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Original Article

Neonatal Urinary Tract Infection in a Tertiary Care Center in Amman, Jordan

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ABSTRACT

Background: The aim of this study was to describe the prevalence of neonatal urinary tract infection (UTI), demographics, and clinical characteristics in a single referral tertiary neonatal intensive care unit.
Methods: The medical records of 118 neonates diagnosed with neonatal UTI were reviewed over a 7-year period.
Results: The prevalence of neonatal UTI was 1.5%. The male to female ratio was 1.6:1. In this study, 61% of the neonates were preterm babies. The mean age of diagnosis was 19.55±19.5 days. Pyuria was observed in 20% of the cases, and *Escherichia coli* was the most common pathogen. Hospital-acquired UTI was observed in 76% of the cases, and community-acquired UTI was noticed in 24% of the subjects. Prolonged jaundice was the most common presenting symptom of UTI followed by sepsis. An abnormal ultrasound was found in 29% of the neonates with hydronephrosis as the most associated anomaly. There was a high rate of extended spectrum-beta lactamase organisms and a high rate of antimicrobial resistance.
Conclusion: The occurrence of neonatal UTI was rare in the study population. In addition, hydronephrosis was the most common anomaly. Proper antibiotic stewardship is needed to halt the increasing antimicrobial resistance of uropathogens.

Keywords: Extended spectrum beta-lactamase producing bacteria, Neonates, Preterm, Urinary tract infection

Introduction

Urinary tract infection (UTI) is a common infection in children of all age groups, including the neonatal period. The prevalence rate of UTI varies from an overall of 0.1-1% in all neonates to 4-25% in preterm neonates (1, 2). The estimated prevalence in infants younger than 2 months ranges from 4.6% to 14% (3-5). The clinical manifestations are quite variable ranging from fever, decreased feeding, and decreased activity to prolonged jaundice. Neonatal UTI is a serious illness with significant morbidity and requires treatment from 7-14 days. The empirical choice of antibiotics is ampicillin and a third-generation cephalosporin or an aminoglycoside. *Escherichia coli* (*E. coli*) has been the most prevalent cultured organism of neonatal UTI (4, 6).

Recently, there has been a growing number of *E. coli* species resistant to aminoglycosides that could be explained by perinatal factors as antepartum and intrapartum maternal antibiotic exposure and neonatal factors as lower gestational age (7). The American Academy of Pediatrics published recommendations for the diagnosis, treatment, and evaluation of initial UTI in febrile infants and young children.

No recommendations for neonates less than 2 months have been made; therefore, guidelines regarding the diagnosis, management, and investigation of neonatal UTI are still lacking (8). The prevalence of abnormal ultrasound findings and congenital urinary tract abnormalities in neonatal UTI ranges from 20% to 50% (5, 9, 10). Few studies have been done on neonatal UTI. The aim of this study was to assess the demographics, clinical presentations, and associated anomalies of

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neonates with UTI in the neonatal intensive care unit (NICU) at Jordan University Hospital in Amman, Jordan.

Methods

This was a retrospective study covering a 7-year period during January 2011 to October 2017. It included all neonates with a diagnosis of UTI based on a positive urine culture and clinical symptoms of infection admitted to a 30-bed referral tertiary NICU at Jordan University Hospital. The average admissions were 90 newborns/month. Jordan University Hospital is a tertiary hospital with around 4000 deliveries per year.

Urine specimens were obtained according to the American Academy of Pediatrics guidelines (8) by bladder catheterization. Positive urine culture was defined as the growth of a single microorganism of more than 10,000 c.f.u/ml. One urine culture was used for each patient. Neonates with mixed growth of cultures were excluded from the study. Antimicrobial susceptibility and presence of extended spectrum-beta lactamase (ESBL) phenotype were determined by the VITEK 2 automated susceptibility system (Bio Merieux, Marcy l Etoile, France) according to the Clinical and Laboratory Standard Institute guidelines.

The enrolled neonates were divided into two groups, including group I (n=90) that was hospital-acquired UTI defined as the development of UTI after 3 days of hospital admission, while group II (n=28) was community-acquired UTI if the culture was obtained ≤ 72 h after hospital admission or the neonate was admitted to the hospital with a diagnosis of UTI.

The data were extracted from electronic health medical records, filled to a standardized checklist form, entered into a standard unified computer database, and analyzed. The list of patients was obtained through the hospital's computer microbiology. The data retrieved from the medical records included the age in admission, age of UTI, gender, gestational age, birth weight, mode of delivery, length of stay in NICU before acquiring UTI, total length of hospital stay, clinical presentation of UTI, organism causing UTI, laboratory tests, performed radiological imaging, underlying renal diseases, previous antibiotic use, other comorbidities, empirical antibiotic therapy, duration of treatment, as well as clinical and microbiological response to empirical therapy. Small for gestational age (SGA) neonates are defined as those newborns with birth weight less than 10th centile for gestational age.

Clinical presentation included the presence of fever, prolonged jaundice defined as jaundice more than 2 weeks of age in term neonates or 3 weeks in preterm neonates, and suspected sepsis defined as decreased feeding or activity or rise in C-reactive protein (CRP). Laboratory data included urine analysis, white blood cell count (WBC), and CRP. Pyuria on urine analysis was defined by the presence of more than five cells per high power field. In addition, positive CRP was defined as > 6 mg/l.

Leukocytosis was defined as leucocyte count higher than the normal value according to age. Our empirical treatment for early-onset sepsis is ampicillin and a third-generation cephalosporin or an aminoglycoside and carbapenem and vancomycin for late-onset sepsis. The prescribed antibiotics were changed according to antimicrobial sensitivity results.

In our protocol, an ultrasound was done for all patients with UTI, and a micturating cystourethrogram (MCUG) was done in only those with abnormal ultrasound findings. The requirement for informed consent was waived due to the retrospective nature of the study. This study was approved by the Scientific Research Committee at the University of Jordan in Amman, Jordan, and the Ethical Committee at Jordan University Hospital.

Statistical analysis

Statistical analysis was performed using SPSS software (version 20). Standard descriptive statistical calculations (mean±standard deviation) and frequencies were used for quantitative and qualitative data, respectively. The Chi-square test and one-way analysis of variance were used to evaluate significant differences between the groups. The threshold for statistical significance was set at $P < 0.05$.

Results

Demographic characteristics

A total of 7608 neonates were admitted to the NICU during the study period, out of whom 118 neonates were identified with UTI. The rate of neonatal UTI was reported as 1.5% in the present study. The SGA was identified in 16% (n=19) of the neonates. Approximately, 39% (n=46) of the neonates were term neonates, and two-thirds (61%; n=72) of them were preterm newborns. Out of all preterm neonates, 38.8% (n=28), 51.4% (n=37), and 9.7% (n=7) of them were late preterm

Table 1. Demographics of 118 neonates admitted with urinary tract infection

Clinical presentation	Number (%)
Mean age of urinary tract infection in days (mean±standard deviation)	19.5±19.5
Mean birth weight (kg)±standard deviation	2.2±0.8
Gender	
Male	73 (62%)
Female	45 (38%)
Number of preterm neonates	72 (61.0%)
Presence of fever	10 (8%)
Suspected sepsis	37 (31%)
Prolonged jaundice	63 (53%)
Positive CRP[1]	33 (28%)
Rise in CRP	30 (25%)
Mean CRP level± standard deviation	19±49
Pyuria on urine analysis[2]	15/77 (20%)
Mean serum white blood cell count	11±6

[1](calculated in those who had a urine analysis)
[2](C-reactive protein)

(34-36 weeks), very preterm (28-33 weeks), and extremely preterm (<28 weeks). In addition, the male to female ratio was 1.6:1. Mean gestational age was 34.5±3.6 weeks, and mean birth weight was 2180±820 g. The mean age of UTI was 19.55±19.5 days, and the median age was 13 days. The mean duration of UTI treatment was 9±2.8 days. In this study, the demographics are shown in Table 1.

Clinical Characteristics

Prolonged jaundice was the most common presenting symptom of UTI followed by suspected sepsis (Table 1). Urosepsis was seen in 6% (n=7) of the neonates, and the organisms identified in blood culture were three *Klebsiella*, two *Acinetobacter,* one *E. coli*, and one *Pseudomonas.* Pyuria was seen in 20% of the cases (out of 77 cases, in 15 neonates who had a urine analysis). Hospital-acquired UTI was found in 76% (n= 90) of the neonate, while community-acquired UTI occurred in 24% (n=28) of the newborns. In hospital-acquired UTI, the mean length of hospital stay before the acquisition of UTI was 17.9±19.9 days, and the previous use of antibiotics was seen in 55% (n=65) of the patients.

An ultrasound was done in 84% (n=99) of all UTI cases, and it was abnormal in 29% (n=29) of the neonates. The MCUG was carried out on 22 cases, and it was abnormal in two of them. Underlying renal anomalies seen in 29 neonates were hydronephrosis in 19 neonates, neurogenic bladder in association with myelomeningocele in 4 cases, grade 5 vesicoureteric reflux in 1 patient, and other congenital urinary anomalies in 5 newborns. Moreover, two cases were reported with polycystic kidney disease, one neonate was noticed with a posterior urethral valve, one subject was identified with horseshoe kidney, and one newborn was observed with pelviureteric junction obstruction. Other associated anomalies were found in 12% (n=14) of the neonates and were mainly neurological abnormalities.

Table 2. Type of microorganisms in study group

Type of organism	Number (%)
Escherichia coli	48 (40.7%)
Klebsiella	27 (22.9%)
Enterococcus	19 (16.1%)
Enterobacter	6 (5.1%)
Candida	6 (5.1%)
Acinetobacter	5 (4.2%)
Group B Streptococcus	2 (1.7%)
Others	5 (4.2%)

Microbial pattern

In this study, different organisms were shown in Table 2. *E. coli* and *Klebsiella* were most frequently isolated in 75 neonates, 60% (n=45) of whom were ESBL producing organisms. Candida UTIs were seen in six hospital-acquired patients, four of them were preterm and half of them had a previous course of antibiotics. A comparison between ESBL and nonESBL cases showed a significant difference in the percentage of preterm babies in the ESBL group (73.3% versus 46.7%; P=0.019) There was no difference in clinical presentation and other demographical data between the two groups (Table 3).

A comparison between hospital- and community-acquired UTI showed a similar percentage of ESBL infections in both groups and a higher percentage of preterm babies in hospital-acquired UTI (Table 4). A comparison between term and preterm babies (Table 5) showed a higher percentage of pyuria in term neonates than preterm babies (34% versus 7%) and a higher percentage of hospital-acquired UTI and ESBL UTI in the preterm group.

The resistance rate of our *E. coli* and *Klebsiella* isolates were 80% to amoxicillin-clavulanate, 64% to third-generation cephalosporins, 32% to amikacin, 43% to gentamycin, and 4% to carbapenems. The resistance rate in the ESBL group was 100% to amoxicillin-clavulanate, 48.8% to amikacin, 55.5% to gentamycin, 53.3% to quinolones, 66.6% to nitrofurantoin, and 4.44% to carbapenems. However, in the nonESBL group, the resistance rate was 50% to amoxicillin-clavulanate, 6.66% to amikacin, 23.3% to gentamycin, 13.3% to quinolones, 33.3% to nitrofurantoin, and 3.33 % to carbapenems.

Table 3. Comparison between extended spectrum-beta lactamase and nonextended spectrum-beta lactamase urinary tract infection

	ESBL Number (%) 45 (60.0%)	NonESBL Number (%) 30 (40.0%)	P-value
Mean age of urinary tract infection (days)	20.4±20.0	18.5±16.8	0.653
Average birth weight (kg)	2.0±0.7	2.2 ±0.8	0.279
Gender			
Male	27 (60.0%)	18 (60.0%)	1.000
Female	18 (40.0%)	12 (40.0%)	
Mode of delivery			
Normal delivery	16 (35.6%)	13 (43.3%)	0.489
Cesarean delivery	29 (64.4%)	17 (56.7%)	
Preterm	33 (73.3%)	14 (46.7%)	0.019
Organism			
Escherichia coli	27 (60.0%)	21 (70.0%)	0.377
Klebsiella spp	18 (40.0%)	9 (30.0%)	
Type of infection Hospital-acquired Community-acquired	34 (75.60%) 11 (24.4%)	20 (66.7%) 10 (33.3%)	0.401
Suspected sepsis	14 (31.1%)	10 (33.3%)	0.840
Fever	4 (8.9%)	4 (13.3%)	0.541
Prolonged jaundice	21 (46.7%)	16 (53.3%)	0.572
Presence of renal anomalies	7 (15.6%)	7 (23.3 %)	0.397

ESBL: Extended spectrum-beta lactamase

Table 4. Comparison between hospital- and community-acquired urinary tract infections

	Hospital-acquired UTI Number (%) 90 (76.3%)	Community-acquired UTI Number (%) 28 (23.7%)	P-value
Mean age of UTI (days) Mean±standard deviation	21.4±19.9	13.7±17.3	0.071
Mean birth weight (kg)	1.9±0.8	2.7±0.6	0.000
Gender			
Male	53 (58.9 %)	20 (71.4%)	0.233
Female	37 (41.1%)	8 (28.6%)	
Mode of delivery			
Normal delivery	32 (35.6%)	15 (53.6%)	0.089
Cesarean section	58 (64.4%)	13 (46.4%)	
Preterm	63 (70.0%)	9 (32.1%)	0.000
Organism			
Escherichia coli	33 (36.7%)	15 (53.6%)	0.240
Klebsiella	21 (23.3%)	6 (21.4%)	
Number of extended spectrum-beta lactamase organism	34 (63.0%)	11 (52.4%)	0.401
Suspected sepsis	29 (32.2%)	8 (28.6%)	0.716
Fever	6 (6.7%)	4 (14.3%)	0.206

UTI: Urinary tract infection

Table 5. Comparison between preterm and term neonates

	Preterm Number (%) 72 (61.0%)	Term Number (%) 46 (36.0%)	P-value
Clinical presentation			
Prolonged jaundice	36 (50.0 %)	27 (58.7%)	0.356
Suspected sepsis	18 (25.0%)	19 (41.3%)	0.063
Pyuria[1] on urine analysis	3 (7%)	12 (34%)	0.001
Type of organism			
Escherichia coli	28 (38.9%)	20 (43.5%)	0.525
Klebsiella	19 (26.4%)	8 (17.4%)	
Number of extended spectrum-beta lactamase positive organisms	33 (70.2 %)	12 (42.9%)	0.019
Number of hospital-acquired infections	63 (87.5%)	27 (58.7%)	0.000
Presence of renal anomalies	17 (23.6%)	12 (26.1%)	0.761

[1]Pyuria (the percentage was calculated in those who had a urine analysis)

Discussion

In our NICU, the rate of neonatal UTI was 1.5%, which was similar to that in a study by Weems et al. (11). The UTI was more predominant in males with a ratio of around 1.6:1. It is well-known that UTI is more frequent in boys in the first 3 months of life with a gender distribution of 3-4:1 as reported in other studies (5, 10, 12-14). The high prevalence of UTI in males in this age group was attributed to the bacterial colonization of the skin, particularly the prepuce of uncircumcised boys leading to ascending infection. The average age of UTI was 19.55±19.5 days, which was similar to those in other studies (13).

In our study, prolonged jaundice and sepsis were the most common clinical presentations of UTI as supported by other studies (10, 15, 16). The UTI was presented as prolonged jaundice in 53% of our patients. Tola et al. (17) in a systematic review and meta-analysis performed in Iran reported a UTI prevalence of 11% in neonates with prolonged jaundice. Murat et al. (18) from Turkey reported a UTI incidence of 16.7% in neonates with early neonatal jaundice.

In our cohort, 60% of the cases were preterm babies. Preterm babies are at higher risk of UTI based on multiple risk factors, including increased susceptibility, due to immature immune status, prolonged hospitalization, and multiple interventions, including intravascular catheters and exposure to antibiotics. Previous studies have shown a high prevalence of UTI in preterm babies reaching 11.3% and recommended doing urine analysis in preterm neonates with late-onset sepsis because it was not uncommon (19). In a study carried out by Tamim et al. (20), 25% of preterm babies had UTI.

In our study, *E. coli* was the predominant pathogen in 50% of the neonates, which was similar to the findings of a study by Weems (11), but lower than those in other studies where they contributed to 70-88% of their neonatal UTI cases (4-6, 10, 12, 15, 21). However, enterococcus was reported to be the most common pathogen in other studies (22).

Klebsiella was more frequently seen in preterm neonates than in term newborns as identified in other studies, but it was not statistically significant (23). The absence of pyuria did not rule out UTI. In our cohort, it was seen in only 20% of our patients and detected in 7% of the preterm and 34% of the term babies with a statistically significant difference as in previous studies (10). The lower percentage of pyuria in preterm neonates could be explained by the immature inflammatory response of the endothelial cells to infection.

The mean WBC in our cohort was not elevated, and a normal CRP was found in 72% of the neonates indicating that they are poor predictors in UTI diagnosis. In a study on the clinical predictors of UTI in NICU (24), only increased chronological age was statistically associated with a positive culture, while peripheral WBC count and CRP do not help discriminate between the patients with and without UTI.

A high percentage (60%) of our *E. coli* and *Klebsiella* infections were ESBL producing bacteria, with a similar prevalence in hospital- and community-acquired infections indicating a higher prevalence of community-acquired ESBL UTI in the neonates. In a study conducted on the fecal colonization of bacteria in Jordanian infants (25), it was observed that 36.9% of fecal *E. coli* were ESBL producers, indicating a high carriage rate that predisposes them to infections with these organisms. In a study in China carried out on 229 neonates who developed UTI in NICU, more than 85% of their *E. coli* and *Klebsiella* isolates were resistant to cephalosporins (25).

The ESBL producing bacteria were mainly encountered in hospital-acquired infection until recently when the prevalence of pediatric community-acquired ESBL UTI has started rising (26). A recent systematic review and meta-analysis showed a 14% pooled prevalence of pediatric UTI caused by ESBL producing Enterobacteriaceae in different countries (27).

An abnormal ultrasound was found in 29% of our cohort. The most common abnormality was hydronephrosis, which is similar to the findings of other studies (9, 11, 28, 29). The prevalence of congenital urinary tract anomalies in preterm and neonates younger than 2 months hospitalized for a UTI remains high with 20% to 50% having an abnormal finding on ultrasound (5, 10, 13). However, the prevalence of major anatomic abnormalities is less than 6% in neonatal UTI as supported by the results of studies conducted by Cleper et al. and Lisa et al. (21, 29). Nevertheless, other studies found a high rate of vesicoureteric reflux reaching 20% (11-13, 21).

The MCUG was abnormal in 9% of the patients, which was similar to the findings of other studies (28, 29). A routine MCUG after UTI in the NICU has a low yield and may be reserved for infants with severe or persistent abnormalities on ultrasound (9, 28). Because when the ultrasound is normal, the risk of missing a significant congenital

abnormality is extremely low (12). Previous studies have addressed the need for MCUG in neonates and infants less than 3 months with a first febrile UTI and concluded that the presence of *E. coli* and normal renal ultrasound findings allow us to safely avoid MCUG (30).

Our total cohort of *E. coli* and *Klebsiella* isolates showed a total resistance of 32% to amikacin and 43% to gentamycin, which is similar to the results of a study in Iran (6). In the United States, gentamycin resistance in neonatal isolates has been reported to be between 12% and 15% (31). Our study is limited by its retrospective nature and reliance on medical records. We had a small number of patients who underwent an MCUG, and this would underestimate the prevalence of reflux in our neonates. This was the first study carried out on neonatal UTI in Jordan.

In conclusion, UTIs rarely occur in NICU patients, but specific diagnostic criteria and required imaging are still lacking. Prolonged jaundice and suspected sepsis were the main presenting symptoms. Hydronephrosis was the most common anomaly among the neonates. We had a high percentage of ESBL organisms in our cohort, and proper antibiotic stewardship is needed to halt the increasing antimicrobial resistance of our uropathogens. Further studies are required to standardize the diagnosis and management of UTI in this population.

Conclusion

The occurrence of neonatal UTI was rare in the study population. In addition, hydronephrosis was the most common anomaly. Proper antibiotic stewardship was needed to halt the increasing antimicrobial resistance of uropathogens.

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Conflicts of interests

None.

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