Trends in Intravenous Antibiotic Duration for Urinary Tract Infections in Young Infants

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abstract

OBJECTIVES: To assess trends in the duration of intravenous (IV) antibiotics for urinary tract infections (UTIs) in infants ≤60 days old between 2005 and 2015 and determine if the duration of IV antibiotic treatment is associated with readmission.

METHODS: Retrospective analysis of infants ≤60 days old diagnosed with a UTI who were admitted to a children's hospital and received IV antibiotics. Infants were excluded if they had a previous surgery or comorbidities, bacteremia, or admission to the ICU. Data were analyzed from the Pediatric Health Information System database from 2005 through 2015. The primary outcome was readmission within 30 days for a UTI.

RESULTS: The proportion of infants ≤60 days old receiving 4 or more days of IV antibiotics (long IV treatment) decreased from 50% in 2005 to 19% in 2015. The proportion of infants ≤60 days old receiving long IV treatment at 46 children's hospitals varied between 3% and 59% and did not correlate with readmission (correlation coefficient 0.13; $P = .37$). In multivariable analysis, readmission for a UTI was associated with younger age and female sex but not duration of IV antibiotic therapy (adjusted odds ratio for long IV treatment: 0.93 [95% confidence interval 0.52–1.67]).

CONCLUSIONS: The proportion of infants ≤60 days old receiving long IV treatment decreased substantially from 2005 to 2015 without an increase in hospital readmissions. These findings support the safety of short-course IV antibiotic therapy for appropriately selected neonates.

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WHAT'S KNOWN ON THIS SUBJECT: A previous study from 1999 to 2004 of infants <6 months old with a urinary tract infection showed that intravenous antibiotic treatment of 3 or fewer days may be equivalent to longer-duration treatment.

WHAT THIS STUDY ADDS: In healthy infants ≤60 days old with a urinary tract infection, the proportion receiving long-duration (≥4 days) intravenous antibiotic treatment varies widely by children's hospital and decreased dramatically between 2005 and 2015 without an increase in the readmission rate.

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Urinary tract infections (UTIs) are a common reason for hospitalization in young infants, with >20 000 children <1 year of age hospitalized for UTIs each year in the United States.[1–4] Data from randomized controlled trials in mostly older infants and children support initial oral therapy to avoid unnecessary hospitalization and health care costs.[5,6] In children 2 to 24 months of age, the American Academy of Pediatrics guidelines from 2011 (reaffirmed in 2016) state that "initiating treatment orally or parenterally is equally efficacious."[7,8]

Infants ≤60 days old often initially receive parenteral antibiotics as part of an evaluation for invasive bacterial infection. The optimal duration of intravenous (IV) antibiotic therapy when a UTI is diagnosed in these younger infants is not known.[7] As a result, significant practice variability exists.[6,9–14]

Using data from 1999 to 2004, Brady et al[14] found no difference in readmissions between infants 0 and 6 months old who received short-course (≤3 days) versus long-course (≥4 day) IV antibiotic therapy, including subanalyses of infants 0 to 1 months old and 1 to 2 months old. In light of these data, the aforementioned randomized controlled trials (from 1999 to 2007) showing the safety of oral antibiotic therapy, and the American Academy of Pediatrics recommendations for oral therapy in older infants, we hypothesized that the percentage of infants ≤60 days old who were treated with short-duration IV therapy increased over the previous decade.

Short-duration IV therapy could provide several potential benefits compared with long-duration therapy. Shorter hospitalizations would incur fewer direct medical costs, increase hospital bed availability, and be less disruptive to parent-infant bonding.[15] In addition, shorter hospitalization could reduce the risk of nosocomial infection[16] and adverse events, such as IV infiltrates.

The purpose of the current study was to examine recent trends in the treatment of UTIs in otherwise healthy infants ≤60 days old who were admitted as inpatients between 2005 and 2015. We also evaluated the association between the duration of IV antibiotic treatment and readmissions.

METHODS

Institutional Review Board

The study was approved by the institutional review board at Ann & Robert H. Lurie Children's Hospital of Chicago.

Data Source

This was a retrospective cohort study using data from the Pediatric Health Information System (PHIS), which is an administrative and billing database maintained by the Children's Hospital Association (CHA).[17] The 46 CHA hospitals that participated in the PHIS database during the study are located in 25 states, in 17 of the 20 major metropolitan areas in the United States, and represent 70% of freestanding children's hospitals. Data include the 9th and 10th revisions of the *International Classification of Diseases* coding for medical diagnoses and procedures, demographic characteristics, and billed transactions and use data for pharmacy, radiology, and laboratory charges accrued during the clinical encounter. Microbiology and other laboratory data, including the method of urine collection (eg, urine bag or catheterization), are not available in the PHIS database.

Inclusion Criteria

Patients were included if they were admitted to 1 of the 46 participating hospitals between 2005 and 2015, were ≤60 days old on admission to the inpatient or observation unit, received IV antibiotics within the first 2 days of hospitalization, and had a primary discharge diagnosis of a UTI (see Fig 1).

Exclusion Criteria

Children with the following diagnoses or procedures in the PHIS database were excluded to ensure a generally healthy cohort without other indications for prolonged IV antibiotic therapy: other bacterial infections, including bacteremia (and UTI with bacteremia); genitourinary abnormalities, including both previously known disorders and those discovered during the admission for the UTI; previous major surgical procedures; and a complex medical disease beyond common neonatal conditions (see Supplemental Tables 3 and 4). In addition, for patients with multiple admissions for UTIs in the first 60 days of life, only the index admission was included. Patients with procedural codes for peripherally inserted central catheters were omitted because they might have received outpatient IV therapy. Patients who were billed for a stay in the pediatric or neonatal ICU or had a hospital length of stay of >14 days were not included because they might have had significant comorbidities, other uncoded diagnoses, or an atypical course. Patients were also excluded if they received antibiotics not typically used as empirical treatment in neonates with fever or to treat UTIs (Fig 1). The specific antibiotic given was not further analyzed.

Main Exposures

Short-duration IV antibiotic treatment was defined as the receipt of ≤3 calendar days of IV antibiotics, and long-duration treatment was defined as the receipt of ≥4 calendar days of IV antibiotics.[14] One or more doses of an antibiotic on a given calendar day was considered a full

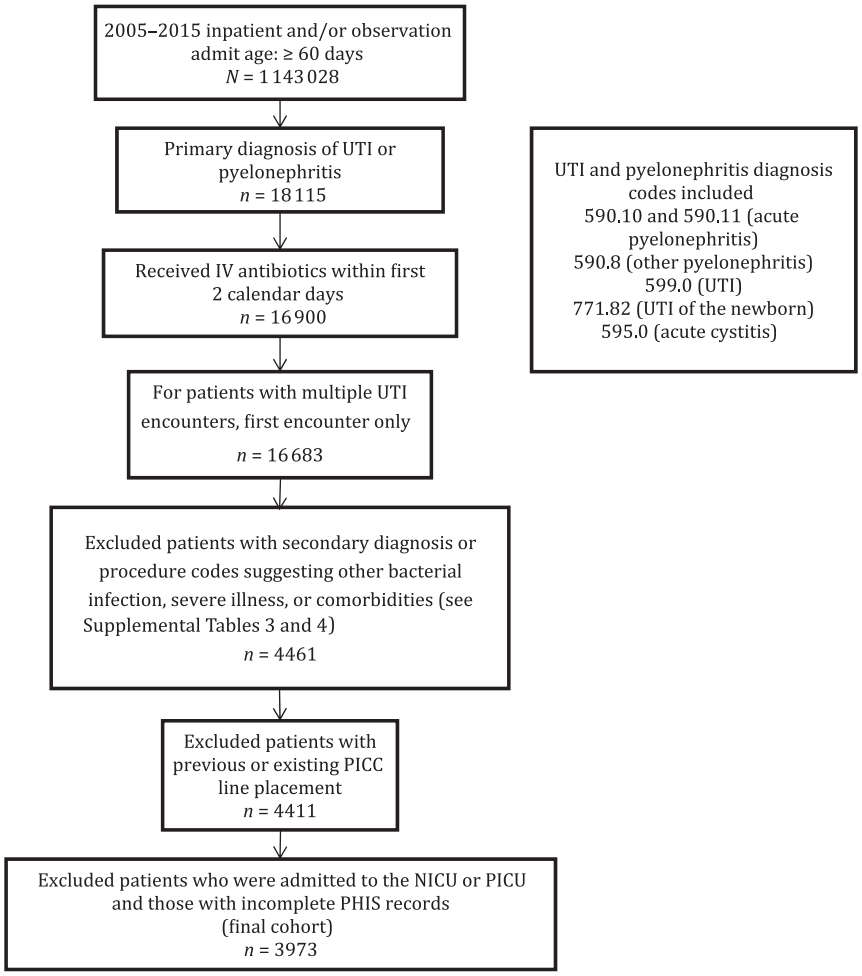

FIGURE 1
Selection of the final cohort. PICC, peripherally inserted central catheter.

day of therapy. The duration of IV antibiotic therapy was determined on the basis of the billing charges for an antibiotic on a calendar day. We could not determine the total number of antibiotic doses given, only whether IV antibiotics were received on a particular day.

Outcome Measures

The main outcomes were readmission for a UTI, which is defined as any readmission within 30 days of the index discharge with a primary diagnosis of UTI and all-cause readmission within 30 days of index discharge.

Statistical Methods

Descriptive statistics were performed for categorical and continuous variables. The readmission rate was calculated as the proportion of patients admitted for UTIs who were readmitted within 30 days. Variability in the readmission rate by year and hospital was assessed with Spearman correlations and χ^2 testing. Multivariable logistic regression was used to examine the association between the primary exposure variable (short versus long IV treatment) and the odds of readmission for a UTI and for all causes within 30 days. Categorical variables included as covariates (selected a priori) were as follows: age group (<15, 15–29, 30–44, and 45–60 days), race and/or ethnicity, and sex. Interaction terms for both age and sex with the duration of IV therapy were included in the final model if significant at $P < .05$. Clustering of patients within a hospital was accounted for by using a random intercept for each hospital. A similar model was created to evaluate all-cause readmission within 30 days. Statistical analyses were performed with RStudio version 0.99.902 (R Studio, Boston, MA) and SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Overall, there were 3973 patients included in the study; 1234 patients received long-duration IV antibiotic therapy, and 2739 patients received short-duration IV antibiotic therapy.

Across all hospitals, the percentage of infants ≤60 days old receiving long IV treatment decreased over time, with 50% receiving long IV treatment at the beginning of the study period in 2005 and 19% receiving long IV treatment at the end of the study period in 2015. The percent receiving long-duration IV antibiotic treatment in 1 year was not significantly correlated with the UTI readmission rate (Fig 2; correlation coefficient −0.53; $P = .09$).

Of the 32 hospitals reporting data in both 2005 and 2015, 21 had a decreased proportion of long therapy in 2015 compared with 2005. Six of the hospitals had an increased proportion of long therapy in 2015 compared with 2005, and 5 were the same. Among hospitals reporting data in both 2015 and 2005, the average change was an increase in short-duration therapy of 21 percentage points for 2015 compared with 2005.

Over the course of the study period, the proportion of neonatal hospital admissions receiving long IV treatment varied across hospitals from 3% to 59%. In 2015, the proportion receiving long IV treatment varied across hospitals from 0% to 67%, with 17

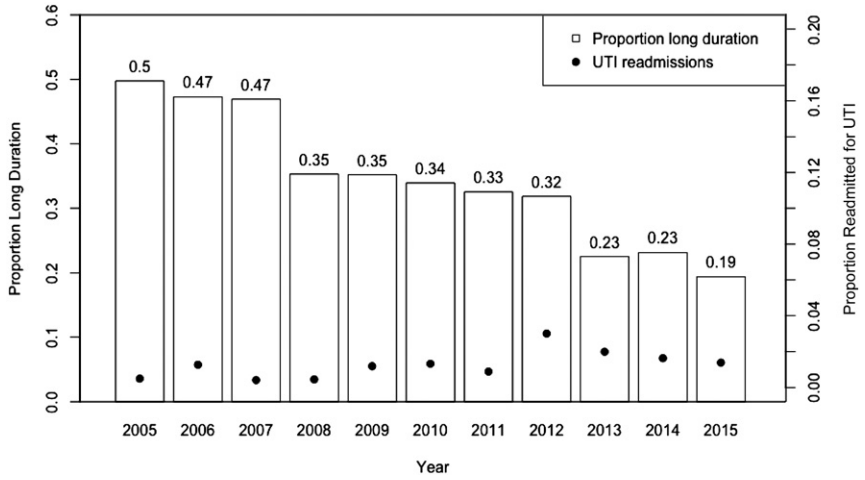

FIGURE 2
Proportion of patients receiving long-duration IV antibiotics by year compared with the proportion of patients readmitted for UTIs by year.

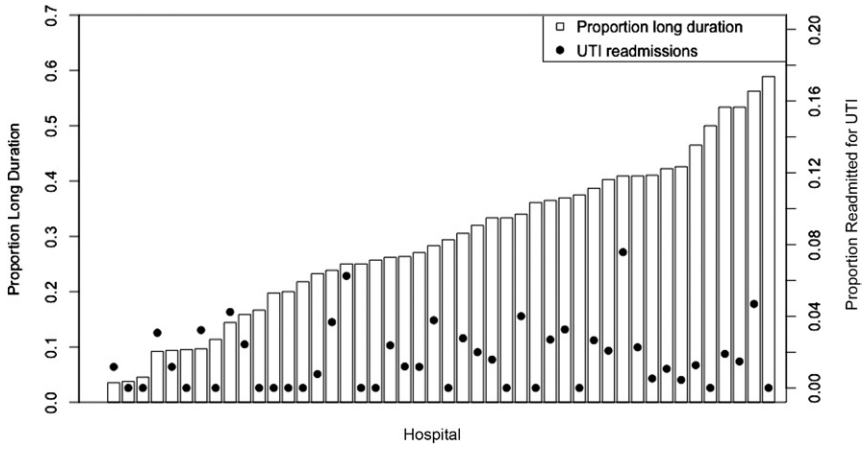

FIGURE 3
Proportion of patients receiving long-duration IV antibiotics by hospital compared with the proportion readmitted for UTIs, 2005–2015.

of 46 hospitals applying only short-duration IV therapy. The 30-day readmission rate for UTIs varied from 0% to 7.6% among the 46 hospitals over the course of the study. There was no significant correlation between the proportion of subjects receiving long IV treatment and the readmission rate by hospital for UTIs (Fig 3; correlation coefficient 0.13; $P = .37$).

On unadjusted comparisons, there was no difference between the 2 groups in the rate of readmissions for UTIs within 30 days (1.5% in both groups). Similarly, there was no difference in all-cause readmissions (4.1% in short-duration group and 5.0% in the long-duration group; see Table 1).

In the logistic regression analysis (Table 2), there was no relationship between the duration of IV antibiotics (long versus short) and risk of readmission for UTIs (odds ratio [OR] for long 0.93; 95% confidence interval [CI] 0.52–1.67). Female sex was significantly associated with readmission for UTIs within 30 days. Readmission for UTIs was more likely in the youngest age group than in the oldest. Including an interaction term for age with the duration of IV antibiotic therapy did not improve the model. The adjusted readmission rate for UTIs was 1.5% in the long-duration group and 1.6% in the short-duration group overall. For the different age groups, the adjusted readmission rates were 2.5% for <15 days old, 1.6% for 15 to 29 days old, 1.5% for 30 to 44 days old, and 1.2% for 45 to 60 days old.

When evaluating by age group and the duration of therapy for long-duration IV antibiotics, the adjusted readmission rates for UTIs were 2.3% for <15 days old, 1.5% for 15 to 29 days old, 1.3% for 30 to 44 days old, and 1.0% for 45 to 60 days old. For short-duration IV antibiotics, the adjusted readmission rates for UTIs were 2.6% for <15 days old, 1.7% for 15 to 29 days old, 1.5% for 30 to 44 days old, and 1.2% for 45 to 60 days old.

There was no difference in the risk of all-cause readmission on the basis of the duration of IV antibiotic therapy (Table 2; OR for long 1.16; 95% CI 0.83–1.62). Non-Hispanic white infants were more likely to be readmitted than infants categorized as another race or ethnicity (ie, not white, Hispanic, Asian American, or African American). Infants in the youngest 2 age groups were more likely to be readmitted compared with infants aged 45 to 60 days.

DISCUSSION

In this large retrospective cohort study of infants ≤60 days old, we examined the association between the duration of IV therapy for UTIs and the rate of readmission. Despite considerable variability in practice at different children's hospitals, we observed no association between the receipt of shorter-course IV therapy (≤3 days) and increased odds of readmission for UTIs compared with the receipt of longer courses. Furthermore, despite a shift away from long-course IV therapy during the study period, no increase in the rate of readmission occurred

TABLE 1 Characteristics of Long- and Short-Duration IV Antibiotic Groups Among Patients 60 Days or Younger Diagnosed With a UTI

Characteristics	*n* (%)		*P*
	Long (*N* = 1234)	Short (*N* = 2739)	
Age group, d			<.001
<15	263 (21.3)	272 (9.9)	
15–29	459 (37.2)	563 (20.6)	
30–44	307 (24.9)	844 (30.8)	
45–60	205 (16.6)	1060 (38.7)	
Race and ethnicity			<.001
Non-Hispanic white	364 (29.5)	1093 (39.9)	
Non-Hispanic African American	191 (15.5)	367 (13.4)	
Hispanic	502 (40.7)	897 (32.7)	
Asian American	41 (3.3)	90 (3.3)	
Other	136 (11.0)	292 (10.7)	
Payer			<.001
Private	262 (21.2)	817 (29.8)	
Government	876 (71.0)	1767 (64.5)	
Other	96 (7.8)	155 (5.7)	
Female sex	446 (36.1)	1304 (47.6)	<.001
UTI readmission	19 (1.5)	42 (1.5)	0.99
All-cause readmission	62 (5.0)	112 (4.1)	.21

TABLE 2 Multiple Logistic Regression Model of the Risk of UTI and All-Cause Readmission

Characteristics	Adjusted OR for UTI Readmissions (95% CI)	Adjusted OR for All-Cause Readmissions (95% CI)
Race and ethnicity		
Other	Reference	Reference
Non-Hispanic white	2.13 (0.74–6.11)	2.78 (1.38–5.60)*
Non-Hispanic African American	0.87 (0.23–3.31)	1.64 (0.74–3.65)
Hispanic	1.44 (0.47–4.37)	1.98 (0.97–4.06)
Asian American	2.79 (0.61–12.76)	2.35 (0.82–6.75)
Sex		
Male	Reference	Reference
Female	1.91 (1.09–3.33)*	1.26 (0.91–1.75)
Age, d		
45–60	Reference	Reference
30–44	1.34 (0.66–2.70)	1.23 (0.80–1.88)
15–29	1.72 (0.82–3.61)	1.67 (1.09–2.57)*
<15	2.48 (1.13–5.44)*	1.79 (1.09–2.92)*
IV antibiotics duration		
Short	Reference	Reference
Long	0.93 (0.52–1.67)	1.16 (0.83–1.62)

* $P < .05$.

between 2005 and 2015. These findings further support the safety of short-course IV antibiotic therapy for appropriately selected neonates.

The variability in IV treatment duration by hospital observed in this study is consistent with that of previous studies on UTIs. In particular, Brady et al[14] found that between 15% and 87% of infants 0 to 6 months old with UTIs received long-duration IV antibiotics from 1999 to 2004. This study also found no difference in the rate of readmissions for UTIs within 30 days on the basis of the duration of IV antibiotic treatment even in the subset of infants <2 months of age.

To complement the study by Brady et al,[14] we focused on a younger and healthier group of infants. First, we limited our patient population to infants ≤60 days old with a primary diagnosis of UTI to increase the likelihood that the treatment received was for a UTI rather than for another infection. In a recent study of the PHIS database by Tieder et al,[18] the use of a primary rather than primary-or-secondary diagnosis of UTI increased the positive predictive value of the billing code for representing true UTI from 85% to 93% when using provider documentation as a gold standard. We also explicitly excluded patients with other bacterial infections (including bacteremia), patients admitted to the ICU, patients with genitourinary abnormalities (including vesicoureteral reflux and hydronephrosis), and patients with a history of surgery. We compared the rates of all-cause readmissions between the groups, which were similar, suggesting similar baseline medical complexity. With the combination of the inclusion and exclusion criteria used in our study, we likely were able to reduce the number of included infants who may have had other comorbidities and thus limit confounding when assessing hospital readmission.

Female infants in this study had a higher rate of readmissions for UTIs, which is consistent with the known increased risk of UTIs in female infants, at least compared with circumcised boys.[3,7] Although the readmission rates (UTI and all-cause) were higher for infants <15 days old, the absolute increase in the rate of readmission was low and not associated with the duration of IV therapy. The increased rate of readmission for infants <15 days old may be due to the increased rate of infection in this age group and unrelated to previous treatment of UTIs. Non-Hispanic white infants were more likely than infants of other races to be readmitted for all causes, although not for UTIs. The reasons for this difference are unclear but may be related to better access to medical care.

This study has several limitations. First, clinical and laboratory data that may indicate differences in

risk of infection (eg, circumcision status) and clinical severity (eg, persistent fever or infection with a resistant pathogen) were not available in the PHIS database. Our data were also limited by a lack of information about the method of urine specimen collection and by antibiotic duration based on billing data rather than the medication administration record. Although it is possible that infants who received short-course IV therapy had less severe symptoms, this would not explain the significant interinstitutional variation in the duration of IV antibiotics. Furthermore, because these were all freestanding children's hospitals, the spectrum of severity of illness across centers would most likely be similar, so the duration of IV therapy likely has more to do with local practice patterns than with severity of illness. There is also no reason to believe that the severity of UTIs has decreased between 2005 and 2015, during which time the proportion receiving long-duration IV antibiotics decreased dramatically. A large prospective study may be helpful in this population to further assess whether there are differences in the clinical severity of UTIs in the patients who are not seen when examining billing data. Regardless, individualized clinical decision-making regarding some infants with atypical presentations or comorbidities is still required to determine the duration of IV therapy. Secondly, it is possible that children may have been readmitted to other, non-CHA hospitals after their index admissions, although we suspect this is likely to be uncommon. We also would not expect the pattern of these readmissions to differ by the duration of IV therapy received. We did not measure the duration of any oral therapy before admission, although we suspect initial outpatient treatment of UTIs would be uncommon in this age group. Finally, we could not measure the duration of oral therapy after discharge.

CONCLUSIONS

IV antibiotic treatment duration for UTIs in infants ≤60 days old continued to vary greatly by hospital over the past 10 years. However, the proportion receiving long-duration IV antibiotic therapy has decreased substantially over that period without any significant increase in the readmission rate for UTIs. Furthermore, when compared directly, we found that the duration of IV antibiotics was not associated with readmission. These data support the use of short-duration IV therapy for UTIs in healthy infants 60 days or younger.

ABBREVIATIONS

CHA: Children's Hospital Association
CI: confidence interval
IV: intravenous
OR: odds ratio
PHIS: Pediatric Health Information System
UTI: urinary tract infection

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