Prevalence of urinary tract infection in febrile infants

Alejandro Hoberman, MD, Han-Pu Chao, MD,[a] David M. Keller, MD,[b] Robert Hickey, MD,[c] Holly W. Davis, MD, and Demetrius Ellis, MD

From the Departments of Pediatrics and Nephrology, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania

Urinary tract infection (UTI), a relatively common cause of fever in infancy, usually consists of pyelonephritis and may cause permanent renal damage. This study assessed (1) the prevalence of UTI in febrile infants (temperature ≥38.3° C) with differing demographic and clinical characteristics and (2) the usefulness of urinalysis in diagnosing UTI. We diagnosed UTI in 50 (5.3%) of 945 febrile infants if we found ≥10,000 colony-forming units of a single pathogen per milliliter in a urine specimen obtained by catheterization. Prevalences were similar in (1) infants aged ≤2 months undergoing examination for sepsis (4.6%), (2) infants aged >2 months in whom UTI was suspected, usually because no source of fever was apparent (5.9%), and (3) infants with no suspected UTI, most of whom had other illnesses (5.1%). Female and white infants had significantly more UTIs, respectively, than male and black infants. In all, 17% of white female infants with temperature ≥39° C had UTI, significantly more ($p < 0.05$) than any other grouping of infants by sex, race, and temperature. Febrile infants with no apparent source of fever were twice as likely to have UTI (7.5%) as those with a possible source of fever such as otitis media (3.5%) ($p = 0.02$). Only 1 (1.6%) of 62 subjects with an unequivocal source of fever, such as meningitis, had UTI. As indicators of UTI, pyuria and bacteriuria had sensitivities of 54% and 86% and specificities of 96% and 63%, respectively. In infants with fever, clinicians should consider UTI a potential source and consider a urine culture as part of the diagnostic evaluation. (J Pediatr 1993;123:17-23)

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Reprint requests: Alejandro Hoberman, MD, Department of Pediatrics, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, 3705 Fifth Ave. at De Soto St., Pittsburgh, PA 15213.

[a]Now in the Department of Pediatrics, University of Michigan Medical Center and Mott Children's Hospital, Ann Arbor.

[b]Now in the Department of Pediatrics, University of Massachusetts Medical Center, Worcester.

[c]Now in the Department of Pediatrics, Ohio State University School of Medicine and Columbus Children's Hospital, Columbus.

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Initial episodes of urinary tract infection occur more commonly in infancy than at any other age.[1-3] Predisposing factors include congenital obstruction, ureterovesical valve dysfunction, immaturity of host defenses, and exposure through fecal soiling to pathogens that can enter the urinary tract. In febrile infants the reported prevalence of UTI has ranged from 4.1% to 7.5%.[4-6] The variability in prevalence appears attributable to differences among studies in the age, sex, and race of subjects, methods of urine collection, and criteria for the diagnosis of UTI. The limitations of previous studies include imprecise criteria for selecting sub-

CFU	Colony-forming unit
CI	Confidence interval
ED	Emergency department
UTI	Urinary tract infection
VUR	Vesicoureteral reflux

jects,[4, 5] restriction of the study population to febrile infants whose urine specimens were cultured routinely as part of a sepsis evaluation,[6] and the use of bag-collected urine specimens.[4, 5] To our knowledge, no study has examined the prevalence of UTI in febrile infants identified differentially as having, or not having, another apparent source of fever.

Whereas fever appears to be consistently present in infants with UTI, no other signs or symptoms, singly or in combination, accurately predict the presence of UTI. The difficulty of correctly diagnosing UTI in infants was evident in a study by Bauchner et al.,[5] in which all episodes of illness ultimately diagnosed as UTI had initially been assigned other diagnoses, including acute otitis media, gastroenteritis, upper respiratory tract infection, and bronchiolitis.

Although microscopic urinalysis for leukocytes and bacteria is often used as a diagnostic test for UTI, the sensitivity, specificity, and predictive values of this test have varied greatly according to the patient population studied, the definition of a positive culture result, and the method of microscopic analysis.[6-13]

We undertook the present study, using only urine specimens obtained by catheterization, (1) to determine more precisely than in previous studies the prevalence of UTI among demographically distinct groups of febrile infants with and without an apparent source of fever and (2) to assess the validity of microscopic urinalysis—as distinct from urine culture—in the diagnosis of UTI in febrile infants.

METHODS

Subjects. All febrile infants aged ≤1 year who were seen in the emergency department of the Children's Hospital of Pittsburgh (CHP) from February 1990 through January 1991 were potential study subjects. Eligibility was limited to infants with a rectal temperature ≥38.3° C (100.9° F) recorded in the ED, or a history of a rectal temperature ≥38.3° C or axillary temperature ≥37.4° C having been recorded within the previous 24 hours. Infants who had received an antimicrobial agent or had undergone bladder catheterization within 48 hours were excluded.

Clinical procedures. A urine culture specimen was obtained routinely as part of the evaluation of all febrile infants aged ≤2 months. In study-eligible infants aged >2 months, a urine culture specimen was obtained at the discretion of the examining resident physician. When a urine specimen had not been obtained as part of an infant's evaluation, and when an investigator was available in the ED (8 AM to 9 PM weekdays and on some weekends), parental permission was requested for the infant to undergo bladder catheterization. Demographic information and recorded rectal temperature were abstracted from the ED record by an investigator or a research nurse. When an investigator was available to interview the parent, a history was systematically obtained and recorded concerning the presence or absence, during the preceding 48 hours, of a group of specified signs and symptoms.

Microscopic urinalysis, urine culture, and diagnosis of UTI. All urine specimens were obtained by bladder catheterization. Urinalysis was performed in a clinic-based laboratory. Specimens of ≥1.0 ml were centrifuged at 2000 rpm for 10 minutes; specimens of <1.0 ml were analyzed uncentrifuged. Specimens were not stained, and were examined microscopically for pyuria, reported as the number of leukocytes per high-power field, and for bacteriuria, reported as none, trace, light, moderate, or heavy amount per high-power field.

For infants whose urine cultures were ordered by the examining physician, standard quantitative cultures were grown in the CHP microbiology laboratory. A loop calibrated to deliver approximately 0.001 ml was used to inoculate plates containing sheep blood agar, Columbia colistin-nalidixic acid agar, and MacConkey agar. All plates were incubated at 35° to 37° C and examined at 24 and 48 hours for colony count and bacterial identification. For infants whose urine cultures had not been ordered by the examining physician but were being grown for study purposes, urine specimens were cultured in the clinic-based laboratory, on a dipslide (Dip-N-Count, Starplex Scientific, Mississauga, Ontario, Canada) consisting of a paddle containing MacConkey and Cled agar on one side each. A sterile Pasteur pipette was used to drip urine uniformly over the agar on each side of the paddle, which was then held vertically to allow excess urine to drain. The slides were incubated at 35° to 37° C and examined at 24 and 48 hours for colony count. Slides with a growth of at least two colonies (equivalent to 1000 colony-forming units per milliliter) were sent to the microbiology laboratory for subculture and identification. Results of both standard quantitative and dipslide cultures were considered positive if ≥10,000 CFU of a single type of organism per milliliter were present. Results of cultures showing <10,000 CFU of a single type of organism per milliliter or showing two or more types of organisms were considered negative. The diagnosis of UTI was based on a positive urine culture result.

Dipslides versus quantitative urine cultures. After completion of the prevalence component of the study as just described, a comparative study was carried out in an effort to assess the validity of the dipslide method. All urine specimens obtained by bladder catheterization in the ED during a 2-month period were divided by nurses using sterile technique into two aliquots. One aliquot was sent to the microbiology laboratory for standard quantitative culture, and the other to the clinic-based laboratory for dipslide culture.

Classification of discharge diagnoses. For each infant the ED physician's discharge diagnosis was subsequently classified by each of two investigators independently into one of three categories: (1) no identified source of fever (e.g., rule out sepsis, rule out bacteremia, rash, dehydration), (2) possible source of fever (e.g., otitis media, upper respiratory tract infection, croup, bronchiolitis, gastroenteritis, viral syndrome, immunization reaction); and (3) unequivocal source of fever (e.g., meningitis, pneumonia, septic arthritis, varicella, herpetic gingivostomatitis). Differences in classification were resolved by a consensus procedure involving one or more additional investigators.

Management and follow-up. After diagnosis, UTI was managed by the infants' primary care providers, resident or attending physicians, or study investigators. All infants received appropriate antimicrobial therapy and, when deemed necessary, were admitted to the hospital. Patients who identified no primary care provider were offered follow-up renal ultrasonography, voiding cystourethrography, and continuing care at CHP. Follow-up information was obtained from medical record review or discussions with primary care providers, or both. Anomalies of the urinary tract were recorded on the basis of radiologists' evaluations. Vesicoureteral reflux was graded according to the five-grade system of the International Reflux Study Committee.[14] When reflux was bilateral and the grade on the two sides differed, the higher grade was recorded.

Statistical analysis. Relationships between categoric variables were analyzed by using the Fisher Exact Test or the chi-square test. All statistical tests were two tailed. Log-linear analysis was used to detect associations between demographic and clinical characteristics and the prevalence of UTI. In calculating sensitivity, specificity, and positive and negative predictive values for pyuria and bacteruria, we used urine culture results as the validating standard.

RESULTS

Study population. A total of 2455 infants were seen in the ED for care of a febrile illness during the 1-year study period. Of these, 287 were excluded because they had received antimicrobial agents or undergone bladder catheterization within the previous 48 hours. Urine culture specimens were obtained as a matter of routine from 306 infants who were febrile and aged $\leq$2 months, and on 443 infants aged >2 months because of a suspicion of UTI. In addition, during the periods that investigators were available, the parents of 370 infants from whom a urine specimen had not been obtained for diagnosis were asked to consent to their infants' being catheterized; 213 (57.6%) agreed, and usable urine culture results were obtained on 196 of these infants. The 945 infants on whom urine culture results were obtained constitute the study population.

The distributions of age, sex, race, and diagnostic category regarding source of fever (unequivocal, possible, or none identified) were similar among infants seen during periods when an investigator was available and when an investigator was unavailable. However, the proportion of infants with temperature $\geq$39° C when seen was higher during periods when an investigator was unavailable (623/1307; 48%) than when an investigator was available (339/861; 39%) (p <0.05). All demographic and clinical characteristics were similar in infants whose parents did, and did not, consent to their infants' being catheterized for study purposes. Of the 204 male infants catheterized when an investigator was present, 98% had been circumcised.

Prevalence of UTI. Of the 945 febrile infants from whom urine culture specimens had been obtained, the results were positive ($\geq$10,000 CFU of a single pathogen [per milliliter] only) in 50 (5.3%; 95% confidence interval, 3.9% to 6.7%). In 38 (76%) of these infants the concentration of bacteria was $\geq$100,000 CFU/ml. Culture results were positive in 14 of the 306 infants aged $\leq$2 months being examined for sepsis (4.6%; 95% CI, 2.2% to 6.9%); in 26 of the 443 infants aged >2 months in whom UTI was suspected (5.9%; 95% CI, 3.7% to 8.1%); and in 10 of the 196 infants for whom cultures had not been ordered but whose parents consented to participate in the study (5.1%; 95% CI, 2.0% to 8.2%).

The prevalence of UTI in relation to five variables—age, sex, race, temperature, and the presence or absence of an apparent source of fever—is summarized in Table I. The prevalence was similar in infants aged $\leq$2 months and infants aged >2 months; higher among female than male infants; and higher among white than black infants. No association was apparent between the prevalence of UTI and infants' temperature as recorded in the ED. If sex, race, and temperature were combined, UTI was found in 16.9% of white female infants whose highest temperature had been $\geq$39° C, a significantly higher proportion than in any other grouping of infants (p <0.05). Using log-linear analysis, we found that each of the latter three variables was significantly associated, individually and in combination, with the presence of UTI (p =0.0035). Urinary tract infection was more prevalent among infants with no identified source of fever than among infants with a condition identified as a possible source of fever, and least prevalent among infants with an unequivocal source of fever.

Signs and symptoms. Information about the presence or absence of signs and symptoms commonly ascribed to UTI was obtained by an investigator by interview of the parents of 416 infants. Vomiting, diarrhea, irritability, and poor feeding were present in 40%, 30%, 80%, and 65%, respectively, of 20 infants with UTI, and in 32%, 42%, 76%, and 65%, respectively, of 396 infants without UTI. None of the differences between the UTI and non-UTI groups was sta-

Table I. Prevalence of UTI according to age, sex, race, height of temperature, and source of fever

	n	Positive culture			p
		No.	%	(95% CI)	
Age (days)					
≤60	306	14	4.6	(2.2-6.9)	0.5
61-365	639	36	5.6	(3.8-7.4)	
Sex					
Male	526	13	2.5	(1.1-3.8)	<0.0001
Female	419	37	8.8	(6.1-11.5)	
Race					
White	533	35	6.6	(4.5-8.7)	0.04
Black	392	14	3.6	(1.7-5.4)	
Other	20	1	5.0	(−4.6-14.6)	
Temperature at presentation					
<38.3° C	233	11	4.7	(2.0-7.4)	
38.3° C to 38.9° C	287	12	4.2	(1.9-6.5)	0.22
≥39°C	424	27	6.4	(4.0-8.7)	
Not available	1	0	0	(0-0)	
Highest temperature by history					
<38.3° C	41	2	4.9	(−1.7-11.5)	
38.3° C to 38.9 ° C	363	13	3.6	(1.7-5.5)	0.08
≥39° C	541	35	6.5	(4.4-8.5)	
Source of fever					
Unequivocal	62	1	1.6	(−1.5-10.5)	
Possible	429	15	3.5	(1.8-5.2)	0.02
No source	454	34	7.5	(5.1-9.9)	
TOTAL	945	50	5.3	(3.9-6.7)	

Table II. Sensitivity, specificity, positive predictive value, and negative predictive value of microscopic urinalysis (pyuria and bacteriuria) in identifying positive urine culture results (N = 856)

Criteria	Sensitivity	Specificity	PPV	NPV
Any WBC/HPF	0.77	0.47	0.07	0.97
≥5 WBC/HPF	0.54	0.96	0.45	0.97
≥10 WBC/HPF	0.32	0.99	0.64	0.96
Any bacteria	0.86	0.63	0.11	0.99
Heavy bacteria	0.16	0.99	0.70	0.96

75% centrifuged, 10% uncentrifuged, 15% no information.
PPV, Positive predictive value; *NPV*, negative predictive value; *WBC*, white blood cells; *HPF*, high-power field.

tistically significant. Other signs and symptoms, including cough, nasal discharge, ear pulling, and diaper rash, also occurred with approximately equal frequency in the two groups.

Microscopic urinalysis. Of the 945 urine specimens obtained, 89 were of insufficient volume to permit microscopic urinalysis. For the remaining 856 specimens, Table II shows the sensitivity, specificity, positive predictive value, and negative predictive value of microscopic pyuria and of bacteriuria of varying degrees in relation to the presence of a positive urine culture result. The sensitivity of bacteriuria (defined as any number of bacteria per high-power-field) was lower in infants aged ≤2 months (0.64) than in infants aged >2 months (0.94) (p =0.03), and the specificity of bacteriuria was lower in centrifuged urine (0.59) than in noncentrifuged urine (0.74) (p =0.02).

Methods of urine culture. In the prevalence component of the study, among the 50 specimens that yielded positive culture results, the proportion of specimens that had 10,000 to 100,000 CFU/ml (rather than >100,000 CFU/ml) was higher in the subgroup cultured by the dipslide method than in the subgroup cultured by the standard quantitative method. That growth at these lower concentrations was a valid indicator of UTI is suggested by findings in four of the five infants who had positive culture results, with colony counts between 10,000 and 50,000 CFU/ml. Of these four infants, two gave additional culture specimens that in each instance showed the same pathogen, *Escherichia coli*, in concentrations of 10,000 and 100,000 CFU/ml, respectively. Cultures of specimens from the other two infants grew enterococci in concentrations of 10,000 and 50,000 CFU/ml, respectively, suggesting that, because the infants were febrile, they had UTI. The fifth infant's specimen yielded *E. coli* in a concentration of 10,000 CFU/ml, but an additional culture specimen was not obtained.

In our comparison of dipslide and standard quantitative cultures, established after completion of the prevalence

component of the study, 103 urine specimens obtained by catheterization were cultured by both methods. The results showed agreement in 99 instances: six specimens had ≥100,000 CFU of the same organism (per milliliter) by both methods, and 93 specimens showed no growth by either method. Of the four specimens giving discordant results, three had standard quantitative cultures showing no growth but dipslide cultures showing 10,000 CFU *E. coli* per millliter, 10,000 CFU *Klebsiella pneumoniae* per milliliter, and 15,000 CFU coagulase-positive staphylococci per milliliter, respectively, whereas one specimen had a standard quantitative culture showing 2000 CFU enterococci per milliliter and a dipslide culture showing 25,000 CFU enterococci per milliliter.

Imaging studies. Of the 50 infants in whom UTI was diagnosed in the prevalence component of the study, follow-up sonograms and voiding cystourethrograms were obtained for 36: 29 of 40 in whom UTI had been initially suspected, and 7 of 10 whose parents consented to participate in the study. Abnormalities of the urinary tract were found in 12 infants—grade II or III VUR in 4 infants, grade IV or V VUR in 3 infants, pelvicalicectasis in 2 infants, and dysplastic kidney, ureteral duplication, and bilateral hydroureter in 1 infant each.

DISCUSSION

Urinary tract infection is an important clinical problem in infants because, in those who are febrile, the infection usually consists of acute pyelonephritis,[1-3], which may adversely affect renal function later in life. The risk of renal parenchymal damage from UTI—manifested by subsequent renal scarring—is strongly related to age at the time of UTI, being highest in infancy and declining markedly with increasing age.[15] Renal scarring is associated with the later development of hypertension, preeclampsia, eclampsia, and end-stage renal disease.[16-19]

Standard pediatric textbooks recommend including a urine culture in the diagnostic evaluation of febrile infants <3 months of age. However, for febrile infants ≥3 months of age, whose history or physical examination does not suggest serious illness, recommendations are for expectant follow-up only.[20, 21] Further, a recent survey of 1600 pediatricians, family practitioners, and emergency medicine physicians found that half would treat a highly febrile 4-month-old infant with an antibiotic without first obtaining a urine culture specimen.[22]

Our study was designed to avoid the limitations of previous studies of the prevalence of UTI in infants. All urine specimens were obtained by bladder catheterization, subjects' ages spanned the entire first year of life, and outcomes were analyzed in relation to demographic and clinical variables. Absence of bias in the selection of study subjects was evidenced by the similarity of demographic and clinical characteristics in enrolled and nonenrolled infants. Because urinalysis results were not used as criteria for obtaining urine culture specimens and because, among infants >2 months of age, prevalence rates of UTI in those with initially suspected UTI were similar to prevalence rates in those with no suspected UTI, but whose parents consented to participate in the study, we believe that ascertainment bias did not distort our results. The proportions of infants who had follow-up studies performed also were similar in these two groups of infants (29/40 and 7/10, respectively).

The prevalence of UTI reported here is consistent with rates reported previously.[4-6] Neither the presence of pertinent clinical signs and symptoms nor the presence of leukocytes and bacteria on microscopic examination of the urine—both commonly used as potential indicators of UTI—was an accurate predictor of positive urine culture results. The presence of pyuria, defined as ≥5 leukocytes per high-power field, was a relatively insensitive indicator of UTI. Had urine culture been omitted because of the absence of pyuria, nearly half of the UTIs would not have been diagnosed. The presence of bacteriuria, defined as any number of bacteria per high-power field, was a more sensitive indicator, but it was not specific enough to identify infants with UTI accurately. The diagnostic limitations, in this and other studies,[6-13] of microscopic pyuria and bacteriuria—defined on the basis of numbers of leukocytes and bacteria counted per high-power field in centrifuged specimens of urine—may be due to lack of standards concerning the volume of urine studied, the duration of centrifugation, the volume used for resuspension, and the size of the drop and the number of fields examined microscopically.

A notable finding of our study was the disproportionately high prevalence (16.9%) of UTI among white infant girls with a temperature ≥39° C, a significantly higher proportion than in any other grouping of infants by sex, race, and temperature. Roberts et al.[4] had reported a relatively high prevalence of UTI in female children less than 2 years of age (7.4%), but analysis according to race or to height of temperature was not reported. Earlier, Kunin et al.[23] had reported that, among school-aged children, the prevalence of symptomatic and of asymptomatic bacteriuria was higher in white than in black girls. Our finding that UTI was particularly prevalent among white female infants with high fever suggests that clinicians should particularly suspect the presence of UTI in this subgroup of infants. Among the male infants whom we studied, the low proportion of those uncircumcised (2%) precluded analysis of any association of the prevalence of UTI with circumcision status.

A limitation of our study was our use of two differing urine culture methods. To limit the study's cost, we used dipslide cultures rather than standard quantitative cultures

in infants from whom a urine specimen had not been obtained as part of the examining physician's evaluation. Several studies have reported dipslide cultures to be valid, with standard quantitative cultures used as the gold standard.[24, 25] In our comparison of the results of dipslide and standard quantitative cultures of 103 urine specimens obtained by catheterization, all specimens with ≥100,000 CFU/ml on the standard quantitative culture had at least that quantity on the dipstick-slide culture. However, dipslide cultures were more likely than standard quantitative cultures to detect lower colony counts of bacteria, in the range of 10,000 to 50,000 CFU/ml. An explanation may lie in the differing amounts of urine cultured by the two methods. Although catheterization of infants often yields only a few milliliters of urine, this amount, dripped over the slide's paddle, is far greater than the 0.001 ml delivered by the calibrated loop used for inoculating quantitative culture media.

Our observation that the rate of positive urine culture results was approximately the same among febrile infants whose examining physicians considered UTI a diagnostic possibility as among febrile infants with no suspected UTI suggests that UTI may be underdiagnosed in febrile infants. Except when a source of fever is unequivocal, as defined previously, UTI should always be included in the differential diagnosis of fever during the first year of life. In our study, 15 of the 50 infants ultimately found to have positive urine culture results had initially received diagnoses other than UTI. Some or all of these diagnoses may have been correct, in which case the positive urine culture results would have reflected either coincident asymptomatic bacteriuria or concomitant UTI. Wettergreen et al.[26] reported a mean point prevalence of asymptomatic bacteriuria of 0.57% (range, 0.17% to 1.56%, the latter value in uncircumcised male infants aged <2 months). Because the 5.3% level of prevalence among our febrile infants was substantially greater than the mean value reported by Wettergreen et al. in symptom-free infants, we do not consider that asymptomatic bacteriuria, incidental to but not the cause of febrile illness, is a likely explanation for most of the positive urine culture results in our study. Antimicrobial treatment appropriate for other acute bacterial infections may, in many instances, also constitute adequate treatment for acute UTI, but failure to identify UTI as such would ordinarily preclude obtaining appropriate follow-up studies aimed at identifying VUR and structural urinary tract abnormalities. Infants with such abnormalities should receive antimicrobial prophylaxis, and in some cases surgical intervention, to reduce recurrences of acute pyelonephritis that may increase the risk of renal scarring, with its potentially serious long-term consequences.[16-19]

We conclude that until more sensitive techniques are available for immediately diagnosing UTI in febrile infants, and except when the cause of fever in such infants is unequivocal as defined previously, clinicians should be alert to the possibility that febrile infants may have UTI and should consider obtaining a urine culture specimen as part of their diagnostic evaluation. Further study of the prevalence of UTI among white female infants with high fever would be desirable, as would study of methods to enhance the accuracy of urinalysis as a diagnostic test for UTI.

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