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Urinary tract infection concordance with positive blood and cerebrospinal fluid cultures in the neonatal intensive care unit

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Abstract

Objective—Urinary tract infections (UTI) are common in the neonatal intensive care unit (NICU). Blood, urine, and cerebrospinal fluid (CSF) cultures are frequently obtained to evaluate for infection. We sought to determine the concordance between positive urine cultures and blood or CSF cultures.

Study design—Infants <121 days of age with a UTI admitted to 322 NICUs managed by the Pediatrix Medical Group from 1997–2010 were identified. UTIs were defined by isolation of a single pathogenic organism in a urine sample obtained by catheterization or suprapubic tap. The UTI was concordant if the same organism was identified in the blood or CSF within 3 days of the urine culture.

Results—Of 5681 infants with a urine culture, 984 had 1162 UTIs. Nine hundred seventy-six UTIs (84%) had a blood culture collected within 3 days, and 127 (13%) were concordant. Of the 1162 UTIs, 77 (7%) had a CSF culture collected within 3 days, and 2 (3%) were concordant.

Conclusion—Collection of a urine culture in infants evaluated for late-onset sepsis is important. Concordance was observed in 13% of blood cultures and 3% of CSF cultures. These findings may be related to the initiation of empirical antimicrobial therapy before evaluation for disseminated infection or poor blood culture sensitivity.

Keywords

infant; sepsis

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Conflict of interest

Dr. Benjamin receives support from the United States government for his work in pediatric and neonatal clinical pharmacology (1R01HD057956-02, 1R01FD003519-01, 1U10-HD45962-06, 1K24HD058735-01, and Government Contract HHSN267200700051C), from the non-profit organization Thrasher Research Foundation for his work in neonatal candidiasis (http://www.thrasherresearch.org), and from industry for neonatal and pediatric drug development (http://www.dcri.duke.edu/research/coi.jsp). Dr. Smith received support from NICHD 1K23HD060040-01 and DHHS-1R18AE000028-01. Dr. Downey received support from T-32 Multidisciplinary Neonatal Training Grant (2T32 HD043728-06, PI Goldberg). Dr. Watt received support from a T-32 Multidisciplinary Pediatric Training Grant (5T32HD043029-09, PI St. Geme). Dr. Cohen-Wolkowiez received support from the United States government for his work in pediatric and neonatal clinical pharmacology (Government Contract HHSN267200700051C, PI Benjamin) and from NICHD (1K23HD064814-01). No sponsoring agency played a role in the study design; collection, analysis, and interpretation of the data; writing of the report; or the decision to submit the manuscript for publication. The authors have no additional conflicts of interest to disclose.

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Introduction

Urinary tract infections (UTIs) are common among infants admitted to the neonatal intensive care unit (NICU) and are most common in very low birth weight infants (<1500 g birth weight), with a cumulative incidence of 3–25%.[1–4] Infants diagnosed with a UTI are often evaluated with blood and cerebrospinal fluid (CSF) cultures to assess dissemination of infection. Failure to identify the extent of the infection may lead to inadequate treatment.

Published data evaluating the concordance between UTIs and blood and CSF cultures in infants are scarce, and most reports represent single-center experiences.[3–5] Evaluation of concordance is further complicated by the frequent delay in obtaining CSF cultures in infants until there is a positive blood culture result or concern for instability or respiratory compromise.[6]

Determining concordance between urine, blood, and CSF cultures may influence diagnostic evaluations, duration of treatment, and type of antimicrobial therapy, thereby improving clinical decision-making. Here, we report the concordance of urine cultures with blood and CSF cultures obtained from a large cohort of infants admitted to NICUs in North America.

Methods

Study design and setting

We identified all infants <121 days of age admitted to 322 NICUs in North America managed by the Pediatrix Medical Group from 1997–2010. These NICUs represent units in both academic and community settings. The administrative database was created using a computer-assisted tool that generates clinical progress notes. We obtained infant and maternal demographic data and the results of all cultures collected during the first 120 days of life. Patients with missing urine culture data were excluded from the analysis.

Definitions and participants

We defined a UTI as isolation of a single pathogenic organism from a urine culture obtained by catheterization or suprapubic tap. We grouped pathogenic organisms into 3 clinically relevant categories: gram-negative rods (GNR), gram-positive cocci (GPC), and *Candida*. We excluded UTIs for organisms typically considered contaminants, including non-speciated streptococci*, Bacillus sp., Corynebacterium sp., diphtheroids sp.,* gram-positive rods (not including *Listeria sp.), Lactobacillus sp., Micrococcus sp., Stomatococcus sp.,* and *Bacteroides sp.* Coagulase-negative staphylococci (CoNS) infections were defined as definite, probable, or possible. 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 sepsis. We included definite and probable CoNS infections in our analysis.

Urine cultures collected by bag were excluded. Multiple positive urine cultures for the same organism within 21 days were considered collectively as a single UTI. We considered UTIs occurring >21 days apart as separate episodes. We defined concordance between UTIs and blood or CSF cultures as isolation of the same pathogenic organism in blood or CSF within 3 days before or after a UTI diagnosis. Those blood cultures obtained on the same day as a positive urine culture or within a UTI episode with multiple positive urine cultures were described as same-day blood cultures.

Gestational age was determined by the best estimate of last menstrual period, obstetrical record, or clinical examination. Maternal antibiotic use was recorded by the clinician on admission of the infant to the NICU. Urinalysis data and organism quantification in urine culture were not available in the database.

Statistical methods

We compared demographic distributions among infants with and without concordant UTIs using Fisher's exact or chi-square tests. We performed univariable logistic regression analysis between concordant UTIs and gestational age, birth weight, organism group, day of blood culture in relation to urine culture, maternal race/ethnicity, mechanical ventilation on day of life 1, prolonged rupture of membranes (>18 hours), exposure to any antenatal antibiotics, and inborn status clustered by patient. Predictors identified in the univariable analysis were included in a multivariable logistic regression model with stepwise selection (*P* value for removal >0.1). We did not evaluate predictors of concordance between UTIs and CSF cultures because only 2 episodes were found to be concordant. We examined concordance between UTIs and blood cultures according to the day when the blood culture was obtained relative to the UTI with the Fisher's exact or chi-square tests. STATA 12 (College Station, TX) was used to perform the statistical analysis. A $P<0.05$ was considered statistically significant for all tests. Permission to conduct this analysis was provided by the Duke University Institutional Review Board.

Results

We identified 553,035 infants <121 postnatal days of age with at least 1 culture (blood, urine, or CSF) collected (Table 1). The majority of the infants in this cohort were inborn (467,355/553,035 [84.5%]). Of these, 5681 infants had 8029 urine cultures obtained by catheterization or suprapubic tap. One thousand four hundred sixty (18%) of these were obtained in the first 3 days of life. Nine hundred eighty-four infants met our UTI definition. The majority of infants (86%) had a single UTI, 10% had 2 UTIs, 3% had 3 UTIs, and <1% had 4 or more UTIs for a total of 1162 UTIs. Only 36 (3%) of these UTIs occurred in the first 3 days of life. Infants with negative urine cultures had a mean birth weight of 1885 g (5^{th}, 95^{th} percentiles; 600, 3660) and a mean gestational age of 31.9 weeks (24, 40). The mean birth weight of infants with positive urine cultures was 1397 g (560, 3402), and the mean gestational age was 29.1 weeks (24, 39).

On average, infants developed a UTI on day of life 42 (3, 121). For infants <1000 g, 1000–1499 g, 1500–2499 g, and ≥2500 g, the mean day of life of diagnosis of a UTI was 55 (8, 143), 38 (9, 103), 33 (4, 107), and 20 (1, 79), respectively.

Gram-negative organisms were the most frequently isolated organisms from urine cultures (50%), followed by gram-positive organisms (32%), and *Candida* (15%). The most common pathogenic organisms isolated in the urine were *Escherichia coli* (18%), *Candida* sp. (15%), CoNS (14%), and *Enterococcus* (13%).

Of the 1162 UTI episodes, 976 (84%) and 77 (7%) had an associated blood or CSF culture obtained within 3 days, respectively. Of those UTIs, 127/976 (13%) were concordant with blood cultures and 2/77 (3%) with CSF cultures. There were 24,562 infants with bacteremia, and 1780 (6.8%) had a urine culture obtained by catheterization or suprapubic tap during the infection period. The group of infants with concordant UTIs had a higher proportion of infants <26 weeks' gestational age (37% vs. 26%, $P=0.03$) and were more likely to receive mechanical ventilation on day of life 1 (68% vs. 57%, $P=0.02$) (Table 2).

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Candida UTIs had higher rates of concordance among urine and blood cultures (41/179 [23%]) compared with GNRs or GPCs (Table 3). When stratified by birth weight, this remained true in all groups except for those infants ≥ 2500 g, where gram-positive UTIs were most likely to be concordant (Table 4). *Staphylococcus aureus* was the most likely species to be concordant (5/13 [38%]), followed by *Candida*, group B *Streptococcus* (GBS; 6/27 [22%]), and CoNS (30/163 [18%]) (Table 3). There were 2 UTIs concordant with CSF; 1 with GBS and 1 with CoNS. There were 6842/8029 (85%) urine cultures that had at least 1 blood culture obtained within 3 days. The majority (5307/6842 [78%] of these blood cultures were obtained on the same day as the urine culture, while 2070/6842 (30%) were collected within 3 days prior to the urine culture and 1620/6842 (24%) were collected within 3 days following the urine culture. More than 1 blood culture was drawn in some of the infection episodes.

Predictors of concordance between organisms found in UTIs and blood cultures by univariable regression analysis included type of UTI causative organism, receipt of mechanical ventilation on day of life 1, and gestational age less than 26 weeks. However, only organism group remained a significant predictor in the multivariable model (Table 5).

Discussion

Infants <8 weeks of age evaluated in the emergency department routinely have a urine culture collected by catheterization or suprapubic tap as part of a sepsis evaluation.[7] It is strongly recommended that infants >2 months and children <2 years of age with a fever from an unknown source should be evaluated for a UTI.[8] However, premature infants—one of the populations most susceptible to UTIs[1]—do not always have urine collected for a sepsis evaluation.

Few studies have reported on concordance between urine and blood cultures in hospitalized infants, particularly those born prematurely. In this cohort of 6681 infants with 8029 urine cultures obtained by catheterization or suprapubic tap, we found that 13% of UTIs in infants admitted to a NICU are concordant with blood cultures. *Staphylococcus aureus* UTIs were most likely to be concordant (38%), followed by *Candida* (23%). While gram-negative organisms were the most frequent causative organisms for neonatal UTIs, they were concordant with blood cultures only 6% of the time.

A retrospective single-center study evaluated 189 infants <1500 g birth weight who had both blood and urine cultures collected between day of life 6 and 150.[3] Forty-eight (25%) infants had positive urine cultures, and 18/48 (38%) of the positive urine cultures had a concordant blood culture. Another single-center retrospective study investigated 6198 preterm infants (1127 <1500 g at birth).[4] Fifty-six (0.9%) of all infants developed UTIs diagnosed by catheterization or suprapubic tap. Six of 56 (11%) infants had the same organism isolated from both the blood and urine cultures. Finally, a retrospective single-center study[5] of 57 infants (36 with birth weights <1000 g) with 60 hospital-acquired UTIs after day of life 7 found that 16/60 (27%) UTIs had concordant blood cultures. Fungal UTIs were concordant in 13/25 (52%) of UTIs, and bacterial UTIs were concordant in 3/35 (8%). The proportion of concordant UTIs in this study is 13% and on the lower end of the range relative to previous reports. Exposure to empirical antibiotics prior to collection of urine or blood cultures may account for the lower observed concordance. Exposure to empirical antibiotic therapy may also explain the low concordance observed when blood cultures were obtained in the 3 days after the urine culture.

In our study, CoNS was the most common gram-positive organism isolated in the urine and was concordant with a blood culture in 30/163 (18%) of cases. It is unclear if the high concordance observed among CoNS UTIs and blood cultures suggests true infection, given that this organism colonizes the skin[9,10] and may contaminate both urine and blood cultures at the time of collection. This is particularly important in small infants, for whom catheterization may be technically difficult and require multiple attempts. However, many premature infants in the NICU have central venous catheters and other risk factors for late-onset sepsis.[11–13] CoNS is the most common cause of late-onset sepsis in the NICU.[11,14–16] Additionally, the frequency and concordance of CoNS UTIs are not unique to the present report. In a study of infants with birth weights <1500 g with UTIs caused by CoNS, 7/9 (78%) had a concordant blood culture.[3]

Infants in our cohort with UTIs were predominantly male (64% in those with concordant UTIs and 66% in those without). This is consistent with previous literature demonstrating that hospitalized male infants, particularly with birth weights <1000 g, are at higher risk of UTIs compared with female infants.[1,2,4,17,18] However, over the first several months, the incidence of UTIs decreases in males and increases in females and, by 1 year of age, UTIs are more frequent in females.[18,19]

Our finding of few concordant CSF cultures is consistent with previous studies. In a study of 56 premature infants with a UTI who underwent a full sepsis evaluation, no pathogens were isolated in the CSF.[4] A prospective study of 82 infants ≤60 days of age presenting to the emergency department with UTIs who underwent a lumbar puncture found only 1 (1%) infant with a positive CSF culture.[20] The low frequency of concordance observed between UTI and CSF cultures in the present study should be interpreted with caution as only 7% of infants with urine cultures had CSF cultures obtained. Administration of empirical antibiotic therapy prior to obtaining a CSF culture may contribute to the low number of concordant meningitis cases. Additionally, it has been reported that a third of all infants with a positive CSF culture will have a negative blood culture.[21] This finding underscores the importance of performing lumbar punctures in infants with suspected sepsis.

Collection of a urine culture in infants evaluated for late-onset sepsis is important. Because only 13% of UTIs are concordant, the blood culture cannot be relied upon as a screen. Cultures should be obtained when possible by either catheterization or suprapubic tap any time infection is suspected.

This study is the largest report to date on UTI concordance with blood and CSF cultures in infants admitted to a NICU. The cohort was assembled from 322 NICUs in North America, including both academic and community sites, making these findings generalizable to a wide range of NICU populations. This study is limited, however, by the lack of quantification (colony counts) of pathogens in urine cultures, urinalysis data, organism sensitivities to antibiotics, information on exposure to empirical antimicrobial therapy, and information related to urinary tract anomalies. In addition, we were unable to differentiate between cultures obtained by catheterization or suprapubic tap.

We observed concordance between blood and urine cultures in 13% of UTIs among infants admitted to the NICU. Future investigations should examine contamination rates of various types of urine samples (catheterization vs. bagged specimens), the usefulness of colony counts, and long-term outcomes following urinary tract infection.

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Table 1

Demographics of infants with urine cultures

	Infants with negative urine cultures, N=4697 (%)	Infants with positive urine cultures, N=984 (%)	*P*
Birth weight (g)			<0.01
<1000	1323 (28%)	462 (47%)	
1000–1499	843 (18%)	222 (23%)	
1500–2499	1045 (22%)	138 (14%)	
≥2500	1466 (31%)	161 (16%)	
Gestational age (weeks)			<0.01
<26	635 (14%)	268 (27%)	
26–28	949 (20%)	278 (28%)	
29–33	1131 (24%)	230 (23%)	
34–36	812 (17%)	80 (8%)	
≥37	1170 (25%)	128 (13%)	
Sex			<0.01
Male	2587 (55%)	648 (66%)	
Race/ethnicity			<0.01
White	1771 (39%)	444 (46%)	
Black	661 (14%)	205 (21%)	
Hispanic	1979 (43%)	270 (28%)	
Other	182 (4%)	46 (5%)	
Delivery			0.92
Cesarean section	2807 (60%)	590 (60%)	
Mechanical ventilation on day of life 1			<0.01
Yes	1909 (41%)	578 (59%)	

Table 2

Demographics of infants with UTIs who had both urine and blood or CSF cultured

	Infants without concordant UTIs, N=858	Infants with concordant UTIs, N=126	*P*
Birth weight (g)			0.29
<1000	393 (46%)	69 (55%)	
1000–1499	196 (23%)	26 (21%)	
1500–2499	124 (14%)	14 (11%)	
≥2500	144 (17%)	17 (13%)	
Gestational age (weeks)			0.03
<26	222 (26%)	46 (37%)	
26–28	250 (29%)	28 (22%)	
29–33	197 (23%)	33 (26%)	
34–36	75 (9%)	5 (4%)	
≥37	114 (13%)	14 (11%)	
Sex			0.68
Male	567 (66%)	81 (64%)	
Race/ethnicity			0.76
White	384 (46%)	60 (48%)	
Black	178 (21%)	27 (22)%	
Hispanic	240 (29%)	30 (24%)	
Other	39 (5%)	7 (6%)	
Delivery			0.80
Cesarean section	513 (60%)	77 (61%)	
Mechanical ventilation on day of life 1			0.02
Yes	492 (57%)	86 (68%)	

Abbreviation: UTI, urinary tract infection.

Table 3

Proportion of UTIs concordant with blood and CSF cultures

Organism	Blood	CSF
Gram-positive cocci	52/318(16%)	2/24 (8%)
CoNS	30/146 (21%)	1/9 (11%)
Enterococcus	10/128 (8%)	0/10(0%)
Group B *Streptococcus*	6/24 (25%)	1/2 (50%)
Staphylococcus aureus	5/12 (42%)	0/2 (0%)
Gram-negative rods	34/478 (7%)	0/34 (0%)
Escherichia coli	10/173 (6%)	0/13 (0%)
Enterobacter	12/108 (11%)	0/8 (0%)
Klebsiella	4/92 (4%)	0/5 (0%)
Serratia	3/35 (9%)	0/2 (0%)
Pseudomonas	2/27 (7%)	0/4 (0%)
Proteus	2/13 (15%)	0/0
Candida	41/147 (28%)	0/19 (0%)

Abbreviations: CSF, cerebrospinal fluid; CoNS, coagulase-negative staphylococci.

Table 4

Proportion of UTIs concordant with blood cultures stratified by birth weight

Organism	<1000 g (N=568)	1000–1499 g (N=264)	1500–2499 g (N=157)	≥2500 g (N=172)
Gram-positive cocci	21/148 (14%)	13/96 (14%)	7/66 (11%)	11/58 (20%)
CoNS	18/80 (23%)	8/39 (21%)	2/23 (9%)	2/21 (10%)
Enterococcus	3/57 (5%)	2/46 (4%)	2/32 (6%)	3/17 (18%)
Group B *Streptococcus*	0/2 (0%)	2/5 (40%)	1/7 (14%)	3/13 (23%)
Staphylococcus aureus	0/5 (0%)	1/2 (50%)	1/1 (100%)	3/5 (60%)
Gram-negative rods	18/281 (6%)	7/121 (6%)	4/76 (5%)	5/101 (5%)
Escherichia coli	4/85 (5%)	3/42 (7%)	1/31 (3%)	2/51 (4%)
Enterobacter	7/68 (10%)	2/26 (8%)	2/18 (11%)	1/15 (7%)
Klebsiella	2/55 (4%)	2/30 (7%)	0/11 (0%)	0/17 (0%)
Serratia	3/24 (13%)	0/7 (0%)	0/3 (0%)	0/5 (0%)
Pseudomonas	1/24 (4%)	0/3 (0%)	0/5 (0%)	1/3 (33%)
Proteus	1/8 (13%)	0/3 (0%)	1/2 (50%)	0/2 (0%)
Candida	31/121 (26%)	6/35 (17%)	3/13 (23%)	1/9 (11%)

Abbreviations: CoNS, coagulase-negative staphylococci.

Table 5

Predictors of concordance with blood cultures by univariable and multivariable regression

	Univariable regression		Multivariable regression	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Organism type				
Gram-negative rods	1.00		1.00	
Gram-positive cocci	2.64 (1.69, 4.13)	<0.01	2.37 (1.63, 4.59)	<0.01
Candida	4.76 (2.90, 7.82)	<0.01	6.14 (3.50, 10.79)	<0.01
Sex				
Female	1.00		-	
Male	0.88 (0.59, 1.29)	0.51	-	
Gestational age				
<26 weeks	1.00		-	
≥26 weeks	0.67 (0.44, 0.98)	0.04	-	
Birth weight				
<1000 g	1.00		-	
≥1000 g	0.76 (0.52, 1.10)	0.14	-	
Mechanical ventilation on day of life 1				
No	1.00		-	
Yes	1.40 (0.95, 2.09)	0.09	-	
PROM				
No	1.00		-	
Yes	0.76 (0.49, 1.19)	0.24	-	
Antenatal antibiotics				
No	1.00		-	
Yes	0.96 (0.66, 1.39)	0.82	-	
Inborn				
No	1.00		-	
Yes	0.80 (0.51, 1.26)	0.33	-	

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; CoNS, coagulase-negative staphylococci; OR, odds ratio; PROM, premature rupture of membranes.