

# Urinary Tract Infection in Febrile Infants Younger Than Eight Weeks of Age

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**ABSTRACT.** *Objective.* To assess the usefulness of laboratory parameters, including peripheral white blood cell (WBC) count, C-reactive protein (CRP) concentration, erythrocyte sedimentation rate (ESR), and microscopic urinalysis (UA), for identifying febrile infants younger than 8 weeks of age at risk for urinary tract infection (UTI), and comparison of standard UA and hemocytometer WBC counts for predicting the presence of UTI.

*Methods.* A total of 162 febrile children <8 weeks of age were enrolled in this prospective study. All underwent clinical evaluation and laboratory investigation, including WBC count and differential; ESR; CRP; blood culture; a lumbar puncture for cell count and differential, glucose level, protein level, Gram stain, and culture; and a UA and urine culture. All urine specimens were obtained by suprapubic aspiration and microscopically analyzed with standard UA as well as with hemocytometer WBC counts. Quantitative urine cultures were performed. Sensitivity, specificity, accuracy, likelihood ratios, and receiver operating characteristic (ROC) curves were determined for each of the screening tests.

*Results.* There were 22 positive urine culture results of at least 100 colony-forming unit/mL. Eighteen of these 22 patients were males, and all were uncircumcised. There were significant differences for pyuria  $\geq 5$  WBCs/hpf, pyuria  $\geq 10$  WBC/ $\mu$ L, CRP >20 mg/L, and ESR >30 mm/hour between culture-positive and culture-negative groups ( $P < .05$ ). The ROC area for hemocytometer WBC count, standard UA, peripheral WBC count, ESR, and CRP concentration were  $.909 \pm .045$ ,  $.791 \pm .065$ ,  $.544 \pm .074$ ,  $.787 \pm .060$ , and  $.822 \pm .036$ , respectively. The ROC curve analysis indicates that the CRP, ESR, and standard UA were powerful but imperfect tools with which to discriminate for UTI in potentially infected neonates. Hemocytometer WBC counts had the highest sensitivity, specificity, accuracy, and likelihood ratios for identifying very young infants with positive urine culture results. For all assessments, hemocytometer WBC counts were significantly different, compared with the standard urinalysis. ESR, CRP, and peripheral WBC counts were not helpful in identifying UTI in febrile infants.

*Conclusion.* UTI had a prevalence of 13.6% in febrile infants <8 weeks of age. The CRP, ESR, and standard UA were imperfect tools in discriminating for UTI, and the sensitivity of these laboratory parameters was relatively

low. Hemocytometer WBC count was a significantly better predictor of UTI in febrile infants. *Pediatrics* 2000; 105(2). URL: <http://www.pediatrics.org/cgi/content/full/105/2/e20>; urinary tract infection, standard urinalysis, hemocytometer white blood cell counts, receiver operator characteristic curves.

ABBREVIATIONS. UTI, urinary tract infection; UA, urinalysis; hpf, high-power microscopic field; WBC, white blood cell; CFU, colony-forming unit; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MMH, Mackay Memorial Hospital; ROC, receiver operator characteristic curves; AUC, area under the curve; LR, likelihood ratio.

Urinary tract infection (UTI) is a frequent serious bacterial infection in young infants.<sup>1</sup> UTI is often associated with vesicoureteral reflux or urinary tract obstruction,<sup>2</sup> conditions associated with a higher risk of recurrent UTI.<sup>3</sup> Moreover, UTI is believed to be the leading cause of renal scarring,<sup>4,5</sup> one of the most common causes of end-stage renal disease in children.<sup>6,7</sup>

The presumptive diagnosis of UTI in children is often based on the results of microscopic urinalysis (UA), and most infections remain undiagnosed if tests are not performed routinely to detect them. Febrile infants <8 weeks of age are frequently admitted for rigorous diagnostic examinations, including consideration of UTI, and for administration of parenteral antibiotics for treatment of possible serious bacterial infection. The evaluation and management of febrile infants remain controversial. Previous studies have attempted to identify those febrile infants at risk for serious bacterial infection using data ranging from clinical impressions to the use of multiple laboratory examinations.<sup>8-12</sup>

Microscopic UA in pediatric primary care facilities is often performed on centrifuged specimens and reported as cells per high-power microscopic field (hpf), that is, a standard UA. The sensitivity, specificity, and positive predictive value of the standard UA are so low that only a third to half of patients with positive urine culture results can be identified correctly.<sup>13-15</sup> Dukes<sup>16,17</sup> described a more accurate microscopic analysis of uncentrifuged urine performed with a hemocytometer and reporting cells per cubic millimeter, herein referred to as hemocytometer white blood cell (WBC) counts. Stamm<sup>18</sup> defined pyuria as the presence of  $\geq 10$  WBCs/ $\mu$ L in uncentrifuged urine and found it to be very sensitive,

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identifying 96% of symptomatic adult patients with bacteriuria of  $\geq 1000$  colony-forming unit (CFU)/mL.

The present study was undertaken to evaluate a group of febrile infants younger than 8 weeks of age 1) to assess the usefulness of the WBC count, C-reactive protein (CRP) concentration, erythrocyte sedimentation rate (ESR), and UA for identifying infants at risk for UTI; and 2) to compare standard WBC counts and hemocytometer WBC counts in identifying very young infants with positive urine culture results.

## METHODS

We prospectively studied all febrile (rectal temperature  $>38^{\circ}\text{C}$ ) infants younger than 8 weeks of age who presented to the Pediatric Clinic or Emergency Department of Mackay Memorial Hospital (MMH), from September 1, 1997, through August 31, 1998. All infants were hospitalized. Infants who had received an antibiotic agent or who had undergone suprapubic bladder aspiration or bladder catheterization within 24 hours were excluded.

Every infant underwent a history and physical examination, and a full evaluation for sepsis was performed, including peripheral WBC count and differential; ESR; CRP; blood culture; a lumbar puncture for cell count and differential, glucose level, protein level, Gram stain, and culture; and a UA and urine culture. Blood, urine, and cerebrospinal fluid specimens were cultured using standard media and techniques. Blood samples were cultured on aerobic, anaerobic, and hypertonic media. Stool specimens were cultured when indicated.

All urine specimens were obtained by suprapubic bladder aspiration. The bladder tap was performed after the infant had been well hydrated intravenously or one half to 1 hour after feeding. Eligibility was limited to urine specimens of  $>5$  mL obtained on a single aspiration. All urinalyses were performed in a certified clinical laboratory. Specimens were analyzed with both standard UA and hemocytometer WBC counts simultaneously. For the standard UA, specimens were centrifuged at 2000 rpm for 10 minutes and were examined microscopically for pyuria reported as the number of leukocytes per high-power field. For hemocytometer WBC counts, the uncentrifuged urine specimens were examined microscopically on a KOVA Slide 10 (Hycor Biomedical, Inc, Irvine, CA) chamber by the same technician. The KOVA Slide 10 chamber is a glass disposable cell counting chamber with methodology based on Neubauer ruling that is similar to the Neubauer hemocytometer. One milliliter of undiluted, uncentrifuged urine was trapped by a KOVA pipet and was transferred to the notch on a KOVA Slide 10 chamber hemocytometer. By capillary action  $6.6\ \mu\text{L}$  of the sample was drawn into the chamber. Average leukocyte contained per small grid were counted on the chamber and multiplied by 90 to obtain total cells per  $\mu\text{L}$ .

Quantitative urine cultures were performed in the MMH Microbiology Laboratory. A loop calibrated to deliver  $\sim 0.01$  mL was used to inoculate plates containing sheep blood agar, Columbia CAN agar, and MacConkey agar. All plates were incubated at  $35^{\circ}$  to  $37^{\circ}\text{C}$  and examined at 24 to 48 hours for colony count and bacterial identification.

For standard UA, pyuria was defined as at least 5 WBCs/hpf. For hemocytometer WBC counts, pyuria was defined as at least 10 WBCs/ $\mu\text{L}$ . Growth of a single urinary pathogen at a concentration of at least 100 CFU/mL was defined as positive and considered diagnostic of UTI.<sup>15</sup> Cultures with growth of mixed organisms or nonpathogenic Gram-positive cocci were considered contaminated.

A receiver operating characteristic (ROC) curve was constructed to describe the diagnostic properties of the peripheral WBC count, CRP, ESR, standard UA, and hemocytometer WBC counts. The ROC curves are plots of the probability of a true-positive rate against false-negative rate at various cutoff levels obtained for each laboratory parameter. The curve demonstrates the empirical relationship between sensitivity and specificity. The area under the curve (AUC) quantifies a test's discriminating power into a single figure. A test can have an AUC value of between .5 (which represents a true UTI being diagnosed by chance) and 1.0 (which represents perfect discrimination of UTI from other conditions). The difference in the AUCs was analyzed with a  $\chi^2$  test.

Sensitivity, specificity, accuracy, and likelihood ratios (LR) for

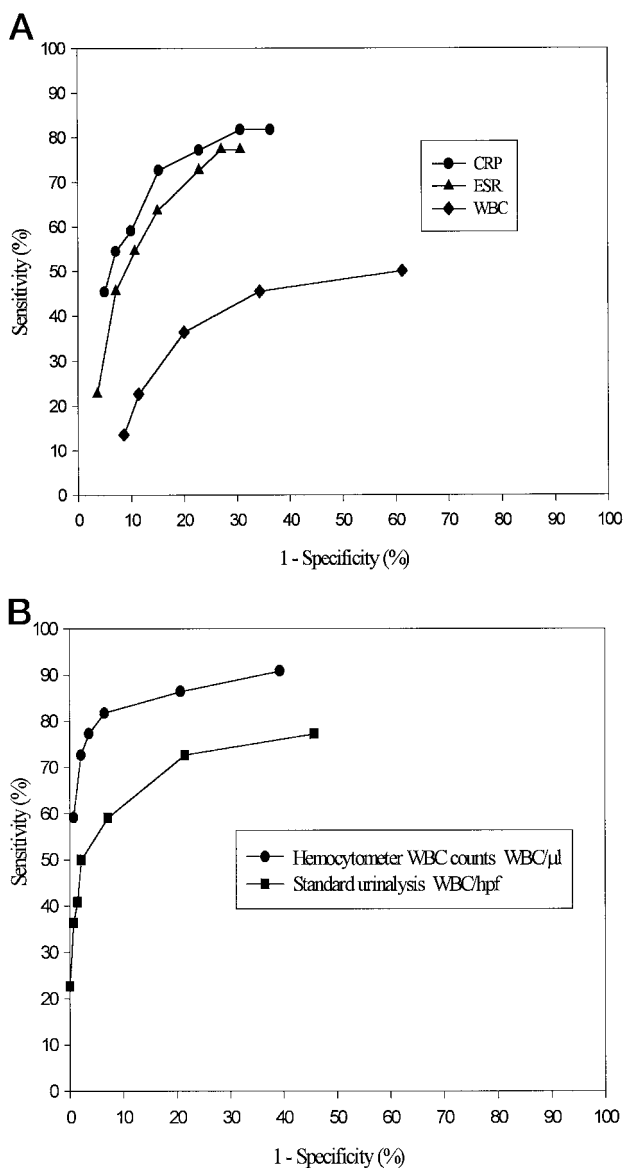
laboratory parameters, with the decision cutoff criterion, were calculated. The  $\chi^2$  test (or Fisher's exact test when the numbers were small) was used for comparison of diagnostic sensitivity and specificity;  $P < .05$  was considered statistically significant. The LR(+) for a positive test result is the ratio of the frequency of a finding among the diseased patients (true-positive rate) and among the nondiseased patients (false-positive rate), or the sensitivity/(1 - specificity). The LR(-) for a negative or normal test result is the false-negative fraction divided by the true-negative fraction, or the (1 - sensitivity)/specificity. A test result with an LR of  $>1.0$  raises the probability of disease and is often referred as a positive test result. A test result with an LR of  $<1.0$  lowers the probability of disease and is often called a negative test result. Unlike the positive and negative predictive values, the LR is independent of the prevalence of the disease among the studied patients.

## RESULTS

Of 223 febrile infants who presented to our hospital during the study period, 61 (27.4%) were excluded: 8 for previous antibiotic treatment, 14 for failure to aspirate urine, 16 for urine specimens of  $<5$  mL, and 23 for  $>1$  aspiration. A total of 162 infants  $<2$  months of age were enrolled in this study of whom 94 were boys. All infants were hospitalized and initially treated with parenteral antibiotics. All patients had negative blood and CSF culture results. Of the 162 febrile infants, 22 (13.6%) had positive urine culture results. Four were female and 18 were male. All the infected boys were uncircumcised. Of the 22 positive urine culture results, 16 (73%) had colony counts  $\geq 100\ 000$  CFU/mL. The remaining had between 100 and 50 000 CFU/mL. Eighteen infants had *Escherichia coli* infection, 15 (83%) of these had bacterial colony counts  $\geq 100\ 000$  CFU/mL. The pathogens from the other 4 infants were *Pseudomonas aeruginosa*  $\geq 10\ 000$  CFU/mL (2 infants), *Klebsiella pneumoniae*  $\geq 100\ 000$  CFU/mL (1 infant), and group B streptococcus  $\geq 10\ 000$  CFU/mL (1 infant). Of the 22 infants with UTI, 13 had pyuria  $\geq 5$  WBCs/hpf, 18 had pyuria  $\geq 10$  WBCs/ $\mu\text{L}$ , 13 had CRP  $>20$  mg/L, 16 had ESR  $>30$  mm/hour, and 8 had WBC  $>15\ 000/\mu\text{L}$ . There were significant differences ( $P < .05$ ) between infants with and without UTI for pyuria  $\geq 5$  WBCs/hpf, pyuria  $\geq 10$  WBCs/ $\mu\text{L}$ , CRP  $>20$  mg/L, and ESR  $>30$  mm/hour.

The ROC curves for each laboratory test are presented in Fig 1. There were no significant differences between the AUCs of the standard UA, CRP, and ESR. The AUC of the hemocytometer WBC counts was significantly better than that of any other laboratory parameter ( $P < .05$ ). The AUC of the total WBC was significantly smaller than any of the rest ( $P < .05$ ).

Comparison of sensitivity, specificity, accuracy, and LR for CRP  $>20$  mg/L, ESR  $>30$  mm/hour, peripheral WBC  $>15\ 000/\mu\text{L}$ , pyuria  $\geq 5$  WBCs/hpf, and pyuria  $\geq 10$  WBCs/ $\mu\text{L}$ , in relation to the presence of a positive urine culture result is shown in Table 1. None of the blood tests were sensitive indicators of UTI. The most sensitive indicator for UTI was pyuria  $\geq 10$  WBCs/ $\mu\text{L}$  ( $P < .05$ ). Pyuria  $\geq 5$  WBCs/hpf had poor sensitivity but high specificity. The combination of pyuria  $\geq 10$  WBCs/ $\mu\text{L}$  and CRP  $>20$  mg/L increased the specificity to 98%. The specificity of pyuria  $\geq 10$  WBCs/ $\mu\text{L}$  combined with a positive ESR was 97%. The sensitivity of these combinations decreased significantly to 54% and 72%, respectively ( $P < .05$ ).



**Fig 1.** ROC curves in febrile infants younger than 8 weeks of age with UTI showing the sensitivity and specificity of WBC, ESR, CRP (A), standard UA, and hemocytometer WBC counts (B). The ROC area for WBC count, ESR, CRP, standard UA, and hemocytometer WBC counts was  $.544 \pm .074$ ,  $.787 \pm .060$ ,  $.822 \pm .036$ ,  $.791 \pm .065$ , and  $.909 \pm .045$ , respectively.

For febrile infants in our study, UTI was significantly more likely when the urine had  $\geq 5$  WBCs/hpf or  $\geq 10$  WBCs/ $\mu\text{L}$ . A febrile infant with pyuria  $\geq 10$  WBCs/ $\mu\text{L}$  had a greater likelihood of infection than with pyuria of  $\geq 5$  WBCs/hpf. In contrast, UTI was

highly unlikely when there was a normal hemocytometer WBC counts result.

## DISCUSSION

UTI had a prevalence in our series of 13.6% in febrile infants  $< 8$  weeks of age, suggesting that UTIs may be a relatively common cause of fever in these patients. Males comprised 82% of the infants with UTI in our sample.

None of our patients with UTI had associated bacteremia. This contrasts with the results of Ginsburg and McCracken,<sup>19</sup> in which sepsis was documented in 31% of neonates and 21% of infants 1 to 2 months of age, and that of Wiswell and Geschke,<sup>20</sup> bacteremia in 36.4% of uncircumcised male infants with UTI. These results also differ from those of Bachur and Caputo,<sup>21</sup> who, in a retrospective analysis of 354 children  $\leq 2$  years of age with UTI, found all cases of bacteremia were observed in children  $< 6$  months of age, and that one third of young infants with bacteremia were  $< 2$  months of age. This discrepancy in the rate of positive blood culture results may result from differences in our study population. MMH is a medical center that provides inpatient medical care to people from all over Taipei and surrounding towns. All febrile infants  $< 2$  months of age who are referred to MMH or seen in the MMH Pediatric Clinic or emergency room are evaluated and hospitalized. Therefore, our sample reflects the general population of febrile infants with UTI rather than primarily those who seem to be too sick to treat as outpatients. The results of our study support those of Krober et al<sup>22</sup> and Crain and Gershel,<sup>15</sup> who studied similar patient populations.

CRP  $> 20$  mg/L, ESR  $> 30$  mm/hour, and WBC  $> 15\,000/\mu\text{L}$  are key findings in various studies on febrile infants.<sup>8-12</sup> The diagnostic value of these parameters for predicting serious bacterial infection in febrile infants, however, is conflicting.<sup>8-12</sup> Our investigation showed that febrile infants with CRP  $> 20$  mg/L and ESR  $> 30$  mm/hour were at risk for UTI ( $P < .05$ ) but that a WBC count  $> 15\,000/\mu\text{L}$  was not significantly associated with UTI ( $P > .05$ ). Although the specificity of ESR and CRP was high, their sensitivity relatively low, demonstrating that elevated CRP and ESR are poor predictors for identifying UTI in febrile infants. Our results corroborate the findings of Crain and Gershel,<sup>15</sup> whose sample was similar to ours. In that report of 442 hospitalized febrile infants younger than 8 weeks of age studied prospectively, reliable clinical or laboratory indicators of UTI were lacking.

The presence of pyuria  $\geq 5$  WBC/hpf has been

**TABLE 1.** Comparison of the Results of Diagnostic Test in Relation to the Presence of a Positive Urine Culture Result

	Hemocytometer WBC Counts $\geq 10$ WBCs/ $\mu\text{L}$	Standard UA $\geq 5$ WBCs/hpf	CRP $> 20$ mg/L	ESR $> 30$ mm/h	Peripheral WBC $> 15\,000/\mu\text{L}$
Sensitivity	82%	59%	59%	73%	36%
Specificity	94%	93%	90%	78%	80%
Accuracy	92%	88%	86%	77%	74%
LR(+)	12.7	8.3	5.9	3.3	1.8
LR(-)	.19	.44	.45	.35	.80

LR(+) indicates likelihood ratio for positive test result; LR(-), likelihood ratio for negative test result.

found to be a poor predictor of a positive urine culture.<sup>13-15</sup> In our report, the sensitivity (59%) of the standard UA was relatively low for predicting a positive urine culture result, compatible with previous studies of febrile infants and children.<sup>14,15,23</sup> The hemocytometer WBC counts reported here showed significantly greater sensitivity for identifying febrile infants with UTI, compared with the standard UA. These results in young infants were similar to those in young children with UTI.<sup>24-27</sup> In studies by Hoberman and Wald<sup>26,27</sup> on febrile children <24 months of age, 89.6~91.2% of catheterized urine specimens with bacterial colony counts  $\geq 50\,000$  CFU/mL had at least 10 WBCs/ $\mu$ L, discriminating true UTI from bacteriuria associated with contamination or colonization of the urinary tract. Hoberman et al<sup>24</sup> further compared standard UA versus hemocytometer WBC counts combined with bacteriuria using sensitivity, specificity, and positive and negative predictive values, in 698 febrile children for whom catheterized urine specimens were obtained. There was a significantly higher sensitivity (84.5%) and positive predictive value (93.1%) of the hemocytometer WBC counts combined with bacteriuria to detect UTI.

The diagnostic accuracy and the interpretation of microscopic UA are influenced by the preparation of the specimen (centrifuged vs uncentrifuged), and the method of quantifying and reporting leukocytes (per microscopic high-power field vs per cubic millimeter). Hemocytometer WBC counts allow counting of a fixed volume of urine and facilitate accurate counting by providing a small, marked visual field and uniform illumination. The method reduces variability in results by avoiding the concentration and resuspension of solid elements attained by centrifugation.

Our study favors the use of hemocytometer WBC counts to evaluate febrile infants for UTI. The greater sensitivity of the hemocytometer WBC counts compared with the standard UA substantially increases its accuracy in diagnosing UTI. We conclude that hemocytometer WBC counts is of definite value as an aid in early diagnosis of UTI in febrile infants <8 weeks of age.

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