Urinary Tract Infection Epidemiology in United States Neonatal Intensive Care Units

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Abstract

Objective: Characterize the incidence, associated clinical factors, timing of infection, microbiology, and incidence of concordant blood culture of urinary tract infections (UTIs) in very low birth weight (VLBW, <1500g) infants.

Design: Multicenter cohort study of VLBW infants with gestational age (GA) 32 weeks, still hospitalized on postnatal day 7, and discharged 2010–2018 from Pediatrix Medical Group neonatal intensive care units. Demographic and clinical characteristics of infants with and without UTI were compared. Multivariable logistic regression evaluated adjusted odds of UTI diagnosis.

Results: Of 86,492 included infants, 5,988 (7%) had a UTI. The most common pathogen was *Enterococcus* spp. (20%), followed by *Escherichia coli* (19%) and *Klebsiella* spp. (18%). *Candida* spp. (6%) was the most common non-bacterial pathogen. Concordant positive blood culture was present in 8% of infants with a UTI diagnoses. UTI was associated with lower GA, male sex, vaginal delivery, prenatal steroid exposure, and longer length of hospitalization.

Conclusion: UTI is a common cause of infection in VLBW infants, especially among the smallest, most premature, male infants, and those with longer length of hospitalization. Neonatal

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clinicians should consider obtaining urine culture in the setting of late-onset sepsis evaluations in VLBW infants.

Urinary tract infection (UTI) is a common cause of late-onset sepsis (LOS) in very low birth weight infants (VLBW, birth weight <1500g) and is responsible for substantial morbidity in this population.[1] The signs of UTI in VLBW infants are non-specific, including increased apnea, bradycardia and desaturation episodes, feeding intolerance, temperature instability, and lethargy.[2–4] Given the non-specific signs, awareness of associated clinical factors may raise clinical suspicion and accelerate timely diagnosis and treatment. Clinical decompensation secondary to UTI in VLBW infants may result in need for increased respiratory support, interruption of enteral feeding, and escalation of other medical therapies. UTI can also coincide with bacteremia and necrotizing enterocolitis (NEC) in this population.[5,6] UTI may lead to sepsis, and scarring can lead to renal damage, which in turn may result in renal insufficiency, proteinuria, and hypertension later in life.[7] UTI in premature infants may further compound increased risk for renal impairment in the setting of postnatal nephrogenesis, exposure to nephrotoxic medications, and hyperoxia.[8] A recent study of 18 premature infants born at mean gestational age (GA) 29.4 weeks with a single episode of UTI and structurally normal kidneys showed no increased risk for recurrent UTI or kidney disease in the first two decades of life; however, this pilot study was limited by small sample size.[9] In older infants in the outpatient setting, UTI may be a harbinger of major urinary tract anatomical abnormalities; however, severe structural anomalies requiring further treatment are present in less than 5% of VLBW infants with UTIs.[10]

The incidence of UTI in VLBW infants is reported to be between 3–8.5%[11,12]; however, estimates vary widely in published literature.[13] Earlier studies have shown a higher UTI incidence with lower birth weight, lower GA, and presence of renal anomalies.[11,12] Male VLBW infants appear to be at higher risk compared to females.[13] Other reported associated factors for UTI in VLBW infants include mechanical ventilation, central line access, older postnatal age, and duration of hospitalization.[11,12,14] Prior studies of the epidemiology of UTI in VLBW infants are limited to single-center studies and relatively small sample sizes. Despite the higher incidence of UTI in premature infants, multicenter studies are lacking and are critical to standardize guidelines for diagnosis, treatment, and management in the VLBW population. Our objective was to evaluate the incidence, microbiology, and associated clinical factors of UTI in a large, multicenter cohort of VLBW infants to inform risk stratification and management of UTI in this population. Our hypothesis was that lower birthweight, lower GA, male sex, higher severity of initial illness (with 5-minute Apgar score as a marker), and vaginal delivery would be associated with increased risk of UTI.

Methods

Study design and data source

We conducted a multicenter cohort study of infants discharged from the neonatal intensive care unit (NICU) from 2010 to 2018. Deidentified data were obtained from the Pediatrix Clinical Data Warehouse (Sunrise, FL USA), a multicenter clinical database including patients from nearly 400 NICU sites in 35 states and Puerto Rico. NICUs included in the Pediatrix Clinical Data Warehouse are community and academic centers throughout North America and ranged from Level I through IV. Clinicians in these NICUs generate infant data daily including admission history and physicals, daily progress notes, and discharge summaries with demographics, administered medications, laboratory results, microbiologic culture results, limited dosing information, and diagnoses available. From the daily notes, data are extracted and consolidated into the Pediatrix Clinical Data Warehouse.[15] Infants with birth weight 1500g, gestational age 32 weeks, and still hospitalized on postnatal day 7 were included. In order to focus this analysis on typical VLBW infants, those with severe and uncommon urinary tract abnormalities including diagnosis of neurogenic bladder, cystic kidney disease, bilateral renal agenesis, horseshoe kidney, ectopic kidney, renal dysplasia, renal hypoplasia, multicystic dysplastic kidney, megaureter, ureter duplication, ureter agenesis, ectopic ureter, ureteropelvic junction obstruction, congenital mesoblastic nephroma, exstrophy of urinary bladder, and Prune Belly syndrome were excluded. Infants diagnosed with hydronephrosis or pelviectasis were not excluded. We extracted information on prenatal characteristics, demographics, exposure to medications and interventions while in the hospital, and in-hospital clinical outcomes. Permission to conduct this analysis was provided by the Duke University Institutional Review Board (Durham, NC USA).

Definitions and participants

The following data were collected from birth until discharge or death: GA at birth; exposure to prenatal steroids; Apgar score at 5 minutes of life; sex; birth weight; small for GA (SGA) status; mode of delivery; postnatal age (PNA) at time of positive urine culture; microbiology of urine culture; and microbiology of blood cultures drawn within 3 days of UTI. UTI was defined as isolation of a single pathogenic organism from urine culture collected on or after postnatal day 3. Urine cultures with isolation of more than one organism were considered a contaminant. Multiple positive urine cultures for the same organism within 21 days were considered collectively as a single UTI. Biochemical urine studies, such as urinalysis, were not available for analysis. Method of urine culture collection and colony counts of positive urine cultures were not available for analysis. We excluded UTI occurrences for organisms typically considered contaminants, including non-speciated Streptococci, *Bacillus* spp., *Corynebacterium* spp., Gram-positive rods (not including *Listeria sp.*), *Lactobacillus* spp., *Micrococcus* spp., *Stomatococcus* spp., and *Bacteroides* spp. Coagulase-negative *Staphylococcus* (CoNS) infections were determined to be definite, probable, or possible.[16] Definite and probable blood and urine CoNS infections were used in the analysis. We defined a definite CoNS infection as 2 positive cultures drawn on the same day; probable CoNS infection as 2 positive cultures within a 4-day period, 3 positive cultures within a 7-day period, or 4 positive cultures within a 10-day period; and possible CoNS infection as a culture positive for CoNS that did not meet criteria for definite or probable CoNS infection.

Concordant blood culture was defined as isolation of the same pathogenic organism in blood within 3 days before or after collection of positive urine culture. SGA status was defined as birth weight less than tenth percentile for GA as determined by Olsen growth chart.[17]

Statistical analysis

Summary statistics for the variables of interest, including sex, GA, birth weight, prenatal steroid exposure, SGA status, 5-minute Apgar score, mode of delivery, and length of hospitalization were calculated among infants who were diagnosed with at least one UTI, those with at least one urine culture obtained without a UTI, and those without a urine culture obtained during hospitalization. Microbiologic pathogens of first positive urine cultures were tabulated. Postnatal age at first positive urine culture was described. We calculated the incidence of concordant positive blood culture within 3 days of positive urine culture. To evaluate differences between groups, Chi-square tests were used for categorical variables, and Wilcoxon rank sum tests were used for continuous variables. The unadjusted odds of UTI diagnosis were calculated for all variables of interest, including birth weight, GA, 5-minute Apgar, SGA status, sex, prenatal steroid exposure, and mode of delivery. Multivariable logistic regression was used to evaluate the adjusted odds of UTI diagnosis among all infants in the cohort, regardless of whether a urine culture was obtained during hospitalization. All significant variables in univariable analysis were considered for inclusion in the multivariable model; site was included as a random effect. Birth weight and GA were collinear in the multivariable logistic regression; therefore, only GA was used in the multivariable logistic regression to avoid multicollinearity. Olsen growth curves for infants born at 22 weeks GA are not currently defined; therefore, SGA status was not used in the final multivariable model. Length of hospitalization in days was added to the multivariable model to account for variable lengths of hospitalization. Standard assumption diagnostics were conducted prior to selection of the final model. From the final multivariable model, odds ratios (ORs) with 95% confidence intervals (CIs) were determined. A second multivariable logistic regression was constructed using the same method as above and included only infants with at least one urine culture obtained during hospitalization. STATA 16.1 (College Station, TX) was used to perform the statistical analysis. A *p<0.05* was considered statistically significant for all tests.

Results

The median GA of the entire cohort was 28 weeks (quarter 1 [Q1], quarter 3 [Q3]: 26, 30) with median birth weight of 1.078kg (Q1, Q3: 0.820, 1.300). Of 86,492 included infants (Figure 1), 5988 (7%) infants had a UTI (Table 1). The group with UTI had a higher proportion of males, lower GAs, and lower birth weights (Table 1). Positive urine cultures were obtained on median postnatal day 36 (Q1, Q3: 21, 60) (Figure 2). *Enterococcus* spp. was the most common pathogen (20%), followed by *Escherichia coli* (*E. coli*) (19%) and *Klebsiella* spp. (18%) (Table 3). *Candida* spp. (6%) was the most common non-bacterial pathogen. Regarding LOS evaluations during hospitalization, 25% of infants had urine and blood cultures, 2% of infants had urine but no blood culture, 24% of infants had blood but no urine culture, and 49% had neither obtained. Concordant positive blood culture was present in 8% of infants with UTI diagnosis (n=474). Six percent (300/5283) of infants

with at least one UTI died, while 5% (3854/74,162) of infants without a UTI died before discharge. In the multivariable analysis of the entire cohort, infants 24 weeks GA had the highest risk of UTI (Table 2). Compared to infants 29–32 weeks GA, infants 24 weeks GA had an increased adjusted odds ratio (aOR) of UTI of 2.03 (95% CI 1.83–2.26) and infants 25–28 weeks GA had aOR 1.76 (95% CI 1.63–1.90). Other factors associated with UTI included male sex (aOR 2.53; 95% CI 2.38–2.70), vaginal delivery (aOR 1.12; 95% CI 1.05–1.20), prenatal steroid exposure (aOR 1.15; 95% CI 1.06–1.25), and longer length of hospitalization (aOR 1.02; 95% CI 1.02–1.02). A multivariable analysis including only infants with at least one urine culture obtained during hospitalization had similar results (Supplemental Material).

Discussion

In this large cohort study of VLBW infants, UTI was associated with lower GA, male sex, vaginal delivery, prenatal steroid exposure, and longer length of hospitalization. Seven percent of infants had a UTI diagnosis, which is similar to published literature, with incidences of UTI in VLBW infants ranging from 3.2% to 8.5%.[2,4,12,13] This seven percent is the same as the prevalence of UTI in febrile infants in the general population.[18] The relatively high incidence of UTI in VLBW infants highlights the importance of obtaining urine cultures in LOS evaluations in this population. Timing of UTI in our cohort, with highest incidence postnatal days 8 to 30, is similar to findings in other previous studies.[2,4,6,19]

Enterococcus spp., *E. coli, Klebsiella* spp., and *Enterobacter* spp. were the most common cause pathogens grown in urine culture in this cohort. Other studies have also frequently noted Gram negative pathogens as the most common pathogens in the premature infant population. In a single-center study of 1127 VLBW infants with 60 UTIs identified between 1995–2003, *Klebsiella* spp. was the most common at 43% of positive urine cultures.[4] *Klebsiella* spp. was also the most common pathogen in a single-center study of 762 VLBW infants with 66 UTIs identified between 1990–2001[13] and another single-center study of 232 VLBW infants with 32 UTIs identified between 2005–2015.[12] Other studies have shown *E. coli* to be the most common pathogen, including a single-center study of 572 VBLW infants with 20 UTIs identified conducted between 2004–2006.[2] The rate of *Enterococcus* spp. positive urine cultures in this cohort was similar to previous studies completed in premature infants, which showed *Enterococcus* spp. growth in 7.9 to 17.9% of positive urine cultures.[6,10–12,14,19] *Enterococcus* spp. appears to be more common in the hospitalized premature population compared to older children in the outpatient setting.[20] This may in part be due to the preponderance of males with UTIs in the VLBW population, as *Enterococcus* spp. appears to be more common in male infants and children of all age groups compared to females.[20] However, *E. coli* remains the most common UTI pathogen in male children overall.[20] It is possible that some *Enterococcus* spp. positive cultures were not true UTI, as non-catheterized urine specimens included in the analysis may have contributed to contaminated urine cultures. Our study showed a relatively low incidence of coagulase-negative *Staphylococcus* (CoNS) at 4% of positive urine cultures, whereas other studies of UTIs in infants in the NICU showed CoNS in 10% to 28% of positive urine cultures.[2,5,10,19,21] This relatively low incidence of CoNS in this cohort may be due

to including only definite and probable CoNS infections, while excluding possible CoNS infections. The rate of *Candida* spp. positive urine cultures in this cohort is similar to other studies of UTIs in preterm infants with percentages ranging from 7.3–15%.[5,13,22] The choice of empiric coverage should be based on local susceptibility patterns for the most common pathogens outlined in this study. Understanding the spectrum of pathogens causing UTI in VLBW is necessary to ensure proper antimicrobial coverage, especially in the setting of increasing proportion of antibiotic-resistant organisms causing infections in the NICU.[23–25]

Concordant positive blood culture in 8% of infants with a UTI diagnoses in this cohort is similar to prior studies, with the incidence of concordant positive blood cultures ranging from 8.8–13%.[4,5,13] The incidence of concordant positive blood cultures has been reported as high as 38% in a retrospective single-center study of 189 VLBW infants, although the incidence of UTI 48/189 (25%) was high in that study.[26] Concordant positive blood and urine cultures may have resulted from primary bacteremia with hematogenous seeding of the urinary system, or from primary UTI with resultant bacteremia.

This study identified several associated clinical factors for UTI, including lower GA, male sex, vaginal delivery, prenatal steroid exposure, and longer length of hospitalization. Lower GA and male sex have previously been shown to be associated with increased risk of UTI in smaller and single-center observation studies, which are confirmed here.[13,14] Premature infants are at increased risk for many infections, including UTI, likely due to immature immune systems, along with increased need for invasive procedures. As GA is strongly associated with all causes of late onset sepsis, GA alone does not differentiate risk among UTI, bacteremia, and meningitis, although this association does reinforce the increased risk of infection in low GA infants. The OR for UTI in males compared to females in this cohort was 2.53 (95% CI 2.38–2.70); this finding is similar to a single-center study conducted 1995–2003 that included 1127 VLBW infants and showed OR 2.96 (95% CI 1.28–6.85).[4] While reliable data regarding circumcision was not available in this dataset, given the low GAs examined in this study, very few male infants would have been eligible for circumcision at time of first UTI. Vaginal delivery was associated with increased odds of UTI compared to C-section, which may be due to exposure to vaginal bacterial flora during the birthing process. Prenatal steroid exposure was associated with increased odds for UTI compared to no prenatal steroid exposure, which has not been studied previously. While steroid exposure may alter immune responses,[27,28] this increased risk of UTI in the setting of prenatal steroid exposure could be due to increased survival among infants with prenatal steroid exposure and, therefore, greater opportunity to develop a UTI. Longer length of hospitalization has been shown to be associated with UTI diagnosis, which is confirmed here.[11,12] Infants with longer lengths of hospitalization have greater opportunity to develop and be diagnosed with a UTI, and likely have greater severity of illness, which may also be associated with increased UTI risk.

A strength of this cohort study is the large sample size derived from 367 community and academic NICUs across the United States. While the regression model examining associated clinical factors for UTI presented here includes all infants in the cohort regardless of whether urine culture was collected during hospitalization, a similar model including only

infants with at least one urine culture collected during hospitalization had similar results (Supplemental Material).

This study has several limitations. There is likely misclassification of some positive urine isolates as UTI, since additional diagnostic criteria for UTI, including biochemical urine studies (e.g., urinalysis), were not analyzed and colony counts were not available for analysis. We expect that any differential misclassification due to our less specific (but not less sensitive) definition of UTI would bias OR's in the direction of the null. Therefore, we may currently underestimate the factors associated with UTI in VLBW infants than would a more specific definition of UTI. Additionally, method of urine culture collection was not available for analysis; therefore, non-catheterized or indwelling catheter urine specimens included in the analysis may have contributed to contaminated urine cultures. There may be clinical and demographic factors associated with UTI in VLBW infants that were not examined in this study. Variations in clinical practice and unit policies on thresholds to obtain urine culture may have influenced our study, as UTIs may have gone undiagnosed if urine culture was not obtained.

Conclusion

In this large cohort study of VLBW infants, clinical factors associated with UTI diagnosis included lower GA, male sex, vaginal delivery, prenatal steroid exposure, and longer length of hospitalization. The most common pathogen was *Enterococcus* spp., followed by *E. coli*, *Klebsiella* spp., *Enterobacter* spp., and *Candida* spp. Concordant positive blood culture was present in 8% of these UTI diagnoses. UTI remains a common cause of LOS in VLBW infants, especially among the smallest, most premature, male infants, and those with greater severity of illness. Neonatal clinicians should consider obtaining urine culture in the setting of LOS evaluations in VLBW infants. Results from this study may increase awareness of UTI risk in this population and aid in risk stratification to improve diagnosis and outcomes of UTI in VLBW infants. Next steps should include study of preventative measures that may reduce the incidence of UTI in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflict of interest disclosures:

RGG has received support from industry for research services (https://dcri.org/about-us/conflict-of-interest/). The authors have no other conflicts of interest relevant to this article to disclose.

Data availability statement:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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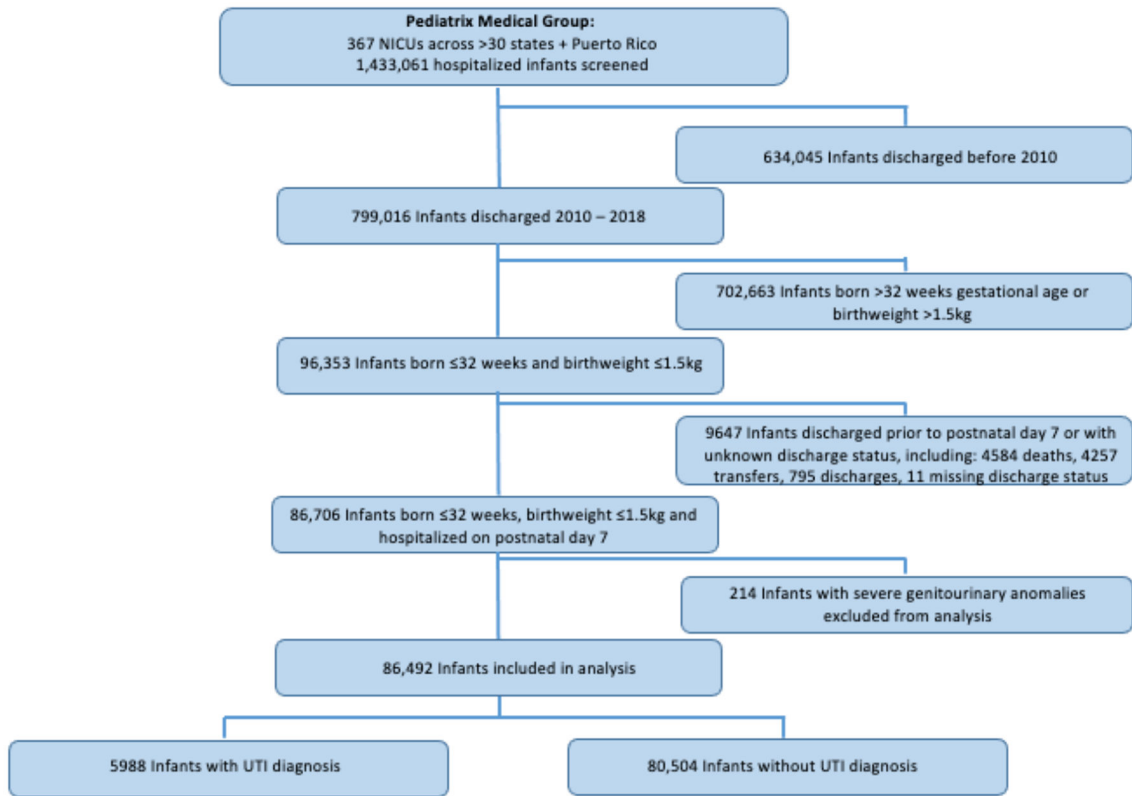
Figure 1. Flow Diagram

This figure displays a flow diagram of the initial study population, exclusions, and the final number of infants included in the analysis.

ELBW = extremely low birth weight; NICU = neonatal intensive care unit; UTI = urinary tract infection; VLBW = very low birth weight
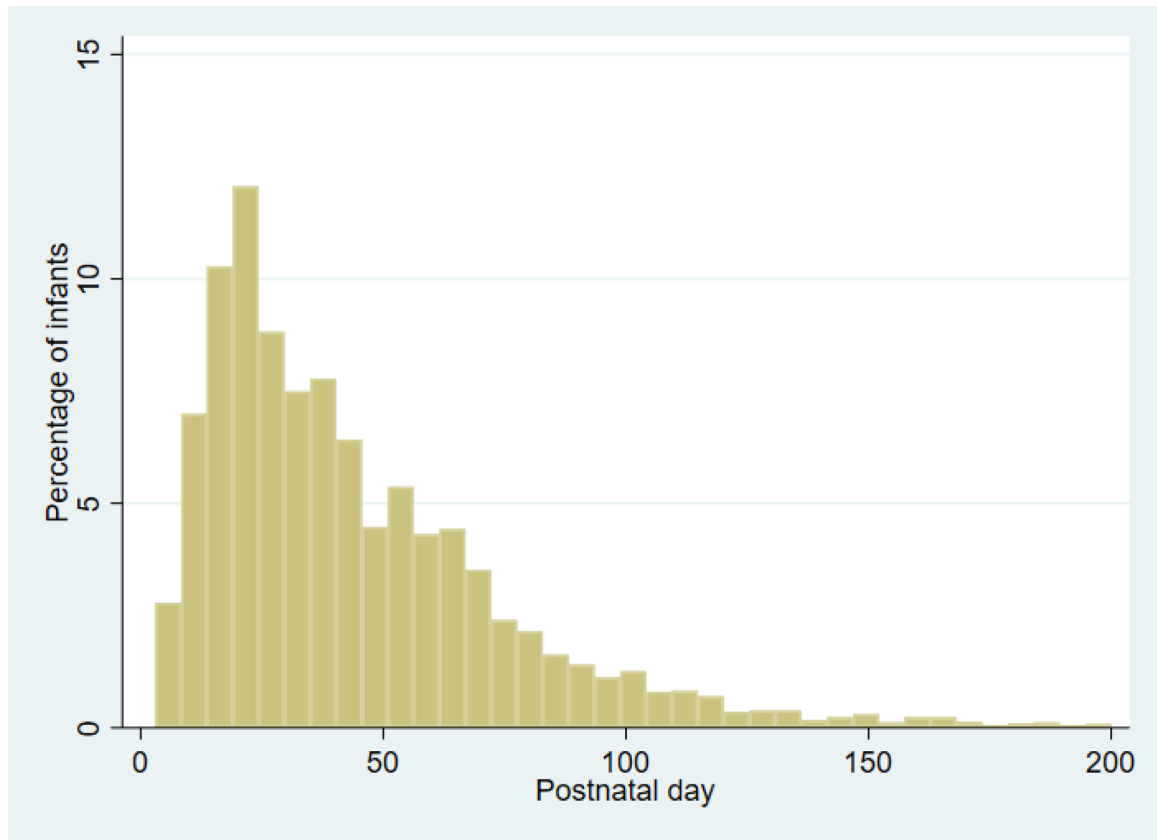
Figure 2. Postnatal Day of First Positive Urine Culture
This figure displays the percentage of infants with first positive urine culture on which postnatal day. Positive urine cultures were most common in infants postnatal age 8–30 days.

Table 1.

Demographics and Clinical Characteristics of Infants with Positive Urine Culture, Negative Urine Culture, and No Urine Culture Collected during Hospitalization

Characteristics	Positive Urine Culture(s) N=5988 (%)	Negative Urine Culture(s) N=16,786 (%)	No Urine Culture N=63,718 (%)
Male	4190 (70)	8637 (51)	30,808 (48)
Gestational age (weeks)			
24	1294 (22)	2733 (16)	5153 (8)
25–28	3427 (57)	8931 (53)	25,687 (40)
29–32	1267 (21)	5122 (31)	32,878 (52)
Small for gestational age	1020 (17)	4062 (24)	10,986 (17)
5-minute Apgar score			
0–3	490 (8)	1225 (7)	2944 (5)
4–6	1375 (24)	3558 (22)	10,081 (16)
7–10	3978 (68)	11,571 (71)	48,920 (79)
Birth weight (grams)			
<500	191 (3)	631 (4)	899 (1)
500–999	3622 (60)	9469 (56)	21,352 (34)
1,000–1500	2175 (36)	6686 (40)	41,467 (65)
Vaginal delivery	1719 (29)	4169 (25)	15,335 (24)
Prenatal steroid exposure	5001 (84)	13,776 (82)	53,415 (84)
Length of hospitalization (days), median (IQR)	91 [68–120]	78 [53–106]	54 [39–76]

UTI = Urinary Tract Infection; IQR = interquartile range

Table 2.

Multivariable Logistic Regression Analysis of Demographic and Clinical Characteristics associated with UTI among All Infants in the Cohort

Characteristics	OR (95% CI)	p-value
Sex		
Female	(Reference)	—
Male	2.53 (2.38–2.70)	<0.001
Gestational age (weeks)		
24	2.03 (1.83–2.26)	<0.001
25–28	1.76 (1.63–1.90)	<0.001
29–32	(Reference)	—
5-minute Apgar Score		
0–3	1.09 (0.98–1.23)	0.13
4–6	1.08 (1.00–1.16)	0.05
7–10	(Reference)	—
Vaginal delivery	1.12 (1.05–1.20)	0.001
Prenatal steroids	1.15 (1.06–1.25)	0.001
Length of hospitalization (days)	1.02 (1.02–1.02)	<0.001

CI = confidence interval; OR = odds ratio; UTI = urinary tract infection

Table 3.

Pathogens Causing First Urinary Tract Infection *

Organism	Frequency	Percent
Enterococcus spp.	1201	20
Escherichia coli	1167	19
Klebsiella spp.	1081	18
Enterobacter	723	12
Candida spp.	375	6
Other	265	4
CoNS	220	4
Other GNR	178	3
GBS	148	2
Staphylococcus aureus	140	2
Citrobacter spp.	138	2
Serratia spp.	136	2
Proteus spp.	110	2
Pseudomonas spp.	84	1

*
All pathogens with percentage of cultures 1% are shown.

CoNS = Coagulase-negative Staphylococcus; GBS = group B Streptococcus; GNR = gram-negative rods, not otherwise specified