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Length of Intravenous Antibiotic Therapy and Treatment Failure in Infants With Urinary Tract Infections

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Abstract

OBJECTIVE: The goal was to determine the association between short-duration (≤3 days) and long-duration (≥4 days) intravenous antibiotic therapy and treatment failure in a cohort of young infants hospitalized with urinary tract infections (UTIs).

METHODS: We conducted a retrospective cohort study of infants <6 months of age who were hospitalized with UTIs between 1999 and 2004 at 24 children's hospitals in the Pediatric Health Information System. Our main model adjusted for all covariates, propensity scores, and clustering according to hospital to evaluate the effect of short versus long courses of inpatient intravenous antibiotic therapy on treatment failure, defined as readmission because of UTI within 30 days.

RESULTS: Of the 12 333 infants who met the inclusion criteria, 240 (1.9%) experienced treatment failure. The treatment failure rates were 1.6% for children who received short-course intravenous antibiotic treatment and 2.2% for children who received long-course treatment. Treatment courses varied substantially across hospitals and with patient-level characteristics. After multivariate adjustment, including propensity scores, there was no significant association between treatment group and outcomes, with an odds ratio for long versus short treatment of 1.02 (95% confidence interval: 0.77–1.35). Known presence of genitourinary abnormalities, but not age, predicted treatment failure.

CONCLUSIONS: Treatment failure for generally healthy young infants hospitalized with UTIs is uncommon and is not associated with the duration of intravenous antibiotic treatment. Treating more infants with short courses of intravenous antibiotic therapy might decrease resource use without affecting readmission rates. *Pediatrics* 2010;126: 196–203

Keywords

urinary tract infection; therapy; children; infants; hospital medicine

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Urinary tract infections (UTIs) are the most common cause of serious bacterial infections among young children and are identified for ~5% of febrile infants.[1–4] Among infants with febrile UTIs, imaging studies reveal pyelonephritis in the majority (~60%) of cases.[5] Pyelonephritis is associated with increased risk for renal scarring.[5–8] Prompt initiation of appropriate antibiotic therapy decreases this risk.[9,10]

Consensus guidelines and meta-analyses consistently have supported 7 to 14 days of antibiotic therapy for children with UTIs.[11–13] Greater uncertainty exists regarding the proper route for initial antibiotic therapy and what additional benefit, if any, is conferred by longer courses of intravenous antibiotic therapy. Two randomized, controlled trials failed to show any difference for patients who received initial parenteral versus oral antibiotic therapy, with respect to renal scarring at 6 and 12 months or markers of resolution, such as time to defervescence and proportion of sterile urine cultures.[14,15] Neither study included infants <1 month of age, and the numbers of infants between 1 and 2 months of age included in each study arm were quite small, which leads to questions regarding the power of these studies to detect clinically meaningful treatment outcome differences for these youngest patients. Considerable variability in length of stay (and likely intravenous antibiotic therapy use) for these patients continues to exist.[16] We undertook a retrospective cohort study of the relationship between length of intravenous antibiotic therapy and treatment failure for infants <6 months of age who were hospitalized with UTIs, to test our hypotheses that the length of therapy would be highly variable and the treatment failure rates would be similar regardless of the length of intravenous therapy.

METHODS

Design

We performed a retrospective cohort study with a large sample of infants hospitalized with UTIs at 24 freestanding children's hospitals throughout the United States.

Data Source

We used the Pediatric Health Information System (PHIS), an administrative database that currently contains clinical and financial details of >6 million patient cases from 42 freestanding children's hospitals affiliated with the Child Health Corporation of American (Overland Park, KS). During our study period, 27 hospitals were submitting data to the PHIS. The database contains diagnosis and procedure codes and billed transaction/utilization data for inpatient encounters among participating children's hospitals throughout the nation. Member hospitals represent most of the major metropolitan areas across the United States. At submission, data are deidentified, and 175 reliability and validity checks are applied. Any data that do not meet specific error thresholds are rejected. Each hospital must correct the errors, resubmit the data, and meet the threshold before the data are loaded into the PHIS.

Study Population

The source population for our cohort was all children in the PHIS with admission dates between January 1, 1999, and December 31, 2004. All children <6 months of age with a primary or secondary discharge diagnosis code for acute UTI or pyelonephritis

(International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], code 590.10, 590.11, 590.80, or 599.0) were included in the initial cohort.

In an effort to define a cohort of generally healthy children with primary UTIs, we excluded children with secondary diagnosis codes suggesting comorbid chronic conditions, including malignancies, diabetes mellitus, HIV infection, sickle cell disease, other congenital immunodeficiencies, and spina bifida, as well as children with diagnosis codes suggesting a secondary or catheter-associated UTI (eg, burns or trauma) (n = 473). We also excluded children who received >14 days of intravenous antibiotic treatment or were hospitalized for >14 days (n = 2520), both of which suggested a more-complicated course. Three of the initial 27 hospitals (with 1108 records) were found to lack intravenous antibiotic exposure data recorded according to day; therefore, all records from those hospitals were excluded from analyses. Because they were not at risk of treatment failure, as defined in our study, we also excluded from analyses data for infants who died during the index hospitalization (n = 338). Finally, data for 170 children with procedure code 38.93 (venous catheterization, not elsewhere classified) were excluded from the primary analysis because the possibility of receipt of intravenous antibiotic treatment at home did not allow us to assess exposure fully. The accuracy of this code in the PHIS was validated previously.[17]

Exposure Classification

The primary exposure variable was duration of intravenous antibiotic therapy in the hospital. This was examined as a dichotomous variable, defined as short-course (≤3 days) versus long-course (≥4 days) treatment, and as a continuous variable (days of intravenous antibiotic treatment). Three days was chosen as the cutoff point because it was the median length of therapy. We counted any day on which a child received ≥1 dose of intravenously administered antibiotics as a full day, expressed as an integer.

Outcome Measures

The primary outcome was treatment failure, defined as rehospitalization within 30 days after discharge with an ICD-9-CM code related to UTI present at admission. We chose 30 days because this time would allow ≥2 weeks without antibiotics for all infants who completed a typical 10- to 14-day course, including oral antibiotic treatment at home. A UTI diagnosis within this period likely would be related to treatment failure.[18] UTIs occurring >30 days after discharge more likely would be recurrent UTIs. To test a treatment failure definition with increased specificity, we also performed the analysis with the outcome measure defined as rehospitalization with a UTI diagnosis code within 15 days after discharge.

Covariates

We extracted data on age, race, ethnicity, gender, insurance status, and bacteremia, as well as a constructed variable indicating the presence of diagnosis codes for functional or anatomic disorders of the genitourinary tract. Bacteremia was defined on the basis of ICD-9-CM code 790.7 or 0.38 (septicemia). The ICD-9-CM codes included in the constructed genitourinary variable were those for vesicoureteral reflux (VUR) (code 593.7), obstructive defects of the renal pelvis and ureter (code 753.2x), and posterior urethral valves (code 753.6). We also

extracted data on the initial severity of illness by using class assignment v20, a 4-level severity indicator derived from All Patient Refined Diagnosis-Related Group grouping.

Statistical Analyses

Summary statistics for each variable were analyzed descriptively with counts and proportions. The bivariate association between each covariate and the primary exposure group (long-course versus short-course intrave nous antibiotic treatment) was analyzed by using the $\chi 2$ test. Next, each covariate was placed as an independent variable in a logistic regression model of long-course intravenous antibiotic exposure.

The $\chi 2$ test was used for unadjusted comparisons between dichotomous primary exposure and treatment failure and between covariates and treatment failure. The primary exposure group and other covariates initially were placed in a logistic regression model of treatment failure. Next, each demographic covariate was placed in a propensity score model to determine the probability of each record to receive long-course intravenous antibiotic treatment (*c* statistic of 0.69). Propensity scores are particularly helpful in addressing confounding by indication for treatment.[19,20] Adjustment for propensity scores limits this bias and approximates randomized receipt of treatment, as in a trial. We calculated propensity scores by using multivariate logistic regression and then grouped scores into quintiles for use in the main treatment failure model. The propensity score quintile, intravenous antibiotic therapy exposure, and other covariates were modeled as independent variables in a random-effects logistic regression model that accounted for clustering according to hospital. Treatment failure was the primary outcome. This association also was tested with stratification according to age, in 1-month increments, in the propensity score model. Because readmission was a relatively infrequent event, data also were analyzed with Poisson regression, to confirm findings.[21] Finally, we performed a posthoc power analysis to evaluate our study's power to detect a 1% difference in treatment failure rates between exposure groups.[22] We used SAS 9.1 (SAS Institute, Cary, NC) for all data analyses. The study was approved by the institutional review board at Cincinnati Children's Hospital Medical Center.

RESULTS

Subject Characteristics

A total of 12 333 records in the data set met our inclusion and exclusion criteria. Of the final cohort, 1930 patients had known genitourinary anomalies, with 1353 (70.1%) having VUR alone.

The characteristics of patients in the short-course and long-course treatment groups are presented in Table 1. In bivariate analyses, male gender, neonatal status, black race, Hispanic ethnicity, nonprivate insurance, known bacteremia, and known functional or anatomic disorders of the genitourinary tract were each associated with increased likelihood of receiving a long course of intravenous antibiotic treatment. Each of these covariates also was significantly associated with treatment group in multivariate analyses. The proportions of children who received long-course intravenous antibiotic treatment also varied significantly

among hospitals, from 15% to 87% ($P < .001$) (Fig 1). This significant association remained when hospital was placed with each patient-level covariate as independent variables in a logistic regression model of treatment group ($P < .001$).

Treatment Failure

Of the 12 333 children in the analytic cohort, 240 (1.9%) experienced treatment failure, defined as readmission within 30 days after discharge. Children who received a short course of intravenous antibiotic treatment had a 1.6% rate of treatment failure, whereas children who received a long course had a 2.2% rate of treatment failure. The unadjusted $\chi 2$ test yielded a significant P value of .02. Unadjusted readmission rates stratified according to other covariates are presented in Table 2. Among tested covariates, only the presence of known genitourinary abnormalities was significantly associated with treatment failure.

In the main model shown in Table 3, with adjustment for propensity score quintile and clustering within hospitals, there was no significant association between long-course versus short-course intravenous antibiotic therapy and treatment failure (odds ratio [OR]: 1.02 [95% confidence interval [CI]: 0.77–1.35]). In addition, no significant association was identified when intravenous antibiotic therapy was modeled as a continuous variable in this model (OR: 1.00 [95% CI: 0.95–1.06]). A Poisson regression also failed to find a significant association between treatment group and treatment failure. Our posthoc power analysis for comparison of proportions showed that we had >95% power to detect a 1% increase in absolute risk of treat ment failure in our main model. When the model was stratified according to age in 1-month increments, no association between antibiotic therapy and treatment failure was found for children <4 months or 5 to 6 months of age. Infants 4 to 5 months of age who were treated with long-course intravenous antibiotic therapy did have a significantly increased risk of treatment failure (OR: 8.82 [95% CI: 1.99–39.09]). Of the 1056 infants 4 to 5 months of age, 2 (0.4%) in the short-course therapy group and 20 (4.0%) in the long-course therapy group experienced treatment failure.

Of the 240 children who experienced treatment failure, defined as readmission with a UTI diagnosis code within 30 days, 143 (59.6%) were readmitted within 15 days. Similarly, in the adjusted model, there was no association between treatment failure, defined as readmission within 15 days, and long versus short treatment (OR: 0.99 [95% CI: 0.70–1.39]).

Among the 170 children with a procedure code for a central venous catheter, the median number of days of intravenous antibiotic treatment during hospitalization was 6 days (interquartile range: 3–8 days). The unadjusted treatment failure rate in this group was 1.2% (2 children were readmitted within 30 days).

DISCUSSION

In this large cohort study of young infants hospitalized with UTIs, readmission was a relatively uncommon event. Short (≤3 days) and long (≥4 days) courses of inpatient intravenous antibiotic treatment were equally effective in preventing hospital readmission within 30 days. However, the proportions of infants treated with courses of the 2 lengths

varied widely according to patient-level characteristics. Gender, age, race, ethnicity, insurance status, severity of illness, bacteremia, and known abnormalities of the genitourinary tract each predicted treatment length, although only severity of illness and known genitourinary abnormalities showed associations with outcomes in the final model. As we expected, these patient-level characteristics were quite different between the 2 treatment groups. It is not surprising that patients judged as being sicker or possessing other potentially high-risk characteristics (eg, very young age) were more likely to receive longer courses of intravenous antibiotic treatment. This led to concern regarding confounding by indication, because the sickest patients were likely more prone both to receive long-course intravenous antibiotic treatment and to experience treatment failure. The significant association between group and treatment failure in the unadjusted analysis supports this concern. The use of propensity scores (and, to a lesser extent, the severity-of-illness covariate) is designed to address confounding by indication in observational data. Inclusion of the propensity score in the regression model resulted in an OR for treatment group very close to 1.

We observed particularly striking variability in practices at the hospital level (Fig 1). This variation was not fully explained by differences in patient characteristics. Although we were somewhat surprised by the magnitude of this variation, it is consistent with previous findings that practices vary widely when the evidence base is less firmly established.[23]

The only significant covariates for treatment failure were severity of illness and the presence of known abnormalities of the genitourinary tract, the majority of which were VUR. We did not find any other studies that reported anincreasedriskoftreatmentfailurefor children with VUR. Although concerns have existed that VUR may be a risk factor for recurrent UTIs, a controlled trial did not find an association.[24,25] It is im portant to note that, with our methods, we could not discern whether children with VUR and other abnormalities of the genitourinary tract had clear clinical manifestations of treatment failure (eg, recurrence of fever or positive urine culture results) or whether knowledge of these abnormalities made the families of these children more likely to return for evaluations and/or made the clinicians caring for these children more likely to admit them to the hospital. In other words, the observed association between genitourinary abnormalities and readmission to the hospital within 30 days might have been driven by the perceived high-risk status of individual infants, rather than discernable differences in clinical course.

We noted with interest that young age was not a risk factor for readmission. Our results suggest that the majority of young infants can be treated with shorter courses of intravenous antibiotic therapy without increased odds of treatment failure. Although we did not observe an increased risk of treatment failure among neonates, we think that concern about the erratic absorption of orally administered antibiotics in this group might lead to more deliberate, cautious use of short courses of intravenous therapy.[26–28] These results do support the idea that early transition maybeasuccessfulstrategyinthetreat ment of neonates with infections caused by organisms susceptible to well-absorbed, orally administered antibiotics.[29] The stratified analysis did note an increase in the odds of treatment failure for infants 4 to 5 months of age who were treated with long-course intravenous antibiotic therapy. We cannot think of any reason why these infants would experience a different

negative effect of intravenous antibiotic treatment, compared with infants 3 to 4 months or 5 to 6 months of age. Nevertheless, this result supportsearlytransitiontooraltherapy, as in other age groups.

The main finding in our study was the lack of association between the length of intravenous antibiotic therapy and subsequent treatment failure. This result was consistent across several different models. Because no children in our primary analysis had billing data for peripherally inserted, central catheter lines, we think that children in both groups transitioned to orally administered agents to complete a 7- to 14-day total course. Our findings are in line with the randomized trial findings of Hoberman et al[14] and Montini et al, [15] which showed equivalent times to defervescence for children treated with initial oral versus intravenous antibiotic therapy. Importantly, our study confirmed the effectiveness of short-course intravenous therapy in a substantially larger cohort of infants. The study by Hoberman et al[14] included no neonates, and only 4 children 4 to 7 weeks of age were assigned randomly to initial oral therapy. The study by Montini et al[15] included ~190 infants between 1 and 6 months of age who were assigned randomly to initial intravenous or oral therapy.[15] Hoberman et al[14] and Montini et al[15] showed equivalent rates of renal scarring, as demonstrated by scintigraphy at 6 and 12 months, respectively, for children in the initial oral and intravenous therapy arms. A trial by Benador et al[30] demonstrated similar rates of renal scarring, as determined with 3-month scintigraphy, for children assigned randomly to receive 3 days of intravenous therapy followed by 7 days of oral therapy or a full 10 days of intravenous therapy. Our finding of equivalency of short-course and long-course intravenous therapy in this cohort of young, hospitalized infants, combined with trials showing no effect on renal scarring, indicates that it is reasonable to treat infants, even those as young as 1 to 6 months of age, with short-course (1–3 days) intravenous therapy. Given the relatively substantial cost, inconvenience to families, and increased potential for hospital-acquired complications with prolonged hospitalization, physicians should consider and discuss with families the potential for shorter intravenous courses and earlier discharge. Although our study did not include any nonhospitalized children, our findings in combination with those of the trials discussed above suggest that a full course of oral treatment outside the hospital may be appropriate for the majority of young infants.

Our study did have several limitations. First, there is potential misclassification bias in administrative data. Misclassification of intravenous antibiotic treatment exposure is possible. Our data quality check, which removed 3 of the initial 27 hospitals from analysis, limited this somewhat, as did our decision to use billing data (for which hospitals have particularly robust capture processes) for our main exposure. Al though some misclassification of exposure likely still exists, it is unlikely to differ between outcome groups. Of note, poor adherence (a concern that is often raised to support longer-duration intravenous antibiotic treatment) would bias results away from the null hypothesis. Our study was one of effectiveness more than efficacy of therapy course and therefore would be relevant to actual clinical decision-making. The particular threats regarding misclassification of outcomes are that a child would seek readmission at a non-PHIS hospital or that a meaningful treatment failure would not result in hospitalization. Because our cohort was at high risk, in terms of young age and hospitalization status, we consider it unlikely that children would seek care at an alternative hospital or experience a clinically significant

treatment failure that would not result in hospitalization within 1 month after the index hospital stay. Finally, misclassification through miscoding of UTI diagnosis might occur. Second, our decision to use readmission as the primary outcome measure meant that different patterns of or criteria for re-admission at individual emergency departments and hospitals might have led to different treatment failure rates. We included hospital in the final model to account for clustering and hospital-level differences; therefore, we do not think that this factor is likely to bias substantially our OR estimates for primary exposure or other covariates. Third, although these results should apply to children's hospitals, the generalizability to community hospitals may be more limited. With exclusion of patients with significant comorbidities, however, this population of children with UTIs is likely similar to populations treated at community hospitals. In addition, only 15.6% of children in the cohort had known genitourinary abnormalities (mostly VUR, similar to other community and hospital-based cohorts[18,31]). Finally, our cohort did not include any patients admitted after the end of 2004. It is possible that practice patterns regarding antibiotic therapy have changed; however, the patterns were similar across our study period, and we are not aware of any publications or policy changes that would drive such a shift.

CONCLUSIONS

Treatment failure for young infants hospitalized with UTIs is uncommon, and rates are not decreased with longer inpatient intravenous antibiotic therapy. Severity of illness and the presence of known abnormalities of the genitourinary tract, but not young age, were associated with increased risk for treatment failure. Given the wide variation currently present, it is likely that treating more infants with short-course intravenous antibiotic therapy would decrease the length of hospitalization for children and families without affecting the readmission rate.

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ABBREVIATIONS

UTI	urinary tract infection
PHIS	Pediatric Health Information System
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
VUR	vesicoureteral reflux

OR	odds ratio
CI	confidence interval

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WHAT'S KNOWN ON THIS SUBJECT:

Two randomized, controlled trials failed to show a difference for initial intravenous versus oral therapy for children with febrile UTIs. Those trials had small numbers of young infants, and variation in treatment course for UTIs persists.

WHAT THIS STUDY ADDS:

In a large cohort of infants <6 months of age with UTIs, the authors found no association between duration of intravenous antibiotic treatment and treatment failure, defined as readmission within 30 days. Treatment failure was an uncommon event.

Law School Grade Inflation for a Tough Job Market:

Apparently several law schools have begun to inflate grades so that students look more attractive in a competitive job market. According to an article in The New York Times (Rampell C, June 22, 2010), at least ten schools in the last two years have changed their grading systems to make them more lenient by tacking on a numeric correction factor to raise the grade point average. Others have begun to use a pass/fail system which may reduce the pressures on students, but makes it harder for employers to distinguish between the academic abilities of students. Schools that have done this have been those with a reputation for having a tough grading system compared to others, and if by doing so, the average law student grades increase, it will pressure more and more schools to raise their average grades to ensure their students are fairly evaluated by firms for hiring opportunities. The parallels to our medical schools speak for themselves.

Noted by JFL, MD

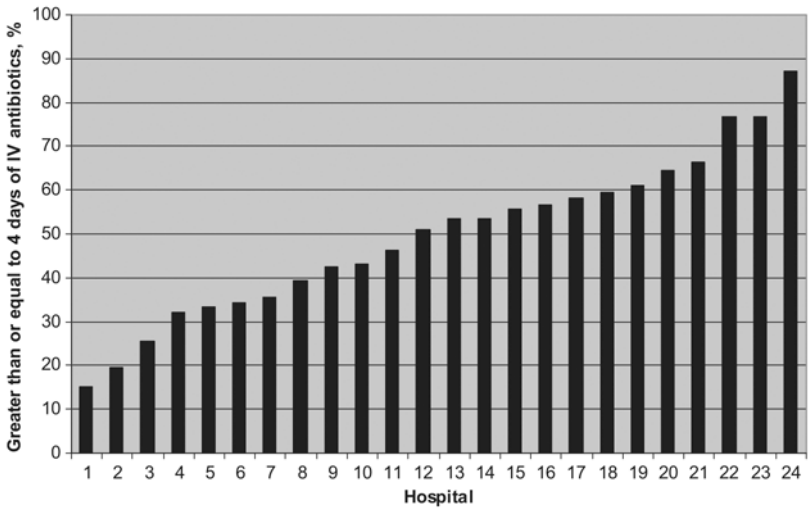

FIGURE 1.

Proportion of infants <6 months of age who received ≥4 days of intravenous antibiotic therapy in each hospital.

TABLE 1

Patient Characteristics for Short and Long Intravenous Antibiotic Therapy Groups

Characteristics	Proportion, % (*n*)		*P*
	Short Therapy (*N* = 5414)	Long Therapy (*N* = 6919)	
Gender			
Male	45.8 (2479)	56.5 (3906)	<.0001
Female	54.2 (2935)	43.5 (3013)	
Age			
<1 mo (neonates)	19.2 (1042)	33.8 (2341)	<.0001
≥1 and <2 mo	27.4 (1484)	27.5 (1902)	
≥2 and <3 mo	22.0 (1190)	17.2 (1188)	
≥3 and <4 mo	14.0 (757)	9.5 (657)	
≥4 and <5 mo	10.3 (557)	7.2 (499)	
≥5 and <6 mo	7.1 (384)	4.8 (332)	
Race			
White	65.3 (3534)	63.8 (4413)	.003
Black	15.9 (862)	18.3 (1263)	
Other	18.8 (1018)	18.0 (1243)	
Ethnicity			
Hispanic	23.1 (1248)	30.7 (2126)	<.0001
Not Hispanic or unknown	76.9 (4166)	69.3 (4793)	
Bacteremia			
Known	0.5 (26)	0.8 (55)	.03
Unknown or not present	99.5 (5388)	99.2 (6864)	
Genitourinary abnormalities			
Known	10.2 (551)	19.9 (1379)	<.0001
Unknown or not present	89.8 (4863)	80.1 (5540)	
Primary payer			
Medicaid	49.9 (2699)	50.1 (3467)	<.0001
Private insurance	27.8 (1504)	20.2 (1395)	
Self-pay	3.9 (212)	3.7 (253)	
Other	18.5 (999)	26.1 (1804)	

TABLE 2

Unadjusted Readmission Rates According to Patient Characteristics and Length of Intravenous Therapy

Characteristics	Readmission Within 30 d, %	*P* for Readmission
Gender		
Male	2.0	.62
Female	1.9	
Age		
<1 mo	2.3	.15
≥1 and <2 mo	2.0	
≥2 and <3 mo	1.5	
≥3 and <4 mo	1.4	
≥4 and <5 mo	2.1	
≥5 and <6 mo	2.2	
Race		
White	2.1	.32
Black	1.6	
Other	1.8	
Ethnicity		
Hispanic	1.8	.41
Unknown	2.0	
Bacteremia		
Known	1.9	.73
Unknown or not present	2.5	
Genitourinary abnormalities		
Known	4.1	<.0001
Unknown or not present	1.5	
Length of intravenous antibiotic therapy		
≤3 d	1.6	.02
≥4 d	2.2	

TABLE 3

Multivariate Adjusted ORs for Treatment Failure

Characteristics	Adjusted OR for Treatment Failure (95% CI)[a]
Gender	
Male	Reference
Female	0.98 (0.72–1.33)
Age	
<1 mo	Reference
≥1 and <2 mo	1.10 (0.73–1.66)
≥2 and <3 mo	0.83 (0.54–1.28)
≥3 and <4 mo	0.86 (0.51–1.45)
≥4 and <5 mo	1.25 (0.61–2.57)
≥5 and <6 mo	1.37 (0.81–2.32)
Race	
White	Reference
Black	0.73 (0.43–1.24)
Other	0.81 (0.52–1.26)
Ethnicity	
Hispanic	Reference
Not Hispanic or unknown	1.37 (0.93–2.03)
Bacteremia	
Known	1.90 (0.45–8.14)
Unknown or not present	Reference
Genitourinary abnormalities	
Known	1.83 (1.20–2.79)
Unknown or not present	Reference
Principle payer	
Medicaid	Reference
Private insurance	1.06 (0.73–1.52)
Self-pay	0.63 (0.33–1.20)
Other	0.88 (0.65–1.17)
Initial severity of illness (per 1-unit increase)	1.56 (1.14–2.15)
Length of intravenous antibiotic therapy	
≤3 d	Reference
≥4 d	1.02 (0.77–1.35)

[a] Treatment failure was defined as readmission within 30 days for UTI, and ORs were adjusted for all characteristics in Table 3 and the propensity score for receiving long intravenous therapy, with accounting for clustering within hospital.