Urinary Tract Infections with Non-*Escherichia coli* Pathogens in Children: An Observational Study

Mitra Naseri [1], Gholam Reza Sarvari [1, *], Niayesh Tafazoli [2] and Nooshin Tafazoli [2]

[1]Pediatric Nephrology Department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[*]*Corresponding author*: Pediatric Nephrology Department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Email: sarvarir@mums.ac.ir

Abstract

Background: Urinary tract infections (UTIs) with non-*Escherichia coli* (*E. coli*) species are associate with urological abnormalities.

Objectives: To compare the prevalence of non-*E. coli* infections in patients with urological anomalies, neurogenic bladder dysfunction, and those with apparently normal urinary systems.

Methods: Pediatric nephrology clinic at a tertiary-care center in east of Iran. Children affected by UTI enrolled from 2003 to 2016. The results of urine culture were noted at enrolment. Cases with nephrolithiasis who had normal voiding cystourethrogram were excluded. After the implementation of imaging and urodynamic examinations, 832 patients enrolled according to the following inclusion criteria: cases with vesicoureteral reflux, urinary obstruction, neurogenic bladder, and patients with apparently normal urinary tract. The prevalence of infections with *E. coli* vs. non-*E. coli* pathogens were compared between different groups of enrolled cases.

Results: In this study, 62.26% of the subjects had a normal urinary system, while 33.77%, 3.97%, and 2.4% of whom had vesicoureteral reflux, neurogenic bladder, and obstruction, respectively. Non-*E. coli* pathogens were responsible for infections in 17.29%, 19.39%, 33.74%, and 17.15% of these cases, respectively. Infections with non-*E. coli* pathogens were significantly more prevalent in cases with neurogenic bladder (P = 0.003). *Pseudomonas* species were responsible for 4/125, 5/118, 5/28, and 0/6 episodes of non-*E. coli* infections in cases with apparently normal urinary system, patients with vesicoureteral reflux, cases with neurogenic bladder, and those with urinary obstruction, respectively (P = 0.004).

Conclusions: Infections with non-*E. coli* and also *Pseudomonas* species are significantly more prevalent in patients with neurogenic bladder dysfunction rather than those with urological abnormalities and/or cases with apparently normal urinary system.

Keywords: UTI, Non-*Escherichia coli*, *Escherichia coli*, Urological Anomalies, Neurogenic Bladder, Children

1. Background

Urinary tract infections (UTIs) are among the most common bacterial infections occurring during childhood. These infections can induce damages to the bladder, kidneys, and ureters (1). Based on the statistics, UTIs have prevalence rates of 1% and 1% - 3% in boys and girls, respectively (2). These infections have the highest frequency among the patients up to the age of one year in both genders (3). Gram-negative Enterobacteriaceae is the main cause of community-acquired UTI (4, 5). The main etiological agent of this infection is *Escherichia coli* (*E. coli*), which accounts for up to 90% of cases, with various frequencies ranging from 47.6% to 85.9 % (5). Although the majority of UTIs are due to *E. coli*, the diagnosis of the infections caused by organisms other than *E. coli* is very important, given their different antimicrobial susceptibility patterns

(6). Atypical UTI includes seriously ill state, poor urine flow, abdominal or bladder mass, raised serum creatinine levels, septicemia, failure to respond to treatment, and infections with non-*E. coli* organisms (7). A non-*E-coli* infection has been suggested as a risk factor for vesicoureteral reflux (VUR). In addition, such kind of infection is associated with an increased risk of UTI recurrence (8-10).

2. Objectives

The identification of predisposing factors for UTI is of paramount importance in the development of novel therapeutic procedures and long-term follow-up. Regarding this, we aimed to compare UTIs due to *E-coli* and non-*E-coli* pathogens in the pediatric population based on the presence or absence of predisposing factors of infection. The main predisposing factors considered in the study were

urological anomalies [vesicoureteral reflux (VUR) and different types of urinary obstruction] and neurogenic bladder.

3. Methods

A cross-sectional retrospective review was conducted on the recorded information of patients with UTI referred to the Nephrology Clinic of a tertiary academic children hospital from October 2003 to October 2016 (i.e., a 13-year period). The patients with the diagnosis of UTI from birth up to 18 years of age were enrolled if they underwent direct cystography, either voiding cystourethrography (VCUG) or direct radionuclide cystography (DRC) with renal bladder ultrasonography (RBUS). If there was radiologic evidence suggestive of urinary obstruction, diuretic renal scans such as TC^{99} EC-renal scan or TC^{99}-DTPA scan were recommended. Moderate to severe hydronephrosis [anteroposterior (AP) diameter of renal pelvis $\geq$ 10 mm $\pm$ hydroureter were considered indications for doing diuretic renal scans. Patients with neurologic deficits such as myelodysplasia, spinal trauma, and cerebral palsy underwent urodynamic studies to assess bladder compliance, capacity, and detrusor sphincter synergy, as well as uninhibited bladder contraction in the filling phase. The diagnosis of neurogenic bladder was confirmed by a combination of findings on physical examination, RBUS, VCUG, and urodynamic study.

The urine sampling was performed by means of urinary bags and midstream methods in no toilet- and toilet-trained patients, respectively. The growth of a single organism with a colony forming unit (CFU) of $\geq$ 10^5 was considered a positive culture and diagnosed as UTI. In toilet-trained patients with symptomatic UTI (e.g., fever and lower urinary tract symptoms), a growth of $\geq$ 10^4 CFU of a single urinary pathogen was regarded as a positive culture. In the samples obtained via urinary bags, the presence of leukocyturia, in addition to positive urine culture, was necessary for the diagnosis of UTI. Leukocyturia was defined as a white blood cell count of (WBC) $\geq$ 5 (or approximately 25 WBCs per liter) in the high power field (HPF) of urinary sediment in a centrifuged urine sample.

After the implementation of imaging studies, patients with nephrolithiasis but no urological anomalies (n = 106), and those with abnormal kidney ultrasound + normal VCUG with no evidence of anatomical obstruction (n = 46) excluded from the study (total excluded cases = 152 patients). Kidney ultrasound findings in the latter group included mild to moderate hydronephrosis, renal agenesis, or horseshoe kidney. The final enrolled cases (n = 832) were categorized into four groups: patient with apparently normal urinary tract (i.e., normal ultrasound and VCUG find-

ings; n = 518), cases with VUR (n = 281), those with urinary obstruction (n = 20), and cases with neurogenic bladder (n = 33) (Figure 1). Ten cases had a combination of VUR and urinary obstruction.

3.1. Statistical Analysis

Data were analyzed using SPSS software, version 16 (SPSS Institute, Inc., Chicago, IL, USA). Experimental data were presented as mean and standard deviation. All variables showed a normal distribution by using the one-sample Kolmogorov-Smirnov test. Chi-square test was used for data analysis. A P value of less than 0.05 was considered statistically significant.

4. Results

Of 832 enrolled patients, 741 (89.0 6%) and 91(10.94%) cases were girls and boys, respectively. Table 1 presents the demographic characteristics of different groups of patients. Totally 508/832 (61.05%) cases had normal kidney US and VCUG. They defined as patients with apparently normal urinary system, 281/832 (33.77%) subjects were diagnosed as the group with VUR, 33/832 (3.97%) as cases with neurogenic bladder, and 20/832 (2.4%) cases had a urinary obstruction. In 10 (1.2%) subjects, VUR was associated with urinary obstruction.

Based on the obtained results of our study, *E. coli* was responsible for 1071/1348 (79.45%) episodes of infections, while 20.55% (n = 277) of UTI episodes were due to non-*E. coli* pathogens (Table 1). The most common non-*E. coli* pathogens in total enrolled cases were *Klebsiella* (81/277; 29.24%), *Staphylococcus* (55/277; 19.85%), *Enterobacter* (48/277; 17.33%), *Proteus* (33/277; 11.91%), *Enterococcus* (26/277; 9.4%) and *Pseudomonas* (14/277; 5.05%) species (Table 2).

Non-*E. coli* pathogens were responsible for 125, 118, 28, and 6 episodes of infection in cases with apparently normal urinary tract, patients with VUR, case with neurogenic bladder, and those with urinary obstruction, respectively (P = 0.003). Based on the obtained results, non-*E. coli* infections were significantly more prevalent in cases with neurogenic bladder compared to three other groups of patients. *Pseudomonas* species were responsible for 3.2% (4/125), 4.23% (5/118), 17.85% (5/28), and no episode of infection (0%) in cases with apparently normal urinary tract, patients with VUR, cases with neurogenic bladder, and those with urinary obstruction, respectively (P = 0.004). It means that infection with *Pseudomonas* species was significantly more prevalent in patients with neurogenic bladder compared to other groups. *Klebsiella* was the most common non-*E. coli* pathogens in all groups of the patients (Figure 2).
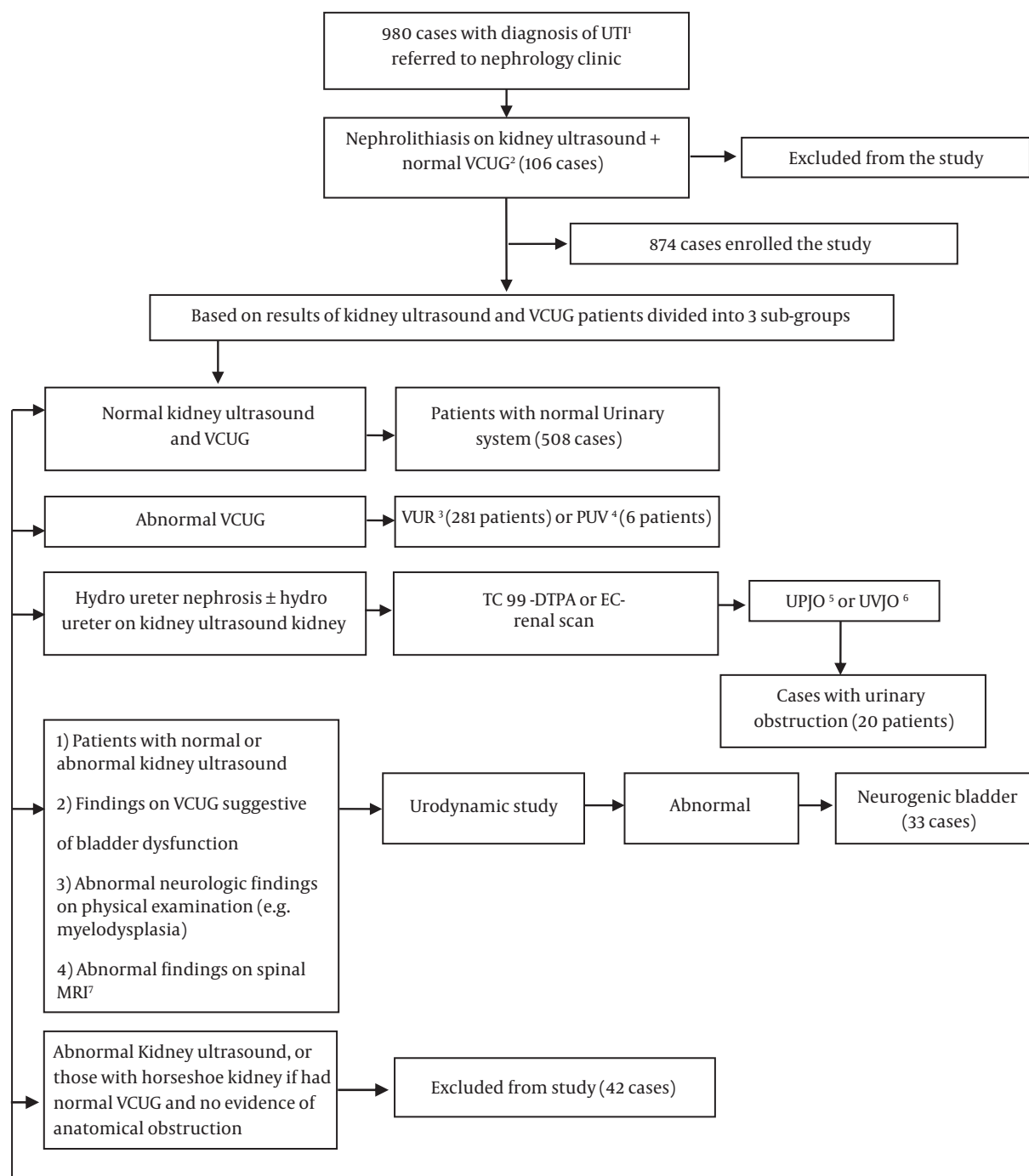
Figure 1. sample selection based on the exclusion and inclusion criteria. 1, Urinary tract infection; 2, voiding cystoureterography; 3, vesicoureteral reflux; 4, posterior ureteral valve; 5, ureteropelvic junction obstruction; 6, ureterovesical junction obstruction; 7, magnetic resonance imaging.

5. Discussion

The results of the current study revealed that *E. coli* was the cause of UTI in the majority of the cases. Moreover, it was the most frequent etiologic agent in all four groups of patients. Most of the patients were female and had febrile UTI. We found a significantly higher frequency of non-*E. coli*

Table 1. Demographic Characteristics and Distribution of *E. coli* Vs. Non-*E. coli* Infections in Different Groups of Patients[a]

| Groups of Patients | Age, mo | Gender | | *E. coli* Infections | Non-*E. coli* Infections | Total |
		Girls	Boys			
Normal urinary tract (508 cases)	44.05 ± 37.21	470 (92.52)	38 (7.48)	598 (82.71)	125 (17.29)	723 (100)
Patients with VUR (281 patients)	25.38 ± 26.66	242 (86.12)	39 (13.88)	389 (76.72)	118 (23.27)	507 (100)
Cases with neurogenic bladder (33 cases)	37.8 ± 43.39	23 (69.7)	10 (30.3)	55 (66.26)	28 (33.74)	83 (100)
Subjects with urinary obstruction (20 cases)	13.8 ± 14.75	9 (45)	11 (55)	29 (82.85)	6 (17.15)	35 (100)
Total cases (832 patients)[b]	38.48 ± 36.11	741 (89.06)[c]	91 (10.94)[d]	1071 (79.45)	277 (20.55)	1348 (100)

Abbreviation: VUR, vesicoureteral reflux.
[a] Values are expressed as No. (%) or mean ± SD.
[b] In 10 patients, vesicoureteral reflux was associated with urinary obstruction
[c] Three girls had vesicoureteral reflux in association with urinary obstruction
[d] Seven boys had vesicoureteral reflux in association with urinary obstruction.

Table 2. Prevalence of Different Non-*E. coli* Pathogens in the Four Study Groups[a]

Non-*E. coli* Pathogens	Normal Urinary System	Cases with VUR	Neurogenic Bladder	Urinary Obstruction	Total
Kelebsiella	34 (27.2)	35 (29.66)	8 (28.57)	4 (66.66)	81 (29.24)
Staphylococcus	27 (21.6)	24 (20.34)	4 (14.3)	0 (0)	55 (19.86)
Enterobacter	26 (20.8)	19 (16.1)	3 (10.71)	0 (0)	48 (17.33)
Proteus	15 (12)	16 (13.56)	2 (7.14)	0 (0)	33 (11.91)
Enterococcus	11 (8.8)	12 (10.17)	3 (10.71)	0 (0)	26 (9.39)
Pseudomonas	4 (3.2)	5 (4.23)	5 (17.86)	0 (0)	14 (5.05)
Citerobacter	6 (4.8)	1 (0.84)	1 (3.57)	1 (16.67)	9 (3.25)
Group B *Streptococcus*	1 (0.8)	4 (3.4)	1 (3.57)	0 (0)	6 (2.17)
Group A *Streptococcus*	0 (0)	2 (1.7)	0 (0)	0 (0)	2 (0.72)
Acinetobacter	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.36)
Serattia	0 (0)	0 (0)	1 (3.57)	0 (0)	1 (0.36)
Morganella morganii	0 (0)	0 (0)	0 (0)	1 (16.67)	1 (0.36)
Total	125 (45.13)	118 (42.6)	28 (10.1)	6 (2.17)	277 (100)

Abbreviation: VUR, vesicoureteral reflux.
[a] Values are expressed as No. (%).

infections in cases with neurogenic bladder vs. those with apparently normal urinary tract and patients with urological anomalies (VUR and urinary obstruction). Shaikh et al. (6) reported that Hispanic children and cases with moderate to severe VUR (VUR grade 3 - 5) are more prone to develop UTI caused by non-*E. coli* organisms.

The present study was targeted toward the assessment of the rate of UTI caused by *E. coli* and non-*E. coli* pathogens among Iranian children. Our results revealed a higher prevalence of UTI among females than males. Nonetheless, this rate has been reported to be higher in males than in females in other studies (3, 11). This discrepancy may be due to the use of various sampling methods. In this regard, in a study performed by Spahiu and Hasbahta (3), 63.88% of the infections were reported to be caused by *E. coli* pathogens. Furthermore, Halerstein (11) and Shaikh et al. (6) reported this rate as 75%. In the present study, *E. coli* was the cause of UTI in 79.5 % of the infections. Friedman et al. (12) found a higher association of non-*E. coli* disease with urinary tract anomalies (77%), including VUR (50%) and UPJO (9%).

Despite different studies on pediatric UTIs, our knowledge about non-*E. coli* pathogens is incomplete (1). A bet-
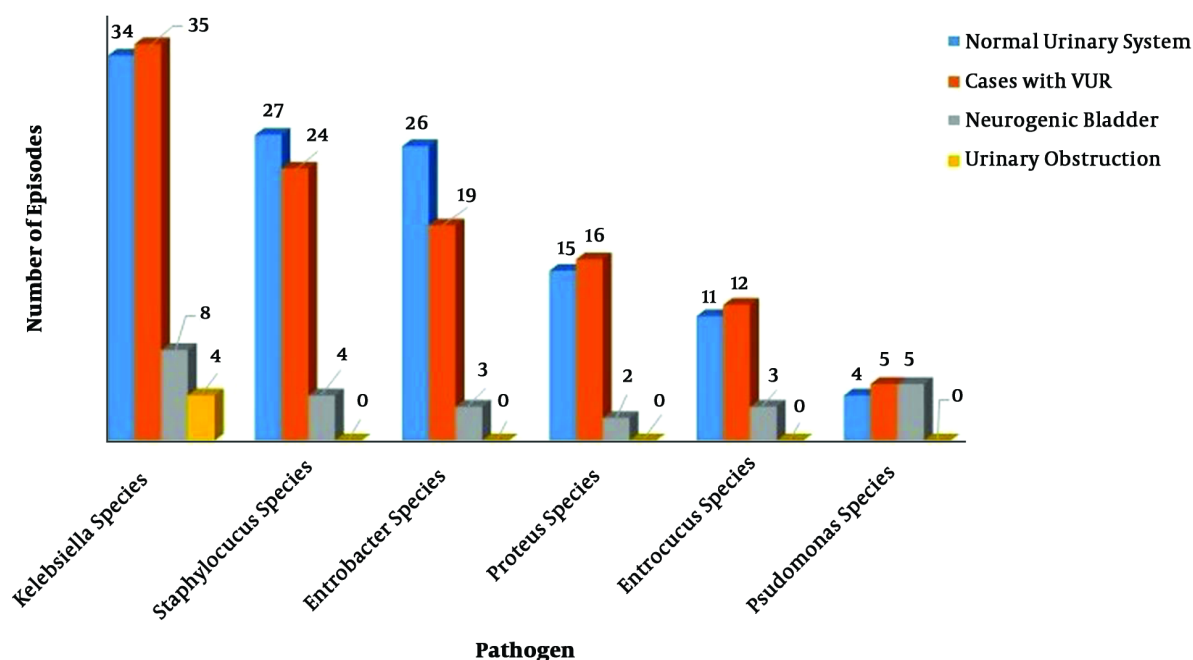
Figure 2. The most common non-*E. coil* pathogens in different groups of the patients.

ter understanding of the non-*E. coli* pathogens accounting for the development of UTI can contribute to the prevention and management of this disease. Based on the literature, a total of 10 -20% of UTI episodes are due to non-*E. coli* pathogens. *Klebsiella*, *Enterobacter*, *Pseudomonas*, and *Staphylococcus* species are the most common non-*E. coli* pathogens accounted for pediatric UTIs (3). In the current study, approximately 20% of the infections were due to non-*E. coli* pathogens, 29.24% of which were due to *Klebsiella*. *Klebsiella* accounted for 81/1348 (6%) of total UTI episodes. Compared to the study by Spahiu and Hasbahta (3), the prevalence rate of UTIs developed by *Klebsiella* was about four-fold of our series (23.06% Vs. 6%, respectively). They found *Proteus mirabilis*, *Citrobacter*, and *Staphylococcus saprophyticus* as the second to fifth most common non-*E. coli* uropathogens in their cases. In our series, *Proteus* and *Citrobacter* were responsible for 2.45% and 0.66% of total UTI episodes, respectively. *Staphylococcus* species were accounted for 4.08% of total episodes of UTIs. In the current study, the second to fifth most common non-*E. coli* uropathogens were *Staphylococcus*, *Enterobacter*, and *Proteus* species, respectively.

In a study carried out by Friedman et al. (12), in terms of clinical and laboratory characteristics of UTI, there was a significant difference between the infants and children.

They reported that patients with non-*E. coli* UTIs younger, have milder clinical signs, and need a longer hospital stay in comparison to those with *E. coli*-related UTIs. Moreover, they showed a higher rate of urinary tract anomalies in patients with non-*E. coli* UTIs compared to those affected by *E. coli* species. In the current study, *E. coli* and non-*E. coli* pathogens accounted for 77% and 23% of infections in cases with VUR, and 82% and 18% of UTIs in a patient with urinary obstruction.

The results obtained by Honkinen et al. (13) showed a stronger association between non-*E. coli* UTIs (i.e., *Klebsiella* or *Enterococcus* UTIs) and VUR than between *E. coli* UTIs and VUR, in contrast to this study, we did not find a significant association between non-*E. coli* infections and VUR. Based on a study carried out by Shaikh et al. (6), the UTIs are caused by non-*E. coli* pathogens are more observed among children with grade III or IV VUR and those without fever. They showed that the rate of high-grade VUR in children with non-*E. coli* UTIs was twice the rate of the UTIs caused by *E. coli* (6). This result has also been confirmed in previous studies (13, 14). Therefore, inconsistent with the findings of other studies, we found that non-*E. coli* UTIs cannot be suggested as a predictive factor for the diagnosis of anatomic anomalies. Nonetheless, our results indicated a significantly higher prevalence of non-*E. coli* UTIs in pa-

tients with neurogenic bladder dysfunction.

The value of non-*E. coli* virulence factors in patients with neurogenic bladder has not been established yet. To the best of our knowledge, no sequence type or phylogenetic group of non-*E. coli* has been observed in the urine culture of the patients suffering from the neurogenic bladder. In addition, there are no data demonstrating how they are genetically related to other pathogens (6).

In a study, 25 children with neurogenic bladder receiving clean intermittent characterization were assessed for UTI. During 24 weeks, weekly urine samples were obtained through a urinary catheter. In 56% of cases, the urine culture was positive. The most prevalent organisms were *E. coli*, *Klebsiella*, Coagulase-negative *staphylococci*, *Corynebacterium*, and *Enterococcus* species, respectively. In our series, the most common organisms among patients with diagnosis of neurogenic bladder were *E. coli*, *Klebsiella*, *Pseudomonas*, *Staphylococcus*, *Enterobacter*, and *Enterococcus* species, respectively.

A relationship has been reported between the higher rate of *E. coli* UTIs in patients with a normal urinary tract and higher virulence of *E. coli* in comparison to non-*E. coli* strains. Abnormal urinary tract is more susceptible to infection with the less virulent non-*E. coli* bacteria (15). Shaikh et al. (6) found a high number of urinary tract anomalies in patients with non-*E. coli* UTI necessitates the administration of prolonged antibiotic therapy and longer hospital stay. They found antibiotic treatment before hospitalization as a main risk factor for non-*E. coli* UTIs. Non-*E. coli* species are more likely to be resistant to the first-generation cephalosporins and nitrofurantoin (16).

Honkinen et al. (13) reported VUR in 1/3 of children affected by *E. coli* UTIs. They also found a double rate of VUR in patients whose first episodes of UTIs were due to *Klebsiella* or *Enterococcus* (non-*E. coli* pathogens). In our series, *E. coli* was the pathogen responsible for first episodes of UTIs in 326/551 (59.16%) VUR⁻ and 233/281 (82.9%) VUR⁺ patients. *Klebsiella* accounted for 48/832(5.77%) of the first episodes of UTIs, including 25/281(8.9%) patients with VUR. In VUR⁻ cases, 23/551 (4.17%) episodes of the first UTIs were due to *Klebsiella*. It indicated that *Klebsiella* infections at the first UTIs were 2.13 times more common in patients with Vs. those without VUR. In the current study, *Enterococcus* was responsible for 12/832 (1.44%) of the first episodes of UTI, including 7/281 (2.5%) episodes in patients with and 5/551(0.8%) episodes in those without VUR. *Enterococcus* was not responsible for the first episodes of UTI in any patient with urinary obstruction or neurogenic bladder.

5.1. Conclusions

The findings of the present study indicate the patients with neurogenic bladder dysfunction are more prone to develop not only non-*E. coli* UTIs but also *Pseudomonas* infections than those with normal urinary tract or urological anomalies. We demonstrated that neither presence of VUR nor its severity (severe vs. mild to moderate VUR) are not significantly associate with non-*E. coli* UTIs. Doing similar studies in patients with voiding dysfunction ± VUR seems to be attractive. Voiding dysfunction or non-neurogenic bladder, an entity mimics clinical manifestation and radiologic findings of neurogenic bladder, is common among the pediatric population affected by UTI. Such evaluation can determine whether, similar to the patients with neurogenic bladder, those with voiding dysfunction are more prone to develop non-*E. coli* UTIs or not?

Footnotes

References

1. Bitsori M, Maraki S, Koukouraki S, Galanakis E. Pseudomonas aeruginosa urinary tract infection in children: risk factors and outcomes. *J Urol*. 2012;**187**(1):260–4. doi: 10.1016/j.juro.2011.09.035. [PubMed: 22114821].

2. Bhutta ZA. Acute gastroenteritis in children. In: Kliegman RM, Stanton BF, Geme JWS, Schor NF, editors. *Nelson Textbook of Pediatrics*. Philadelphia: Elsevier; 2016. p. 1854–73.

3. Spahiu L, Hasbahta V. Most frequent causes of urinary tract infections in children. *Med Arh*. 2010;**64**(2):88–90. [PubMed: 20514772].

4. Schlager TA. Urinary tract infections in infants and children. *Microbiol Spectr*. 2016;**4**(5). doi: 10.1128/microbiolspec.UTI-0022-2016. [PubMed: 28087926].

5. Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. *Am J Med*. 2002;**113 Suppl 1A**:14S–9S. doi: 10.1016/s0002-9343(02)01055-0. [PubMed: 12113867].

6. Shaikh N, Wald ER, Keren R, Gotman N, Ivanova A, Carpenter MA, et al. Predictors of non-escherichia coli urinary tract infection. *Pediatr Infect Dis J*. 2016;**35**(11):1266–8. doi: 10.1097/INF.0000000000001301. [PubMed: 27434831]. [PubMed Central: PMC5071137].

7. NICE. *Urinary tract infection in under 16s: diagnosis and management*. National Institute for Clinical Excellence; 2007, [updated 31 October 2018]. Available from: https://www.nice.org.uk/guidance/cg54.

8. Ristola MT, Loyttyniemi E, Hurme T. Factors associated with abnormal imaging and infection recurrence after a first febrile urinary tract infection in children. *Eur J Pediatr Surg*. 2017;**27**(2):142–9. doi: 10.1055/s-0036-1572418. [PubMed: 26855368].

9. Peters CA, Skoog SJ, Arant BJ, Copp HL, Elder JS, Hudson RG, et al. Summary of the AUA guideline on management of primary vesicoureteral reflux in children. *J Urol*. 2010;**184**(3):1134–44. doi: 10.1016/j.juro.2010.05.065. [PubMed: 20650499].

10. Rushton HG. Urinary tract infections in children. Epidemiology, evaluation, and management. *Pediatr Clin North Am*. 1997;**44**(5):1133–69. doi: 10.1016/s0031-3955(05)70551-4. [PubMed: 9326956].

11. Hellerstein S. Long-term consequences of urinary tract infections. *Curr Opin Pediatr*. 2000;**12**(2):125–8. doi: 10.1097/00008480-200004000-00007. [PubMed: 10763761].

12. Friedman S, Reif S, Assia A, Mishaal R, Levy I. Clinical and laboratory characteristics of non-E. coli urinary tract infections. *Arch Dis Child*. 2006;**91**(10):845–6. doi: 10.1136/adc.2005.080721. [PubMed: 16717085]. [PubMed Central: PMC2066003].

13. Honkinen O, Jahnukainen T, Mertsola J, Eskola J, Ruuskanen O. Bacteremic urinary tract infection in children. *Pediatr Infect Dis J*. 2000;**19**(7):630–4. doi: 10.1097/00006454-200007000-00009. [PubMed: 10917221].

14. Jantunen ME, Siitonen A, Ala-Houhala M, Ashorn P, Fohr A, Koskimies O, et al. Predictive factors associated with significant urinary tract abnormalities in infants with pyelonephritis. *Pediatr Infect Dis J*. 2001;**20**(6):597–601. doi: 10.1097/00006454-200106000-00010. [PubMed: 11419502].

15. Johnson JR, Scheutz F, Ulleryd P, Kuskowski MA, O'Bryan TT, Sandberg T. Host-pathogen relationships among Escherichia coli isolates recovered from men with febrile urinary tract infection. *Clin Infect Dis*. 2005;**40**(6):813–22. doi: 10.1086/428048. [PubMed: 15736014].

16. Shaikh N, Hoberman A, Keren R, Ivanova A, Gotman N, Chesney RW, et al. Predictors of antimicrobial resistance among pathogens causing urinary tract infection in children. *J Pediatr*. 2016;**171**:116–21. doi: 10.1016/j.jpeds.2015.12.044. [PubMed: 26794472]. [PubMed Central: PMC4808618].