Pediatr Infect Vaccine. 2020 Apr;27(1):35-44
https://doi.org/10.14776/piv.2020.27.e7
pISSN 2384-1079·eISSN 2384-1087

PIV PEDIATRIC INFECTION & VACCINE

Original Article

Clinical Features of and Antibiotic Resistance in Recurrent Urinary Tract Infection in Children with Vesicoureteral Reflux

So Hyun Eun,[1] **Ji-Man Kang**,[1] **Ji Hong Kim**,[2] **Sang Woon Kim**,[3] **Yong Seung Lee**,[3] **Sang Won Han**,[3] **Jong Gyun Ahn**[1]

[1]Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, the Republic of Korea
[2]Department of Pediatrics, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, the Republic of Korea
[3]Department of Urology and Urological Science Institute, Yonsei University College of Medicine, Seoul, the Republic of Korea

Received: Oct 29, 2019
Revised: Nov 28, 2019
Accepted: Nov 28, 2019

Correspondence to
Jong Gyun Ahn
Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, the Republic of Korea.
E-mail: JGAHN@yuhs.ac

ORCID iDs
So Hyun Eun
https://orcid.org/0000-0002-9598-7519
Ji-Man Kang
https://orcid.org/0000-0002-0678-4964
Ji Hong Kim
https://orcid.org/0000-0001-5352-5423
Sang Woon Kim
https://orcid.org/0000-0002-5790-1948
Yong Seung Lee
https://orcid.org/0000-0003-3778-9888

ABSTRACT

Purpose: This study aimed to investigate the clinical features of recurrent urinary tract infection (UTI) in children with vesicoureteral reflux (VUR) and to compare the causative uropathogen and antibiotic susceptibility between the first and recurrent UTI episodes.
Methods: We retrospectively reviewed the medical records of children with VUR who had recurrent UTI. Group 1 included patients in whom the same pathogen caused the first and recurrent UTI episodes. Group 2 included patients in whom different pathogens caused the first and recurrent UTI episodes.
Results: During a 13-year study period (2005–2018), 77 children with VUR experienced at least one episode of UTI. Among these, 47 patients (61.0%) had recurrent UTI. Of the children with recurrent UTI, 19 (40.4%) were in group 1 and 28 (59.6%) were in group 2. *Escherichia coli* was the most commonly isolated uropathogen (n=37; 39.4%) in both episodes of recurrent UTIs, followed by *Klebsiella pneumoniae* (n=18; 19.1%), *Enterococcus faecalis* (n=14; 14.9%), and *Enterobacter aerogenes* (n=7; 7.4%). Although the difference was not significant, the rate of resistance to the antibiotics ceftazidime, piperacillin/tazobactam, and trimethoprim-sulfamethoxazole increased in patients with the second episode of *E. coli* recurrence in group 1, and that to cefotaxime, ceftazidime, piperacillin/tazobactam, and meropenem increased in children with the second episode of *E. aerogenes* recurrence in group 1.
Conclusions: When selecting empirical antibiotics for recurrent UTI in children with VUR, it is important to consider that the pathogen and antimicrobial susceptibility of the previous UTI are not always the same in recurrent UTIs.

Keywords: Urinary tract infections; Vesico-ureteral reflux; Child; Anti-bacterial agents

INTRODUCTION

Vesicoureteral reflux (VUR) predisposes the patients to acute pyelonephritis by facilitating bacteria from the bladder to enter the kidney, which can result in renal scarring, renin-mediated hypertension, or end-stage renal disease.[1-4] VUR is present in approximately 30%

Sang Won Han
https://orcid.org/0000-0003-0941-1300
Jong Gyun Ahn
https://orcid.org/0000-0001-5748-0015

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: Ahn JG; Data curation: Eun SH, Kim JH, Kim SW, Lee YS, Han SW, Ahn JG; Formal analysis: Eun SH, Ahn JG; Investigation: Eun SH, Kim JH, Kim SW, Lee YS, Han SW, Ahn JG; Methodology: Eun SH, Kim JH, Kim SW, Lee YS, Han SW, Ahn JG; Resources: Eun SH, Kim JH, Kim SW, Lee YS, Han SW, Ahn JG; Software: Eun SH; Supervision: Kang JM, Ahn JG; Validation: Kang JM, Ahn JG; Visualization: Eun SH; Writing - original draft: Eun SH; Writing - review & editing: Kang JM, Ahn JG.

to 40% of children who had a first episode of urinary tract infection (UTI).[5-7] Among patients with febrile UTI, children with VUR are 3 times more likely to have a renal injury than those without VUR.[7] The published Randomized Intervention for VUR trial, a randomized trial of trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis for patients with a history of UTI and diagnosed VUR, showed a reduction in the recurrence rate of UTIs by approximately 50%, from 30% in the group not receiving prophylaxis to 15% in that receiving prophylaxis, but there was no reduction in the rate of renal scarring with antibiotic prophylaxis.[8] Therefore, prompt treatment of intercurrent episodes of UTI in patients with VUR is crucial in preventing possible renal damage.[1]

To date, no precise guideline has been established for the treatment of recurrent UTIs. When recurrent UTI occurs in patients with VUR, empirical antibiotic selection tends to be based on previous results.[1] However, there is little evidence and research on this topic. The recent emergence of drug-resistant uropathogens has made it difficult to select empirical antibiotics when recurrent UTIs develop in patients with VUR.[2,3] The purpose of this study was to investigate the clinical features of recurrent UTI in patients with VUR and to compare the causative uropathogens and antibiotic susceptibility between the first and recurrent UTI episodes.

MATERIALS AND METHODS

This retrospective observational study was performed in 2 tertiary referral hospitals (Severance Children's Hospital and Gangnam Severance Hospital) from April 2005 to February 2018. We reviewed the medical charts of all children with VUR aged ≤18 years, who experienced at least 1 episode of UTI. The research was approved by the Institutional Review Board (No. 4-2018-1086) of the Yonsei University Health System, and the requirements for informed consent were waived because of the retrospective nature of the study.

UTI was defined on the basis of the culture of a single pathogen from a catheter urine specimen culture with a colony count ≥50,000 or from a clean-catch bag-collected specimen culture with ≥100,000 colonies in children with fever (38°C or greater) and pyuria (white blood cell count >5 cells/high power field).[4] Cases were excluded when 2 pathogens were isolated on urine culture. The presence and grade of VUR were determined on voiding cystourethrography (VCUG) according to the system proposed by the International Reflux Study Committee.[9] Data on patient age and sex, grade of VUR, surgical correction, additional urinary tract anomalies, and use of prophylactic antibiotics were collected from the medical records.

Any child with ≥2 UTI episodes during the 12-month follow-up period after the initial UTI was defined as having had recurrent UTIs.[10] Patients with recurrent UTI were also subdivided into 2 groups. We compared the uropathogen and clinical features between the first and second episodes of UTIs. Group 1 was defined as having the same isolated pathogen in the first and second episodes. Group 2 was defined as having different cultured organism in the first and second episodes.

In case of group 1 (same strain), antibiotic susceptibility profiles between the first and second episodes were compared based on the urine culture results. Sensitivity to an antibiotic was defined as the notation of sensitive (S) on the urine culture antibiotic sensitivity results, tested using the VITEK2 (bioMeriéux, Marcy-l'Étoile, France) equipment according to the Clinical and Laboratory Standards Institute standards.[11]

1. Statistical analysis

Descriptive statistics are expressed for continuous and categorical variables using the medians with the interquartile range (IQR) and frequency and percentage, respectively. The χ^2 test (Fisher's exact test) and the Mann-Whitney U test were used for comparison of categorical and continuous variables. Antibiotic sensitivity results between the first and second episodes of relapse were compared using the McNemar's test. A *P*-value of <0.05 was considered statistically significant. All analyses were performed using the SAS version 9.3 statistical package (SAS Institute, Cary, NC, USA).

RESULTS

1. Patient characteristics

During the 13-year study period, 378 patients were screened through diagnostic codes on medical records. A total of 301 patients were excluded based on the medical chart review. The reasons for exclusion are shown in **Fig. 1**. As a result, 77 patients were included in the present study: 50 boys (64.9%) and 27 girls (35.1%). The median age at diagnosis of the first UTI was 6.0 months (IQR, 3.0–14.0 months). UTI was diagnosed in 2 cases by catheterized urine culture and in the rest by bag-collected specimen culture.

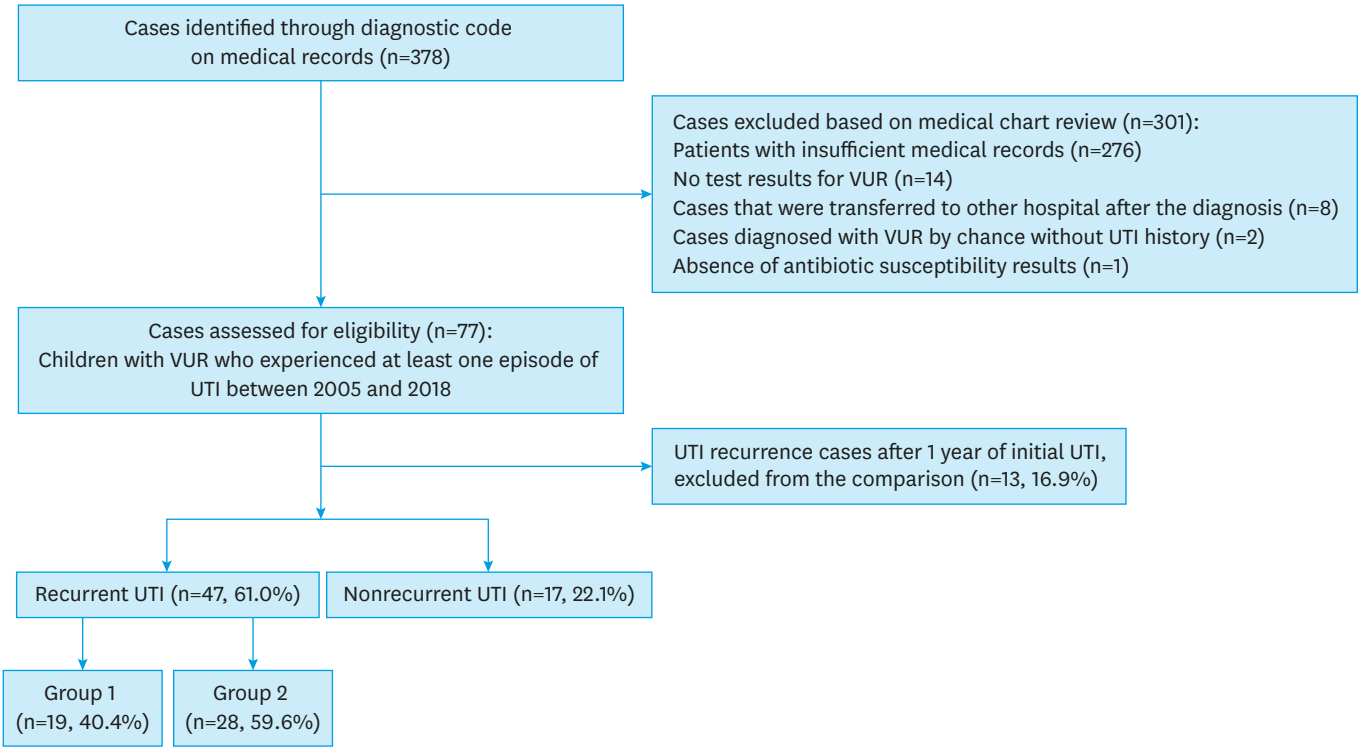

Fig. 1. Flowchart for patient selection. A total of 378 patients were screened through diagnostic codes on medical records from April 1, 2005, to February 28, 2018. A total of 301 patients were excluded due to inadequate study based on the medical chart review. Group 1 was defined as having the same isolated pathogen in the first and second episodes. Group 2 was defined as having different cultured organism in the first and second episodes.
Abbreviations: VUR, **v**esicoureteral reflux; UTI, urinary tract infection.

https://doi.org/10.14776/piv.2020.27.e7

2. Characteristics of the VUR patients with recurrent UTI

Among the 77 patients, 47 (61.0%) had recurrent UTI during 12 months and 17 (22.1%) had nonrecurrent UTI. Thirteen (16.9%) were excluded from the comparison because they recurred after 1 year of the initial UTI episode. VUR was diagnosed after the first UTI in 40 patients, after the second UTI in 10 patients, and after the third UTI in 5 patients. Due to the hydronephrosis identified in prenatal test, 9 patients were diagnosed with VUR by undergoing a VCUG test prior to developing UTI. The median age of first UTI was significantly younger in the recurrent UTI patients (5.0 months; IQR, 2.0–8.0) than in the nonrecurrent UTI patients (9.0 months; IQR, 6.5–19.0; P<0.001). The proportion of surgical correction after first episode of UTI was significantly higher in the nonrecurrent UTI group than in the recurrent UTI patients (58.8% vs. 10.6%, P<0.001). However, there were no significant differences in sex, laterality and grade of VUR, presence of other tract anomalies, and use of prophylactic antibiotics between the recurrent and nonrecurrent UTI groups (**Table 1**).

Of the 47 children with recurrent UTI, 19 patients (40.4%) were in group 1 and 28 patients (59.6%) were in group 2. The median interval between the first and second episodes of UTI was 2.0 months (IQR, 1.0–4.0 months). Prophylactic antibiotics were used in 44 (93.6%) of recurrent UTI group. Except for 2 patients who used prophylactic antibiotics after the second episode of UTI, 42 patients used oral prophylactic antibiotics on average 36.6 days after the diagnosis of first episode of UTI. The antibiotics used in group 1 were TMP-SMX (n=9), 2nd generation cephalosporin (n=5), 3rd generation cephalosporin (n=1), and aminopenicillins

Table 1. Characteristics of VUR patients with or without recurrent UTI

Variable	Total (n=77)	Recurrent UTI (n=47)	Nonrecurrent UTI (n=17)	P-value*
Age of first UTI (mon)	6.0 (3.0–14.0)	5.0 (2.0–8.0)	9.0 (6.5–19.0)	<0.001
Sex				0.443
Male	50 (64.9)	35 (74.5)	11 (64.7)	
Female	27 (35.1)	12 (25.5)	6 (35.3)	
VUR				0.602
Unilateral	44 (57.1)	27 (57.4)	11 (64.7)	
Bilateral	33 (42.9)	20 (42.6)	6 (35.3)	
VUR grade				0.485
1–2	15 (19.5)	11 (23.4)	2 (11.8)	
3–5	62 (80.5)	36 (76.6)	15 (88.2)	
Surgical therapy after 1st episode of UTI (before 2nd episode of UTI in recurrent group)				<0.001
No	60 (77.9)	42 (89.4)	7 (41.2)	
Yes	17 (22.1)	5 (10.6)	10 (58.8)	
Concomitant urinary tract abnormalities†				0.777
No	36 (46.8)	23 (48.9)	9 (52.9)	
Yes	41 (53.2)	24 (51.1)	8 (47.1)	
Prophylactic antibiotics				1.000
No	4 (5.2)	3 (6.4)	1 (5.9)	
Yes	73 (94.8)	44 (93.6)	16 (94.1)	

Data are expressed as number (%) or the medians with the interquartile range.
Abbreviations: UTI, urinary tract infection; VUR, vesicoureteral reflux.
*Thirteen were excluded from the comparison because they recurred after 1 year of the initial UTI episode; †Concomitant urinary tract abnormalities in recurrent UTI group included posterior urethral valve (n=5), ureterovesical junction anomaly (n=4), dysplastic kidney (n=3), vesico-ureteral diverticulum (n=3), renal duplex system (n=2), bladder outlet stenosis (n=2), hypospadias (n=1), autosomal recessive polycystic kidney disease (n=1), cloacal anomaly (n=1), recto-urethral fistula (n=1), and vesico-urachal remnant (n=1). Concomitant urinary tract abnormalities in nonrecurrent UTI group included bulbous urethra ring (n=2), posterior urethral valve (n=1), ureterovesical junction anomaly (n=1), dysplastic kidney (n=1), vesico-ureteral diverticulum (n=1), hypospadias (n=1), and cryptorchidism (n=1).

https://doi.org/10.14776/piv.2020.27.e7

(n=2). The antibiotics used in group 2 were TMP-SMX (n=19), 2nd generation cephalosporin (n=5), and 3rd generation cephalosporin (n=1). The proportion of male patients were significantly higher in group 2 than in group 1 (85.7% vs. 57.9%, *P*=0.045). However, there were no significant differences in the other variables between the 2 groups (**Table 2**).

3. Etiology of the first and second episodes of UTI

Urine culture results of both the first and second episodes of recurrent UTIs are shown in **Table 3**. *Escherichia coli* was the most commonly isolated uropathogen (n=37, 39.4%), followed by *Klebsiella pneumoniae* (n=18, 19.1%), *Enterococcus faecalis* (n=14, 14.9%), *Enterobacter aerogenes* (n=7, 7.4%), and *Pseudomonas aeruginosa* (n=4, 4.3%).

Twenty-seven (57.4% of 47) of the children with VUR with recurrent UTI experienced recurrence of UTI more than once during the 12-month follow-up period after the initial UTI. Twenty (42.6% of 47) patients experienced a single episode of recurrence. The uropathogens involved in each recurrent episode in children with VUR are shown in **Supplementary Table 1**.

E. coli was the most common pathogen (n=20, 52.6%) in group 1 (**Table 3**). In the cases with *E. coli* recurrence in group 1, antibiotic resistance rate to ceftazidime, piperacillin/tazobactam, and TMP-SMX increased in the second episode but was not statistically significant. In addition, antibiotic resistance rate to cefotaxime, ceftazidime, piperacillin/tazobactam, and

Table 2. Characteristics of patients with recurrent UTI

Variable	Total (n=47)	Group 1 (n=19)	Group 2 (n=28)	*P*-value
Age at first UTI (mon)	5.0 (2.0–8.0)	5.0 (3.0–8.0)	4.5 (2.0–7.5)	0.395
Sex				0.045
Male	35 (74.5)	11 (57.9)	24 (85.7)	
Female	12 (25.5)	8 (42.1)	4 (14.3)	
VUR				0.514
Bilateral	27 (57.4)	12 (63.2)	15 (53.6)	
Unilateral	20 (42.6)	7 (36.8)	13 (46.4)	
VUR grade				0.276
1–2	11 (23.4)	6 (31.6)	5 (17.9)	
3–5	36 (76.6)	13 (68.4)	23 (82.1)	
Interval between the first and second episodes of UTI (mon)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–4.75)	0.796
Surgical therapy after 1st episode of UTI (before 2nd episode of UTI)				0.051
No	42 (89.4)	19 (100)	23 (82.1)	
Yes	5 (10.6)	0 (0)	5 (17.9)	
Concomitant urinary tract abnormalities*				0.859
No	23 (48.9)	9 (47.4)	14 (50.0)	
Yes	24 (51.1)	10 (52.6)	14 (50.0)	
Prophylactic antibiotics				0.557
No	3 (6.4)	2 (10.5)	1 (3.6)	
Yes	44 (93.6)	17 (89.5)	27 (96.4)	

Data are expressed as number (%) or the medians with the interquartile range.
Group 1 was defined as having the same cultured pathogen in the first and recurrent episodes. Group 2 was defined as having different cultured pathogens between the first and recurrent episodes.
Abbreviations: UTI, urinary tract infection; VUR, vesicoureteral reflux.
*Concomitant urinary tract abnormalities in group 1 included posterior urethral valve (n=4), ureterovesical junction anomaly (n=1), renal duplex system (n=1), hypospadias (n=1), cloacal anomaly (n=1), vesico-urachal remnant (n=1) and recto-urethral fistula (n=1). Concomitant urinary tract abnormalities in group 2 included ureterovesical junction anomaly (n=3), dysplastic kidney (n=3), vesico-ureteral diverticulum (n=3), bladder outlet stenosis (n=2), posterior urethral valve (n=1), renal duplex system (n=1), and autosomal recessive polycystic kidney disease (n=1).

https://doi.org/10.14776/piv.2020.27.e7

Table 3. Urine culture results in recurrent urinary tract infection episodes

Strains isolated from urine culture	Total episodes	First episode	Second episode
Escherichia coli	37 (39.4)	17 (18.1)	20 (21.3)
Klebsiella pneumoniae	18 (19.1)	7 (7.4)	11 (11.7)
Enterococcus faecalis	14 (14.9)	7 (7.4)	7 (7.4)
Enterobacter aerogenes	7 (7.4)	4 (4.3)	3 (3.2)
Pseudomonas aeruginosa	4 (4.3)	3 (3.2)	1 (1.1)
Enterobacter cloacae	3 (3.2)	3 (3.2)	0 (0.0)
Citrobacter freundii	2 (2.1)	1 (1.1)	1 (1.1)
Klebsiella oxytoca	2 (2.1)	0 (0.0)	2 (2.1)
Enterococcus faecium	2 (2.1)	2 (2.1)	0 (0.0)
Other*	5 (5.3)	3 (3.2)	2 (2.1)
Total	94 (100)	47 (50)	47 (50)
Group 1			
E. coli	20 (52.6)	10 (26.3)	10 (26.3)
K. pneumoniae	10 (26.3)	5 (13.2)	5 (13.2)
E. aerogenes	4 (10.5)	2 (5.3)	2 (5.3)
E. faecalis	2 (5.3)	1 (2.6)	1 (2.6)
P. aeruginosa	2 (5.3)	1 (2.6)	1 (2.6)
Total	38 (100)	19 (50)	19 (50)
Group 2			
E. coli	17 (30.4)	7 (12.5)	10 (17.9)
E. faecalis	12 (21.4)	6 (10.7)	6 (10.7)
K. pneumoniae	8 (14.3)	2 (3.6)	6 (10.7)
E. aerogenes	3 (5.4)	2 (3.6)	1 (1.8)
E. cloacae	3 (5.4)	3 (5.4)	0 (0.0)
P. aeruginosa	2 (3.6)	2 (3.6)	0 (0.0)
C. freundii	2 (3.6)	1 (1.8)	1 (1.8)
K. oxytoca	2 (3.6)	0 (0.0)	2 (3.6)
E. faecium	2 (3.6)	2 (3.6)	0 (0.0)
Other*	5 (8.9)	3 (5.4)	2 (3.6)
Total	56 (100)	28 (50)	28 (50)

Data are expressed as number (%).
Group 1 was defined as having the same cultured pathogen in the first and recurrent episodes. Group 2 was defined as having different cultured pathogens between the first and recurrent episodes.
**Acinetovactoer pittii*, *Enterobacter amnigenus*, *Klebsiella planticola*, *Morganella morganii*, *Proteus vulgaris*.

meropenem increased in patients with second episode of *E. aerogenes* recurrence in group 1, although the difference was not significant (**Table 4**).

DISCUSSION

This study showed that the uropathogen between the previous and recurrent episodes may differ in cases of recurrent UTI in children with VUR. Furthermore, we found a difference in antibiotic susceptibility even between the first and second episodes of UTI by the same pathogen in group 1, but the difference was not statistically significant.

In our study, there was a male predominance in children with VUR. These findings are in contrast to the results of Chand et al.,[12] who reported that females were twice as likely to have VUR as males. However, our results correspond with the result of an earlier study in Korea, which reported that among the children diagnosed with VUR, 91 (61.9%) were boys and 56 (38.1%) were girls.[13] In addition, there are several reports stating that the sex difference in children with VUR is lower in countries where circumcision is not routinely performed.[14,15] Further research is needed to determine if circumcision during infancy affects the sex difference in VUR.

https://doi.org/10.14776/piv.2020.27.e7

Table 4. Urine culture results and the antimicrobials susceptibility in group 1

Pathogens	No. of strain (%)	Antimicrobial susceptibility of the first UTI episode								Antimicrobial susceptibility of the second UTI episode							
Gram-positive bacteria	2 (5.3)	AMP	Gent	CIP	Vanco	LZD	OXA			AMP	Gent	CIP	Vanco	LZD	OXA		
Enterococcus faecalis	2 (5.3)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	0/1	0/1			1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)		
Gram-negative bacteria	36 (94.7)	AMK	Gent	CTX	Ceftaz	PIP-TZ	MER	Levo	TMP-SMX	AMK	Gent	CTX	Ceftaz	PIP-TZ	MER	Levo	TMP-SMX
Escherichia coli	20 (52.6)	10/10 (100)	5/10 (50)	5/10 (50)	6/10 (60)	7/10 (70)	10/10 (100)	3/10 (30)	6/10 (60)	10/10 (100)	6/10 (60)	5/10 (50)	5/10 (50)	5/10 (50)	10/10 (100)	5/10 (50)	4/10 (40)
Klebsiella pneumoniae	10 (26.3)	5/5 (100)	1/5 (20)	1/5 (20)	3/5 (60)	4/5 (80)	4/5 (80)	4/5 (80)	1/5 (20)	5/5 (100)	1/5 (20)	1/5 (20)	3/5 (60)	4/5 (80)	4/5 (80)	4/5 (80)	1/5 (20)
Enterobacter aerogenes	4 (10.5)	2/2 (100)	2/2 (100)	1/2 (50)	1/2 (50)	1/2 (50)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	0/2 (0)	0/2 (0)	0/2 (0)	1/2 (50)	2/2 (100)	2/2 (100)
Pseudomonas aeruginosa	2 (5.3)	1/1 (100)	1/1 (100)	-	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	-	1/1 (100)	1/1 (100)	-	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	-
Total	38 (100)																

Antibiotic susceptibility results that differ from the first episode are shaded in the second episode with 2 levels of intensities: lighter shade, increase in susceptibility percentage; darker shade, decrease in susceptibility percentage.
Group 1 was defined as having the same cultured pathogen in the first and recurrent episodes.
Abbreviations: UTI, urinary tract infection; AMK, amikacin; AMP, ampicillin; CIP, ciprofloxacin; Ceftaz, ceftazidime; CTX, cefotaxime; Gent, gentamicin; Levo, levofloxacin; LZD, linezolid; MER, meropenem; OXA, oxacillin; PIP-TZ, piperacillin/tazobactam; TMP-SMX, trimethoprim-sulfamethoxazole; Vanco, vancomycin.

The age at the diagnosis of the first UTI in the present study was significantly younger in the recurrent UTI patients than in the nonrecurrent patients. These results correspond with those of earlier studies which reported that the younger the first UTI then the higher the risk is for recurrent UTIs in children with VUR.[16,17] These findings are seen even in children with normal urinary tract systems without VUR. Shim et al.[18] have shown in a group of 190 children less than 12 months of age with normal urinary systems that the recurrence rate in infants less than 6 months of age was 25.0%, which was significantly higher than the 5.3% in older infants (P=0.008). Therefore, these results suggest that clinicians evaluating fever in young infants with a history of UTI should maintain a high index of suspicion for recurrent UTI.

Our results showed that 57.8% of recurrent UTI cases in children with VUR were caused by pathogens different from the first episode of UTI, which are in agreement with those of Wu et al.,[19] who reported that 64.7% of recurrent UTI patients with VUR developed reinfection. UTIs are caused primarily by bacteria in the gastrointestinal and vaginal tracts. Antibiotics used in the first episode of UTI may cause changes in the composition of colonic bacteria, and as a result, the second episode of UTI could be caused by a new bacterial strain in the altered gut microbiota. Numerous studies that have confirmed that antibiotics alter the composition and functions of the human intestinal microbiota support our hypothesis.[20,21]

In this study, boys had a greater rate of group 2, whereas girls had a greater rate of group 1. This is probably due to the differences in the anatomical structures of the genitourinary tract between the 2 sexes. The vaginal tract could act as the local reservoir of the same bacterial strain when UTI recurs. Several studies have found that most strains obtained from patients with relapse infections were biofilm producers in vitro.[22-24] Uropathogens can persist within the vaginal tissue by biofilm formation and serve as a source of relapse UTIs in females. Future research on the etiology differences of UTI in males and females is needed. Several studies have demonstrated, using pulsed field gel electrophoresis (PFGE), that 50% to 68% of strains causing relapse symptomatic UTI were similar to the index strains, suggesting that most relapsed UTIs are endogenous relapses rather than reinfections by new strains.[15,25-28]

https://doi.org/10.14776/piv.2020.27.e7

In relapses of both *E. coli* and *K. pneumoniae* in group 1 of this study, the antibiotic susceptibility results of the first and second episodes were slightly different but not statistically significant. These findings suggest that even in relapses by endogenous strains, antimicrobial susceptibility patterns at recurrence may be different from those in the previous episode. Therefore, empirical antibiotics should be selected according to the treatment effects in association with clinical features. Further studies on the antibiotic susceptibility of relapse strains are needed.

This study has some limitations. First, this was a retrospective study with a small sample size and was performed at 2 tertiary referral hospitals. Owing to the nature of the referral hospitals, VUR had already been diagnosed at other hospitals, leading to an increased exclusion of potential subjects. Further multicenter studies are required to validate the study results. Second, we did not evaluate the association between the appropriateness of the empirical antimicrobial regimen and the clinical outcomes according to the antimicrobial susceptibility test results in each episode of UTI. Third, in group 1, we did not perform further tests such as PFGE; thus, it was unclear whether the bacterial strain cultured in the second episode was similar to that in the first episode.

The major strength of this study is that to our knowledge, it is the first study to compare the causative uropathogens between the first and second episode of UTI in children with VUR. Our study can make a significant contribution to the literature because it shows the importance of carefully selecting antibiotics, considering that the pathogen and the antibiotic susceptibility results between the first and second episodes may differ. This can lead to changes in policies in the treatment of recurrent UTI in patients with VUR.

In conclusion, it is difficult to clinically determine whether the recurrence is caused by the same or different species as the previous infection in case of recurrent UTI in children with VUR. Even in recurrence caused by the same pathogen in the first episode, the antibiotic susceptibility results between the first and second episodes were slightly different. Therefore, when selecting empirical antibiotics in recurrent UTI, it should be taken into account that the uropathogen and antimicrobial susceptibility of the previous UTI are not always the same in recurrent UTIs.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Uropathogens for each recurrent episode in children

Click here to view

REFERENCES

1. Skoog SJ, Peters CA, Arant BS Jr, Copp HL, Elder JS, Hudson RG, et al. Pediatric vesicoureteral reflux guidelines panel summary report: clinical practice guidelines for screening siblings of children with vesicoureteral reflux and neonates/infants with prenatal hydronephrosis. J Urol 2010;184:1145-51.
PUBMED | CROSSREF
2. Younis N, Quol K, Al-Momani T, Al-Awaisheh F, Al-Kayed D. Antibiotic resistance in children with recurrent or complicated urinary tract infection. JNMA J Nepal Med Assoc 2009;48:14-9.
PUBMED

3. Lu KC, Chen PY, Huang FL, Yu HW, Kao CH, Fu LS, et al. Is combination antimicrobial therapy required for urinary tract infection in children? J Microbiol Immunol Infect 2003;36:56-60.
PUBMED
4. Zorc JJ, Kiddoo DA, Shaw KN. Diagnosis and management of pediatric urinary tract infections. Clin Microbiol Rev 2005;18:417-22.
PUBMED | CROSSREF
5. Downs SM. Technical report: urinary tract infections in febrile infants and young children. The Urinary Tract Subcommittee of the American Academy of Pediatrics Committee on Quality Improvement. Pediatrics 1999;103:e54.
PUBMED | CROSSREF
6. Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. N Engl J Med 2003;348:195-202.
PUBMED | CROSSREF
7. Jerardi KE, Jackson EC. Urinary tract infections. In: Kliegman RM, St. Geme JW III, Blum NJ, Shah SS, Tasker RC, Wilson KM, editors. Nelson textbook of pediatrics. 21st ed. Philadephia: Elsevier Inc., 2020:2789-95.
8. RIVUR Trial Investigators, Hoberman A, Greenfield SP, Mattoo TK, Keren R, Mathews R, et al. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med 2014;370:2367-76.
PUBMED | CROSSREF
9. Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Möbius TE. International system of radiographic grading of vesicoureteric reflux. International reflux study in children. Pediatr Radiol 1985;15:105-9.
PUBMED | CROSSREF
10. Aydin A, Ahmed K, Zaman I, Khan MS, Dasgupta P. Recurrent urinary tract infections in women. Int Urogynecol J 2015;26:795-804.
PUBMED | CROSSREF
11. Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard—eighth edition. CLSI document M07-A10. Wayne: Clinical and Laboratory Standards Institute, 2009:1-65.
12. Chand DH, Rhoades T, Poe SA, Kraus S, Strife CF. Incidence and severity of vesicoureteral reflux in children related to age, gender, race and diagnosis. J Urol 2003;170:1548-50.
PUBMED | CROSSREF
13. Jang HC, Lee KH, Park JS. Primary vesico-ureteral reflux: comparison of factors between infants and children. Korean J Urol 2011;52:206-9.
PUBMED | CROSSREF
14. Montini G, Rigon L, Zucchetta P, Fregonese F, Toffolo A, Gobber D, et al. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. Pediatrics 2008;122:1064-71.
PUBMED | CROSSREF
15. Roussey-Kesler G, Gadjos V, Idres N, Horen B, Ichay L, Leclair MD, et al. Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. J Urol 2008;179:674-9.
PUBMED | CROSSREF
16. Dias CS, Silva JM, Diniz JS, Lima EM, Marciano RC, Lana LG, et al. Risk factors for recurrent urinary tract infections in a cohort of patients with primary vesicoureteral reflux. Pediatr Infect Dis J 2010;29:139-44.
PUBMED | CROSSREF
17. Park S, Song SH, Lee C, Kim JW, Kim KS. Bacterial pathogens in first febrile urinary tract infection affect breakthrough infections in infants with vesicoureteral reflux treated with prophylactic antibiotics. Urology 2013;81:1342-5.
PUBMED | CROSSREF
18. Shim YH, Lee JW, Lee SJ. The risk factors of recurrent urinary tract infection in infants with normal urinary systems. Pediatr Nephrol 2009;24:309-12.
PUBMED | CROSSREF
19. Wu TH, Huang FL, Fu LS, Chou CM, Chien YL, Huang CM, et al. Treatment of recurrent complicated urinary tract infections in children with vesicoureteral reflux. J Microbiol Immunol Infect 2016;49:717-22.
PUBMED | CROSSREF
20. Lange K, Buerger M, Stallmach A, Bruns T. Effects of antibiotics on gut microbiota. Dig Dis 2016;34:260-8.
PUBMED | CROSSREF

21. Becattini S, Taur Y, Pamer EG. Antibiotic-induced changes in the intestinal microbiota and disease. Trends Mol Med 2016;22:458-78.
PUBMED | CROSSREF

22. Soto SM. Importance of biofilms in urinary tract infections: new therapeutic approaches. Adv Biol 2014;2014:543974.
CROSSREF

23. Sanchez CJ Jr, Mende K, Beckius ML, Akers KS, Romano DR, Wenke JC, et al. Biofilm formation by clinical isolates and the implications in chronic infections. BMC Infect Dis 2013;13:47.
PUBMED | CROSSREF

24. Hooton TM. Pathogenesis of urinary tract infections: an update. J Antimicrob Chemother 2000;46 Suppl A:1-7.
PUBMED | CROSSREF

25. Jantunen ME, Saxén H, Salo E, Siitonen A. Recurrent urinary tract infections in infancy: relapses or reinfections? J Infect Dis 2002;185:375-9.
PUBMED | CROSSREF

26. Russo TA, Stapleton A, Wenderoth S, Hooton TM, Stamm WE. Chromosomal restriction fragment length polymorphism analysis of *Escherichia coli* strains causing recurrent urinary tract infections in young women. J Infect Dis 1995;172:440-5.
PUBMED | CROSSREF

27. Foxman B, Zhang L, Tallman P, Palin K, Rode C, Bloch C, et al. Virulence characteristics of *Escherichia coli* causing first urinary tract infection predict risk of second infection. J Infect Dis 1995;172:1536-41.
PUBMED | CROSSREF

28. Craig JC, Simpson JM, Williams GJ, Lowe A, Reynolds GJ, McTaggart SJ, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children. N Engl J Med 2009;361:1748-59.
PUBMED | CROSSREF

요약

목적: 본 연구의 목적은 방광 요관 역류(vesicoureteral reflux) 환아에서 재발성 요로감염의 임상양상을 조사하고, 첫 번째 및 재발성 요로감염 간의 원인균과 항생제 감수성 결과를 비교하는 것이다.
방법: 방관 요관 역류로 진단된 소아 환자 중에서 요로감염이 발생한 환자의 의무기록을 후향적으로 검토하였다. 첫 번째와 두 번째 요로감염 건에서 같은 균종이 동정된 경우를 1군으로, 다른 균종이 동정된 경우를 2군으로 분류하여 분석하였다.
결과: 2005년 4월부터 2018년 2월까지 총 13년 간의 연구 기간 동안, 총 77명의 방관 요관 역류 환아가 적어도 한 번 이상의 요로감염을 경험하였다. 이 중 47명의 환자(61.0%)가 재발성 요로감염 소견을 보였다. 재발성 요로감염 환자 중에서 1군은 19명(40.4%)이었고, 2군은 28명(59.6%)이었다. *Escherichia coli* (n=37, 39.4%)는 재발성 요로감염 환자의 첫 번째 및 두 번째 요로감염 건에서 가장 흔하게 분리된 원인균이었고, 그 다음으로는 *Klebsiella pneumoniae* (n=18, 19.1%), *Enterococcus faecalis* (n=14, 14.9%), *Enterobacter aerogenes* (n=7, 7.4%), 및 *Pseudomonas aeruginosa* (n=4, 4.3%) 순이었다. 비록 통계적 차이는 없었지만, *E. coli*에 의한 재발 시, 같은 균에 의한 재발 임에도 ceftazidime, piperacillin/tazobactam과 trimethoprim-sulfamethoxazole에 대한 항생제 내성의 비율이 첫 번째보다 두 번째 감염에서 증가하였고, *E. aerogenes*에 의한 재발에서도 cefotaxime, ceftazidime, piperacillin/tazobactam 및 meropenem에 대한 항생제 내성의 비율이 첫 번째보다 두 번째 감염에서 증가하였다.
결론: 방관 요관 역류 환아의 재발성 요로감염에서 경험적 항생제를 선택할 때, 이전 감염의 병원균 및 항균제 감수성 결과가 재발 시에 항상 동일하지는 않다는 점을 염두에 두어야 한다.