JPPT | Single Center Retrospective Study

Association Between Antibiotic Duration and Recurrence of Urinary Tract Infection in the Neonatal Critical Care Unit

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OBJECTIVES Urinary tract infection (UTI) is the most common bacterial infection in infants. Current practice guidelines suggest a treatment duration of 7 to 14 days. Suboptimal therapy may increase the risk for recurrent UTIs leading to renal scarring and possibly chronic kidney disease. The primary objective is to evaluate the duration of therapy for UTIs and its association with the incidence of recurrent UTIs in a neonatal intensive care unit (NICU). The secondary objectives are to identify the risk factors and the most common organisms for recurrent UTIs.

METHODS Patients were identified via the diagnosis codes for UTIs and were included if admitted to the NICU and if they received antibiotics prior to hospital discharge. Patients were divided into 2 groups: antibiotic treatment for 7 days or fewer and antibiotic treatment for greater than 7 days.

RESULTS Eighty-six infants were included in the study. Twenty-six patients received antibiotics for 7 days or fewer, and 60 for more than 7 days. In the study, the median birth weight was 977 g and the median gestational age was 27.6 weeks. There was no significant difference in the rate of recurrent UTIs between the 2 groups ($p = 0.66$). However, in the subgroup analysis, the incidence was higher for patients receiving antibiotic therapy for fewer than 7 days versus 7 days ($p = 0.03$).

CONCLUSION There was no difference in recurrence of UTI between treatment groups (≤7 days versus >7 days), and recurrence was seen in a higher percentage of patients with a urinary tract anomaly.

ABBREVIATIONS AAP, American Academy of Pediatrics; CFU, colony-forming unit; ESBL extended-spectrum beta-lactamase; ICD-10, International Classification of Diseases 10; IV, intravenous; NICU, neonatal intensive care unit; UTI, urinary tract infection

KEYWORDS antibiotic; duration of therapy; neonatal infection; pyelonephritis; recurrent urinary tract infection

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Introduction

Urinary tract infection (UTI) is the most common serious bacterial infection in febrile neonates and infants. There is an estimated prevalence of 4.6% to 13.6% in infants younger than 2 months.[1] Among infants with febrile UTIs, pyelonephritis accounts for approximately 60% of cases. Within the neonatal population, very low birth weight preterm neonates have the highest incidence of UTIs.[2] This population is also more likely to have renal scarring with their first infection, which can lead to long-term complications such as hypertension and chronic kidney disease.[3] Owing to the possible translocation of bacteria into the bloodstream, these patients are also at a higher risk of developing urosepsis, further complicating their treatment course.[4]

Congenital anomalies of the kidney and urinary tract in neonates and infants are associated with an increased risk for recurrent infections.[5] Additional risk factors reported in the literature vary; however, the American Academy of Pediatrics (AAP) specifically identified males younger than 3 months and males who are uncircumcised at higher risk for recurrent UTIs.[6]

The AAP 2011 practice guideline for managing UTIs has recommendations for febrile infants from the ages of 2 to 24 months. The guideline suggests that the diagnosis should be made by bacteriuria, pyuria, or both in the urinalysis (with confirmation by a positive urine culture finding). A positive urine culture result is defined as ≥50,000 colony-forming units (CFUs)/mL from a catheterized sample. A treatment duration of 7 to 14 days was recommended and targeting a longer duration was suggested for pyelonephritis.[6]

Though there has been increasing literature on shorter durations of antibiotic therapy in pediatric UTIs,

the duration of therapy needed to treat neonatal UTIs and prevent recurrence warrants further investigation because these patients are at higher risk of chronic complications such as renal scarring.[8] Specifically for neonates and infants younger than 2 months in the neonatal intensive care unit (NICU), there is little guidance on the adequate duration for the treatment of UTIs. The AAP guideline also does not address prematurity so infants who have a corrected age of less than 2 months might not necessarily be included in those recommendations.[6] We therefore aimed to determine if the duration of antibiotic therapy for the initial UTI treatment course will affect the rate of recurrent UTIs and which factors may be associated with increased risk.

Methods

Design and Data Source. For this single-center retrospective study, we evaluated the medical records of all patients in a 102-bed, level III NICU with a diagnosis of UTI between January 1, 2007, and October 31, 2020, at a tertiary care facility. Patients were included in the study regardless of post-menstrual age at the time of UTI diagnosis. The patients were identified by using the International Classification of Disease-10 (ICD-10) codes for urinary tract infections.[7]

Study Population. Patients were included if they had their first UTI diagnosis at our institution. A UTI was defined as having 1 of the 4 criteria: pyuria or bacteriuria in the urinalysis, ≥50,000 CFUs/mL on the culture sample, or symptomatic with <50,000 CFUs/mL.[6] Symptomatic was defined as clinical status change noted in medical record that resulted in a sepsis workup with initiation of antibiotics and obtainment of cultures. Patients were excluded if they required extracorporeal membrane oxygenation or renal replacement therapy during their hospital admission. The patients were also excluded if they were treated for 3 days or fewer, if appropriate documentation of antibiotic therapy was unavailable in the medical record, or if the treatment course was completed in outpatient care. A 72-hour or less evaluation period was selected because some rule-out periods extended beyond the standard 48 hours pending finalization of culture results from microbiology. For the primary analysis, patients were divided into 2 groups: short antibiotic course (7 days or fewer) and long course (greater than 7 days). Days of antibiotics were defined as the number of days on appropriate therapy, based on urine culture susceptibilities. Therapy was considered appropriate when the organism that grew was susceptible to the antibiotic the patient was receiving at appropriate doses.

Outcome Measures. Clinical, laboratory, and radiographic data were collected via manual chart reviews. Clinical and demographic data included gestational age, postnatal age at the time of first UTI diagnosis, birth weight, weight at first diagnosis, sex, race or ethnicity, and urogenital anomalies. Circumcision status was not included as a data point because it is standard practice at our institution for this to be performed in outpatient care after discharge. Laboratory variables included urinalysis, complete blood count, direct bilirubin concentration, cultures (blood, urine, cerebral spinal fluid, sputum), and concomitant infections. When evaluating the urinalysis, we defined pyuria and bacteriuria as the presence of greater than 5 white blood cells on the high-power field microscope and the presence of bacteria, respectively.[6] Concomitant infection was defined as a positive blood, wound, cerebral spinal fluid, or sputum culture finding 24 hours before or after the first UTI diagnosis. An elevated direct bilirubin was defined as a value greater than 2 mg/dL. For urine cultures, information including collection methods, organisms, and antibiotic susceptibilities was collected. The different types of urine collection methods at our institution include catheterization, suprapubic aspiration, and clean catch. Catheterization is attempted first for all patients, followed by suprapubic aspiration. A clean catch is only performed when there are contraindications for the above methods.

To define a positive UTI result, we used the criteria established in the AAP 2011 guideline[6] but modified it to only include 1 of the 4 criteria to confirm the diagnosis. This is because obtaining a urinalysis is not standard practice in our NICU.

Patients were considered to have a recurrent UTI if they met 1 of the 4 criteria for UTI diagnosis at least 2 weeks after the initial positive urine culture finding.[6,8] Our institution does not routinely repeat urine cultures as a test of cure, therefore we felt this definition for recurrent UTI was appropriate because any cultures obtained 2 weeks or after treatment would have been collected as a new sepsis evaluation.

Additional data collected include imaging results for renal ultrasonography and voiding cystourethrogram, antibiotic agents administered, route of therapy, and duration of appropriate therapy.

Descriptive analysis and chi-square test were used for baseline demographics. For categorical variables, the chi-square test or Fisher exact test was performed. The Mann-Whitney *U* test was used for continuous variables. A p value of less than 0.05 was established as statistically significant. Sample size estimation was not calculated owing to the lack of literature on the optimal duration of intravenous (IV) antibiotic therapy for the treatment of UTIs in NICU.

Objectives. The primary objective of this study was to investigate an association between recurrent UTIs and the duration of antibiotic therapy. The secondary objectives were to determine the risk factors and most common pathogens associated with causing recurrent UTIs.

Results

Demographic. Of the 102 NICU patients identified by using ICD-10 codes for UTIs and chart review,

Table 1. Patient Characteristic (N = 86)

	≤7 Days* n = 26	>7 Days† n = 60	p value
Gestational age, median (IQR), wk	28 (25–33)	27.6 (25–33)	0.71
Birth weight, median (IQR), g	1040 (792.5–1625)	960 (770–1740)	0.43
Postnatal age at time of first UTI, median (IQR), days	30 (15.5–45.5)	25.5 (12–37)	0.99
Weight at time of first UTI, median (IQR), g	1774.5 (1002.5–2277.5)	1395.5 (1020–2765)	0.25
Sex, male, n (%)	20 (77)	43 (72)	0.61
Race, n (%)			
White	9 (34)	32 (53)	0.11
African American	14 (54)	16 (27)	0.01
Other	1 (4)	3 (5)	0.82
Unknown	2 (8)	9 (15)	0.35
Comorbid renal abnormality, n (%)			
Hydronephrosis	3 (12)	11 (18)	0.43
Vesicourethral reflux (any grade)	5 (19)	11 (18)	0.92
Other	2 (8)	6 (10)	0.74

UTI, urinary tract infection

* Median days (range): 7 (4–7).
† Median days (range): 10 (8–24).

86 patients met the criteria for inclusion. Sixteen patients were excluded owing to the following: 5 patients were admitted before the implementation of an electronic medical record and did not have adequate documentation of antibiotics administered, 9 patients received antibiotics for less than 72 hours, 1 patient completed antibiotic therapy in outpatient care, and 1 patient did not complete therapy owing to withdrawal of care (see Supplemental Figure).

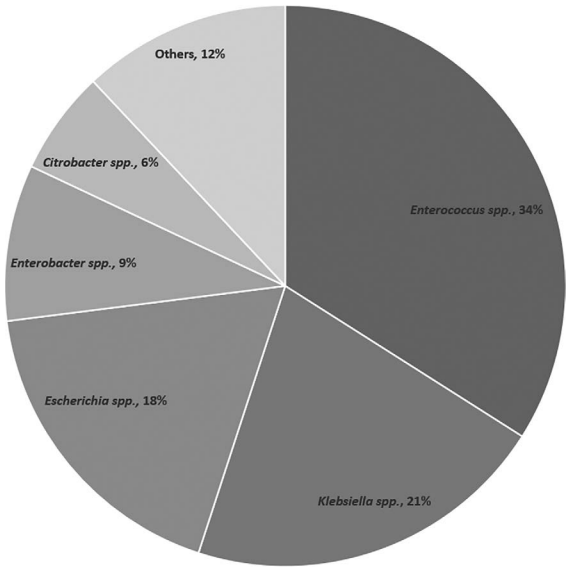
There were 26 patients in the short duration group (≤7 days of therapy) with a median gestational age of 28 weeks (IQR, 25–33) and median birth weight of 1040 g (IQR, 792.5–1625). For the long duration group (>7 days of therapy), there were 60 patients with a median gestational age of 27.6 weeks (IQR, 25–33) and median birth weight of 960 g (IQR, 770–1740). At the time of the first UTI diagnosis, the median postnatal age was 30 days (IQR, 15.5–45.5) for the short duration group and 25.5 days (IQR, 12–37) for the long duration group. There were no statistical differences between the 2 groups' demographics except for a higher percentage of African American patients in the short duration group (54% versus 27%, p = 0.01). Of the 86 patients, 91% underwent a renal ultrasonography, and 74% completed a voiding cystourethrogram. There were no statistical differences between the various urinary tract anomalies among the groups. Patient characteristics are summarized in Table 1.

Primary and Secondary Outcomes. The incidence of recurrent UTIs in the short versus long duration of therapy groups occurred in 7 (27%) and 19 (32%) infants, respectively (p = 0.66). There were no statistically significant differences in concomitant infections, sex, race, and age younger than 3 months for the secondary outcomes evaluating risk factors for recurrent UTIs. There was a higher percentage of patients in the recurrent group with some type of renal or urinary tract anomaly (58%) than in the nonrecurrent group (40%) although not statistically different (p = 0.63) (Table 2). Among the 26 patients with recurrent UTIs, 33 organisms were identified in the first urine culture. Of those 26 patients, 7 patients had a polymicrobial infection. The most common species were *Enterococcus* (n = 11, 33%), followed by *Klebsiella* (n = 7, 21%) and

Table 2. Secondary Objectives (Risk Factor)

	Recurrent n = 26	Not Recurrent n = 60	p value
Concomitant infection, n (%)	7 (27)	14 (23)	0.72
Male, n (%)	18 (69)	45 (75)	0.56
African American, n (%)	8 (31)	22 (37)	0.59
White, n (%)	13 (50)	28 (47)	0.55
Postnatal age less than 90 days, n (%)	25 (96)	57 (95)	0.81
Hydronephrosis, n (%)	5 (19)	9 (15)	0.63
Vesicourethral reflux (any grade), n (%)	7 (27)	9 (15)	0.19
Other renal anomalies, n (%)	3 (12)	5 (8)	0.63

Figure. Organisms from first urine culture.



Escherichia (n = 6, 18%) spp. See the Figure for a summary of the organisms cultured.

Subgroup Analyses. There were 2 subgroup analyses performed to remove patients with concomitant infections, which resulted in 66 patients. The first analysis divided the long duration treatment group into 8 to 10 days and greater than 10 days and found no statistical difference when compared with patients who received antibiotic therapy for 7 days or fewer.

In a second subgroup analysis where we evaluated fewer than 7 days versus 7 days (see Table 3), we found that patients who received antibiotic therapy for fewer than 7 days had a statistically higher incidence of recurrent UTIs (p = 0.03).

Discussion

In this retrospective study evaluating the association between antibiotic duration of therapy and the incidence of recurrent UTIs in the NICU, we did not identify a difference in the rate of recurrent UTIs comparing a short antibiotic course (≤7 days) and a long antibiotic course (>7 days). It is important to note that the antibiotic course for all the patients in the study was given parenterally. Because there are no existing guidelines for the treatment of UTIs in neonates and infants in the NICU, we used AAP as a reference for what the standard treatment duration would be for our patient population. We established 7 days or fewer as our short antibiotic course and wanted to investigate if a decrease in recurrent UTIs was seen in patients treated for longer than 7 days. For our study, we excluded patients who required extracorporeal membrane oxygenation or renal replacement therapy during their admission because this complicates the treatment course and these were independent risk factors for urinary tract infections.[9]

A systematic review by Hikmat and colleagues[10] suggests that an IV antibiotic duration of fewer than or equal to 7 days for bacteremic UTIs and 3 days for non-bacteremic UTIs should be considered for infants of age 90 days or younger.[10] In comparison to our study, it is important to note that in the study of Lewis-de los Angeles,[11] the patients enrolled were primarily non-ICU patients. The study also did not evaluate the entire treatment course, only the duration of parenteral antibiotics. In another study, Desai and colleagues[12] evaluated the duration of parenteral antibiotic therapy for the treatment of bacteremic UTIs in young infants. The authors did not identify a difference between recurrent UTIs in patients who received a short course of 7 days or fewer compared with a long course of greater than 7 days. Again, it is important to note that most of these patients were not from the ICU.

In our study, though there was no statistical difference in the incidence of recurrent UTIs between our 2 groups in the initial evaluation, a subgroup analysis was performed to determine if a decrease in the treatment duration would affect the recurrence of UTIs. For our subgroup analyses, we removed patients with concomitant infections, which could affect the duration of therapy and rate of recurrence. Our first subgroup analysis was composed of 3 groups: 7 days or fewer, 8 to 10 days, and greater than 10 days. There was no difference in the incidence of recurrent UTIs in our first subgroup analysis (p = 0.62).

This is consistent with the findings of Fox and colleagues[13] that an antibiotic course of at least 7 days is as effective as a longer course of greater than 10 days for the treatment of pyelonephritis. The second subgroup analysis divided the short duration group into a fewer-than-7-days and a 7-day group. For our second subgroup analysis, we found a lower rate of UTI recurrence when patients received a full 7-day course as opposed to fewer than 7 days. This finding aligns with the AAP guideline for duration of therapy of at least 7 days for pediatric patients 2 to 24 months of age[6] (Table 3).

Marsh and colleagues[14] reported that few clinical presentations influenced the duration of antibiotics other than age younger than 7 days and urinary tract anomalies. Although we did not evaluate for clinical factors that determined the duration of treatment, we identified that symptomatic patients with a lower urinalysis bacterial colony count (<50,000 CFUs/mL) were more likely to receive a shorter course of antibiotics (p < 0.001) (Table 3).

In our study, we also sought to identify risk factors for recurrent UTIs in neonates and infants. Patient characteristics such as age, sex, race, circumcision status, and urogenital anomalies have been identified

Table 3. Subgroup Analysis (Short Duration of Therapy Breakdown)

	<7 Days n = 10	7 Days n = 11	p value
Recurrent UTI, n (%)	5 (50)	1 (9)	0.03
CFUs/mL <50K, n (%)	8 (80)	5 (45)	<0.001

CFUs, colony-forming units; UTI, urinary tract infection

as factors that may influence the rate of recurrent infection.[15] In our baseline demographics, the only difference noted was a larger number of African American patients in the short duration group (p = 0.01) and more White patients in the long duration group (p = 0.11) (Table 1). When evaluating race as a factor for recurrent UTIs, we did not see a difference in the number of either African American patients (p = 0.59) or White patients (p = 0.55) (Table 2). This differs from the findings of Keren and colleagues[5] in which they identified White race as a risk factor for recurrent infection.

Along with demographic data, we also collected direct bilirubin serum concentrations 24 hours before or after the diagnosis of UTI because direct hyperbilirubinemia can be an early indicator for UTIs in neonates. Many of our patients, however, had a normal direct bilirubin value or did not have a documented concentration value (data not shown). This is interesting because Ozcan and colleagues[15] found that neonates with UTIs were more likely to have elevated total and direct bilirubin serum concentrations.

Although we did not identify a relationship between serum bilirubin concentration and urinary tract infections, we noted a trend between recurrent UTIs and congenital renal anomalies, as there was a higher percentage of patients with a recurring infection and some type of urogenital anomaly (Table 2). This aligns with the findings of Dias and colleagues[16] that vesicoureteral reflux and other urinary tract anomalies can increase the risk of recurrent UTIs. In one study, after excluding neonates with congenital urogenital anomalies, the authors did not find any abnormal changes in renal ultrasound findings during the first year of life in neonates who previously had a UTI. This again could support that the risk of recurrent UTIs and renal complications is associated with anomalies of the kidney and urinary tract.[17]

Our study also evaluated the organisms cultured from the urine of patients diagnosed with UTIs. Because catheterization is the primary collection method at our institution, most urine samples were collected by this method. There were 82 (95%) collected by catheterization, 3 (4%) by suprapubic aspiration, and 1 (1%) by a clean catch. One of the reasons we evaluated the organisms cultured was because of the increased prevalence of drug-resistant organisms such as ESBL (extended-spectrum beta-lactamase)–producing *Escherichia coli* and *Enterobacteriaceae* spp.[18] In our study, the 2 most common organisms identified during the initial UTI were *Enterococcus* and *Klebsiella* species. This is similar to the findings by Levy and colleagues[19] where *Klebsiella* species contributed to 43% of the UTIs. Other studies have also reported that non–*Escherichia coli* species are more prevalent in UTIs in younger patients.[19–21] An interesting finding by Falup-Pecurariu and colleagues[22] was a high rate of ESBL-positive cultures—29% of their *Escherichia coli* and 42.9% of their *Klebsiella* species—but we only identified 1 patient (1%) with an ESBL-positive organism.

When evaluating patients with recurrent UTIs, most patients in our study had a positive urine culture finding with the same organism as the initial culture and remained pan-susceptible or were positive for a different organism (data not shown). Other studies have found recurrent infections to be associated with increased risk for multidrug-resistant organism.[19,23,24] This was also observed in one of our patients with a recurrent UTI in which the same organism with resistance to additional antimicrobial agents was noted.

Current AAP guidelines have recommendations for obtaining a urinalysis in conjunction with a urine culture for patients at least 2 months of age.[6] In our study, only 10% of patients had a urinalysis performed. Of those patients, 67% had a positive finding for urine culture collected around the same time. This is to be expected because it is not routine practice for providers to obtain a urinalysis in our NICU. With this, we suggest that obtaining a urinalysis in patients younger than 2 months may help evaluate the need to initiate antimicrobial therapy before urine cultures are finalized. This may also provide guidance on whether or not to treat when urine culture results reveal fewer than 50,000 CFUs/mL.

Though our study was not powered to detect a difference, the results did provide new information for the treatment of UTIs in neonates and infants admitted to the NICU. This study is a first to evaluate parenteral antibiotic treatment duration for UTIs in neonates and infants younger than 2 months in the NICU. Our NICU is also a level III center with a diverse patient population, which adds to our generalizability. There were, however, several limitations to our study due to its retrospective nature and small sample size. One limitation is that our study was underpowered owing to the low rates of UTIs at our institution. Additionally, changes in our electronic medical record prohibited us from including more patients to power the study. Other limitations to our study included not identifying the organisms from the concomitant infections and the inability to evaluate effects of circumcision on recurrent UTIs. Additionally, we did not evaluate antibiotic dosing as a possible factor contributing to recurrent UTIs. We did not evaluate total duration of therapy in each group because days of therapy was only used to assign

patients to the appropriate group. We were unable to assess circumcision because most circumcisions were performed in outpatient care. We were also unable to obtain readmission data for UTIs.

Conclusion

Though no difference was observed in UTI recurrence when comparing patients who received antibiotic therapy for 7 days or fewer or for greater than 7 days, our subgroup analyses suggest a minimum of 7 days of IV antibiotic treatment may reduce the incidence of recurrent UTIs in the NICU. More studies are needed to evaluate an optimal duration of therapy within the NICU population.

Article Information

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References

1. Lai A, Rove KO, Amin S, et al. Diagnosis and management of urinary tract infections in premature and term infants. *NeoReview.* 2018;19(6):e337–e347.
2. Mohseny AB, Velze VV, Steggerda SJ, et al. Late-onset sepsis due to urinary tract infection in very preterm neonates is not uncommon. *Eur J Pediatr*. 2018;177(1): 33–38.
3. Lotem G, Yael B, Nir S, et al. Long-term follow-up of premature infants with urinary tract infection. *Eur J Pediatr*. 2021;180(9):3059–3066.
4. Arshad M, Seed PC. Urinary tract infections in the infant. *Clin Perinatol*. 2015;42(1):17–28.
5. Keren R, Shaikh N, Pohl N, et al. Risk factors for recurrent urinary tract infection and renal scarring. *Pediatrics*. 2015;136(1):e12–e21.
6. Roberts KB, Downs SM, Finnel SME, et al. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128(3):595–610.
7. World Health Organization. *International statistical classification of diseases and related health problems* (11th ed.). https://icd.who.int/. Accessed October 10, 2021.
8. Conway PH, Cnaan A, Zaoutis T, et al. Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. *JAMA*. 2007;298(2):179–186.
9. Cashen K, Reeder R, Dalton HJ, et al. Acquired infection during neonatal and pediatric extracorporeal membrane oxygenation. *Perfusion*. 2018;33(6):472–482.
10. Hikmat S, Lawerance J, Gwee A. short intravenous antibiotic courses for urinary tract infections in young infants: a systematic review. *Pediatrics*. 2022;149(2):e2021052466.
11. Lewis-de los Angeles WW, Thurm C, Hersh AL, et al. Trends in intravenous antibiotic duration for urinary tract infections in young Infants. *Pediatrics*. 2017;140(6):e20171021.
12. Desai S, Aronson PL, Shabanova V, et al. Parenteral antibiotic therapy duration in young infants with bacteremic urinary tract infections. *Pediatrics*. 2019;144(3):e20183844.
13. Fox MT, Amoah J, Hsy AJ. Comparative effectiveness of antibiotic treatment duration in children with pyelonephritis. *JAMA Netw Open*. 2020;3(5):e203951.
14. Marsh MC, Watson JR, Hill N, et al. Relationship between clinical factors and duration of IV antibiotic treatment in neonatal UTI. *Hosp Pediatr.* 2020;10(743):2019–0325.
15. Özcan M, Sarici SÜ, Yurdugül Y, et al. Association between early idiopathic neonatal jaundice and urinary tract infections. *Clin Med Insights Pediatr*. 2017;11:1–7.
16. Dias CS, Silva JM, Diniz JS, et al. Risk factors for recurrent urinary tract infections in a cohort of patients with primary vesicoureteral reflux. *Pediatr Infect Dis J*. 2010;29(2):139–144.
17. Goldberg L, Borovitz Y, Sokolover N, et al. Long-term follow-up of premature infants with urinary tract infection. *Eur J Pediatr*. 2021;180(9):3059–3066.
18. Michael M, Hodson EM, Craig JC, et al. Short compared with standard duration of antibiotic treatment for urinary tract infection: a systematic review of randomized controlled trials. *Arch Dis Child.* 2002;87(2):118–123.
19. Levy I, Comarsca J, Davidovitis M, et al. Urinary tract infection in preterm infants: the protective role of breastfeeding. *Pediatr Nephrol*. 2009;24(3):527–531.
20. Flores-Mireles AL, Walker JN. Caparpn M, Hultgren S. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol*. 2015;13(5):269–284.
21. Swekersson S, Jodal U, Ahren C, et al. Urinary tract infection in infants: the significance of low bacterial count. *Pediatr Nephrol.* 2016;31(2):239–245.
22. Falup-Pecurariu O, Leibovitz E, Vorovenci C, et al. First UTI episode in life in infants <1 year of age: epidemiologic, clinical, microbiologic and disease recurrence characteristics. *Pediatr Nephrol*. 2020;61:613–619.

23. Flokas ME, Detsis M, Alevizakos M, Mylonakis E. Prevalence of ESBL-producing *Enterobacteriaceae* in paediatric urinary tract infections: a systematic review and meta-analysis. *J Infect*. 2016;73(6):547–557.
24. Mahony M, McMullan B, Brown J, Kennedy SE. Multidrug-resistant organisms in urinary tract infections in children. *Pediatr Nephrol*. 2020;35(9):1563–1.