Prevalence of Concomitant Acute Bacterial Meningitis in Neonates with Febrile Urinary Tract Infection: A Retrospective Cross-Sectional Study

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Objective To describe the frequency of concomitant acute bacterial meningitis (ABM) in neonates with febrile urinary tract infection (UTI).

Study design This was a retrospective cross-sectional study from 2005 to 2013 of infants ≤30 days old evaluated in the emergency department of a quaternary care children's hospital with fever and laboratory-confirmed UTI. Definite ABM was defined as cerebrospinal fluid (CSF) culture with growth of pathogenic bacteria and probable ABM if pleocytosis with ≥ 20 white blood cell was present in an antibiotic-pretreated patient. The timing of lumbar puncture and first antibiotic dose was recorded to assess for antibiotic pretreatment.

Results A total of 236 neonates with UTI were included. Mean age was 18.6 days (SD 6.2); 79% were male infants. Twenty-three (9.7%) had bacteremia. Fourteen (6%) were pretreated. No neonate (0%; 95% CI 0%-1.6%) had definite ABM and 2 (0.8%; 95% CI 0.1%-3.0%) neonates with bloody CSF had probable ABM. CSF white blood cell count was 25 and 183 for these 2 infants, and CSF red blood cell count was 3100 and 61 932, respectively. Another neonate had herpes simplex virus meningoencephalitis.

Conclusions The frequency of ABM in neonates with febrile UTI is low. Further prospective studies are needed to evaluate the safety of a tiered approach to evaluate for serious bacterial infection, in which lumbar puncture potentially could be avoided in well-appearing febrile neonates with suspected UTI. *(J Pediatr 2017;184:199-203).*

Urinary tract infections (UTIs) are the most common bacterial cause of fever in young infants.[1,2] Controversy exists as to whether cerebrospinal fluid (CSF) testing is needed for all young infants with UTIs. Studies have shown that acute bacterial meningitis (ABM) is rare beyond the neonatal period.[3-7] In a review of 14 studies, predominantly of children in the first 90 days of life, the prevalence of concomitant ABM in children with UTIs ranged from 0% to 2%.[5] One retrospective study of 1609 infants 29-60 days old with febrile UTI found ABM in 0.3% of infants.[7] Many of these studies were limited by their retrospective nature, lack of a standard definition for UTI, and potential for over-diagnosis of UTI because of inclusion of urine specimens collected using a bag.[5]

Fewer data are available for neonates, a population at higher risk for ABM because of immunologic immaturity and concern for bacterial seeding of the CSF.[8] This risk leads to more lumbar punctures (LPs) being performed in neonates than in older infants,[9] but the need to obtain CSF in all neonates with suspected UTI is unclear. There is already substantial practice variation in the acquisition of CSF, with studies showing that CSF is obtained from 47% to 72% of young infants across various centers.[4,6,9,10] The frequency of ABM has varied substantially, with reports of neonatal ABM ranging from 0% to 2.6% of febrile neonates in whom CSF is obtained.[11-17] These studies have additional limitations with poor precision of the estimate of ABM because of inclusion of small numbers of neonates with laboratory-confirmed UTI and lack of a systematic determination of antibiotic pretreatment prior to lumbar puncture.[12-19] We determined the frequency of concomitant ABM in a population of febrile neonates with UTI while measuring antibiotic pretreatment.

Methods

We conducted a retrospective cross-sectional study from January 1, 2005, to June 30, 2013, of neonates presenting to the emergency department (ED) at Texas Children's Hospital, a large freestanding children's hospital. Patients were identified via a microbiology database for positive urine cultures and cross-referenced with medical record list of patients with discharge diagnosis of UTI using *International Classification of Diseases, Ninth Revision* codes: 599.0D UTI, 599.0FA febrile UTI, or 771.82A neonatal UTI. Electronic medical records

ABM	Acute bacterial meningitis	LPs	Lumbar punctures
CFUs	Colony forming units	PCR	Polymerase chain reaction
CSF	Cerebrospinal fluid	UTIs	Urinary tract infections
ED	Emergency department	WBC	White blood cell
HSV	Herpes simplex virus		

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were reviewed, and data were recorded on a standard data collection form. The study was approved by the institutional review board.

To be included in the study, the infant had to be <30 days of age, present to the ED with fever >100.4°F (38.0°C) rectally or by historical report, have a laboratory-confirmed UTI, and have CSF obtained via lumbar puncture. UTI was defined as any growth on a culture collected by suprapubic aspiration. For urine collected by catheterization, either ≥50 000 colony forming units (CFUs) of a pathogen on urine culture or >10 000 CFU/mL plus a suggestive urinalysis was considered a UTI.[7] Urinalysis was suggestive of UTI if positive leukocyte esterase or microscopy with white blood cell (WBC) count was ≥5 per high-powered field.[20,21] Enhanced urinalysis was unavailable.

Infants whose urine samples were collected by methods other than suprapubic aspiration or catheterization were excluded. Additional exclusion criteria were a hospital-acquired UTI, history of spina bifida/myelomeningocele, and history of spinal instrumentation.

Population Characteristics

Baseline data collected included age, prematurity, ethnicity, sex, pathogen recovered from urine culture, method of acquiring urine specimen, grade of vesicoureteral reflux, obstructive and nonobstructive anatomic anomalies on imaging, comorbidities (severe systemic diseases including complex heart, chronic lung, metabolic or neurologic diseases),[7] history of previous UTI, history of previous hospitalization, circumcision status, and clinical appearance (ill, well, or undetermined). Ill appearance was defined as at least 2 of the following within the physical examination portion of the admission note: "ill-appearing," "dehydrated," "respiratory distress," "irritability," "pallor," "mottling," or "cyanosis."[7,22,23] Neonates with just one of these terms, with contradictory terms ("pale pink"), or with other vital sign related descriptors ("tachycardia," "tachypnea") were considered undetermined appearance. In absence of any of the above-described features, neonates were considered well appearing. Other data collected were the number of days of fever at time of presentation, shock upon presentation (systolic blood pressure <60, receipt of >40 mL/kg of normal saline, or vasopressors),[7] peripheral WBC count, absolute neutrophil count, absolute band count, bacteremia, and admission unit. Antibiotic pretreatment prior to CSF culture, total number of lumbar puncture attempts, CSF WBCs, CSF red blood cells, and viral testing of CSF were recorded. Antibiotic pretreatment was determined by comparing the time of lumbar puncture with the time of first receipt of antibiotics. Medical records also were reviewed to determine whether there was any antibiotic given before arrival to ED. Urinalysis dipstick results (defined as positive if positive for leukocyte esterase) and microscopy results (positive defined as presence of ≥5 WBC per high-powered field) also were recorded.[20,21]

Outcome

The outcome was the percentage of patients with ABM, defined as either definite or probable. Definite bacterial meningitis was defined as any bacterial growth on CSF culture. Probable bacterial meningitis was defined as pleocytosis in the presence of antibiotic pretreatment with no viral pathogen identified in the CSF. Neonates with readmission within 30 days for bacterial meningitis caused by the same pathogen also were considered to have probable bacterial meningitis. Pleocytosis was defined as >20 WBC/mm^3.[24]

Data Analyses

Summary statistics were used to describe frequencies, measures of central tendency, and dispersion for baseline and outcome variables. Data was analyzed using Stata v 13 (StataCorp, College Station, Texas).

Results

In total, 342 infants were identified who met inclusion criteria for age, fever, and UTI. Of these, 236 infants ultimately were included; 106 infants were excluded for the following reasons: 52 had missing data to verify eligibility, 45 had hospital-acquired UTI, and 9 had no CSF sample. Of the 9 infants with no CSF, none had a return ED visit or readmission within 30 days of discharge.

The study population included a predominance of uncircumcised males and well appearing neonates. (**Table I**). One infant had a previous UTI. Only 3 infants (1.3%) had a previous hospitalization for any reason. Infants came to attention after a median of 1 day of fever (range 1-10 days). Five infants (2.1%) had signs of shock at the time of ED evaluation. Fourteen infants (5.9%) had been pretreated with antibiotics before LP; the antibiotics used were ampicillin (n = 12),

Table I. Characteristics of study population

Characteristics	Total population n = 236
Mean age, d (SD)	18.6 (6.2)
Male (%)	187/236 (79.2)
Ethnicity (%)	
Hispanic	142/236 (60.2)
Non-Hispanic White	38/236 (16.1)
Non-Hispanic Black	36/236 (15.3)
Asian	9/236 (3.8)
Missing	8/236 (3.4)
Other	3/236 (1.3)
Clinical appearance (%)	
Ill	14/236 (5.9)
Well	186/236 (78.8)
Undetermined	36/236 (15.3)
Premature	18/233 (7.7)
Comorbidities	3/236 (1.3)
Circumcision status (%)	
Uncircumcised male	137/187 (73.3)
Circumcised male	18/187 (9.6)
Missing	32/187 (17.1)
Genitourinary tract anomalies (%)*	28/235 (11.9)
Obstructive	8/235 (3.4)
Nonobstructive	20/235 (8.5)
Vesicoureteral reflux (%)	55/217 (25.3)
Grades I-III	36/217 (16.6)
Grades IV-V	19/217 (8.8)

*All genitourinary tract anomalies were detected by renal bladder ultrasound scan except for 1 neonate with a genitourinary sinus detected by voiding cystourethrogram.