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Characteristics of First Febrile Urinary Tract Infection in Young Infants: Clinical and Imaging Studies

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Abstract

Background: In young infants, presenting signs and symptoms of urinary tract infection (UTI) usually non-specific and can be a manifestation of congenital urinary tract defects. There is no practice guideline for UTI and few studies about extended-spectrum β-lactamase (ESBL) in children aged under 2 months**.** Our objectives were to determine signs and symptoms, laboratory findings, and imaging results of UTI in patients aged under 2 months, and to compare these parameters between ESBL and non-ESBL groups.

Methods: We conducted a retrospective study of patients aged under 2 months who met the following diagnostic criteria for UTI: positive leukocyte esterase, positive nitrite, or growth of ≥ 50,000 CFU/mL single pathogen from a catheterized specimen. Data on their clinical manifestation, laboratory and imaging results were collected.

Results: A total of 88 patients were included, with a male predominance of 69.3%. Fever was the most common clinical manifestation (96.6%), and *Escherichia coli* was the most common pathogen (69.3%). Moderate-to-severe hydronephrosis was identified in 26.1% of ultrasonographic results, while 25.9% of voiding cystourethrography revealed vesicoureteral reflux grade III-IV. Abnormal urine characteristics and *Klebsiella pneumoniae* were identified as risk factors for abnormal imaging results. Prevalence of ESBL-producing UTI was 18.7%, and ESBL group had longer duration of defervescence. Cloudy urine and *Enterobacter cloacae* were identified as clues for suspicion of ESBL.

Conclusion: Characteristics of first febrile UTI in young infants were higher prevalence in males and high prevalence of ESBL-producing UTI. Additionally, our study identified *Klebsiella pneumoniae* as a risk factor for abnormal imaging results.

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Introduction

Urinary tract infections (UTIs) are one of the most common infections in children, can be a manifestation of congenital defects of the urinary tract, such as vesicoureteral reflux, posterior urethral valve, and ureteropelvic junction obstruction [1]. The signs and symptoms of UTIs vary depending on the age of the child, with young infants often presenting with non-specific symptoms, such as fever, dysuria, foul-smelling urine, drowsiness, poor intake and failure to thrive [2]. Urinalysis can also under-detect UTIs due to their cut-off values [3,4]. The early diagnosis and treatment of UTIs are crucial for good outcomes and to prevent complications, such as septicemia, renal scarring and secondary hypertension.

The American Academy of Pediatrics has published a practice guideline for children aged 2-24 months [5], but in Thailand, there is only a practice guideline for children aged 2 months to 5 years. There is limited data of UTIs in children aged under 2 months of age in Thailand. The objectives of our study are to determine signs and symptoms, laboratory findings and imaging results of UTIs in patients under 2 months of age.

Materials and Methods

This was a retrospective study conducted at King Chulalongkorn Memorial Hospital. from January 2010 to December 2020. Patients who were 1 day to 2 months old and hospitalized with febrile UTIs were included in the study. UTIs were defined as abnormal urinalysis (positive leukocyte esterase and nitrite**,** white blood cell **(**WBC) >5 cells/high power field (HFP) or more than 1 bacterial organism/oil power field in urine gram stain**)** or urine culture from urethral catheterization growing more than 50,000 colony forming unit/mL. Exclusion criteria included patients diagnosed with UTI but who did not meet the diagnostic criteria**,** recurrent UTIs and incomplete data.

The medical records of patients, including clinical manifestations, laboratory results, and imaging studies, were reviewed retrospectively. Clinical manifestations included age, sex, prenatal history, and presentations such as fever, vomiting, poor intake, diarrhea, septic shock, drowsiness, seizure, cloudy urine, foul-smelling urine, and hematuria. Laboratory tests included complete blood count, blood urea nitrogen (BUN), serum creatinine, electrolytes, urinalysis (WBC, RBC, leukocyte esterase, nitrite, urine gram strain), and causative microorganism from urine culture. Imaging studies included renal and bladder ultrasonography (RBUS) and voiding cystourethrography (VCUG).

Statistical analysis

Data was analyzed statistically with STATA version 15.1 (Texas 77845 USA). Most of the patient characteristics, laboratory results and imaging studies were reported as percentages. The age of diagnosis and some of laboratory results (WBC count, serum BUN, serum creatinine) were reported using median and interquartile range. Risk factors for extended-spectrum beta-lactamase (ESBL) UTIs, abnormal RBUS and VCUG were reported using multivariate regression analysis (Odd ratio, 95% confidence interval, p-value)**.**

Results

A total of 88 patients met the inclusion criteria and their data was collected for this study. Table 1 showed the characteristics of all patients. The male to female ratio was 7:3, with median of age at diagnosis of 37 days (IQR 30-60). Fifteen of the 61 male patients (24.6%) were also diagnosed with phimosis. Abnormal prenatal KUB ultrasound results were found in 18 patients (20.5%). Most of the patients had a full-term birth in their perinatal history.

Clinical manifestations of patients included fever (96.6%), vomiting (10.3%), cloudy urine (9.1%), poor intake (8%), diarrhea (5.7%), foul-smelling urine (2.3%), septic shock (2.3%), drowsiness (1.1%), seizure (1.1%), hematuria (1.1%).

Table 2 shows the results of the blood test, urinalysis, and urine cultures that were collected. The median white WBC count in the complete blood count (CBC) was 16,255 cells/µL. The median serum BUN was 7 mg/dL and the median serum creatinine was 0.3 mg/dL. The median urine specific gravity in urinalysis was 1.007 (IQR 1.004-1.015), 63 patients (71.6%) had positive results for leukocytes, and 59 patients (67.1%) had positive results for nitrite. Eight patients (9.1%) had negative results in urine cultures, while the most common pathogen among those with positive results (90.9%) was *Escherichia coli* (69.3%), followed by *Klebsiella pneumoniae* (14.8%), *Pseudomonas aeruginosa* (3.4%), and *Enterobacter cloacae* (3.4%).

In RBUS, 23 patients (26.1%) had moderate to severe hydronephrosis, while 65 patients (73.9%) had normal to mild hydronephrosis. VCUG results were available for only 54 of the 88 studied patients, with 37 (68.5%) having normal results and 11 (37.5%) having abnormal VCUG (VUR grade I-V).

The risk factors for abnormal US KUB results were analyzed, and cloudy urine (adjusted Odd ratio (aOR) 5.69, 95%CI 1.14 to 28.43, p-value 0.034) and Klebsiella pneumoniae (aOR 6.37, 95%CI 1.74 to 23.21, p-value = 0.005) were identified as two risk factors (Table 3). The analysis of risk factors for VUR grade III-V in VCUG results (Table 4) indicated that *Klebsiella pneumoniae* was statistically significant (aOR 6.32, 95% CI 1.19 to 33.3, p-value = 0.03).

During the course of collecting data on urine culture results, we identified a high prevalence of extended-spectrum beta-lactamase (ESBL)-producing bacteria, such as *E. coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*.

We therefore set out to further analyze ESBL-producing bacteria by dividing the 88 patients into two groups, ESBL and non-ESBL. Our secondary objectives were to compare patient characteristics, laboratory results, and imaging studies between the two groups and identify any clues for suspicion of ESBL.

Secondary objectives

Our study revealed no statistically significant differences between the ESBL and non-ESBL groups in terms of demographic factors such as gender, age at diagnosis, phimosis, prenatal history, or perinatal history (as seen in Table 1). However, there were some noticeable differences in clinical symptoms between the two groups. Patients in the ESBL group were more likely to experience cloudy urine, a longer duration of defervescence, and recurrent UTIs compared to those in the non-ESBL group.

In terms of laboratory results, only the blood creatinine level showed a difference between the two groups (Table 1). Urine cultures did not reveal any significant differences in the presence of pathogens, such as *E. coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*, between the ESBL and non-ESBL groups. The RBUS and VCUG (Table 2) results also showed no significant differences in the degree of hydronephrosis or VUR between the two groups.

Table 1: Characteristics of patients.

	Total (N=88)	No ESBL (N=74)	ESBL (N=14)	P-value
Sex: male	61 (69.3%)	51 (68.9%)	10 (71.4%)	0.852
Median age at diagnosis (days)	37 (30-60)	43 (30-60)	30 (16-60)	0.22
Phimosis	15 (24.6%)	12 (23.5%)	3 (30%)	0.696
Prenatal history of abnormal KUB ultrasonography	18 (20.5%)	16 (21.6%)	2 (14.3%)	0.725
Preterm	12 (13.6%)	10 (13.5%)	2 (14.3%)	0.938
Clinical presentation				
- Fever	85 (96.6%)	71 (96%)	14 (100%)	0.443
- Vomiting	9 (10.3%)	9 (12.2%)	0	0.344
- Cloudy urine	8 (9.1%)	4 (5.4%)	4 (28.6%)	0.02
- Poor intake	7 (8%)	6 (8.1%)	1 (7.1%)	0.903
- Diarrhea	5 (5.7%)	5 (6.8%)	0	0.317
- Septic shock	2 (2.3%)	2 (2.7%)	0	0.534
- Foul-smelling urine	2 (2.3%)	1 (1.4%)	1 (7.1%)	0.294
- Seizure	1 (1.1%)	1 (1.4%)	0	0.662
- Drowsiness	1 (1.1%)	1 (1.4%)	0	0.662
- Hematuria	1 (1.1%)	1 (1.4%)	0	0.662
Duration of defervescence (day), median (IQR)	2 (2-3)	2 (2-2)	4 (2-5)	0.030
Recurrent UTIs, n (%)	15 (17.1%)	10 (13.5)	5 (35.7)	0.043

ESBL: Extended-spectrum β-lactamase; UTI: Urinary tract infection.

Table 2: Laboratory findings and imaging results.

	Total (N=88)	No ESBL (N=74)	ESBL (N=14)	P-value
Blood test				
- WBC (cells/μL)	16,255 (11,575-19,515)	15975 (11,580-19,240)	17,070 (10,020-23,310)	0.698
- BUN (mg/dL)	7 (6-10)	7 (6-10)	7.5 (4-11)	0.728
- Creatinine (mg/dL)	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.4 (0.3-0.5)	0.009
Urine analysis				
Specific gravity	1.007 (1.004-1.015)	1.006 (1.004-1.015)	1.01 (1.004-1.015)	0.755
Positive leukocyte esterase	63 (71.6%)	55 (743%)	8 (57.1%)	0.191
Positive nitrite	59 (67.1%)	48 (64.9%)	11 (78.6%)	0.372
WBC - < 5 cells/HPF - ≥ 5 cells/HPF	 17 (19.3%) 71 (80.7%)	 16 (21.6%) 58 (78.4%)	 1 (7.1%) 13 (92.9%)	0.452
Urine Culture - *Escherichia coli* - *Klebsiella pneumoniae* - *Enterobacter cloacae complex* - Others	 61 (69.3%) 13 (14.8%) 3 (3.4%) 3 (3.4%)	 51 (68.9%) 10 (13.5%) 1 (1.4%) 3 (3.4%)	 10 (71.4%) 3 (21.4%) 2 (14.3%) -	 0.852 0.427 0.065
RBUS - Normal-Mild hydronephrosis - Moderate-Severe hydronephrosis	N=88 65 (73.9%) 23 (26.1%)	N=74 57 (77%) 17 (23%)	N=14 8 (57.1%) 6 (42.9%)	 0.530 0.258
VCUG	N=54	N=44	N=10	
- Normal	37 (68.5%)	31 (70.5%)	6 (60%)	0.776
- Abnormal, n - VUR grade I-II - VUR grade III-IV	17 (31.5%) 3 (5.5%) 14 (25.9%)	13 (29.5%) 2 11	4 (40%) 1 3	0.650

BUN: Blood Urea Nitrogen; RBUS: Renal And Bladder Sonography; WBC: White Blood Cell; VCUG: Voiding Cystourethrography; VUR: Vesicoureteral Reflux.

Table 3: Risk factors for moderate to severe hydronephrosis on renal and bladder ultrasonography.

	n/N	Univariate		Multivariate	
		OR (95%CI)	P-value	aOR (95%CI)	P-value
Sex: male	16/61 (26.2%)	1.02 (0.36-2.85)	0.976		
Phimosis	2/15 (13.3%)	0.38 (0.08-1.84)	0.229		
Preterm	3/12 (25%)	0.93 (0.22-3.79)	0.923		
Cloudy urine	5/8 (62.5%)	5.74 (1.25-26.37)	0.025	5.69 (1.14-28.43)	0.034
Klebsiella pneumoniae	8/13 (61.5%)	6.4 (1.83-22.39)	0.004	6.37 (1.74-23.21)	0.005

OR: Odd ratios; aOR: adjusted Odd ratios Using logistics regression, Multivariate models were developed by adjusting for covariates with p<0.10 in univariate models.

Table 4: Risk factors for VUR grade III-V from voiding cystourethrography.

	n/N	Univariate		Multivariate	
		OR (95%CI)	P-value	aOR (95%CI)	P-value
Sex: male	11/33 (33.3%)	3 (0.72-12.42)	0.130		
Phimosis	1/10 (10%)	0.26 (0.03-2.31)	0.229		
Cloudy urine	4/7 (57.1%)	4.93 (0.95-25.74)	0.058		
Klebsiella pneumoniae	5/8 (62.5%)	6.85 (1.37-34.1)	0.019	6.32 (1.19-33.30	0.03
Enterobacter cloacae complex	1/3 (33%)	1.09 (0.09-12.96)	0.943		

OR: Odd ratios; aOR: adjusted Odd ratios Using logistics regression, Multivariate models were developed by adjusting for covariates with p<0.10 in univariate models.

Discussion

Our study revealed that male infants under the age of two months were more prone to urinary tract infections (UTIs) compared to their female counterparts, which is consistent with prior research [6]. All male infants were not circumcised, which may increase their risk for UTIs [7].

The most common presenting sign in this study was fever, which was observed in 96.6% of cases. These findings are in line with previous studies that have also reported fever as the primary symptom, accompanied by non-specific clinical findings [6, 8, 9]. In contrast, only 12.5% of cases in our study exhibited urinary complaints, suggesting that UTI should not be immediately suspected based solely on these symptoms.

The urinalysis results showed a low specific gravity, with a median of 1.007 (IQR 1.004-1.015), and positive leukocyte esterase in 71.6% of cases and a positive nitrite test in 67.1% of cases. Notably, 17 patients out of the total of 88 had a WBC count of less than 5 cells/HPF but still had a positive urine culture. This is consistent with the findings of Shaik et al., who reported that about 10% of children with confirmed UTIs by urine cultures had normal WBC counts in their urinalysis despite experiencing urinary symptoms [10]. Moreover, Nadeem et al. have suggested that the optimal pyuria cut-off point for predicting positive urine culture results in young children varies with urine concentration. In particular, they found that at low concentrations (specific gravity less than 1.011), a pyuria threshold of 3 WBCs/HPF had the best predictive value for UTI [11]. According to Rivanowitch et al, infants younger than two months of age who were diagnosed with UTIs had normal urinalysis results but positive urine cultures.[12] Thus, we recommend that empirical antibiotics be prescribed in cases of pyuria, and that urine culture investigations be conducted to confirm the presence of a UTI.

The most frequently isolated organism in our study was *E. coli*, followed by *Klebsiella* spp., which is consistent with previous findings [6,13,14]. Notably, eight patients who had received empirical antibiotic treatment before urine culture had negative culture results. Furthermore, we observed a high prevalence of ESBL-producing UTI, with 15 cultures (18.7%) showing this pattern. This rate is higher than that reported in a previous study by Flokas et al [15]. (14%, 95% CI 8-21). Our study's findings echo those of previous research in highlighting an increasing number of patients with community-acquired ESBL-producing UTI, which is concerning due to its association with elevated morbidity and mortality [15,16].

Our study revealed that the ESBL group had a longer duration of fever after initiating antibiotics (4 days, IQR 2-5) compared to the non-ESBL group (2 days, IQR 2-3), and experienced more recurrent UTIs (35.7% vs. 13.5%, p = 0.043). These findings are consistent with previous studies that have reported longer defervescence after treatment initiation and a higher likelihood of recurrent UTIs in patients with ESBL UTIs [16]. Risk factors for ESBL UTIs include previous UTIs, recent antibiotic use, urinary tract anomalies such as VUR, and recent hospital admission [15-18]. Although the number of cases was insufficient for statistical analysis, univariate analysis showed that cloudy urine (95%CI = 6.11, 1.54-24.2, p = 0.01) and *Enterobacter cloacae* (95%CI = 11.83, 0.99-140.9, p = 0.05) were statistically significant.

Imaging studies can help identify risk factors and structural abnormalities in the urinary tract that can be modified to decrease the likelihood of recurrent UTIs. RBUS serves as an initial screening tool for anatomic abnormalities because of its non-invasive method. In this study, RBUS revealed moderate to severe hydronephrosis in 26.1% of cases, whereas other studies have found abnormal results in approximately 15-37% [19,20]. Cloudy urine and *Klebsiella pneumoniae* were identified as risk factors for moderate to severe hydronephrosis. Chong et al. reported that non-*E. coli* UTI was an independent risk factor associated with imaging abnormalities and recurrent UTI [21].

VCUG is considered the gold standard for detecting VUR, especially in younger children who are at higher risk for acute pyelonephritis and scarring with grade III-V VUR, according to a meta-analysis of AUA guidelines [22]. In this study, 54 out of 84 patients who underwent VCUG showed abnormal results, with 5.6% having VUR grade I-II and 25.9% having VUR grade III-V. This is slightly lower than the rates reported in previous studies, which found VUR in 22-37.8% of children with a first episode of pyelonephritis [13,23]. Klebsiella pneumoniae was identified as a risk factor for VUR grade III-V, which is consistent with previous studies that have shown non-E. coli UTIs to be associated with higher grades of VUR [24,25]. Interestingly, 5 out of 14 patients with mild hydronephrosis in this study were found to have VUR grade III-V, suggesting that mild hydronephrosis may not always be a reliable predictor of VUR. It's worth noting that RBUS may miss dilating VUR in some cases, with previous studies reporting a miss rate of 24-33% [26,27].

There are several limitations to our study that should be acknowledged. Firstly, as a retrospective study, there might be missing data from medical records. Secondly, this study was conducted at a single center and had a relatively small sample size, which may limit the generalizability of our findings. Additionally, some of the risk factors for abnormal imaging results and ESBL UTIs may have limited statistical power due to the small number of cases.

Conclusion

In conclusion, our retrospective study found a higher prevalence of ESBL-producing UTI than expected in young infants with first febrile UTIs, with a significant male predominance. Risk factors for abnormal imaging results included *Klebsiella pneumoniae* infections. These findings highlight the importance of appropriate diagnosis and management of UTIs in young infants, and suggest the need for continued surveillance of ESBL-producing organisms in this population.

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Disclosure

The author has no conflicts of interest to declare.

Author contribution

A.B. and T.D. designed the study; A.B. collected and analyzed data; A.B. and T.D. wrote the manuscript.

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