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Risk factors for recurrent urinary tract infections in young infants under the age of 24 months

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Purpose: Recurrent urinary tract infections (UTIs) in children is a major challenge for pediatricians. This study was designed to investigate the risk factors for recurrent UTIs and determine the association between recurrent UTIs and clinical findings, including growth patterns in infants and children younger than 24 months of age.

Methods: We retrospectively reviewed the medical records of 147 patients <24 months of age with UTIs who were hospitalized between August 2018 and October 2021. The patients were divided into recurrent and single UTI episode groups. Clinical findings and anthropometric and laboratory data were compared between the two groups.

Results: In the recurrent UTI group, the weight-for-length (WFL) percentile at the first UTI diagnosis was lower compared to the single UTI episode group, and the weight-for-age percentile at 3-month and 6-month follow-ups after the first UTI decreased (all $P<0.05$). In univariable logistic regression analysis, higher birth weight, lower WFL percentile, the presence of hydronephrosis, acute pyelonephritis or vesicoureteral reflux, the use of prophylactic antibiotics, and non-*Escherichia coli* infections were associated with the development of recurrent UTIs (all $P<0.05$). However, in the multivariable analysis, only the presence of hydronephrosis and prophylactic antibiotic use were independently related to UTI recurrence ($P<0.05$).

Conclusions: The presence of hydronephrosis at the first UTI can be helpful for predicting UTI recurrence in young children aged <24 months. Antibiotic prophylaxis may be associated with UTI recurrence. Potential growth delay should be carefully monitored in infants with recurrent UTI.

Keywords: Body-weight trajectory; Growth; Hydronephrosis; Recurrence; Urinary tract infections

Introduction

Urinary tract infections (UTIs) are the most common serious bacterial infection in children, with 8.4% of girls and 1.7% of boys experiencing a UTI before age 6 [1]. UTIs account for 5% to 10% of febrile diseases in children younger than 24 months, and the recurrence rate is known to be 10% to 30% [2]. Recurrent UTIs increase the risk of kidney scarring, which is associated with hypertension in about 10% of pediatric patients and with dialysis and transplantation in approximately 20% [3]. Given that the symptoms and signs of UTI, except for fever, do not appear well in children under 2 years of age [4], many studies have tried to identify the risk factors for UTI, as it is important to quickly recognize these factors and prevent UTI recurrence.

In the pediatric population, young age, sex, vesicoureteral reflux (VUR), and bladder bowel dysfunction have received attention as important risk factors for recurrent UTIs [5-9]. In a multicenter prospective cohort study of 500 pediatric patients

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aged 2 months to less than 6 years, the rate of recurrent UTIs was 25.4% in those with VUR and 17.3% in those without VUR. The probability of UTI recurrence was the highest if the VUR stage was 3 or higher, at 28.9% [5]. According to a study by Park et al. [6], younger age at the first UTI, bilateral VUR, grade 4–5 VUR, and hydronephrosis on the initial ultrasonography significantly increased the risk of UTI recurrence. Although the use of prophylactic antibiotics is recommended for children with VUR [7], whether these prophylactic antibiotics prevent UTI is unclear [8]. Craig et al [9]. reported that long-term, low-dose trimethoprim-sulfamethoxazole was associated with a decrease in the number of UTIs in pediatric patients. However, other studies reported that it was not related and only increased the risk of resistant bacteria [10]. Obesity has recently become a more serious and global public health problem [11], but many studies have shown that being underweight also increases the risk of infection. An analysis of 1,747 patients who visited the emergency room at the University of Oklahoma Children's Hospital found that underweight patients had more hospital visits, experienced respiratory diseases more often, and had a higher incidence of fractures than normal and overweight patients [12]. Also, in the United States, underweight children aged 2 to 19 years reported increased rates of surgical site infections following orthopedic surgery [13]. Host resistance to a UTI, especially in the acute phase, is highly dependent on innate immunity [14]. The innate immune system plays an essential role in the prevention of recurrent and invasive UTIs, and irreversible parenchymal tissue damage can occur if this system does not work properly [15]. An investigation of 48 types of serum cytokines and growth factors in female patients aged 18 to 49 without underlying diseases at a single center in the United States reported that factors required for the development and differentiation of monocytes, macrophages, and neutrophils were increased in patients with recurrent UTIs [16]. In another study of patients aged 6 months to less than 21 years, the median urinary neutrophil gelatinase-associated lipocalin (NGAL) level in patients with recurrent UTIs was 15 ng/mL, which was significantly lower than that in the control group of healthy children, at 30 ng/mL [17].

In this study, we hypothesized that abnormal growth trajectories in young infants might be associated with suppressed immune responses and enhanced bacterial vulnerability, namely, UTI recurrence. Therefore, we aimed to identify risk factors for recurrent UTIs, determine whether abnormal growth patterns were related to recurrent UTIs, and compare host inflammatory responses between patients with recurrent UTIs and those with a single UTI episode.

Subjects and Methods

Patient characteristics and inclusion criteria

This was a retrospective observational study of patients who were hospitalized in the Department of Pediatrics and Adolescents at Korea University Ansan Hospital from August 21, 2018, to October 20, 2021, for UTIs. Among them, patients aged 0 to 24 months who were first diagnosed with a UTI and followed up for more than 6 months in an outpatient setting were included. The diagnosis of a first UTI was as follows: (1) hospitalized for febrile UTI, fever (≥38 °C); (2) positive results on urinalysis for pyuria (≥5 white blood cells [WBCs] per high-power field) or nitrate; and (3) a positive urine culture collected from a catheterized specimen (defined as the growth of a single bacterial type to ≥50,000 colony-forming units/mL), and (4) no previous history of UTI. A single UTI was defined as no reinfection within 12 months after the onset of the first UTI. Patients who had 2 or more UTIs within 12 months were included in the recurrent UTI group. Reinfection was defined as infection with either the same bacteria as earlier or a different type of bacteria following a negative bacterial culture after treatment for a previous UTI. Patients were excluded if they satisfied any of the following conditions: (1) acute kidney injury, (2) chronic kidney disease, (3) underlying systemic disease, or (4) congenital anomalies of the kidney and urinary tract except for VUR and/or hydronephrosis (Fig. 1). Patients with systemic diseases, including pulmonary

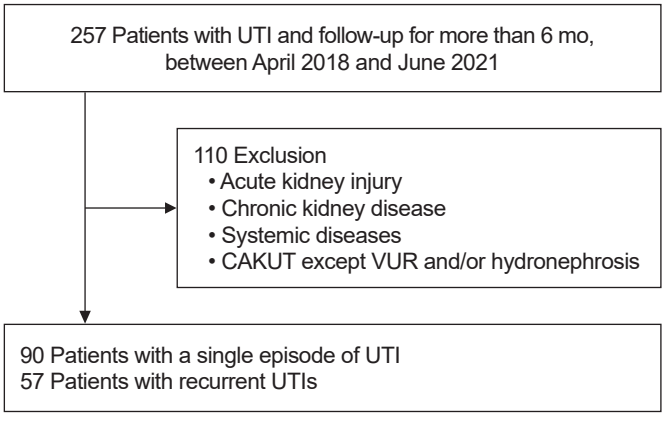

Fig. 1. Study flow diagram. UTI, urinary tract infection; CAKUT, congenital anomalies of the kidney and the urinary tract; VUR, vesicoureteral reflux.

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atresia with ventricular septal defect, metabolic disease, chronic respiratory failure, viral infections, and others, were excluded. Grades 1 to 3 of VUR were assigned to the low grade category, and grades 4 and 5 were assigned to the high grade. Prophylactic antibiotics were used in cases with high grade VUR and acute pyelonephritis (APN) after the initial UTI. Patients were defined to have APN if the uptake of ^{99m}Tc-dimercaptosuccinic acid (DMSA) at 1–5 mCi was decreased in focal, multifocal, or diffuse areas due to defects in the kidney cortex [18,19]. Hydronephrosis was defined as dilatation and distension of the kidney collecting system of one or both kidneys, and the radiology department at our hospital uses the Society for Fetal Urology system to define it [20]. All data were obtained based on the ethical principles for medical research in human subjects established in the Declaration of Helsinki in 1975 and revised in 2000.

Measurements and laboratory assessments

The growth chart for children and adolescents in 2017 [21] was used to determine weight-for-length (WFL) percentiles. Clinical data, including host and immunological factors, imaging data, and growth patterns, were investigated in the single UTI group and the recurrent group. Clinical information on birth weight, prenatal ultrasonography abnormalities, and previous UTI episodes was obtained by questionnaires and medical chart review. WFL was calculated by examining body weight and height at the time of hospitalization for the first UTI. The same was done in the case of recurrence. The weight percentiles of the single UTI group and the recurrent UTI group were compared at the time of admission and after 3 months and 6 months. In addition, to compare the innate immune system, WBCs, the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelets (PLTs), platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP), urinary, and plasma NGAL levels of the two groups were compared at admission and discharge. Urine samples were obtained through urethral catheterization. Kidney ultrasonography and initial DMSA scans were performed at the time of the UTI diagnosis. Voiding cystourethrography was performed if APN or hydronephrosis was present on kidney ultrasonography or if APN was diagnosed on renal DMSA scan.

Statistical analysis

All analyses were conducted using R statistical software (version 4.3.0; The R Foundation). For comparison between the two groups, the Mann-Whitney *U* test or two-sample *t*-test was used for continuous variables, and the Pearson chi-square test or Fisher exact test was used for categorical variables. Continuous variables are presented as the mean ± standard deviation or standard error of the mean. Categorical variables are presented as numbers (%). A paired *t*-test or signed rank test was used to compare weight and weight percentiles in each group, and a two-sample test or the Mann-Whitney *U* test was used to compare weight and weight percentiles between the two groups. Inflammatory responses at admission and discharge were compared in the single and recurrent UTI groups using the Mann-Whitney *U* test. Univariable logistic regression analysis was performed to analyze variables associated with UTI recurrence. Parameters associated with UTI recurrence in univariable logistic regression analysis ($P<0.05$) were included in a multivariable logistic regression analysis. However, among them, VUR was excluded from the multivariable analysis because it was identified as a multicollinearity suspected variable when checking the variance inflation factor. In all statistical analyses, a *P*-value of <0.05 was considered significant.

Results

Patient demographics

Out of 257 patients who were diagnosed with a first UTI and underwent outpatient treatment for more than 6 months, 110 patients were excluded, 90 patients were included in the single UTI group, and 57 patients were included in the recurrent group (Fig. 1). In the recurrent group, the average WFL percentile was lower, and the frequency of prophylactic antibiotic use was higher than those in the single UTI group (all $P<0.05$). There were differences in uropathogens between the two groups ($P<0.05$). Analysis with Pearson chi-square test with Yates continuity correction showed a difference between the *Escherichia coli* and non-*E. coli* groups. Both extended-spectrum β-lactamase-positive and -negative *E. coli* were included in the *E. coli* group. *Klebsiella aerogenes*, *Enterococcus faecalis*, and *Enterobacter cloacae* complex were identified in cases other than *E. coli*. Patients who visited our hospital after taking antibiotics because the bacteria were confirmed at another hospital were excluded from uropathogen variable because no bacteria were found in our hospital. Hydronephrosis, VUR, and hydronephrosis with VUR were significantly higher in the recurrent group than in the single UTI group ($P<0.05$). There were eight patients in the single UTI group and one patient in the recurrent UTI group who did not undergo voiding cystoure-

throgrаphy, so the total number of patients in these categories was 82 and 56, respectively. There were no differences between hemoglobin, WBC, PLT, CRP, urinary, or plasma NGAL levels in the two groups. Since our hospital is a tertiary hospital, patients usually come after a referral from a local hospital. Therefore, we included some cases where bacteria were not confirmed here because the patient took antibiotics for a UTI before coming to our hospital (Table 1).

Comparison of growth pattern changes in single and recurrent UTI groups

The mean weight percentile tended to decrease in both groups from the time of initial diagnosis to the 3-month and 6-month assessments in each group. Weight percentiles at 3 or 6 months after the initial UTI were not different between the two groups. However, weight percentile declines for 6 months after the first UTI diagnosis seemed to be more prominent in the recurrent UTI group compared to the single UTI group. Weight percentiles at 3 and 6 months were significantly reduced in the recurrent UTI group compared to the initial UTI (Table 2, Fig. 2A). However, the WFL percentiles at the first and second UTI admissions were not different in the recurrent UTI group (Fig. 2B).

Comparison of inflammatory responses in patients with single and recurrent UTIs

Inflammatory responses were compared at admission and discharge in the single and recurrent UTI groups. There were no differences in the WBC, NLR, MLR, PLT, PLR, CRP, urinary NGAL/creatinine (Cr), or plasma NGAL levels at admission and discharge between the two groups. Some statistical data were obtained by excluding people with missing values. Urinary NGAL/Cr was measured in 73 single UTI patients, and in 29 recurrent UTI patients at admission and in 83 and 46 patients in each group at discharge. Plasma NGAL concentrations were determined in 88 and 46 patients, respectively, in each group at admission and in 83 and 47 patients in each group at discharge (Table 3).

Univariable and multivariable logistic regression analyses of recurrent UTIs

Univariable and multivariable logistic regression analyses were performed to test each parameter as an independent predictor of UTI recurrence in the recurrent UTI group. Univariable logistic regression analysis showed that higher birth weight, lower WFL percentile, prophylactic antibiotic use, the presence of hydronephrosis, VUR, APN, and non-*E. coli* infections were associated with UTI recurrence (all $P<0.05$). Multivariable logistic regression analysis showed that the prophylactic antibiotic use (odds ratio [OR], 18.8; 95% confidence interval [CI], 3.04–116) and presence of hydronephrosis (OR, 16.8; 95% CI, 4.04–70.2)

Table 1. characteristics and clinical findings

Characteristic	Single UTI (n=90)	Recurrent UTI (n=57)	*P*-value
Age at first UTI diagnosis (mo)	3.79±3.15	3.25±3.52	0.094[a]
Male sex	64 (71.1)	47 (82.5)	0.173[b]
Prematurity	78 (86.7)	48 (84.2)	0.863[b]
Birth weight (g)	3,134±562	3,350±645	0.116[a]
Abnormal prenatal US	4 (4.44)	6 (10.5)	0.187[c]
Weight (kg)	7.21±1.71	6.86±1.62	0.251[a]
Weight percentile	78.3±24.8	80.5±22.8	0.507[a]
Height (cm)	63.4±6.48	62.9±6.41	0.614[a]
Height percentile	73.2±29.3	79.9±27.2	0.050[a]
Weight-for-length percentile	72.7±22.0	63.9±26.1	0.043[a]
Prophylactic antibiotic use	7 (7.78)	31 (54.4)	<0.001[b]
Uropathogens[d]			0.021[b]
E. coli	80 (95.2)	46 (83.6)	
Non-*E. coli*	4 (4.76)	9 (16.4)	
Hydronephrosis	5 (5.56)	19 (33.3)	<0.001[b]
VUR[e]	15 (18.3)	32 (57.1)	<0.001[b]
Low grade[f]	4	6	
High grade[g]	11	26	
Hydronephrosis+VUR[e]	0	9 (15.8)	<0.001[c]
Acute pyelonephritis	51 (56.7)	42 (73.7)	0.056[b]
Hb (g/dL)	10.8±1.08	10.9±1.27	0.572[a]
WBC (/mm^3)	15,485±6,548	15,725±5,264	0.383[a]
PLT (10^3/mm^3)	421±119	401±122	0.409[a]
PLR	92.5±46.4	84.7±40.4	0.354[a]
CRP (mg/L)	4.44±3.87	4.66±3.42	0.513[a]
uNGAL (ng/mL)	562±820	610±877	0.996[a]
uNGAL/Cr	52.9±131	43.4±55.6	0.838[a]
pNGAL (mg/L)	134±126	171±165	0.218[a]
BUN (mg/dL)	9.04±3.54	8.98±3.46	0.590[a]
Cr (mg/dL)	0.54±2.71	0.26±0.06	0.321[a]

Values are presented as mean±standard deviation or number (%).
UTI, urinary tract infection; US, ultrasonography; *E. coli, Escherichia coli;* VUR, vesicoureteral reflux; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; uNGAL, urine neutrophil gelatinase-associated lipocalin; Cr, creatinine; pNGAL, plasma neutrophil gelatinase-associated lipocalin; BUN, blood urea nitrogen.
[a]Mann-Whitney *U* test. [b]Pearson chi-square test with Yates' continuity correction. [c]Fisher exact test for count data. [d]The total number of people for this variable is 84 in the single UTI group and 55 in the recurrent UTI group. [e]The total number of people for these variables is 82 in the single UTI group and 56 in the recurrent UTI group. [f]Low grade: 1 to 3 grade of VUR. [g]High grade: 4 and 5 grade of VUR.

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were significant predictors of UTI recurrence (P<0.05, respectively). VUR was identified as a multicollinearity variable, so it was excluded from the multivariable analysis when checking the variance inflation factor (Table 4).

Discussion

This study aimed to investigate the risk factors for recurrent UTIs in young children and determine if there were differences in growth trajectories between patients with single and recurrent UTIs. When the single UTI group and the recurrent

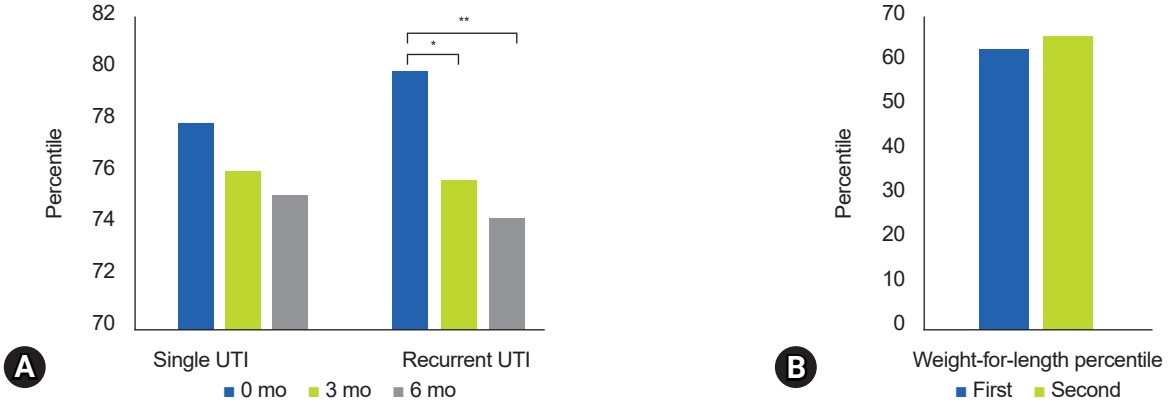

Fig. 2. (A) Comparison of weight percentiles at 0, 3, and 6 months after the first UTI in the single and recurrent UTI groups. (B) Comparison of weight-for-length percentiles in the first and second episodes in the recurrent UTI group. UTI, urinary tract infection. *P<0.05, **P<0.01.

Table 2. Comparisons of weight percentiles of 0, 3, and 6 months after first UTI

	First UTI	After 3 mo	After 6 mo	Diff[a]	P-value[a]	Diff[b]	P-value[b]
Single	78.4±24.9	76.4±24.2	75.5±24.8	−1.99±17.7	0.074[c]	−2.84±23.0	0.094[c]
Recurrent	80.5±22.6	76.0±24.8	74.5±23.1	−4.51±14.2	0.010[c]	−5.93±17.4	0.012[d]
P-value				0.244[e]		0.212[e]	

UTI, urinary tract infection; Diff, differences.
[a]First UTI vs. after 3 mo. [b]First UTI vs. after 6 mo. [c]Singed rank test. [d]Paired t-test. [e]Mann-Whitney test.

Table 3. Comparisons of inflammatory responses between the single and recurrent UTI groups

Variable	At admission			At discharge		
	Single UTI (n=90)	Recurrent UTI (n=57)	P-value[a]	Single UTI (n=90)	Recurrent UTI (n=56)	P-value[a]
WBC (/mm^3)	15,485±6,548	15,725±5,264	0.383	8,483±2,214	8,111±2,313	0.374
NLR	1.74±1.21	1.74±1.03	0.706	0.31±0.16	0.35±0.24	0.538
MLR	0.37±0.21	0.32±0.17	0.139	0.15±0.14	0.16±0.08	0.087
PLT (10^3/mm^3)	421±118	401±122	0.409	474±134	440±140	0.054
PLR	92.5±46.4	84.7±40.4	0.354	88.8±31.7	91.1±37.9	0.939
CRP (mg/L)	4.44±3.87	4.66±3.42	0.513	0.63±0.57	0.68±0.61	0.560
uNGAL/Cr	52.9±131	43.4±55.6	0.838	5.52±4.76	5.94±3.98	0.417
pNGAL (mg/L)	134±126	172±165	0.218	57.2±29.6	80.3±101	0.348

Values are presented as mean±standard deviation.
UTI, urinary tract infection; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLT, platelet; PLR, platelet -to-lymphocyte ratio; CRP, C-reactive protein; uNGAL, urine neutrophil gelatinase-associated lipocalin; Cr, creatinine; pNGAL, plasma neutrophil gelatinase-associated lipocalin.
[a]Wilcoxon rank sum test (or Mann-Whitney test).

Table 4. Univariable and multivariable logistic regression analyses for the recurrent UTI

Variable	Univariable		Multivariable	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
First UTI age	0.95 (0.86–1.06)	0.334		
Male sex	1.91 (0.84–4.34)	0.123		
Abnormal prenatal US	2.53 (0.68–9.39)	0.166		
Birth weight	1.00 (1.00–1.01)	0.040	1.00 (0.99–1.01)	0.286
WFL percentile	0.99 (0.97–1.00)	0.031	0.99 (0.97–1.01)	0.371
Prophylactic antibiotic use	14.1 (5.57–35.9)	<0.001	18.8 (3.04–116)	0.002
Hydronephrosis	8.50 (2.95–24.5)	<0.001	16.8 (4.04–70.2)	<0.001
VUR	5.96 (2.76–12.9)	<0.001		
APN	2.14 (1.04–4.41)	0.039	0.98 (0.36–2.69)	0.967
Uropathogens				
Non-*E. coli*	3.91 (1.14–13.4)	0.030	0.88 (0.16–5.00)	0.889

UTI, urinary tract infection; CI, confidence interval; US, ultrasonography; WFL, weight-for-length; VUR, vesicoureteral reflux; APN, acute pyelonephritis; *E. coli, Escherichia coli.*

UTI group were compared, the recurrent UTI group had a lower WFL percentile and a higher proportion of hydronephrosis and/or VUR and prophylactic antibiotic use. While there were no differences in growth patterns for 6 months between the two groups, weight percentiles in the recurrent UTI group were significantly reduced at 3 and 6 months compared to initial UTI percentiles. The presence of hydronephrosis at the time of the first UTI and prophylactic antibiotic use after the initial UTI were found to be independently associated with recurrent UTIs in children aged <24 months.

Many studies have already reported that VUR [5,8,10] and prenatal hydronephrosis [22] are associated with recurrent UTIs. In a study of 290 children under 5 years of age, recurrent UTIs were associated with kidney defects [8], and UTI recurrence could be predicted in infants under 3 months old when they were infected with bacteria other than *E. coli* at the time of their first febrile UTI [23]. In addition, non-*E. coli* UTI in the first febrile UTI may be useful in predicting imaging abnormalities [23,24]. While we also found that the presence of hydronephrosis, APN, VUR, and non-*E. coli* infections were associated with UTI recurrence, of them, only hydronephrosis was an independent risk factor. Since transient, prenatal, refluxing, and non-refluxing hydronephrosis were all included in our category of patients with hydronephrosis, the causal relationship between congenital or refluxing hydronephrosis and UTI recurrence remains unclear. However, the existence of hydronephrosis itself with or without VUR at the first UTI diagnosis might predict UTI recurrence in children aged <24 months old. To the authors' knowledge, this was the first finding that young children with hydronephrosis at the first UTI diagnosis were at a higher risk of developing recurrent UTIs.

A paper reviewing recurrent UTI studies found that, although controversial, the effectiveness of prophylactic antibiotic therapy was not significant and could even increase the risk of recurrence [2]. Conway et al. [10] found that prophylactic antibiotic use was not associated with a reduced risk of recurrent UTIs but was associated with an increased risk of resistant infections. In the present study, the use of prophylactic antibiotics was found to be a factor related to recurrent UTIs, which may be because more patients with reflux were included in the recurrence group (57.1%) compared to the single UTI group (18.3%). Multivariable analysis showed that antibiotic prophylaxis was an independent risk factor for recurrence. Therefore, the advantages of continuous antibiotic prophylaxis to prevent recurrence in children after the first UTI may be limited in young children. However, there is a need for more randomized controlled trials evaluating the benefits and/or harms of using prophylactic antibiotics in children with UTIs with VUR for a longer period of time.

Our previous paper [25] using Korean National Health Screening data and National Health Insurance Service data showed that the risk of UTIs and APN was higher in underweight boys aged 2 to 6 years compared to the normal weight group after adjusting for age, sex, birth weight, and preterm birth. In a prospective observational chart review study [12], children with underweight status (body mass index less than 5%) had an increased risk of being admitted from the emergency room, even after adjusting for age and sex, especially for respiratory infections and fractures. For many years, the World Health Organization Nutrition Department has been monitor-

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ing trends in child malnutrition using anthropometric measurements (e.g., weight and height) [26]. Underweight status is a direct indicator of chronic and acute malnutrition because it reflects both low height-for-age and low weight-for-age [26,27]. UTIs are more common in malnourished children than in well-nourished children, and the risk of UTIs increases with the severity of malnutrition [28]. In the present study, the recurrent UTI group had a lower WFL percentile than the single UTI group at the first UTI diagnosis. Weight-for-age percentile significantly declined for 6 months in the recurrent UTI group, while there were no differences in the single UTI group. More interestingly, higher birth weight and lower WFL percentile were related to UTI recurrence in univariable analysis. These findings suggest that children with abnormal growth patterns have a high risk of recurrent UTIs. However, large-scale prospective, longitudinal cohort studies may be required to address this issue as the length of the observation period in this study was short, and the information on WFL percentiles was limited.

Severe malnutrition is associated with immune deficiency, which is thought to make affected children more susceptible to serious infections [29]. Urinary secretory immunoglobulin A (IgA), an immunoglobulin synthesized locally at mucosal surfaces, is an important immunological defense that prevents bacterial adhesion to the periurethral epithelium and urothelium [30]. Secretory IgA production may be less secreted in malnourished children, which may predispose them to infections due to immune dysregulation. One study found that patients with recurrent UTIs had lower urinary levels of secretory IgA [31]. Additionally, a rat experiment showed that severe protein malnutrition dramatically suppressed the secretory immune component [32], suggesting that dietary protein plays a site-specific role in the developmental expression of the immune system. NGAL is an iron-carrier protein produced from neutrophilic granules that plays a vital role in the innate immune system response to bacterial infection [33,34]. During infection, bacteria require iron for growth and metabolic activity in the host. Thus, the host activates neutrophils to release NGAL to prevent bacteria from absorbing iron [34]. Malnourished children have decreased transferrin and increased levels of free unbound iron, which may lead to a favorable environment for bacterial growth, leading to urosepsis and UTIs [35]. Although there was no statistically significant difference in our study, urinary NGAL/Cr values tended to be lower in the recurrent UTI group compared to the single UTI group. This is consistent with the previously mentioned study that found the urinary NGAL values were reduced in patients with recurrent UTIs compared to the non-UTI group [17]. This suggests that the host defense system in recurrent UTI group may be more vulnerable. In addition, malnourished children have impaired cell-mediated immunity, phagocytic function, complement levels, and inadequate cytokine production, as well as atrophy of the lymph nodes, tonsils, and thymus, which may make them more susceptible to UTI [35]. CRP and total leukocyte counts, including absolute neutrophil count, are important indicators of acute bacterial infection [36]; NLR and MLR are effective in diagnosing bacterial infections in hospitalized patients with fever [37]. Neutrophils from recurrent UTI patients not only had significantly reduced bactericidal function but also reduced activation ability compared to healthy controls. This reduction in neutrophil function results in incomplete bacterial clearance, which predisposes to recurrent infections [38]. In addition to their essential role in killing bacteria, activated neutrophils can cause extensive parenchymal damage in the infected urinary tract. Neutrophil-derived cyclooxygenase-2 is thought to be a factor causing inflammation associated with severe recurrent cystitis [16]. Neutrophils cause severe tubulointerstitial nephritis in interleukin-8 receptor-deficient mice [39]. Monocytes and macrophages are highly suitable for regulating neutrophil function during UTI [40]. However, the host defense mechanisms that prevent invasive bacterial infections are not fully elucidated [15]. In our study, host inflammatory responses related to WBC, NLR, MLR, CRP, and PLR did not differ between the two groups. This might be due to the fact that both innate and adaptive immune systems are relatively immature in early life and could mask the role of immune defenses in the susceptibility of young children to recurrent UTIs. It is also unclear whether other immune responses play a role in increased vulnerability to recurrent infections. Since we had a low number of patients, the results should be confirmed in a larger cohort of pediatric patients.

This study had the following limitations. First, the study was conducted at a single institution, and the sample size was relatively small. Second, this was a retrospective study. We used only general laboratory values, such as WBC, PLT, CRP, urinary NGAL/Cr, and plasma NGAL values, which were performed when children with UTIs were hospitalized. Underlying innate and adaptive immunity was not fully assessed in the present study. Because there was no data on height during the study period, it was not possible to compare WFL percentiles between the single UTI group and the recurrent group. Using only the

weight percentile may be insufficient for assessing growth trajectories in infancy and childhood. Finally, kidney scarring was not assessed because of insufficient data. A better understanding of the risk factors for kidney scarring and worsening kidney function would be helpful for the management of children with recurrent UTIs. Therefore, multicenter prospective studies involving a large number of patients are needed to address these limitations.

In conclusion, UTI recurrence should be monitored in children with hydronephrosis at the first UTI diagnosis or those using prophylactic antibiotics. Also, when UTI is first diagnosed in infants under 2 years of age, an abnormal growth pattern with a higher birth weight, a lower WFL percentile, and reduced weight percentiles at least 6 months after the first UTI, the presence of VUR and APN, and confirmed infections with bacteria other than *E. coli* may partially account for UTI recurrence.

Ethical statements

The IRB and the Research Ethics Committee of Korea University Ansan Hospital approved this study (IRB number: 2022AS0087). The IRB exempted the requirement for informed consent because of the retrospective nature of this study. Personal identifiers were completely removed, and data were analyzed anonymously.

Conflicts of interest

Hyung Eun Yim, an Editor-in-Chief of the Journal, was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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