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Is urine culture necessary to rule out urinary tract infection in young febrile children?

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Objective. **To determine whether the absence of pyuria on the enhanced urinalysis can be used to eliminate the diagnosis of urinary tract infection, avoiding the need for urine culture and sparing large health care expenditures.**

Design. **Results of an enhanced urinalysis (hemocytometer counts and interpretation of Gram-stained smears) performed on uncentrifuged urine specimens obtained by catheter were correlated with urine cultures in young febrile children at the Children's Hospital of Pittsburgh Emergency Department. In a group of 4253 children (95% febrile) less than 2 years of age, pyuria was defined as ≥10 white blood cells/mm^3, bacteriuria as any bacteria on any of 10 oil immersion fields in a Gram-stained smear and a positive culture as ≥50 000 colony-forming units/ml. A subgroup of 153 children with their first diagnosed urinary tract infection were enrolled in a separate treatment trial, acute phase reactants (peripheral white blood cell count, erythrocyte sedimentation rate and C-reactive protein) were obtained and ^{99}Tc-dimercaptosuccinic acid renal scans were performed.**

Results. **The presence of either pyuria or bacteriuria and the presence of both pyuria and bacteriuria have the highest sensitivity (95%) and positive predictive value (85%), respectively, for identifying positive urine cultures. Because a white blood cell count in a hemocytometer is the technically simpler component of the enhanced urinalysis, we chose to analyze the false negative results and achievable cost savings of using pyuria alone as the sole criterion for omitting urine cultures. If in this study urine cultures had been performed only on specimens from children who had pyuria or were managed presumptively with antibiotics, cultures of 2600 (61%) specimens would have been avoided. Twenty-two of 212 patients with positive urine cultures would not have been identified initially. However, based on interpretation of acute phase reactants, initial ^{99}Tc-dimercaptosuccinic acid scan results, response to management and incidence of renal scarring 6 months later, 14 of the 22 patients most likely had asymptomatic bacteriuria and fever from another cause. The remaining 8 patients probably had early urinary tract infection.**

Conclusions. **The analysis of urine samples obtained by catheter for the presence of significant pyuria (≥10 white blood cells/mm^3) can be used to guide decisions regarding the need for urine culture in young febrile children.**

INTRODUCTION

Urinary tract infection (UTI) in infants and young children is an important clinical problem with a prevalence of 5.3% among febrile subjects seen at the Children's Hospital of Pittsburgh Emergency Department (ED) during a 1-year period.[1] A microscopic analysis of uncentrifuged urine that includes a leukocyte count and a Gram-stained smear (enhanced urinalysis) provides a high sensitivity and positive predictive value (PPV) for the identification of positive urine cultures.[2] Based on data from 2181 urine specimens obtained by catheter from infants and young children with fever, UTI is best defined by both: (1) a leukocyte count of at least 10/mm^3 and (2) growth of a single pathogen at a concentration of at least 50 000 colony-forming units/ml (CFU/ml). These criteria almost always discriminate true UTI from bacteriuria resulting from either contamination of the urine specimen or colonization of the urinary tract (asymptomatic bacteriuria).[3]

During the past 36 months we have used the enhanced urinalysis to identify febrile children <24 months old who are eligible for a randomized clinical trial comparing oral and intravenous antimicrobials for

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treatment of UTI.[4] The high predictive value of pyuria and bacteriuria for positive urine culture has permitted the initiation of antimicrobial therapy and the performance of diagnostic imaging procedures before availability of urine culture results.[5] The current analysis was designed to determine whether the absence of pyuria on the enhanced urinalysis can be used to eliminate the diagnosis of UTI, avoiding the need for urine culture and sparing large health care expenditures.

METHODS

Subjects. This analysis includes 4253 children <24 months of age seen in the hospital's ED from December, 1991, through December, 1994, from whom a urine specimen for urinalysis and culture was obtained by bladder catheterization. Urine specimens were obtained as part of a diagnostic evaluation of fever from 95% of these children; the remaining 5% of urines were from neonates undergoing evaluation for sepsis because of nonspecific symptoms. Of these 4253 patients 153 patients (142 with pyuria and 11 without pyuria) with their first diagnosed UTI were enrolled in a separate study of UTI treatment.[4] The validity of the microscopic urinalysis for diagnosing UTI and the criteria for pyuria and bacteriuria have been reported previously.[2, 3]

Urinalysis. In a certified clinic-based laboratory, uncentrifuged urine was drawn into a Neubauer hemocytometer by capillary action. White blood cells (WBC) were counted on one side of the chamber and multiplied by 1.1 to obtain a total cell count per mm^3. Pyuria was defined as at least 10 WBC/mm^3. Smears were prepared using two drops of uncentrifuged urine on a slide within a standardized marked area 1.5 cm in diameter, air dried and Gram-stained. Smears were considered positive when any bacteria were seen on any of 10 oil immersion fields.

Urine culture. Quantitative urine cultures were performed in the Children's Hospital of Pittsburgh 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 35–37°C and examined at 24 and 48 h for colony count and bacterial identification. A positive urine culture was defined as growth of a single pathogen at a concentration of ≥50 000 CFU/ml. The estimated cost of urine culture was based on Pennsylvania Blue Cross/Blue Shield reimbursement ($65).

Urinary tract infection. UTI was defined as the presence of pyuria (≥10 WBC/mm^3) with growth of a single pathogen at a concentration of ≥50 000 CFU/ml.

Laboratory indicators of inflammation/infection. In addition to the urinalysis and urine culture a blood specimen was drawn at study entry for acute phase reactants from the 153 patients enrolled in the treatment trial: peripheral white blood cell count (PWBC); erythrocyte sedimentation rate (ESR); and C-reactive protein (CRP). For 11 patients who presented without pyuria a blood specimen (for determination of acute phase reactants) was obtained when the initial urine culture became positive, and a repeat microscopic urinalysis showed sustained absence of an inflammatory response (pyuria).

Imaging documentation of inflammation/infection. A ^{99}Tc-dimercaptosuccinic acid (DMSA) renal scan was performed within 48 h of study entry (to ascertain the presence of acute pyelonephritis) and again at 6 months (to determine the presence of renal scarring). DMSA was injected intravenously at a dose based on 5 mCi/1.73 m^2 body surface area (minimum dose, 2 mCi). High resolution magnified images of the kidney were obtained, including posterior and posterior oblique projections using a gamma-camera-computer system equipped with a pinhole collimator (8 min) and posterior views with a parallel collimator (400 000 counts) between 3 and 6 h after injection. DMSA scans were interpreted by a single investigator who was unaware of clinical events, using a standardized rating scale previously validated for intra- and interobserver reliability.[6] Acute pyelonephritis was defined as the presence of (1) focal (single or multiple) or diffuse areas of decreased uptake of DMSA without evidence of cortical loss or (2) diffusely decreased uptake in an enlarged kidney (a less common scintigrahic pattern). Renal scarring was defined as (1) decreased uptake of the radioisotope associated with loss of contours or (2) cortical thinning with decreased volume.

Management. The 142 patients with pyuria and microscopic bacteriuria at their initial medical encounter were enrolled in the study of UTI treatment. They were randomized to receive either oral cefixime or a combination of intravenous cefotaxime and oral cefixime for a total of 14 days. The 11 febrile patients without significant pyuria or microscopic bacteriuria, whose urine cultures were positive the following day, were also enrolled in the study and followed prospectively. Early in the study management of these patients was determined by the primary care provider or the examining resident physician. Seven of the 11 patients were treated with antimicrobials for presumed UTI (Patients 1, 2, 3, 4 and 6) or acute otitis media (Patients 7 and 8). The remaining 4 patients enrolled more recently were not treated. Of the 4253 patients in the current analysis, most (3835) did not have pyuria at the time of the ED visit and therefore were not enrolled in the treatment trial. Medical records of the first 125 patients without pyuria evaluated quarterly during 1994 (total, 500) were reviewed

to determine the frequency with which antimicrobials were presumptively prescribed. This assessment was undertaken because urine culture is recommended to diagnose definitively UTI in patients treated presumptively because antibiotic treatment will preclude subsequent evaluation.

Statistical analysis. Sensitivity, specificity and positive and negative predictive values (NPV) were calculated for the presence of pyuria and/or bacteriuria in the enhanced urinalysis with a positive urine culture as the validating standard. Relationships between categorical variables were analyzed by Fisher's exact test or the chi square test. Relationships between continuous variables were analyzed by the Wilcoxon rank sum test. All statistical tests were two tailed.

RESULTS

Urine specimens obtained by catheter were collected from 4253 children <24 months of age, 95% of whom were febrile, and included specimens from 2181 children reported in a previous study of urinalysis.[3] The diagnostic validity, with the urine culture as gold standard, of the presence of (1) pyuria alone, (2) the combination of pyuria and bacteriuria and (3) either pyuria or bacteriuria are presented in Table 1. The presence of either pyuria or bacteriuria and the presence of both pyuria and bacteriuria have the highest sensitivity and PPV, respectively, for identifying positive urine cultures. Although accurate determination of WBC/mm^3 in uncentrifuged urine specimens is a technically simple procedure, which can be performed easily in the office setting (in compliance with current regulatory requirements), interpretation of a Gram-stained smear is a more difficult task for the inexperienced individual. Accordingly we chose to analyze the false negative results and achievable cost savings if pyuria alone was used as the sole criterion for performing urine cultures.

Only pyuria present; analysis of 22 patients without pyuria. If in the course of this study urine cultures had been performed only on specimens with pyuria, cultures of 3857 specimens would have been avoided. Twenty-two patients without pyuria had positive urine cultures; their laboratory, imaging and clinical data are presented in Table 2.

Patients 1 through 15 were part of the UTI treatment trial of 153 children and both acute phase reactants (PWBC, ESR, CRP) and DMSA scans were obtained from them at entry. Analysis of children in the treatment trial shows that they can be divided into 3 groups according to DMSA scan findings and presence of pyuria. Eleven of these patients had no pyuria and normal DMSA scans at entry. The acute phase reactants of these 11 patients were significantly lower (Table 3) than those of the 114 patients in the trial who had pyuria and DMSA scan evidence of acute pyelonephritis, and the 28 with pyuria but normal DMSA scans (presumed cystitis), supporting the hypothesis that these 11 patients had asymptomatic bacteriuria (ABU).[7] The absence or low level of pyuria is consistent with the absence of inflammatory response in colonized (rather than infected) individuals. In 5 of the 11 patients with presumed ABU an alternate source for their fever was identified: 2 with acute otitis media; 2 with roseola; and 1 with gastroenteritis caused by rotavirus. Initially patients in this group were treated with antimicrobials. However, 2 of the 7 patients who received antimicrobials developed acute pyelonephritis within 3 months. The 4 most recent patients without pyuria were not treated; their bacteriuria cleared spontaneously within 2 weeks and no reinfections have occurred. Ten of the 11 patients with presumed ABU had follow-up DMSA scans at 6 months, including 3 of the 4 untreated patients; all were normal.

In Patients 12 through 15 a repeat urinalysis within 48 h showed pyuria. This finding suggests that the initial urinalysis was obtained before development of a local inflammatory response in children with early UTI. Six-month follow-up DMSA scans were normal for all four patients.

The remaining patients (Patients 16 to 22) were not

TABLE 1. Sensitivity, specificity and predictive values of pyuria* (P), pyuria and bacteriuria† (P and B) and pyuria or bacteriuria (P or B)

	Culture-positive‡	Culture-negative		Culture-positive	Culture-negative		Culture-positive	Culture-negative
P+	190	206	P and B+	186	34	P or B+	203	300
P−	22	3835	P and B−	26	4007	Neither P nor B	9	3741
	%			%			%	
Sensitivity	89.6 (85.5–93.7)§			87.7 (83.3–92.2)			95.8 (93.0–98.5)	
Specificity	94.9 (94.2–95.6)			99.2 (98.9–99.4)			92.6 (91.8–93.4)	
PPV	48.0 (43.1–52.9)			84.6 (79.8–89.3)			40.4 (36.1–44.6)	
NPV	99.4 (99.2–99.7)			99.4 (99.1–99.6)			99.8 (99.6–99.9)	
Prevalence	4.98			4.98			4.98	

* Pyuria defined as ≥10 white blood cells/mm^3.

† Bacteriuria defined as any bacteria on any of 10 oil immersion fields in a Gram-stained smear.

‡ Culture-positive defined as growth of a single pathogen at a concentration of ≥50 000 CFU/ml.

§ Numbers in parentheses, 95% confidence interval.

TABLE 2. Laboratory, imaging and clinical data of patients who presented without pyuria on initial "enhanced urinalysis"

Patient	UA (WBC/mm^3)	UA Bacteria on Gram stain	Urine Culture (CFU/ml)	PWBC ($\times 10^3$/mm^3)	ESR (mm/h)	CRP (μg/ml)	Renal US	Entry DMSA	VCUG	Clinical Data
1	9	Present	>100 000 *Escherichia coli*	12.4	28	2.6	nl	nl	nl	iv abx
2	0	None	>100 000 *E. coli*	19.6	20	0.6	nl	nl	VUR (II)	iv abx
3	5	None	>100 000 *Pseudomonas aeruginosa*	16.6	nd	nd	nl	nl	nl	iv abx
4	4	Present	>100 000 *E. coli*	8.8	19	2.7	nl	nl	nl	po abx
5	5	Present	>100 000 *Klebsiella pneumoniae*	11	9	0.6	nl	nl	nl	Roseola rash; not treated
6	1	Present	80 000 *E. coli*	8.5	20	0.6	nl	nl	nl	iv abx (1 day)
7	5	Present	>100 000 *E. coli*	7	24	2.8	nl	nl	nl	po abx for AOM
8	6	None	50 000 *E. coli*	13.5	8	0.6	nl	nl	nl	po abx for AOM
9	4	None	>100 000 *E. coli*	6.2	4	nd	nl	nl	nl	Roseola rash; not treated
10	3	None	65 000 enterococcus	9.6	nd	nd	nd	nl	nd	Not treated; pyloric stenosis
11	2	None	>100 000 *E. coli*	6.5	12	0.6	nl	nl	nl	Not treated; gastroenteritis caused by rotavirus
12	1	Present	>100 000 *E. coli*	8.1	8	0.6	nl	nl	nl	Repeat UA at 24 h 21 WBC/mm^3, bacteria present; po abx
13	0	Present	>100 000 *E. coli*	13.6	10	0.6	nl	nl	nl	Roseola rash, po abx
14	8	None	>100 000 *E. coli*	10.3	30*	9.6*	nl	APN	VUR (II)	*Laboratory results at 24 h. UA: 800 WBC/mm^3, bacteria present; PWBC: 20.1; po abx
15	2	Present	>100 000 *E. coli*	13.1	18	0.8	nl	nl	nl	Afebrile at the time of initial UA, asymptomatic for 2 days, at Day 4 febrile, UA: 17 WBC/mm^3, 65 000 *E. coli*
16	1	None	>100 000 enterococcus	13.7	nd	nd	nd	nd	nd	Roseola rash, repeat UA showed no pyuria; po abx
17	0	None	62 000 *K. pneumoniae*	11.7	nd	nd	nd	nd	nd	DTP immunization same day, iv abx
18	1	Present	>100 000 *E. coli*	nd	nd	nd	nl	nd	nl	Gastroenteritis, repeat specimen; no pyuria and negative culture; not treated
19	3	None	>100 000 *E. coli*	18.2	nd	nd	nd	nd	nd	po abx
20	6	Present	>100 000 *E. coli*	40	nd	nd	Pelvo-caliectasis	nd	VUR (IV)	iv abx
21	8	Present	>100 000 *E. coli*	23.9	nd	nd	nd	nd	nd	iv abx
22	9	Present	>100 000 enterococcus	21.2	57	nd	nl	nd	VUR (II)	iv abx

UA, urinalysis; AOM, acute otitis media; VUR, vesicoureteral reflux; DTP, diphtheria-tetanus-pertussis; US, ultrasound; VCUG, voiding cystourethrogram; nd, not done; nl, normal; Abx, antibiotics.

part of the treatment trial and thus did not have DMSA scans or determination of acute phase reactants. Patients 16 to 18 most likely had asymptomatic bacteriuria. Patient 19 was treated with trimethoprim-sulfamethoxazole by her private pediatrician, had an uneventful course and had no recurrences within the following year. Imaging studies were not performed at the discretion of the primary care provider. Insufficient data prevent accurate classification of this patient. We assume she had a true UTI.

Patients 20 to 22, as outlined previously for Patients 12 to 15, probably had early UTI; they were promptly treated with intravenous antimicrobials.

TABLE 3. Mean acute phase reactants in patients with positive urine cultures (N = 153)*

	N	PWBC	ESR	CRP
Acute pyelonephritis	114	22.4	44.9	10.1
Cystitis	28	14.6	26.8	2.7
Asymptomatic bacteriuria	11	11.7	15.3	1.3
Total	153			

* All comparisons $P < 0.05$; Wilcoxon rank sum test.

Either pyuria (hemocytometer) or bacteriuria (Gram-stained smear). If results of the Gram-stained smear were available and criteria for urine culture included the presence of either pyuria or any bacteria in the smear, 10 of the 22 previously discussed patients would not have been identified (Patients 2, 3, 8, 9, 10, 11, 14, 16, 17 and 19).

Cost analysis. Table 4 compares two strategies for screening for UTI in young febrile children without an identified source of fever. In the method used in this 36-month study, a urine culture was performed on all 4253 specimens at a reimbursable cost of $276 500. Two hundred twelve cultures were positive. If only the

TABLE 4. Cost considerations when screening for UTI

Urine Culture	No. Screened	No. Positive	Cost
All specimens	4253	212	$276 500
Specimens with pyuria	396	190	$ 25 750
Children treated presumptively with antibiotics	1257		$ 81 705

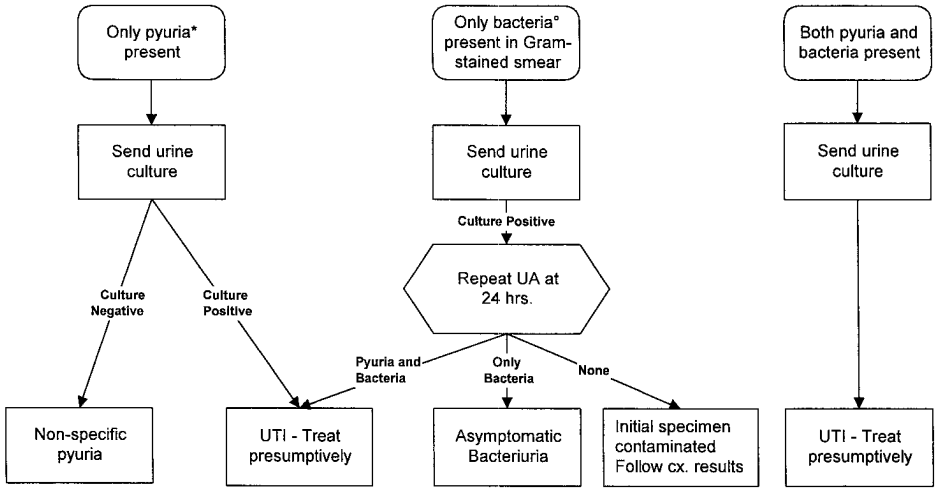

FIG. 1. Algorithm for interpretation of enhanced urinalysis results. *UA*, enhanced urinalysis; *Cx*, urine culture.

396 specimens with pyuria had been cultured, 190 patients would have been identified at a reimbursable cost of $25 750. Of 22 patients who would not have been cultured, 14 were presumed to have ABU and 8 were presumed to have an early stage of UTI because of subsequent pyuria on repeat urinalysis, elevated acute phase reactants or insufficient data. Our review of 500 ED records showed that 1257 (38.6%) of 3257 febrile children <24 months old who did not have pyuria at presentation were presumptively managed with antimicrobials. For those patients treated at the outset a urine culture is necessary because treatment may obscure a missed diagnosis of UTI. Accordingly culturing urine specimens only on patients with pyuria or those presumptively treated with antimicrobials would have resulted in expenditures of approximately $107 500, thereby saving $169 000 by not culturing all specimens.

DISCUSSION

The evaluation and management of infants and young children with fever without an apparent source remain controversial. The virtual disappearance of invasive disease caused by *Haemophilus influenzae* type b after the introduction of conjugate vaccines has reduced the threat of potentially serious invasive bacterial infections in early childhood. UTI, however, remains the most common serious bacterial illness among febrile infants and young children and may lead to permanent renal damage. Published critical pathways or practice guidelines appear to be based on data from the pre *H. influenzae* type b conjugate vaccine era and often recommend extensive diagnostic procedures.[8] Several studies have highlighted the limitations of the standard urinalysis for identifying UTI in infants and young children and have recommended performance of both urinalysis and urine culture.[1, 9, 10] Alternative methods such as dipstick urinalysis, although attractive because of ease of performance, prove to be inadequate as a screen for UTI.[3]

Hemocytometer WBC counts of an uncentrifuged urine specimen can be performed in an office- or hospital-based laboratory with minimal training. Performance of Gram-stained smears, however, is most appropriate for the hospital-based laboratory. In the hospital setting where both tests can readily be performed, the PPV of the combination of pyuria and bacteriuria, 85%, allows prompt institution of antimicrobial therapy before culture results are available, whereas the lower positive predictive value of the single finding of either pyuria or bacteriuria, 40%, justifies delaying treatment decisions until culture results are available. In the office setting where only hemocytometer counts are likely to be performed, culturing only specimens with pyuria will result in the identification of almost all patients with true UTI. Although the urine culture is traditionally regarded as the gold standard of UTI, positive urine cultures may occur secondary to contamination or in cases of ABU, leading to a false diagnosis of UTI.

In this report, if pyuria alone had been used to determine the need for urine culture, 22 of 212 patients would not have been initially identified. However, Patients 1 to 11 and 16 to 18 had an initial urinalysis and most had a repeat urinalysis within 24 h without pyuria. The sustained absence of an inflammatory response constitutes strong evidence that disease was absent. Results of acute phase reactants and the absence of renal scarring further support the likelihood that these patients had ABU. The

occurrence of bacteriuria without pyuria in 0.5% of urine specimens in this study is consistent with the 0.6% point prevalence of ABU reported by Wettergren et al.[11] among 3581 infants. Management of this condition remains controversial; many experts recommend withholding antibiotics because eradication of low virulence organisms may be followed by colonization with more virulent species that cause pyelonephritis.[12, 13] Accordingly failure to identify patients with ABU may be of no consequence. A reevaluation of the diagnostic validity of pyuria alone for identifying true UTI results in a sensitivity of 96%, a specificity of 95%, a PPV of 48% and an NPV of 99.8%. The remaining 8 patients with early UTI, the true false negatives, would most likely have been diagnosed within 24 h because of persistent fever.

Figure 1 shows an algorithm for the use of the enhanced urinalysis. There are several circumstances in which a urine culture should always be obtained regardless of urinalysis findings. These include children who (1) have had a previous UTI, (2) have abnormalities of the urinary tract or (3) will be treated with antibiotics presumptively. To detect a false negative urinalysis (one in which the absence of pyuria has been misleading), the enhanced urinalysis should be repeated within 24 to 48 h if there is persistence of fever without an identified source. This practice will identify the patient from whom a specimen may have been obtained so early in the illness that a local inflammatory response had not yet been mounted. For other children, whose treatment may be guided by results of the enhanced urinalysis, Figure 1 provides guidelines.

The microscopic evaluation of urine samples obtained by catheter for significant pyuria with or without Gram-stained smears identifies febrile infants and young children for whom a urine culture is warranted. It is an easy and inexpensive procedure that can be performed in the hospital- or office-based laboratory and allows the primary care provider to accurately diagnose a serious condition.

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