

# Parenteral Antibiotic Therapy Duration in Young Infants With Bacteremic Urinary Tract Infections

Sanyukta Desai, MD,<sup>a</sup> Paul L. Aronson, MD, MHS,<sup>b,c,d</sup> Veronika Shabanova, PhD,<sup>b,e</sup> Mark I. Neuman, MD, MPH,<sup>f</sup> Frances Balamuth, MD, PhD,<sup>g,h</sup> Christopher M. Pruitt, MD,<sup>i</sup> Adrienne G. DePorre, MD,<sup>j</sup> Lise E. Nigrovic, MD, MPH,<sup>k</sup> Sahar N. Rooholamini, MD, MPH,<sup>k</sup> Marie E. Wang, MD, MPH,<sup>l</sup> Richard D. Marble, MD,<sup>m</sup> Derek J. Williams, MD, MPH,<sup>n</sup> Laura Sartori, MD,<sup>o</sup> Rianna C. Leazer, MD,<sup>p</sup> Christine Mitchell, BSN,<sup>g</sup> Samir S. Shah, MD, MSCE,<sup>q,d</sup> ON BEHALF OF THE FEBRILE YOUNG INFANT RESEARCH COLLABORATIVE

**OBJECTIVES:** To determine the association between parenteral antibiotic duration and outcomes in infants  $\leq 60$  days old with bacteremic urinary tract infection (UTI).

abstract

**METHODS:** This multicenter retrospective cohort study included infants  $\leq 60$  days old who had concomitant growth of a pathogen in blood and urine cultures at 11 children's hospitals between 2011 and 2016. Short-course parenteral antibiotic duration was defined as  $\leq 7$  days, and long-course parenteral antibiotic duration was defined as  $> 7$  days. Propensity scores, calculated using patient characteristics, were used to determine the likelihood of receiving long-course parenteral antibiotics. We conducted inverse probability weighting to achieve covariate balance and applied marginal structural models to the weighted population to examine the association between parenteral antibiotic duration and outcomes (30-day UTI recurrence, 30-day all-cause reutilization, and length of stay).

**RESULTS:** Among 115 infants with bacteremic UTI, 58 (50%) infants received short-course parenteral antibiotics. Infants who received long-course parenteral antibiotics were more likely to be ill appearing and have growth of a non-*Escherichia coli* organism. There was no difference in adjusted 30-day UTI recurrence between the long- and short-course groups (adjusted risk difference: 3%; 95% confidence interval:  $-5.8$  to  $12.7$ ) or 30-day all-cause reutilization (risk difference: 3%; 95% confidence interval:  $-14.5$  to  $20.6$ ).

**CONCLUSIONS:** Young infants with bacteremic UTI who received  $\leq 7$  days of parenteral antibiotics did not have more frequent recurrent UTIs or hospital reutilization compared with infants who received long-course therapy. Short-course parenteral therapy with early conversion to oral antibiotics may be considered in this population.



Divisions of <sup>a</sup>Hospital Medicine and <sup>q</sup>Infectious Diseases, Department of Pediatrics, College of Medicine, University of Cincinnati and Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; <sup>d</sup>Sections of Pediatric Emergency Medicine and <sup>e</sup>General Pediatrics and <sup>b</sup>Departments of Pediatrics and <sup>c</sup>Emergency Medicine, Yale School of Medicine, Yale University, New Haven, Connecticut; <sup>f</sup>Division of Emergency Medicine, Department of Pediatrics, Harvard Medical School, Harvard University and Boston Children's Hospital, Boston, Massachusetts; <sup>g</sup>Division of Emergency Medicine and <sup>h</sup>Center for Pediatric Clinical Effectiveness, Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania and Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; <sup>i</sup>Division of Pediatric Emergency Medicine, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama; <sup>j</sup>Division of Hospital Medicine, Department of Pediatrics, Children's Mercy Hospital, Kansas City, Missouri; <sup>k</sup>Division of Hospital Medicine, Department of Pediatrics, School of Medicine, University of Washington and Seattle Children's Hospital, Seattle, Washington; <sup>l</sup>Division of Pediatric Hospital Medicine, Department of Pediatrics, School of Medicine, Stanford University and Lucile Packard Children's Hospital Stanford, Palo Alto, California; <sup>m</sup>Division of Emergency Medicine, Feinberg School of Medicine, Northwestern University and Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois; (Continued)

**WHAT'S KNOWN ON THIS SUBJECT:** Infants  $\leq 60$  days old with bacteremic urinary tract infection often receive prolonged courses of parenteral antibiotics. The safety of short-course parenteral antibiotic therapy has not been established in this population.

**WHAT THIS STUDY ADDS:** In this multicenter study of infants  $\leq 60$  days old with bacteremic urinary tract infection, infants receiving  $\leq 7$  days of parenteral antibiotics did not experience more frequent UTI recurrence or hospital reutilization compared with infants receiving  $> 7$  days of parenteral therapy.

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Urinary tract infection (UTI) is 1 of the most common bacterial infections in infants  $\leq 60$  days of age.<sup>1-3</sup> Approximately 8% to 10% of young infants with UTI have concomitant bacteremia.<sup>2,4,5</sup> However, no evidence-based guidelines exist to direct management in this population, particularly regarding optimal parenteral (ie, intravenous and/or intramuscular [IV/IM]) antibiotic duration.

Although several studies have supported the safety of short-course parenteral antibiotic therapy with early conversion to oral antibiotics in young infants with uncomplicated UTI,<sup>6-8</sup> the safety of short-course parenteral antibiotic therapy in young infants with bacteremic UTI has not been established. As a result, infants with bacteremic UTI often receive prolonged courses of parenteral antibiotics, which can lead to long hospitalizations and increased costs. Furthermore, the peripherally inserted central catheters (PICCs) often required to deliver prolonged parenteral antibiotic therapy expose infants to added risks, including catheter-associated bloodstream infections as well as mechanical and thrombotic central-line complications.<sup>9,10</sup> The benefit of prolonged parenteral antibiotic therapy is unclear in this population.<sup>6,8,11</sup>

Our objective for this study was to examine the association between parenteral antibiotic duration and clinical outcomes in infants  $\leq 60$  days old with bacteremic UTI.

## METHODS

### Study Design

This study was nested within a multicenter retrospective cohort study<sup>12,13</sup> of young infants evaluated for invasive bacterial infections in the emergency departments (EDs) of 11 geographically diverse children's hospitals (Supplemental Table 3). The

study was approved by each site's institutional review board with a waiver of informed consent and permission for data sharing.

### Study Population

Infants  $\leq 60$  days old who presented to the EDs of the 11 participating hospitals between July 1, 2011, and June 30, 2016, were included in the parent study if they had a bacterial pathogen isolated in blood or cerebrospinal fluid (CSF) culture. Pathogenic bacteria were determined a priori via literature review and expert consensus (Supplemental Table 4).<sup>12,13</sup> For this substudy, we included infants from the parent study who were diagnosed with a UTI and had detection of the same bacterial pathogen in both blood and urine cultures (Fig 1). UTI was defined as growth of  $\geq 50\,000$  colony-forming units (CFUs)/mL of a pathogen in urine culture or growth of  $\geq 10\,000$  CFUs/mL of a pathogen in urine culture plus an abnormal urinalysis (defined as presence of leukocyte esterase, nitrites, or  $>5$  white blood cells per high-power field on urine microscopy).<sup>4,14,15</sup> We excluded infants who had a bag or unknown collection method for urine culture if pathogen growth was  $<100\,000$  CFUs/mL or if multiple organisms were isolated because these organisms could represent contaminants.<sup>16,17</sup> Infants who had concomitant bacterial meningitis, infants with CSF pleocytosis who received antibiotic pretreatment, and infants with examination and laboratory findings consistent with focal infections, such as septic arthritis, were also excluded from our cohort because these infants would likely be prescribed prolonged courses of parenteral antibiotics for treatment of other invasive infections. Finally, we excluded infants who died and those who were transferred out from the participating institution before completion of parenteral antibiotic therapy because we could

not report total duration of IV/IM antibiotic therapy in these patients.

### Data Sources

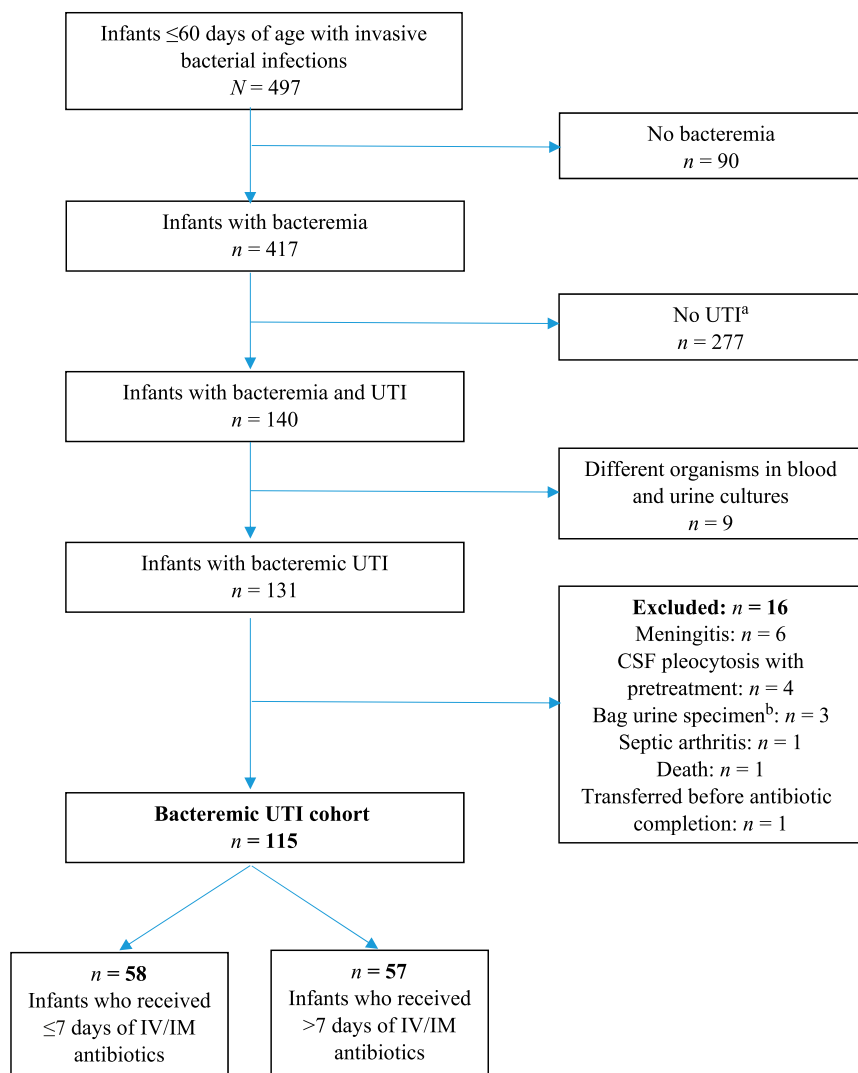
Each site's electronic medical record system or microbiology laboratory was queried to identify all infants who had a positive blood or CSF culture result collected in the ED during the study period. A medical record review was then conducted to confirm eligibility. Information on patient demographics, clinical variables (eg, presence of fever and physical examination findings), laboratory data, parenteral antibiotic duration, adverse events, and 30-day ED revisit or readmission were also obtained via detailed medical record review.

### Exposure

The exposure of interest was duration of parenteral antibiotic therapy. Patients were divided into short-course and long-course exposure groups. Given that we found a somewhat bimodal distribution of parenteral antibiotic duration with a median duration of 7 days (Supplemental Fig 2), we defined short course as receipt of parenteral antibiotics for  $\leq 7$  days and long course as receipt of parenteral antibiotics for  $>7$  days.

### Outcomes

The primary outcome was recurrence of UTI that resulted in an ED revisit or hospitalization within 30 days of discharge from the index hospital admission. For infants who had recurrent UTI, we conducted additional medical record review to obtain information on timing of recurrence, causative organism at recurrence, presence of bacteremia or meningitis at recurrence, diagnosis of vesicoureteral reflux (VUR), and use of prophylactic antibiotics before recurrence. Secondary outcomes included hospital length of stay (LOS), 30-day all-cause reutilization (defined as hospital readmission or ED revisit within 30 days of index discharge),



**FIGURE 1** Flowchart of the study population. <sup>a</sup> UTI definition: positive urine culture result with  $\geq 50\,000$  CFUs/mL or  $\geq 10\,000$  CFUs/mL with an abnormal urinalysis (leukocyte esterase-positive or nitrite-positive or  $>5$  WBCs). <sup>b</sup> Patients who had a bag or unknown method of urine culture collection were excluded if the culture grew  $<100\,000$  CFUs/mL or if  $>1$  organism was isolated. WBC, white blood cell.

and adverse events within 30 days of discharge (ie, readmission to an ICU, need for mechanical ventilation or vasopressor use, or neurologic sequelae).

### Covariates

Covariates of interest included patient age, sex, prematurity (defined as gestational age  $<37$  weeks), complex chronic condition,<sup>18</sup> known genitourinary anomaly, presence of fever (ie, a reported temperature  $\geq 38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) at home, in an

outpatient clinic, or documented in the ED and obtained via any method), ill appearance, ICU stay during the index admission, causative pathogen, and prolonged bacteremia. Ill appearance was defined as any of the following physical examination terms documented on arrival to the ED: “ill appearing,” “toxic,” “limp,” “unresponsive,” “gray,” “cyanotic,” “apnea,” “weak cry,” “poorly perfused,” “grunting,” “listless,” “lethargic,” or “irritable.”<sup>19</sup> If none of these terms were documented, the infant was

classified as not ill appearing. In cases of contradicting documentation of ill appearance between attending physician and trainee, the attending physician’s documentation was used. Prolonged bacteremia was defined as isolation of the initial pathogen on a repeat blood culture drawn at least 24 hours after the initial culture.<sup>20</sup>

### Statistical Analysis

Categorical variables were described by using frequencies and percentages. To adjust for potential confounding by indication for duration of parenteral antibiotic therapy, we generated a propensity score for each patient to estimate the conditional probability of receiving long-course parenteral antibiotic therapy.<sup>21,22</sup> Propensity scores were calculated by using a multivariable logistic regression model that consisted of baseline demographic characteristics (ie, age and sex), past medical history (ie, prematurity, presence of chronic complex condition, and known genitourinary anomaly), and clinical characteristics at presentation (ie, fever, ill appearance, ICU stay, prolonged bacteremia, and causative organism).

We then conducted inverse probability weighting (IPW), aiming to achieve balance in the distribution of covariates between exposure groups by multiplying each study observation by the inverse of its respective propensity score to achieve a statistically balanced pseudo-study population.<sup>21</sup> Distributional balance of covariates between short-course and long-course antibiotic groups after the weighting procedure was examined by using standardized mean differences, with the magnitude of  $\leq 0.1$  indicating acceptable balance (Supplemental Table 5).<sup>21</sup> One variable, prolonged bacteremia, remained unbalanced; however, it was neither significantly associated with the outcomes of recurrent UTI and reutilization, as tested by Fisher’s

exact test, nor with LOS, as tested by the Wilcoxon rank test. To incorporate the effect of study site, we attempted 2 additional models to generate propensity scores: 1 in which study site was used as a fixed-effect predictor in the above logistic regression and a second in which a random intercept was added for each study site. However, neither model yielded adequate balance between covariates. Thus, the multivariable logistic regression model without study site (Supplemental Table 5) was used for the analysis.

To evaluate the association of antibiotic duration with our outcomes of interest, we employed marginal structural models and applied them to our weighted population.<sup>23</sup> We used the logit link function to estimate the probability of recurrent UTI and reutilization in each group and summarized our findings using both relative risk and risk difference. We used the identity link to estimate the adjusted difference in the mean LOS between short-course and long-course treatment groups. Natural log transformation was applied to LOS before its modeling in the marginal structural models. Statistical significance was established at the 2-sided  $\alpha$  level of .05. Data were analyzed by using R version 3.4.3 statistical software<sup>24</sup> and by using the following statistical packages: lme4,<sup>25</sup> tableone,<sup>26</sup> ipw,<sup>27</sup> sandwich,<sup>28</sup> and survey.<sup>29</sup>

## RESULTS

### Patient Characteristics

Of the 497 infants  $\leq 60$  days old in the parent study cohort who had a pathogen isolated in blood or CSF culture, we identified 140 infants with bacteremia and UTI caused by the same pathogen. Applying exclusion criteria, we assembled a cohort of 115 infants  $\leq 60$  days of age with bacteremic UTI (Fig 1). Of this cohort, 52% of infants were

$\leq 28$  days of age, 60% were boys, and 9% were premature (Table 1). A subset of patients had a complex chronic condition or known genitourinary anomaly on admission, and the majority of infants presented with fever (Table 1).

Urine culture was obtained via catheterization for 110 (96%) infants in our cohort. *Escherichia coli* was the most common causative organism and was found in 93 infants (81%). Six infants (5%) grew *Enterococcus faecalis*, 5 (4%) grew *Staphylococcus aureus*, 4 (3%) grew *Klebsiella* spp, 3 (3%) infants grew *Streptococcus agalactiae*, 3 (3%) grew *Enterobacter* spp, and 1 (1%) grew *Citrobacter* spp from blood and urine cultures. Of note, all 5 infants with *S aureus* bacteremia were eventually diagnosed with urinary tract anomalies.

We included a total of 5 patients growing  $>100\,000$  CFUs/mL of *E coli* in a bagged urine specimen. Of these, 4 had evidence of pyuria, and 1 patient did not have a urinalysis conducted. All patients grew *E coli* in the blood with identical antibiotic susceptibilities.

Eight infants (7%) had prolonged bacteremia; all 8 patients with prolonged bacteremia in our cohort grew organisms that were sensitive to the empirical antibiotics they had

been receiving since admission. No patients grew extended-spectrum  $\beta$ -lactamase-producing organisms in a blood or urine culture. All pathogens identified in our cohort were susceptible to an antibiotic with an available oral alternative.

The median duration of parenteral antibiotic therapy was 7 days (range: 2–24 days). The 3 most common parenteral treatment durations were 14 days (27 infants; 23%), 7 days (18 infants; 16%), and 10 days (13 infants; 11%) (Supplemental Fig 2). Overall, 58 (50%) infants received short-course parenteral antibiotics ( $\leq 7$  days), and 57 (50%) infants received long-course parenteral antibiotics. The proportion of infants receiving short-course parenteral antibiotic therapy varied by institution, with a median of 50% (range: 11%–81%). Infants receiving long-course parenteral antibiotic therapy were more likely to be ill appearing on presentation, have growth of a non-*E coli* organism, and have prolonged bacteremia (Table 1).

### Outcomes

Six infants (5%) had a recurrent UTI, each diagnosed between 15 and 30 days after index discharge. Two of the 6 infants received short-course parenteral therapy, and 4 received long-course parenteral antibiotic therapy during the index

**TABLE 1** Baseline Demographic and Clinical Characteristics of Infants With Bacteremic UTI

Patient Characteristics	Overall (N = 115)	Short-Course IV/IM Antibiotics (n = 58)	Long-Course IV/IM Antibiotics (n = 57)	P ( $\chi^2$ Test)
	n (%)	n (%)	n (%)	
Age $\leq 28$ d	60 (52)	25 (43)	35 (61)	.05
Male sex	69 (60)	30 (52)	39 (68)	.06
Prematurity	10 (9)	3/53 (6)	7/54 (13)	.38 <sup>a</sup>
Complex chronic condition	19 (17)	7 (12)	12 (21)	.19
Genitourinary anomaly	17 (15)	6 (10)	11 (19)	.18
Fever	102 (89)	51 (88)	51 (89)	.79
Ill appearance	32 (28)	10 (17)	22 (39)	.01
ICU stay	16 (14)	5 (9)	11 (19)	.10
Prolonged bacteremia	8 (7)	0	8 (14)	.002 <sup>a</sup>
Non- <i>E coli</i> organism	22 (19)	4 (7)	18 (32)	.001 <sup>a</sup>

<sup>a</sup> Fisher's exact test was performed.

hospitalization (Table 2). There was no significant difference in rates of recurrent UTI between the 2 treatment groups (adjusted risk difference: 3%; 95% confidence interval [CI]: -5.8 to 12.7). Both infants in the short-course group who had a recurrent UTI also had a diagnosis of VUR (Supplemental Table 6). One infant in the short-course group had recurrent *E faecalis* bacteremia. This patient had grade 3 to 4 VUR diagnosed during hospitalization for the recurrent UTI and had not been receiving prophylactic antibiotics after discharge from the index hospital admission (Supplemental Table 6). Two of the 4 infants in the long-course group with recurrent UTI had grade 4 VUR and were receiving prophylactic amoxicillin at the time of recurrence. None of the 6 infants with recurrent UTI developed meningitis.

Two of the 6 infants with recurrent UTI grew an organism distinct from the causative organism isolated at the index hospitalization (Supplemental Table 6). Both of these infants had received long-course parenteral antibiotic therapy during their index hospital stay. When evaluating only those infants who had a recurrent UTI with growth of the same pathogen that caused their index UTI, there was no difference in rates of recurrence

between the 2 treatment groups (adjusted risk difference: 0.2%; 95% CI: -7.8 to 8.3) (Table 2).

Fifteen infants (13%) had 30-day all-cause reutilization. There was no significant difference in the rates of reutilization between the 2 treatment groups (adjusted risk difference: 3%; 95% CI: -14.6 to 20.4). The adjusted mean LOS was significantly longer in the long-course group compared with the short-course group (adjusted mean difference: 6 days; 95% CI: 4.0 to 8.8).

Within our cohort, 67 infants were well appearing and had no known complex chronic condition, including genitourinary anomaly. Short-course parenteral antibiotic therapy was prescribed in 40 (60%) healthy, well-appearing infants. Two infants (5%) in the short-course group and 2 infants in the long-course group (7%) had a recurrent UTI.

No infants in our cohort experienced adverse events such as ICU readmission, need for mechanical ventilation or vasopressor use, or signs of neurologic sequelae within 30 days of discharge from the index hospitalization. Thirteen infants in the long-course group were discharged from the hospital with a PICC to complete intravenous (IV) antibiotic therapy. Of these, 1 infant

(8%) had an ED revisit for a PICC-related mechanical complication.

## DISCUSSION

In this multicenter study of young infants with bacteremic UTI, shorter courses of parenteral antibiotic therapy (ie, ≤7 days) were not associated with significantly more frequent UTI recurrence or all-cause reutilization when compared with longer courses of parenteral antibiotic therapy. Adverse events were rare in both groups, and longer courses of antibiotic therapy were associated with longer lengths of hospital stay.

A previous multicenter retrospective study by Schroeder et al<sup>30</sup> of infants ≤90 days old with bacteremic UTI revealed that infants with recurrent UTI did not receive longer parenteral antibiotic treatment when compared with infants without recurrent UTI in an unadjusted analysis. Similar to our study, Schroeder et al<sup>30</sup> reported that infants who received longer courses of parenteral antibiotics were more likely to be younger, have growth of a non-*E coli* organism in blood and urine cultures, and have blood culture positivity for >1 day. Because infants who were perceived to have higher-risk baseline characteristics received longer courses of parenteral antibiotic therapy, we used propensity scores and IPW to mitigate potential confounding by indication.

Our study had several limitations. First, despite the large number of centers included, we identified relatively few infants with bacteremia in the context of UTI. Within our cohort, rates of recurrent UTI and reutilization were low. Therefore, our analysis was not powered to capture small but potentially clinically important differences in outcomes. However, given that the incidence of 30-day adverse outcomes for infants with short-course antibiotics in our study was low, if modest UTI recurrence differences did actually exist, they might prove tolerable for

**TABLE 2** Outcomes of Infants With Bacteremic UTI

Outcome	Short-Course IV/IM Antibiotics (n = 58)	Long-Course IV/IM Antibiotics (n = 57)	Adjusted Relative Risk (95% CI) <sup>a</sup>	Percent Adjusted Risk Difference (95% CI) <sup>a</sup>	Adjusted Mean Difference (95% CI) <sup>a</sup>
Recurrent UTI, n (%)	2 (3)	4 (7)	1.9 (0.3 to 11.6)	3 (-5.8 to 12.7)	—
Recurrent UTI with same organism, n (%)	2 (3)	2 (4)	1.1 (0.1 to 8.4)	0.2 (-7.8 to 8.3)	—
All-cause reutilization, n (%)	6 (10)	9 (16)	1.2 (0.4 to 3.9)	3 (-14.5 to 20.6)	—
LOS, d, adjusted mean (95% CI)	4.5 (4.4 to 4.6)	10.8 (10.7 to 10.9)	—	—	6 (4.0 to 8.8)

<sup>a</sup> IPW was conducted by using propensity scores to achieve covariate balance in patient clinical and demographic characteristics. Marginal structural models were applied to the weighted population to obtain adjusted estimates.



a clinician weighing the aforementioned risks associated with prolonged parenteral antibiotic therapy.

There was also potential for misclassification in infants with recurrent UTI because patients whose recurrence was managed in the outpatient setting or at a different institution would not have been captured by using our data collection methodology. This misclassification could lead to an underestimation of the rate of recurrence. However, given the history of previous bacteremia in our cohort, our patient population is less likely to be managed in the outpatient setting when compared with infants who have uncomplicated UTI. Additionally, the overall rate of recurrence of UTI in our study was similar to that of previous studies of infants with bacteremic UTI.<sup>30,31</sup>

Furthermore, we could not address optimal total duration of therapy for bacteremic UTI in this study because we did not have information on choice or duration of postdischarge oral antibiotic therapy for our cohort.

Finally, it is possible that infants in the short-course parenteral antibiotic group received longer courses of oral antibiotics after discharge compared with infants in the long-course parenteral group. We were not able to evaluate for recurrences of UTI from completion of oral therapy using our data source. Thus, it is possible that a recurrent UTI that occurred 30 days after completion of oral antibiotic therapy in the short-course group was not captured in our 30-day postdischarge window.

The safety of short-course parenteral antibiotic therapy with early conversion to oral antibiotics has been established for the treatment of many invasive pediatric bacterial infections (eg, complicated pneumonia and osteomyelitis) in which prolonged IV antibiotics were previously considered the standard of care.<sup>32,33</sup> Prolonged courses of IV

antibiotics administered via a PICC were associated with increased risk of catheter-associated complications and increased reutilization in these studies. In children who were able to tolerate oral antibiotics, parenteral antibiotic therapy did not confer a clear benefit over oral alternatives with excellent bioavailability.<sup>32,33</sup> However, there are limited data on the bioavailability of oral antibiotics among infants  $\leq 60$  days old. High-dose oral amoxicillin (200 mg/kg per day) has been shown to achieve therapeutic serum concentrations in term neonates with *S agalactiae* bacteremia.<sup>34</sup> Further investigation is needed to establish optimal dosing and bioavailability for oral antibiotics typically used to treat urinary pathogens (eg, aminopenicillins and cephalosporins) in infants  $\leq 60$  days old.

Additionally, it is possible that there is a subset of young infants with bacteremic UTI in whom longer courses of parenteral antibiotics are indicated. For instance, 4 of the 6 infants with recurrent UTI in our cohort were also diagnosed with VUR, and 3 of these infants had Grade 3 or 4 VUR. High-grade VUR is associated with an increased risk of UTI recurrence.<sup>35,36</sup> However, it is not known if longer duration of parenteral antibiotic therapy or longer duration of total therapy is associated with a reduced risk of recurrent UTI in infants with VUR. Future studies should focus on identifying which populations of young infants, if any, may benefit from longer courses of parenteral antibiotic therapy.

## CONCLUSIONS

Young infants with bacteremic UTI who received  $\leq 7$  days of parenteral antibiotic therapy did not have significantly more 30-day recurrent UTIs or hospital reutilization than infants who received longer courses of parenteral therapy. Our data indicates that  $\leq 7$  days of parenteral

antibiotic therapy may be safe in this population. Researchers in future prospective studies should seek to establish the bioavailability and optimal dosing of oral antibiotics in young infants and assess if there are particular subpopulations of infants with bacteremic UTI who may benefit from longer courses of parenteral antibiotic therapy.

## FEBRILE YOUNG INFANT RESEARCH COLLABORATIVE

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## ABBREVIATIONS

CFU: colony-forming unit  
CI: confidence interval  
CSF: cerebrospinal fluid  
ED: emergency department  
IPW: inverse probability weighting  
IV: intravenous  
IV/IM: intravenous and/or intramuscular  
LOS: length of stay  
PICC: peripherally inserted central catheter  
UTI: urinary tract infection  
VUR: vesicoureteral reflux

<sup>a</sup>Divisions of Hospital Medicine and <sup>o</sup>Pediatric Emergency Medicine, Department of Pediatrics, School of Medicine, Vanderbilt University and Monroe Carell Jr Children's Hospital at Vanderbilt, Nashville, Tennessee; and <sup>p</sup>Division of Hospital Medicine, Department of Pediatrics, Children's Hospital of The King's Daughters, Norfolk, Virginia

Dr Desai conceptualized and designed the study, performed local data collection and data analyses, interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript critically for important intellectual content; Dr Aronson contributed to the conceptualization and design of the study, coordinated and supervised data collection locally and nationally, interpreted the data, and reviewed and revised the manuscript critically for important intellectual content; Dr Shabanova designed the statistical approach for this study, performed data analyses, interpreted the data, and reviewed and revised the manuscript critically for important intellectual content; Dr Neuman contributed to the design of the study, collected local data, interpreted the data, and reviewed and revised the manuscript critically for important intellectual content; Drs Balamuth, Pruitt, DePorre, Nigrovic, Rooholamini, Wang, Marble, Williams, Sartori, and Leazer and Ms Mitchell collected local data, interpreted the data, and reviewed and revised the manuscript critically for important intellectual content; Dr Shah conceptualized and designed the study, supervised local data collection and data analyses, interpreted the data, and reviewed and revised the manuscript critically for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Address correspondence to Sanyukta Desai, MD, Division of Hospital Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, MLC 9016, Cincinnati, OH 45229. E-mail: [sanyukta.desai86@gmail.com](mailto:sanyukta.desai86@gmail.com)

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