Original Article

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Risk Factors of Breakthrough Urinary Tract Infection in Children with Primary Vesicoureteral Reflux

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Abstract:

Objective: Vesicoureteral reflux (VUR) is a significant risk factor for urinary tract infections (UTI) in children, potentially leading to renal damage. Antibiotic prophylaxis is essential for the pediatric patients with VUR aiming to reduce the chance of UTI. However, breakthroughs UTI can occurred despite adequate prophylactic antibiotics. We aimed to identify the factors contributing to breakthrough UTIs in the patients with VUR.

Material and Methods: This retrospective study analyzed medical records from 238 children with primary VUR from 2000–2019. This study included children aged less than 10 years old at the time of VUR diagnosis and excluded those with secondary VUR, incomplete medical records, or lost to follow-up. Univariate and multivariate analyses were utilized to determine the predictors of breakthrough UTIs.

Results: This study comprised 238 children diagnosed with VUR, including 133 males and 105 females; 86 patients experienced a breakthrough infection. Multivariate analysis revealed that each additional UTI before prophylactic antibiotics significantly increased the likelihood of breakthrough infections (OR 1.62; 95% CI 1.10–2.37; p-value=0.013). Upper pole renal scarring and generalized abnormal renal scans were also significant risk factors with OR 5.57; 95% CI (2.16–14.40); p-value<0.001 and OR 5.19; 95% CI (1.36–19.75); p-value=0.016, respectively. Bowel bladder symptoms emerged as a substantial risk factor (OR 30.16; 95% CI 1.43–633.86; p-value=0.028), whereas the use of cephalexin appeared protective (OR 0.22; 95% CI 0.05–0.94; p-value=0.042).

Conclusion: The number of UTIs before prophylaxis antibiotics, abnormal renal scan at the upper pole and generalized kidney and bowel bladder symptoms were independent risk factors for breakthrough infections. Moreover, the study showed that the use of cephalexin was a statistically significant protective factor against breakthrough UTI.

Keywords: antibiotic prophylaxis, breakthrough infections, renal scar, urinary tract infection, Vesicoureteral reflux

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Introduction

Vesicoureteral reflux (VUR), characterized by the abnormal flow of urine from the bladder into the ureters or kidneys, is one of the causes of urinary tract infection (UTI) in children[1]. VUR increases the risk of febrile UTI, resulting in renal damage, manifesting as scarring and potentially evolving into more serious complications such as hypertension and renal pathologies[2]. Antibiotic prophylaxis is essential for pediatric patients with VUR in order to reduce the chance of UTI[3]. However, some of these patients who received prophylactic antibiotics encountered breakthrough UTI and needed subsequent surgical treatment. To enhance patient outcomes, it is crucial to identify and understand the myriad of factors influencing the risk of breakthrough UTI in children with primary VUR. The aim of the study was to investigate the risk factors of breakthrough UTI. Hence, this information will provide more awareness to the physicians, parents, and patients and thus help to avoid these hazardous factors, reducing the chance of morbidities.

Material and Methods

After the approval from the institution's ethical committee (MURA 2021/180), we retrospectively reviewed the medical records of the children with primary VUR presenting at Ramathibodi Hospital between 2000 and 2019. Patients with any grade of primary VUR, both male and female, aged less than 10 years old at the time of VUR diagnosis, were included in the study. The exclusion criteria were patients with secondary VUR, such as neurogenic bladder, posterior urethral valves, patients whose medical records were incomplete or missing, and patients who were followed up for less than 1 year after diagnosis.

Data collection

Clinical and demographic data were extracted from medical records, including gender, presenting symptoms comprising UTI, sibling screening, prenatal hydronephrosis, age at VUR diagnosis, Body Mass Index (BMI), number of UTIs before starting prophylactic antibiotics, and estimated Glomerular Filtration Rate (eGFR). Bowel and bladder symptoms were also collected. Patients with symptoms of bowel and bladder dysfunction were classified as the BBD Group, while those without such symptoms were categorized into the Non-BBD Group. The VUR was graded using voiding cystourethrogram (VCUG) findings, and grouped into grades 1-2, grade 3, and grades 4-5. Information regarding the renal scar was obtained from a Technetium-99m-labeled dimercapto-succinic acid (DMSA) scan. The data about UTI including number of febrile UTIs before VUR diagnosis, and type of prophylactic antibiotic drug were recorded. All patients diagnosed with primary VUR were prescribed prophylactic antibiotics, regardless of VUR grades or whether they had a history of UTI. The selection of antibiotic agents depended on the doctor's preference and included amoxicillin, cephalexin, trimethoprim/sulfamethoxazole (TMP-SMX), and nitrofurantoin. The choice of antibiotic depended on physician preference, patient factors, and potential antibiotic resistance patterns.

Definitions

VUR was diagnosed by VCUG and categorized into 5 grades according to the International Reflux Study classification[4]. Renal scar was diagnosed using DMSA. DMSA was performed after VUR was first diagnosed and at least 3 months after the acute UTI to allow for the resolution of acute pyelonephritis-related changes. This timing helps to ensure that the findings reflect chronic renal scarring rather than transient inflammatory changes. Abnormal renal scan was defined as positive if several parenchymal lesions were present; these lesions are areas of reduced or absent uptake of the radioactive tracer, appearing as dark areas on the DMSA images. Generalized abnormal renal scarring was defined as the presence of multiple parenchymal lesions distributed throughout the kidney, rather than being confined to a specific region. These lesions indicate significant renal

damage affecting the kidney extensively, suggesting a more severe and widespread impact of VUR-related renal injury.

Bowel and bladder symptoms refer to changes in the normal functioning of the gastrointestinal tract and the urinary system. We defined bowel bladder abnormalities from the clinical manifestation along with the Bristol Stool Scale to define the hardness of the stool. We collected the symptoms, including urinary frequency and urgency, prolonged voiding intervals, daytime wetting, delayed voiding, urinary incontinence, perineal and penile pain, and constipation. A breakthrough UTI was defined as a febrile UTI after receiving adequate continuous antibiotic prophylaxis. Diagnostic criteria for breakthrough UTI included acute onset of high-grade fever (≥38 °C), pyuria, and a positive urine bacterial culture.

Statistical analysis

Statistical analyses were performed using STATA Version 17. Categorical data, including gender, symptom, VUR grade, side of abnormal renal scan, area of abnormal renal scan, type of antibiotic prophylaxis, antibiotics compliance, bowel and bladder symptoms, and comorbidities, are presented as numbers (%). Continuous data are presented as mean±standard deviation for normal distribution or median (interquartile range) for continuous data with non-normal distribution. Statistical analysis of the difference in proportions between groups was determined using the chi-square test or Fisher's exact test. Prognostic factors were established by univariate analyses and multivariate analysis using binary logistic regression. Multivariate analysis with logistic regression was calculated, and a p-value<0.05 was considered significant.

Results

From January 2000 to December 2019, 238 children diagnosed with VUR were included in the study. Among the 238 patients, 133 were male (55.9%) and 105 were female (44.1%). Eighty-six patients experienced breakthrough UTI while receiving antibiotic prophylaxis. The most common presentation of the VUR was febrile UTI (n=217, 91.2%), followed by sibling screening (n=15, 6.3%), and prenatal hydronephrosis (n=6, 2.5%). At the time of VUR diagnosis, 57 children had grades I-II VUR (23.9%), 63 had grade III (26.5%) and 114 had grades IV-V (49.6%). The prophylactic agents included in the study were trimethoprim/sulfamethoxazole (n=157, 68.8%), cephalexin (n=36, 15.8%), amoxicillin (n=24, 10.5%), nitrofurantoin (n=10 patients, 4.4%) and other antibiotics (n=1, 0.4%), as shown in Table 1.

Regarding the factors predicting breakthrough UTI, number of UTI before receiving prophylaxis antibiotics (OR 1.63; 95% CI 1.10-2.37; p-value=0.013), abnormal renal scan at the upper pole (OR 5.57; 95% CI 2.16-14.40; p-value<0.001), generalized abnormal renal scan (OR 5.19; 95% CI 1.36-19.75; p-value=0.016), and bowel bladder symptoms (OR 30.16; 95% CI 1.43-633.86; p-value=0.028) were considered to increase UTI risk. In contrast, the use of cephalexin (OR 0.22; 95% CI 10.05-0.94; p-value=0.042) was a significant protective factor against breakthrough UTI. However, age and symptoms at diagnosis, side of the abnormal renal scan, VUR grade and associated KUB anomalies were not significantly associated with the risk of breakthrough infections.

Discussion

VUR significantly affects children both physically and emotionally, and it also leads to stress for their families. This is because children with VUR are at a higher risk of recurrent UTI, which can be painful. Moreover, the condition can cause considerable stress for parents, adversely affecting their health and well-being. Our study demonstrated that the number of UTIs before receiving prophylaxis antibiotics, abnormal renal scan at the upper pole and generalized abnormal renal scan and bowel bladder symptoms were

Table 1 Demographic and patient characteristics

Variables	Total (n=238)	No-BT UTI (n=152)	BT UTI (n=86)	p-value
Gender, n(%)				
Male	133 (55.9)	91 (59.9)	42 (48.8)	0.100
Female	105 (44.1)	61 (40.1)	44 (51.2)	
Symptom, n(%)				
UTI	217 (91.2)	139 (91.5)	78 (90.7)	0.929
Screening	15 (6.3)	9 (5.9)	6 (7.0)	
Prenatal HN	6 (2.5)	4 (2.6)	2 (2.3)	
Age at VUR diagnosis (month), median(IQR)	11 (5, 27)	11 (5, 24)	10 (4, 35)	0.666
BMI(kg/m^2), mean±S.D. n=236	16.1±2.6	16.2±2.7	15.9±2.4	0.464
Number of UTI before starting prophylactic ATB, mean±S.D.	2±1	1±0.7	2±1.5	0.020
eGFR(ml/min/1.73 m^2),	94.9±36.4	94.1±36.6	96.3±36.3	0.664
VUR Grade, n(%)				
Grade 1-2	57 (23.9)	44 (28.9)	13 (15.1)	0.030
Grade 3	63 (26.5)	41 (27.0)	22 (25.6)	
Grade 4-5	118 (49.6)	67 (44.1)	51 (59.3)	
Renal scar, n(%) n=95				
No	41 (43.2)	23 (46.0)	18 (40.0)	0.555
Yes	54 (56.8)	27 (54.0)	27 (60.0)	
If yes, side of abnormal renal scan, n(%) n=54				
Left	23 (42.6)	13 (48.2)	10 (37.1)	0.214
Right	18 (33.3)	6 (22.2)	12 (44.4)	
Bilateral	13 (24.1)	8 (29.6)	5 (18.5)	
Area of abnormal renal scan, n=191(%)				
Upper	33 (17.3)	15 (10.3)	18 (40.0)	0.000
Mid	6 (3.1)	2 (1.4)	4 (8.9)	0.028
Lower	7 (3.7)	4 (2.7)	3 (6.7)	0.358
Generalize	13 (6.8)	7 (4.8)	6 (13.3)	0.082
Type antibiotic prophylaxis, n(%) n=222				
Trimethoprim/sulfamethoxazole	157 (68.8)	92 (64.8)	65 (75.6)	0.371
Cephalexin	36 (15.8)	27 (19.0)	9 (10.5)	
Amoxicillin	24 (10.5)	15 (10.6)	9 (10.5)	
Nitrofurantoin	10 (4.4)	7 (4.9)	3 (3.5)	
Others	1 (0.4)	1 (0.7)	0	
Drug compliance, n(%) n=236				
Good	215 (91.1)	141 (94.0)	74 (86.1)	0.039
Poor	21 (8.9)	9 (6.0)	12 (13.9)	
Bowel bladder symptom, n=238(%)				
No	131 (55.0)	93 (61.2)	38 (44.2)	0.011
Yes	107 (45.0)	59 (38.8)	48 (55.8)	
Phimosis, n(%) n=128				
No	76 (59.4)	50 (55.6)	26 (68.4)	0.176
Yes	52 (40.6)	40 (44.4)	12 (31.6)	
Comorbidity, n(%)				
Non-GU abnormality	220 (92.4)	140 (92.1)	80 (93.0)	0.797
GU abnormality	18 (7.6)	12 (7.9)	6 (7.0)	

UTI=urinary tract infection, ATB=antibiotics, BMI=body mass index, HN=hydronephrosis, S.D.=standard deviation, VCUG=voiding cystourethrogram, VUR=vesicoureteral reflux, GU=genitourinary tract

Table 2 Univariate and multivariate analysis of factors predicting breakthrough urinary tract infection

Variable OR (90%CI)	Univariate	p-value OR (95%CI)	Multivariate	p-value
Gender				
Male	base			
Female	1.56 (0.92-2.66)	0.101		
Presenting symptoms				
UTI	base			
Screening	1.19 (0.41-3.46)	0.752		
Prenatal hydronephrosis	0.89 (0.16-4.97)	0.895		
Age at VUR diagnosis (month)	1.05 (0.95-1.15)	0.292		
BMI(kg/m^2) n=236	0.96 (0.86-1.07)	0.464		
Number of UTI before start prophylactic ATB (time)	1.44 (1.08-1.92)	0.013	1.62 (1.10-2.37)	0.013
eGFR(ml/min/1.73 m^2)	1.17 (0.57-2.44)	0.662		
VUR Grade				
Grade 1-2	base		base	
Grade 3	1.82 (0.81-4.06)	0.147	0.94 (0.23-3.81)	0.934
Grade 4-5	2.57 (1.25-5.28)	0.010	2.19 (0.65-7.36)	0.203
Renal scar n=95				
No	base			
Yes	1.28 (0.56-2.89)	0.556		
Side of abnormal renal scan n=54				
Left	base			
Right	2.60 (0.72-9.36)	0.144		
Bilateral	0.81 (0.20-3.25)	0.769		
Area of abnormal renal scan n=191				
Upper	5.82 (2.61-12.97)	<0.001	5.57 (2.16-14.40)	<0.001
Mid	7.02 (1.24-39.72)	0.027	5.29 (0.55-50.96)	0.149
Lower	2.53 (0.54-11.78)	0.235	-	
Generalize	3.05 (0.97-9.61)	0.056	5.19 (1.36-19.75)	0.016
Type of Antibiotic prophylaxis n=222				
Trimethoprim/sulfamethoxazole	base		base	
Cephalexin	0.47 (0.21-1.07)	0.072	0.22 (0.05-0.94)	0.042
Amoxicillin	0.85 (0.35-2.06)	0.718	1.32 (0.33-5.25)	0.691
Nitrofurantoin	0.61 (0.15-2.43)	0.481	0.62 (0.07-4.85)	0.649
Ofloxacin	-	-	-	-
Drug compliance n=236				
Good	base		base	
Poor	2.54 (1.02-6.30)	0.044	0.74 (0.18-2.95)	0.673
Bowel bladder symptoms				
No	base		base	
Yes	1.99 (1.16-3.40)	0.012	30.16 (1.43-633.86)	0.028
Phimosis n=128				
None	base			
Phimosis	0.57 (0.26-1.28)	0.178		
Comorbidity				
Non-GU abnormality	base			
GU abnormality	0.87 (0.31-2.42)	0.797		

ATB=antibiotics, BMI=body mass index, eGFR=estimated glomerular filtration rate, GU=genitourinary tract, UTI=urinary tract infection, VUR=vesicoureteral reflux

risk factors for breakthrough UTIs in children with primary VUR. Conversely, our study exhibited that cephalexin can act as a protective factor against breakthrough UTI.

We found that abnormalities in renal scans, specifically in the upper pole and throughout the kidney, were significantly associated with a higher risk of breakthrough infections. These results support findings by Mingin et al.[5], Koji Shiraishi and Nakamura et al.[6-7] who also identified DMSA scan abnormalities as a key risk factor for breakthrough infections in patients with VUR. Renal scarring may contribute to an increased risk of subsequent UTIs through altering the normal renal parenchyma and reducing the kidney's ability to clear infections effectively. Regarding VUR grading, we found that high-grade VUR increased the risk of breakthrough UTI both in univariate and multivariate analysis; however, it was not statistically significant. The explanation for this may be from the small number of patients included in the study and its effect, which is probably confounded by other factors. This is in contrast to the findings from Jang HC et al.[8], who reported that higher reflux grades were predictive of breakthrough infections (p-value=0.071), and Soylu et al.[9], who found that severe reflux significantly increased the risk of renal scarring, a potential outcome of such infections.

Furthermore, our study also found that patients with bowel and bladder symptoms were more likely to have breakthrough infections than those without these symptoms[10]. Bowel bladder symptoms can exacerbate the risk of breakthrough infection in patients with VUR by increasing urine volume and pressure in the bladder. This increase promotes urine pooling, which encourages bacterial growth, and causes reflux into the ureters and kidneys, thereby raising the risk of infection, which can lead to renal scarring, hypertension, and impaired kidney function. Our research aligned with the findings of Su et al.[11], which showed that despite receiving antibiotic prophylaxis, children with VUR and bowel and bladder dysfunction had a 3.19 times higher risk of breakthrough infections compared to VUR children without these dysfunctions. Similarly, our results are consistent with the study of Davis[3], who suggested that untreated BBD increases the risk of UTI and decreases the likelihood of the spontaneous resolution of VUR. Management strategies typically aim to manage bowel bladder symptoms by promoting behavioral changes, treating constipation, and setting timed voiding schedules. These methods help lower the chances of breakthrough infections and protect renal function.

In addition, we found that each additional UTI before prophylactic antibiotics was associated with a 1.62-fold increase in the likelihood of a breakthrough infection. Frequent UTI suggest that the urinary tract may be colonized by uropathogens that have adapted to the host environment[12]. These bacteria may produce biofilms that make them more difficult to eradicate with antibiotics and serve as reservoirs for recurrent infections. Also, frequent UTIs led to multiple courses of antibiotics, which increased the risk of developing antibiotic-resistant bacteria[13]. These resistant strains were more likely to cause breakthrough infections because general prophylactic antibiotics may not be effective against the microbes. Chronic inflammation in the urinary tract from infection can also change local immune responses. The alteration in immunity can lead to increased difficulty in clearing bacterial infections. Additionally, inflammation can damage urothelial cells, making the urinary tract more vulnerable to bacterial adherence and invasion[14]. This finding suggested that patients with a higher number of UTIs prior to prophylaxis may require closer monitoring or alternative therapeutic strategies to mitigate the risk of breakthrough infections.

Our study showed that cephalexin can act as a protective factor against breakthrough UTIs. Because cephalexin is a beta-lactam antibiotic that interferes with the synthesis of the bacterial cell wall, leading to cell death, this agent is also excreted through the kidneys and maintains a

high concentration in the urine, facilitating antibacterial action within the urinary tract[15]. Consequently, the bacterial load in the urinary tract can be effectively reduced. In contrast, the RIVUR trial primarily used trimethoprim/sulfamethoxazole (TMP-SMX) as the antibiotic for prophylaxis, which was effective in reducing UTI recurrence (hazard ratio, 0.50; 95% CI, 0.34 to 0.74)[16]. However, when choosing among TMP-SMX, cephalexin, and other antibiotics for UTI prophylaxis in children with VUR, several factors should be considered, including individual patient risk for UTIs, local resistance patterns, potential adverse effects, and family history of drug allergies.

The strength of our study is that the data were collected from a significant sample size (238 children) over a long period of time, providing a robust dataset for analysis. Additionally, the findings are directly applicable to clinical settings, guiding physicians in risk stratification and management planning. This includes potentially adding a DMSA scan to routine assessments in order to better pinpoint renal involvement and tailor patient care more precisely.

The limitation of this study is that, as a retrospective study, data collection inherently relied on the review of past medical records, which may contain missing data and inconsistencies, potentially compromising the accuracy and reliability of the data. Additionally, some information was self-reported by patients, which could introduce bias and affect the validity of the results. Moreover, since our study was based on institutional records, we were unable to capture UTIs that may have occurred in rural areas or the patients' hometowns, but were managed elsewhere, leading to potential underreporting.

Conclusion

The number of UTIs before receiving prophylaxis antibiotics, abnormal renal scan at the upper pole, and generalized kidney, and bowel and bladder symptoms were independent risk factors for a breakthrough infection. Conversely, our study also suggested a protective role for cephalexin, a significant factor that could guide therapeutic decisions and prophylactic strategies in managing children with VUR.

Ethical approval

This study was approved by the institution's ethical committee (MURA 2021/180).

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