221
Sodium	r	0.233	0.057	-0.013	0.032	-0.038	0.027
(mmol/L)	*p*-value	0.058	0.355	0.466	0.419	0.405	0.432
Potassium	r	-0.072	-0.021	0.005	-0.048	0.019	0.189
(mmol/L)	*p*-value	0.315	0.447	0.488	0.378	0.453	0.113
C-reactive protein	r	-0.256	-0.459	-0.300	-0.427	-0.271	-0.338
(mg/dL)	*p*-value	0.041	0.001	0.025	0.002	0.040	0.013
Urine S.G.	r	0.067	0.145	-0.193	0.146	-0.155	-0.153
	p-value	0.328	0.174	0.107	0.172	0.160	0.164
Urine albumin	r	0.093	-0.006	-0.233	-0.028	-0.216	-0.062
	p-value	0.266	0.485	0.075	0.427	0.082	0.347
Urine glucose	r	0.021	-0.292	-0.180	-0.200	-0.134	-0.110
	p-value	0.445	0.027	0.124	0.096	0.196	0.241
Urine ketone	r	-0.008	0.093	-0.320	0.026	-0.346	-0.394
	p-value	0.478	0.274	0.018	0.433	0.012	0.004
Urine occult blood	r	0.147	-0.132	-0.210	-0.136	-0.021	-0.112
	p-value	0.328	0.196	0.088	0.190	0.446	0.237
Urine nitrite	r	0.117	0.119	0.447	0.153	0.425	0.328
	p-value	0.432	0.222	0.001	0.161	0.002	0.016
Urine WBC	r	0.112	0.158	0.119	0.088	0.170	0.148
	p-value	0.452	0.153	0.224	0.286	0.138	0.172

eGFR: estimated glomerular filtration rate, UTI: urinary tract infection

△eGFR%: changes in the percentage of eGFR between designated UTI periods, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, S.G.: specific gravity

*Spearman correlation analysis, **Partial correlation analysis controlled by eGFR% at previous UTI

Discussion

In this study, we observed the dynamic changes in antibiotic susceptibility profile and delicate rise and fall of the eGFR% during multiple UTI recurrences for the first time. To our knowledge, this study was the first to compare multiple episodes of UTIs.

The majority of patients who experienced more than three recurrent episodes of UTIs had underlying urologic anomalies and/or VUR; only one patient had no VUR nor underlying urologic anomalies. After identifying the presence of VUR, an anti-reflux surgery was performed in patients who had more than three recurrent episodes of UTIs in our center. Anti-reflux procedure or surgery effectively prevented the recurrence of UTI in patients with isolated VUR. However, patients with cloacal deformities and/or fistula between the urogenital tract and rectum had recurrent UTI even after undergoing anti-reflux surgery (if VUR was present), diversion, or correction of each urogenital and intestinal tract. UTI recurrence in these patients even after anti-reflux interventions can be partly attributed to residual VUR after anti-reflux intervention which wasn't routinely checked after the correction of VUR, or the presence of persistent cloaca requiring several reconstructive procedures for proper function, or the presence of an undiscovered or untreated fistula tract between the urinary tract and rectum.[12] In addition, our study patients with cloacal anomaly always accompanied BBD, rendering themselves to a higher risk of UTI recurrence. Although data on the long-term renal outcomes of cloacal deformities are limited, evaluating the presence of VUR and implementation of pre-emptive management including anti-reflux surgery and antibiotic prophylactic treatment in time of need might be the workable option for patients with persistent cloacal deformities in order to prevent further renal injury due to repeated UTIs.[13]

With regard to the bacterial etiology detected in our study patients with recurrent UTIs, *E. coli* was the most predominant bacterial etiology as previously known. Although infection with *E. coli* and *K. pneumoniae* was most frequently associated with an increase in the number of UTI episodes,

especially with the 7th and 8th UTI episodes, *Enterobacter* species were not detected after the 3rd UTI episode. The decreasing proportion of *Enterobacter* species may be partly attributed to the increase in patients' age; the prevalence *Enterobacter* species and number of UTI episodes inevitably decrease with increasing age.[14,15] Although the reason for the prevalence of *Enterobacter* infection in early infancy is unclear, the length of stay in the neonatal intensive care unit for infants with multiple anomalies might be partly related to the development of opportunistic or nosocomial infections caused by these pathogens,[16] which decrease with infrequent hospitalization and the implementation of invasive measures according to the patients' age. The decreasing diversity in bacterial pathogens mentioned in our study was contrary to the findings of some previous studies, which reported that pathogens other than *E.coli* were frequently detected in patients with recurrent UTIs.[17,18] The decline in pathogenic diversity can be partly associated with the decreased diversity in gut flora, which might have been affected by the frequent exposure to antibiotics and survival of the only resistant strains in these patients with multiple urologic anomalies and UTI recurrence.

We demonstrated the increasing prevalence of resistance to antibiotics including cefotaxime, cefepime, and ciprofloxacin at each UTI episode and the increase in the proportion of ESBL-producing organisms during the study period. Although temporal changes in regional antibiotic resistance might have had some impact on the resistance pattern of uropathogens, we tried to extract the overall trend and distribution of antibiotic resistance in all episodes of UTI. The overall increase in the resistance for such antibiotics rationalizes the significant overall increase in the prescription of piperacillin-tazobactam and carbapenems in patients with an increasing number of UTI episodes. Previous antibiotic use, the geographic distribution of South Asia (a region with a higher prevalence of ESBL-positive isolates), underlying urinary tract anomalies, and recent hospitalization for recurrent UTI were the risk factors reported in previous studies associated with the emergence of multi-drug-resistant uropathogens.[19]

In terms of treating ESBL-producing organisms, our treatment of choice or our second-

line option in case of failure after treatment with first-line antibiotics was piperacillin-tazobactam. Conflicting results regarding the use of piperacillin-tazobactam as an alternative treatment against ESBL-producing organisms isolated from urine samples of patients with UTI have been presented; Gavin et al. demonstrated that UTI could be successfully treated with piperacillin-tazobactam, while another study revealed the unsuccessful inhibition of these infections with piperacillin-tazobactam.[16,20)] In our study, only 1.1% (2 out of 170 with gram-negative pathogens) of the patients had switched from piperacillin-tazobactam to carbapenems; treatment changes were made due to the persistent occurrence of high fever and increase in the levels of inflammatory markers. However, the two cases that switched to carbapenems all showed a negative conversion of urine culture with piperacillin-tazobactam treatment, supporting the use of piperacillin-tazobactam as a 1st-line antibiotics in UTIs with ESBL producing organisms. Changing to 2nd-line antibiotics with a broader spectrum occurred in some patients although they had actual clinical responses to first-line antibiotics. This was based on an antibiogram indicating the *in vitro* non-susceptibility of ESBL-producing pathogens to first-line antibiotics, although high urine concentrations of antibiotics might have effectively eradicated the bacteria, which were resistant per *in vitro* susceptibility testing. However, previous studies showed conflicting results and reported the empirical use of third-generation cephalosporins in the treatment of UTI caused by ESBL-producing organisms. Some of these studies reported a clinical and microbiological response rate of 94%–95% in patients with an infection that is not susceptible to antibiotics without renal scarring or a response rate of 50% in patients with clinical response to third-generation cephalosporins without recurrence.[11,21-24)]

Despite the overall increasing proportion of ESBL-producing uropathogens, these organisms were not present in all episodes of UTI; the ESBL activity was no longer in some of the episodes of UTI recurrence. The rates of clinical response to third-generation cephalosporins and ampicillin-sulbactam improved according to the episodes of UTI although this finding is not considered significant. Alteration in bacterial flora induced by prescribed antibiotics led to the

survival of bacteria that are inherently resistant or have become resistant to those drugs,[25] that is, 1st-line antibiotics (mainly third-generation cephalosporins and ampicillin-sulbactam) for patients with UTIs. Switching to piperacillin-tazobactam or carbapenems at subsequent UTIs and long duration of non-exposure to 1st-line antibiotics might have conveyed responsiveness to those antibiotics with or without loss of ESBL activity as shown in previous studies.[26,27]

TMP-SMX is traditionally used as a 1st-line antibiotic prophylaxis for recurrent UTI due to the fact that the emergence of ESBL-producing bacteria is related to prior use of broad-spectrum antibiotics such as 3rd –generation cephalosporins, amoxicillin, and quinolones, while narrow spectrum antibiotics are less likely to cause resistance with ESBL.[17] Apart from the emergence of ESBL, breakthrough UTIs or resistance frequently occurs after continuous use of TMP-SMX as a prophylactic antibiotic. In a recent gut microbiome metagenomics analysis of South African infants receiving TMP-SMX as a prophylactic treatment for HIV exposure, non-infected infants aged six weeks-six months were evaluated for gut microbiome diversity. α-diversity indicates species diversity in sites within the infant's gut. β-diversity indicates diversity between two different samples obtained from different regions of the infant's gut; a higher β-diversity suggests that the compositions of the sample are different from each other.[28] The authors found no significant difference in α-diversity, but observed a decrease in gut microbiome β-diversity and an increase in antibiotic resistance gene α-diversity between infants with TMP-SMX prophylaxis and those without prophylaxis. Although TMP-SMX was administered for other purposes, this study had implications on gut microbiota dynamics. That is, the use of TMP-SMX may evenly reduce the bacterial load, making its effects undetectable when measuring the α-diversity, but may increase the risk for resistance.

With regard to the impact of previous antibiotic exposure, we analyzed the quantitative relationship between the exposure burden of antibiotics and the emergence of resistance; we estimated the cut-off value for the duration of exposure to cefotaxime and TMP-SMX that can induce

resistance among uropathogens for the first time. Compared to the several previous studies showing the antibiotic prophylaxis including TMP-SMX within six months was associated with the acquisition of resistance to the used antibiotics, or exposure to amoxicillin and amoxicillin-clavulanate within 30 days was associated with the emergence of resistance,[17,30] we showed a more concrete time point of duration and interval of use in which TMP-SMX or 3rd-generation cephalosporin might lead to subsequent resistance to themselves, respectively. As the accumulation of antibiotic use delivers the selective pressure that permits the resistant strains to proliferate, antibiotics withdrawal enable those strains to reverse the selective pressure and regain diversity in gut flora which leads to loss of resistance, although rate and time of loss may vary according to the location where the genes for ESBL are inserted, and the length of time spent on passing the organisms with resistant genes.[31] This partly explains the reason for the difference in time and duration of acquisition or loss of the resistance between different species and antibiotics. The reason for less occurrence of ESBLs after exposure to TMP-SMX needs further elucidation for clear causality; effective prophylaxis with TMP-SMX might have spared the use of broad-spectrum antibiotics for another episode of UTI, and therefore reduced emergence of ESBL-producing species, or TMP-SMX itself could possess a protective property against ESBL production. Further studies including the analysis of microbiome dynamics and passage of resistant species might aid in elucidating these mechanisms.

With the dilemma between protection against the ESBL emergence and the risk of rapid gain of resistance for TMP-SMX itself, clinicians should prudently determine the risk and benefits when using TMP-SMX as routine prophylaxis. In such a case reluctant to use TMP-SMX prophylaxis, nitrofurantoin can safely be an alternative for TMP-SMX[29], although none of the patients in this study have used nitrofurantoin as continuous antibiotic prophylactic treatment; hence, we were unable to evaluate the dynamics of this antibiotic.

Although pediatric patients under age 18 years are seldom exposed to ciprofloxacin as a

treatment or prophylaxis agent, ciprofloxacin resistance rate persistently increased at each UTI episode in our study. Resistance without exposure can be first explained by the transmission of resistant isolates between adults and children in homes, daycare centers, or school settings and by previous use of fluoroquinolones in both humans and animals.[32] Furthermore, with the high prevalence of ESBL-producing uropathogens in the study population, fluoroquinolone resistance might ensue ESBL production; hence, fluoroquinolone resistance develops due to the co-transfer of the *qnr* determinant on ESBL-producing plasmids.[33,34]

Changes in eGFR% at the acute phase of each UTI episode were demonstrated, showing the acute deterioration of renal function in a considerable proportion of patients with low eGFR% at each episode. This study was the first to report the delicate change in eGFR% at each UTI episode. During acute UTI, especially acute pyelonephritis, interstitial infiltration of neutrophils and phagocytes and extensive destruction of the parenchyme by an acute inflammatory process can involve entire lobules of the medulla and cortex, leading to acute renal dysfunction or acute kidney injury in extreme circumstances such as urosepsis.[35] With regard to the overall renal function, a previous study showed a reduction in the eGFR in one side of a scarred kidney after two decades of experiencing UTI recurrence, which started in childhood. Meanwhile, the overall eGFR was preserved in patients with unilateral scarring without any other underlying renal damage.[36] These findings suggest that acute inflammation of either side of the kidneys can lead to an intrinsic renal function defect. Hence, close attention should be paid to the overall renal function of patients with this condition.

We demonstrated the resilient recovery of eGFR% at subsequent UTI episodes with more degree of recovery in eGFR% in UTI patients whose eGFR% deteriorated further during the previous admission. The accumulation of these recuperative powers led to the improvement in eGFR% at the last follow-up as shown in the overall and subgroup analyses. Previous studies also supported this finding; one study demonstrated that 103 febrile UTI patients did not show renal damage after two years of follow-up, and another study with 108 matched patients with or without

renal scar at the time of UTI had preserved renal function after long-term follow-up.[36,37] Although we didn't adjust for the urologic anomalies possibly influencing the renal function of the involved side of the kidney and DMSA scan was not performed at every UTI episode, we showed the overall tendency of recovery after the acute deterioration in renal function between UTI recurrences. Future studies including patients only with totally corrected urologic anomalies, or patients stratified by identical urologic anomalies with a larger sample size might aid in the validation of the eGFR change during UTI recurrences.

Among various clinical variables presented in this study, CRP was associated with a decrease in eGFR at admission. The severity of acute inflammatory reaction associated with CRP seemed to lead to acute renal deterioration, as mentioned above. Although our sample size was not large enough to evaluate other associated variables, previous results from a large cohort of patients with UTI showed that higher peak body temperatures (>39.0℃), high polymorphonuclear leukocyte level (>60%), and higher CRP level (>4 mg/dl) were all associated with renal scarring.[38] Similarly, other previous studies reported that procalcitonin and the duration of fever were the only parameters statistically associated with early renal damage indicated by early defects on DMSA scan.[39] Based on these findings, timely diagnosis and early introduction of antibiotics to minimize inflammatory reaction might aid in the prevention of acute renal deterioration.

The limitation of this study was the small sample size, the retrospective nature of the study, and the different intervals of antibiotic treatment in each patient and episodes of recurrence. This might preclude the clarification of the exact interaction between the use of certain antibiotics and their impact. Moreover, the majority of the urine samples were obtained via urine bags or mid-stream clean-catch technique, and not through catheterization, due to the non-applicability of this method in the emergency room setting of our hospital. The strength of this study is that we were able to evaluate and compare the changes between multiple recurrent UTI episodes in each patient for the first time; hence, we were able to track the dynamics of microbial prevalence and resistance, and

compare the overall eGFR trajectories. Through this, we can capture the direction of multifactorial impacts and drew pieces of evidence adaptable for clinical practice.

Conclusion

With increasing episodes of UTI, resistance to third-generation cephalosporins and the emergence of ESBL-producing pathogens significantly increased. Antibiotic susceptibility in patients with recurrent UTIs was dynamically influenced by previous exposure to particular antibiotics, with certain cut-off values of exposure burden for each antibiotic. Using TMP-SMX as prophylaxis or treatment reduced the possibility of TMP-SMX use as a treatment for subsequent UTIs due to the rapid occurrence of resistance, but less emergence of ESBLs. The decline in renal function was more remarkable when the patient presented with decreased renal function at previous UTI episodes. Patients with recurrent UTI showed a significant decrease in eGFR when CRP elevation was higher at the time of admission. However, results of restoration of normal renal function at subsequent follow-up were more remarkable when the patients' renal function at baseline UTI episode was significantly deteriorated, indicating the high resilience of recovery within each episode of UTI in pediatric patients.

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국문요약

재발성 요로 감염증에 이환된 소아에서
동정균의 항생제 감수성 변화 양상과 신기능의 변화 분석

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목적: 본 연구에서는 소아에서 다회의 재발성 요로 감염증에서 원인균의 항생제 감수성 변화를 다각적으로 분석하고, 각 요로 감염 발생시의 신기능 변화를 추적 분석하고자 하였다.

연구방법: 2004년 1월부터 2019년 9월까지, 3회 이상의 발열성 요로 감염증으로 서울아산병원 어린이병원에 입원하였던 18세 미만의 소아를 대상으로 하여, 이들의 의무기록을 후향적으로 수집하여 연구분석을 진행하였다. eGFR% 은 (eGFR/환자 연령에서 eGFR의 정상 하한값) x 100(%)으로 산출하였으며 eGFR% 이 100% 미만인 경우 감소된 것으로 평가하였다. △eGFR%(n^{th}/$(n+\alpha)^{th}$) 값은 {[eGFR%($(n+\alpha)^{th}$ UTI) − eGFR%($(n^{th}$ UTI)]/eGFR%(n^{th} UTI))} x 100(%) 과 같이 산출하였다.

결과: 총 47명의 환자가 3회 이상의 재발성 요로 감염증에 이환되었다. 모든 회차의 요로 감염에서 대장균이 언제나 가장 주된 원인 균 이었으며, *Enterobacter* species 의 경우 요로 감염 회차가 증가할수록 유의하게 검출이 감소하였다 (p=0.004). Extended−spectrum β−lactamase (ESBL) 생성 균주의 검출 비율 및 cefotaxime, cefepime, ciprofloxacin 에 대한 내성률은 요로 감염 회차에 따라 그 빈도 및 내성률이 증가하였다 (p=0.056, p=0.037, p=0.045, p=0.041). 내성 발생과 관계된 항생제 노출의 정도를 분석하였을 때, 3세대−세팔로스포린 계열

항생제의 경우 21.5일 이상의 투약 기간 (p=0.016) 및 최근 2-4주 이내의 항생제 노출이 내성 발생과 연관됨을 확인하였고 (p=0.022), Trimethoprim-sulfamethoxazole (TMP-SMX) 의 경우는 31일 이상의 투약 기간 (p=0.014) 및 최근 4주 이내의 사용이 동일 항생제에 대한 내성 발생과 유의한 연관이 있음을 확인하였다 (p<0.001). 91.5일 이내의 TMP-SMX 투약력은 이후 요로 감염에서 ESBL 검출의 감소와 연관되었다 (p=0.021). 초회 요로 감염부터 3회차 요로 감염에 이르기까지 각 회차에서 eGFR%은 이전 회차의 eGFR%과 양의 상관관계를 보였다. 여러 임상 지표들과의 연관성을 분석하였을 때, 입원 당시의 C-reactive protein (CRP) 값 만이 각 회차의 eGFR%, 그리고 1-2차, 2-3차, 1-3차의 ΔeGFR% 값과 유의한 음의 상관관계를 보였다 (p< 0.05).

결론: 다회의 요로 감염증이 발생함에 따라 3세대-세파 계열 항생제 저항 및 ESBL 생성원인 균주의 검출이 유의하게 증가하였고, 검출된 원인균의 항생제 감수성은 이전에 노출되었던 항생제의 양과 기간에 따라 역동적으로 변화하였다. 각각의 요로 감염증에서, 이전 감염으로 입원 시 GFR의 저하가 동반되었거나, 해당 감염증으로 입원 당시의 CRP 값이 높을수록 해당 요로 감염증에서의 eGFR% 감소를 보였다.