

Clinical and Demographic Factors Associated With Urinary Tract Infection in Young Febrile Infants

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ABSTRACT. *Objective.* Previous research has identified clinical predictors for urinary tract infection (UTI) to guide urine screening in febrile children <24 months of age. These studies have been limited to single centers, and few have focused on young infants who may be most at risk for complications if a UTI is missed. The objective of this study was to identify clinical and demographic factors associated with UTI in febrile infants who are ≤60 days of age using a prospective multicenter cohort.

Methods. We conducted a multicenter, prospective, cross-sectional study during consecutive bronchiolitis seasons. All febrile (≥38°C) infants who were ≤60 days of age and seen at any of 8 pediatric emergency departments from October through March 1999–2001 were eligible. Clinical appearance was evaluated using the Yale Observation Scale. UTI was defined as growth of a known bacterial pathogen from a catheterized specimen at a level of (1) ≥50 000 cfu/mL or (2) ≥10 000 cfu/mL in association with a positive dipstick test or urinalysis. We used bivariate tests and multiple logistic regression to

identify demographic and clinical factors that were associated with the likelihood of UTI.

Results. A total of 1025 (67%) of 1513 eligible patients were enrolled; 9.0% of enrolled infants received a diagnosis of UTI. Uncircumcised male infants had a higher rate of UTI (21.3%) compared with female (5.0%) and circumcised male (2.3%) infants. Infants with maximum recorded temperature of ≥39°C had a higher rate of UTI (16.3%) than other infants (7.2%). After multivariable adjustment, UTI was associated with being uncircumcised (odds ratio: 10.4; bias-corrected 95% confidence interval: 4.7–31.4) and maximum temperature (odds ratio: 2.4 per °C; 95% confidence interval: 1.5–3.6). Factors that were reported previously to be associated with risk for UTI in infants and toddlers, such as white race and ill appearance, were not significantly associated with risk for UTI in this cohort of young infants.

Conclusions. Being uncircumcised and height of fever were associated with UTI in febrile infants who were ≤60 days of age. Uncircumcised male infants were at particularly high risk and may warrant a different approach to screening and management. *Pediatrics* 2005; 116:644–648; fever, infant, urinary tract infection.

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ABBREVIATIONS. UTI, urinary tract infection; SBI, serious bacterial infection; ED, emergency department; YOS, Yale Observation Scale; RSV, respiratory syncytial virus; cfu, colony-forming units; OR, odds ratio; CI, confidence interval.

Urinary tract infection (UTI) is an important consideration when an infant is evaluated for fever in the first few months of life. In previous studies, UTI has consistently been the most commonly diagnosed serious bacterial infection (SBI), with prevalence varying from 1.8% to 7.5%.^{1–6} An accurate initial diagnosis is important in this setting, as young infants with UTI are at risk for renal scarring and concomitant bacteremia.^{5–9} However, because standard urinalysis and urine dipstick techniques have relatively low sensitivity (65%–88%),^{10,11} UTI is also the most consistently missed SBI in studies that have attempted to define low-risk criteria for the evaluation of fever in this age group.^{1–3}

Previous studies in infants and toddlers have attempted to document predictive factors to guide screening and presumptive management of UTI. These studies have found that gender, white race, circumcision status, and clinical factors predict the presence of UTI.^{12,13} A limitation of these studies was

their single-center implementation, which may limit the generalizability of the findings to patient populations at other centers. In addition, these studies had a limited ability to assess the youngest infants, who may have different propensity and risk factors for UTI and may be at highest risk for complications if the diagnosis is missed. A multicenter study design would allow for collection of data from a larger, more diverse, and more generalizable population of febrile infants. The objective of this study was to identify demographic and clinical factors associated with UTI in infants who were ≤ 60 days of age and being evaluated for fever as part of a multicenter research study in 8 pediatric emergency departments (EDs).

METHODS

Patient Selection

Data for this analysis were collected as part of a prospective cross-sectional study conducted in 8 pediatric EDs during bronchiolitis season, defined as October through March. Detailed methods of this study have been published previously.¹⁴ We collected clinical information associated with UTI during the final 2 years of this study, 1999–2001. All infants who were aged 60 days or younger and presented with rectal temperatures $\geq 38^\circ\text{C}$ by history or in the ED were eligible for enrollment. Infants were excluded when they had received antibiotics within 48 hours of ED presentation or when a parent or guardian refused consent. Patients who met enrollment criteria but were not enrolled prospectively were defined as “missed” patients. The Institutional Review Board at each site approved the study, and informed consent was obtained as required by local institutional guidelines.

Clinical Evaluation

Physicians who evaluated the patients in the ED performed a standard history and physical examination on all enrolled patients, including completion of a Yale Observation Scale (YOS) score to assess ill appearance.¹⁵ Clinical factors that were hypothesized in advance to be associated with UTI and therefore collected and analyzed included age ≤ 28 days, female gender, circumcision status, ill appearance (defined as a YOS > 10), height of fever, and white race. A standardized laboratory evaluation was performed on all enrolled infants, including testing for respiratory syncytial virus (RSV) and bladder catheterization or suprapubic aspiration for urinalysis and urine culture. Standard laboratory screening for UTI varied among institutions; some performed microscopic analysis, whereas others used urine dipstick as an initial screen.

Definitions and Outcome Measures

We defined a positive urinalysis as a trace or greater result for leukocyte esterase and/or nitrite on dipstick or ≥ 5 white blood cells per high-power field on a standard microscopic examination.¹⁶ We defined UTI as the growth of a single known pathogen with colony counts meeting 1 of 3 criteria: (1) ≥ 1000 colony-forming units (cfu)/mL for urine cultures obtained by suprapubic aspiration, (2) $\geq 50\,000$ cfu/mL from a catheterized specimen, or (3) $\geq 10\,000$ cfu/mL from a catheterized specimen in association

with a positive urinalysis. The third criterion was based on research suggesting that colony counts between 10 000 and 50 000 cfu/mL in the absence of pyuria may represent asymptomatic bacteruria.¹⁷

Statistical Analysis

We compared the rate of UTI for each hypothesized variable using the χ^2 test and calculated odds ratios (ORs) with 95% confidence intervals (CIs). To control for multiple variables simultaneously, we performed a multiple logistic regression analysis with UTI as the outcome variable. To obtain more conservative estimates of the CIs of our analyses, we performed bootstrap sampling procedures with 1000 iterations of the analysis using bootstrapped samples of our data. Bootstrapping refers to a process in which random samples of a database are drawn with replacement^{18,19}; this method can be used to obtain conservative estimates of CIs and standard errors. In the bootstrap analysis, we obtained 95% bias-corrected CIs for the variables in the logistic regression analysis. We performed all statistical analyses using SPSS 10.1 (SPSS Inc, Chicago, IL) and Stata (Release 8.0; Stata Corp, College Station, TX) statistical software.

Sample Size Calculations

We followed standard reported methods for sample size estimation in studies using multiple logistic regression, which recommend at least 10 outcomes per independent variable studied.²⁰ Because 6 predictors were hypothesized, at least 60 cases of UTI would be required to perform this analysis with sufficient power.

RESULTS

Patient Population

During the enrollment period, 1513 infants met the study eligibility criteria. Of these, 1025 (68%) were enrolled. For enrolled patients, data were available for $>95\%$ of all study variables. Categorization of enrolled patients by age, gender, and clinical characteristics is shown in Table 1. For the 1025 infants enrolled, age ranged from 1 to 60 days, with a mean age of 35.5 days (SD: ± 14.4 days). The mean gestational age was 39 weeks (SD: ± 1.6 weeks), and 7% of infants had been delivered prematurely, defined as a gestation lasting fewer than 37 weeks. Race categorization was as follows: white, 265 (26%); black, 223 (22%); Hispanic/Latino, 433 (42%); Asian, 68 (7%); and other or unknown, 36 (3%). Boys were significantly more likely to be uncircumcised when they were Hispanic/Latino (78%) or Asian (72%) compared with other infants (28%). The maximum temperature obtained at home or in the ED ranged from 38.0°C to 41.4°C , with a mean temperature of 38.6°C (SD: $\pm 0.5^\circ\text{C}$). The YOS for patients ranged from 6 to 28 with a mean YOS of 7.1 (SD: ± 2.6). RSV testing was obtained in 976 (95%) of infants, and results were positive for 223 (23%).

TABLE 1. Bivariate Analysis of Predictive Factors Associated With UTI ($n = 1025$ Infants)

Predictive Factor	No. With UTI (%)			
	Factor Present	Factor Absent	OR (95% CI)	% of All Patients With the Predictive Factor
Uncircumcised (vs circumcised male)	62/291 (21)	6/262 (2)	11.6 (5.0–26.6)	29
Maximum temperature $>39^\circ\text{C}$ (vs $<39^\circ\text{C}$)	34/209 (16)	57/796 (7)	2.5 (1.6–4.0)	21
Female (vs circumcised male)	22/439 (5)	6/262 (2)	2.2 (0.9–5.5)	44
Age <28 d (vs >28)	37/334 (11)	54/671 (8)	1.4 (0.9–2.2)	33
Ill appearance (YOS >10)	4/71 (6)	87/924 (9)	0.6 (0.2–1.6)	7
White (vs other race)	12/259 (5)	79/44 (11)	0.4 (0.2–0.8)	26

UTI

Urine cultures were obtained for 1005 (98%) of enrolled infants; all were obtained by catheterization. The overall rate of UTI was 9%. Of these, 85 (8.5%) grew $\geq 50\,000$ cfu/mL of a single pathogen, 6 (0.6% patients) grew 10 000 to 49 000 cfu/mL of a pathogen with an associated positive urinalysis or dipstick test, and 6 patients grew 10 000 to 49 000 cfu/mL of a pathogen with a negative dipstick or urinalysis and were considered not to have a UTI. The most common pathogen that caused UTI was *Escherichia coli*, which grew in 73 (80%) cultures. Frequencies of other pathogens were as follows: *Klebsiella pneumoniae*, 8 (9%); *Enterobacter* species, 5 (5%); *Citrobacter* species, 4 (4%); and *Pseudomonas* species, 1 (1%).

Clinical Factors Associated With UTI

The results of bivariate testing for each predictive variable and its association with UTI are presented in Table 1 with ORs and associated 95% CIs (CIs). Being uncircumcised and having a temperature $>39^{\circ}\text{C}$ were associated with an increased risk for UTI, whereas white race was associated with a lower rate of UTI. In multivariable analysis controlling for other factors, being uncircumcised and height of fever remained associated with UTI, whereas white race was no longer significantly associated (Table 2). Furthermore, the estimate for the OR for white race was similar when Hispanic infants were recategorized as white (0.73; boot-strapped bias-corrected 95% CI: 0.44–1.2). Among 68 male infants who were uncircumcised and had temperatures of 39°C or greater, 23 received a diagnosis of UTI (34%; 95% CI: 23–46). Female gender (vs circumcised boys) and age ≤ 28 days showed a trend toward an increase in odds of UTI, although both 95% CIs included 1.

Subanalyses

When the results of RSV testing were added to the model, the ORs for being uncircumcised and temperature were unchanged (9.8 and 2.4, respectively). As reported in a previous analysis, a positive RSV test was associated with a significant reduction in the risk for UTI (OR: 0.46; bias-corrected 95% CI: 0.18–0.92) although the rate of UTI among RSV-positive infants was substantial (4.6%).¹⁴ OR estimates for circumcision status and temperature were similar when UTI was defined alternatively as $\geq 50\,000$ cfu/mL (OR: 14.7 [bias-corrected 95% CI: 5.8–70]; and OR: 2.1 [95% CI: 1.4–3.4], respectively) or $\geq 10\,000$ cfu/mL (OR: 11.8; [95% CI: 5.2–35.9] and 2.4 [95% CI: 1.6–3.5]).

Comparison of Enrolled and Missed Patients

To determine whether selection for enrollment in the study was correlated with the likelihood of UTI, we compared urine culture results between enrolled and missed patients. For the 488 missed patients, urine cultures were obtained for 444 (91%), and among these, the rate of UTI (5.2%) was significantly lower than the 9.0% rate among enrolled patients (OR: 0.55; 95% CI: 0.34–0.88). Much of this difference was attributable to a lower rate of enrollment at the 2 largest hospitals that had lower-than-average population rates of UTI (2.9% and 7.0%) and higher rates of circumcision (81% and 51%) and together accounted for 78% of missed patients. After adjustment by study site, the OR for the difference between rates of UTI among missed and enrolled patients was no longer statistically significant (0.69; 95% CI: 0.42–1.14). Adding study site to the multivariable analysis resulted in similar estimates for the OR of UTI for being uncircumcised (10.1; 95% CI: 4.0–33.8) and maximum temperature (2.5; 95% CI: 1.7–3.8).

DISCUSSION

In this multicenter prospective study of febrile infants who were 60 days of age and younger and evaluated in an ED for fever, circumcision status and height of fever were associated with an increased likelihood of UTI. Other predictors, such as ill appearance and white race, which were associated with UTI in previous studies of infants and toddlers, were not significantly associated with UTI in this study.

The overall risk for UTI observed in this study, 9%, was higher than in previous studies.^{1–4} One difference between the current and previous studies is that here we included infants in the first month of life, who were excluded from some previous studies and may have a higher risk for UTI. Another important difference was the high proportion of uncircumcised boys in the current study (52%), among whom the rate of UTI was 21%. The rates of UTI among circumcised boys (2%) and among girls (5%) were similar to previous estimates.^{1–4} As catheterization of uncircumcised infants may be more difficult as a result of the presence of foreskin, a concern could be raised that some of these positive cultures may be attributable to contamination. However, these cultures grew pure growth of bacteria at high colony counts. In addition, the rate of UTI observed here among uncircumcised boys is very similar to previous studies that have been conducted in populations in which circumcision is not common.^{5,21} Of note, in a recent study from Taiwan, all urine cultures were obtained

TABLE 2. Multivariable Analysis of Predictive Factors Associated With UTI

Predictive Factor	Adjusted OR	Bootstrapped, Bias-corrected 95% CI	P Value
Uncircumcised (vs circumcised)	10.4	4.7–31.4	<.001
Maximum temperature, each $^{\circ}\text{C}$	2.4	1.5–3.6	<.001
Female (vs circumcised male)	2.2	0.9–6.6	.10
Age <28 d (vs >28)	1.6	0.96–2.6	.07
Ill appearance (vs YOS <10)	0.68	0.14–1.6	.49
White (vs other race)	0.79	0.35–1.5	.53

by suprapubic aspiration, and the observed rate of UTI was 19% among 94 febrile uncircumcised male infants who were younger than 8 weeks.²¹ The increase in odds of UTI attributable to the lack of circumcision is also similar to the increase observed in population-based studies of UTI, which have demonstrated a 10-fold increase in incidence of UTI for uncircumcised compared with circumcised male infants during the first year of life.²²

The definition of UTI used in the current study was more conservative than in previous studies, which generally have used $\geq 10\,000$ cfu/mL from a catheterized specimen as a threshold. Hoberman et al¹⁷ assessed patients with growth between 10 000 and 50 000 cfu/mL using enhanced urinalysis, a sensitive form of urinalysis that includes hemocytometer cell count and Gram stain of unspun urine. A substantial proportion of infants with bacterial growth in the urine between 10 000 and 50 000 cfu/mL on culture had normal enhanced urinalysis, and these patients may have had asymptomatic bacteruria. Enhanced urinalysis was not performed routinely at institutions that participated in the current study; however, we used the urinalysis to attempt to distinguish between acute infection and asymptomatic bacteruria in infants with low bacteria counts. In any case, the overall results of the study would have been similar had we chosen 10 000 or 50 000 cfu/mL thresholds, without urinalysis criteria, for the definition of UTI.

The findings reported here may have an impact on efforts to define low-risk criteria for the evaluation of fever in young infants. Currently, circumcision status may not be considered in management decisions, as it was not included among risk factors for SBI reported in key previous studies.¹⁻⁴ We found that circumcision status was often not documented in medical records of missed patients that were reviewed for this study. Although this may have been acceptable in populations with high rates of circumcision, these protocols may not be adequately sensitive in other settings. A group in Pittsburgh recently proposed adding the enhanced urinalysis to previous protocols to reduce the chance of missing a UTI and reported 100% sensitivity for SBI with this approach.⁶ The specificity of the enhanced urinalysis and the effect of this approach on false-positive screening results deserve additional study. However, given the >10 -fold increase in risk for UTI, when evaluating an uncircumcised male infant who is ≤ 60 days of age and has fever, a more conservative approach to screening, such as enhanced urinalysis or perhaps empirical treatment pending cultures in the absence of the enhanced urinalysis, may be appropriate.

Other factors assessed in this study provide additional information about the risk for UTI. Height of fever was associated with the risk for UTI, as has been shown in previous studies of SBI.²³ The increase in risk for UTI for girls compared with circumcised boys was not statistically significant, although it may have reached significance with a larger sample size. Similarly, the difference in rate of UTI among infants who were 28 days and younger compared with older

infants approached statistical significance. White infants were not at increased risk for UTI in this study, which differs from 2 previous studies that assessed infants and toddlers.^{10,11} This difference may represent elimination of a selection bias in this study or differences in the pathophysiology of UTI between younger infants and older infants and toddlers. Some studies have identified underlying Lewis blood group antigens secreted in the urinary tract that seem to reduce bacterial adherence; lack of these antigens has been associated with increased risk for UTI in white women and girls.^{24,25} Secretion of these antigens does not begin until after the first 2 months of life, and this may account for the absence of association between race and UTI in young infants compared with older children.²⁶

There were several potential limitations to this study. One third of the eligible infants were not enrolled, and missed patients had a lower rate of UTI than enrolled patients. Most of this difference was attributable to differential enrollment at sites with lower risk for UTI in their population. It is impossible to include missed infants in the analysis, as key variables such as circumcision status and degree of illness were not reliably available retrospectively. However, it is unlikely that selection bias significantly affected the primary results of the study, as the potential selection bias for the study would also have to be strongly associated with the predictors of interest, such as circumcision status. For example, assuming the extreme case that no UTIs occurred among uncircumcised boys who were missed from the study, the OR for UTI as a result of being uncircumcised overall would nevertheless be 7.2 with a 95% CI extending from 3.6 to 14.6 (data not shown). Another potential limitation was the lack of enrollment outside bronchiolitis season, which was determined by the design of the original study. Because risk for UTI is not known to vary seasonally and we have no biological hypothesis for such an association, there is no reason to suspect that this should bias the study, although this cannot be excluded with the present data. Finally, all infants were enrolled in an ED, and the results may not be generalizable to other clinical settings. Recent results from a large research network of pediatric outpatient practices suggest that there may be important differences in the rate of SBIs between infants who are evaluated in office and ED settings.^{27,28}

In conclusion, our study demonstrates that being uncircumcised and height of fever are associated with an increased risk for UTI in young infants who are assessed for fever in an ED. Febrile uncircumcised boys are at particularly high risk for UTI and may warrant a different approach to screening and treatment.

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SLEEPLESS IN SEAWORLD

"Orca-whale and dolphin mothers and their newborns appear not to sleep for a month after the pups' birth, researchers report. Neither parent nor offspring shows any ill effects from the long waking stint, and the animals don't later compensate with extra sleep. No previously studied mammal stays awake for so long, says Jerry Siegel of the University of California, Los Angeles (UCLA), an investigator in the study. In the months following their wakeful period, baby whales and dolphins—and their mothers—ramped up slowly to sleep amounts typical of normal adults, Siegel and his colleagues report. The infants' sleep pattern contrasts with that of other mammals, which need extra sleep during infancy and gradually sleep less as they age. . . . 'The mystery is that they're . . . dispensing with sleep behavior when so many sleep researchers have assumed that sleep has a vital function,' Siegel says."

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