Pyuria and bacteriuria in urine specimens obtained by catheter from young children with fever

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Results of urinalysis and culture of 2181 urine specimens obtained by catheter from febrile children aged less than 24 months were analyzed to determine the following: (1) an optimal cutoff point in considering a bacterial colony count clinically "significant," (2) the accuracy of leukocyte esterase and nitrite tests in identification of pyuria and bacteriuria, and (3) the utility of pyuria (defined as ≥10 leukocytes/mm³) in the discrimination of urinary tract infection from asymptomatic bacteriuria. Among 110 urine cultures with ≥10,000 colony-forming units per milliliter, 92 (84%) had ≥100,000 CFU/ml, 10 (9%) had 50,000 to 99,000 CFU/ml, and 8 (7%) had 10,000 to 49,000 CFU/ml. Urine specimens with 1000 to 49,000 CFU/ml were more likely than specimens with ≥50,000 CFU/ml to yield Gram-positive or mixed organisms (36/60 vs 7/109; $p < 0.001$). A count of <10 leukocytes/mm³ was almost invariably associated with a sterile culture; a count of ≥10 leukocytes/mm³ was found in 93 of 102 patients with ≥50,000 CFU/ml. The dipstick leukocyte esterase test had sensitivities of 52.9% and 66.7% in detecting ≥10 leukocytes/mm³ and ≥20 leukocytes/mm³, respectively. The dipstick nitrite test had a sensitivity of 31.4% in detecting bacteriuria (≥50,000 CFU/ml). Acute pyelonephritis was diagnosed by a renal scan with dimercaptosuccinic acid labeled with technetium 99m in 50 (77%) of 65 patients with ≥10 leukocytes/mm³ but in none of five patients with <10 leukocytes/mm³ ($p < 0.01$). The findings in these five patients were consistent with colonization of the urinary tract rather than infection. For urine specimens obtained by catheter, we believe that urinary tract infection is best defined by both a leukocyte count ≥10/mm³ and a CFU count ≥50,000/ml. This definition almost always discriminates among true urinary tract infection, bacteriuria resulting from contamination of the urine specimen, and asymptomatic bacteriuria. (J PEDIATR 1994;124:513-9)

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Urinary tract infection is the most common serious bacterial illness among febrile infants and young children, with a reported prevalence between 4.1% and 7.5%.[1-4] Most infants and toddlers with UTI are febrile and it is assumed that they have acute pyelonephritis.[5-7]

"Significant" bacteriuria in urine culture has been the sole standard for the diagnosis of UTI. However, limitations of urine culture include requirement of an incubation period of 24 hours until availability of results, uncertainty concerning the magnitude of a "significant" bacterial colony count, and inability to differentiate asymptomatic bacteriuria from infection.

In a previous study we found that microscopic urinalysis of uncentrifuged urine obtained by catheter, with the use of leukocyte counts performed with a hemocytometer and Gram-stained smears, resulted in a high sensitivity and positive predictive value for identification of positive urine culture results.[8] This study was undertaken to (1) define contamination and significant bacteriuria more precisely, in terms of bacterial colony counts; (2) correlate bacterial colony counts and degree of pyuria; (3) further assess the validity of microscopic urinalysis for diagnosis of UTI; (4) assess the accuracy of nonmicroscopic diagnostic tests for identification of pyuria and positive urine culture results; and (5) determine whether the degree of pyuria discriminates UTI from asymptomatic bacteriuria.

DMSA	Dimercaptosuccinic acid
CFU	Colony-forming units
UTI	Urinary tract infection

See commentary, p. 589.

METHODS

Subjects. All children less than 2 years of age seen in the emergency department of the Children's Hospital of Pittsburgh (CHP) from December 1991 through August 1993, from whom a urine specimen for urinalysis and culture was obtained by bladder catheterization, were eligible for this study. Urine specimens were obtained from 95% of these children during a diagnostic evaluation for fever. Results describing the validity of microscopic urinalysis for diagnosis of UTI in the initial 698 patients have been reported.[8]

Urine culture. Quantitative urine 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 were examined at 24 and 48 hours for colony count and bacterial identification.

Urinalysis. In a certified clinic-based laboratory, uncentrifuged urine was drawn into a Neubauer hemocytometer by capillary action. Leukocytes were counted on one side of the chamber and multiplied by 1.1 to obtain a total cell count per cubic millimeter. Smears were prepared with 2 drops of uncentrifuged urine on a sterile slide within a standardized marked area of 1.5 cm diameter; the sample was air dried and Gram stained. The Multistix 10 SG dipstick (Miles Diagnostics, Elkhart, Ind.) was used to assess the presence of leukocyte esterase and nitrite. Results of the leukocyte esterase test (none, trace, small, moderate, or large) and the nitrite test (positive or negative) were visually interpreted according to standard color charts.

Renal scans with DMSA. Seventy patients with UTI diagnosed for the first time were enrolled in a separate study of UTI treatment. These patients had a renal scan within 48 hours of study entry. Dimercaptosuccinic acid labeled with technetium 99m, prepared within 20 minutes of administration, was injected intravenously at a dose based on 5 mCi of ^{99m}Tc-DMSA per 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 obtained by means of a gamma camera–computer system equipped with a pinhole collimator (150,000 counts), and posterior views obtained with a parallel collimator (400,000 counts), between 3 and 6 hours after injection. The DMSA scans were interpreted by a single investigator without knowledge of clinical events according to a standardized rating scale previously validated for intraobserver and interobserver reliability.[9]

Definitions. Pyuria was defined as the presence of at least 10 leukocytes/mm^3. Results of gram-stained smears were considered positive when any bacteria per 10 oil immersion fields were observed. Urinalysis results were considered positive when both pyuria and any bacteria were present. Cultures with growth of mixed organisms or nonpathogenic Gram-positive cocci were considered contaminated. Acute pyelonephritis was defined as the presence of areas of focal (single or multiple) or diffuse decreased cortical uptake of DMSA without evidence of cortical loss, or the less common scintigraphic pattern of diffuse decreased uptake in an enlarged kidney.

Statistical analysis. The frequency distribution of bacterial colony counts (single and mixed organisms) and of microscopic leukocyte counts was described, and their association was determined. Sensitivity, specificity, and positive and negative predictive values were calculated for the following: (1) microscopic urinalysis, with a positive urine culture finding used as the validating standard, (2) dipstick leukocyte esterase test (results: none vs trace, small, moderate, and large), with both $\geq$10 and $\geq$20 leukocytes/mm^3 as validating standards, and (3) dipstick nitrite test (positive or negative results), with a positive urine culture finding used as the validating standard. Relations between categoric variables were analyzed by means of the Fisher Exact Test or the chi-square test. All statistical tests were two tailed.

RESULTS

Urine specimens obtained by catheter were collected from 2181 children less than 2 years of age, including 698 specimens from a previous study of urinalysis.[8]

Bacteriuria and pyuria. The frequency distribution of bacterial colony counts in cultures of urine specimens obtained by catheter from young febrile children is presented in Fig. 1. Low colony counts (10,000 to 49,000

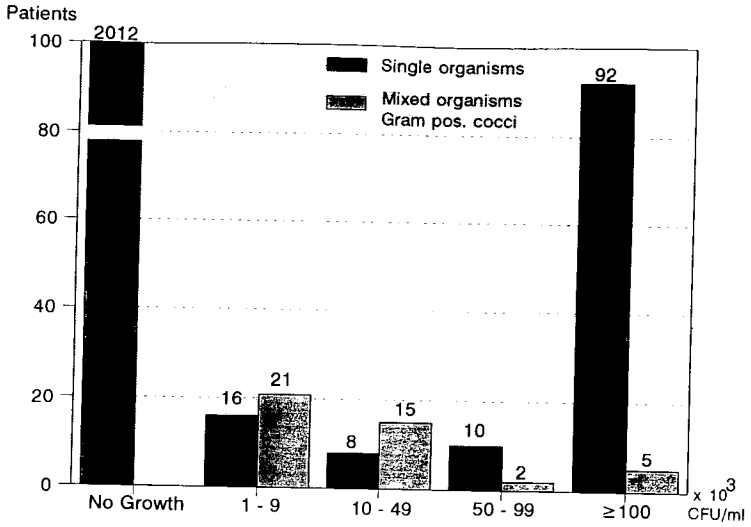

Fig. 1. Frequency distribution of bacterial colony counts in cultures of urine specimens obtained by catheter from young children with fever.

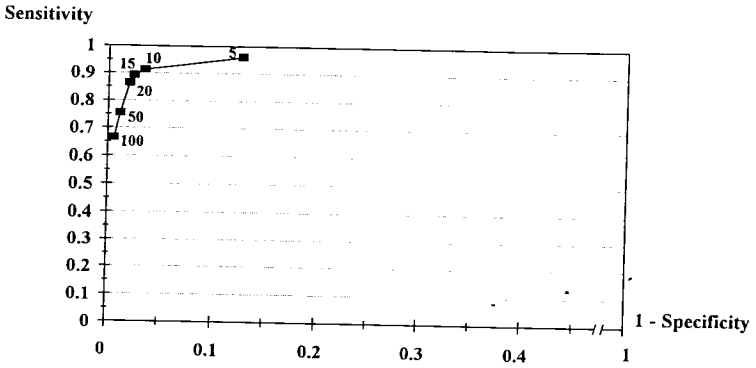

Fig. 2. Receiver-operating characteristic curve of hemocytometer leukocyte counts in urine specimens obtained by catheter from young children with fever.

CFU/ml) of single pathogens were uncommon. Among 102 urine cultures with growth of a single pathogen at a concentration of ≥50,000 CFU/ml, 92 (90.2%) had ≥100,000 CFU/ml. Urine specimens with bacterial colony counts between 1000 and 49,000 CFU/ml were more likely to yield Gram-positive or mixed organisms than specimens with bacterial colony counts ≥50,000 CFU/ml (36/60 vs 7/109; $p < 0.001$). Among the 23 urine cultures with growth at a concentration of 10,000 to 49,000 CFU/ml, single pathogens were isolated from 8 cultures (35%), and mixed or Gram-positive organisms (excluding enterococci) were isolated from 15 cultures (65%). In contrast, single pathogens were recovered from 10 (83%) of 12 cultures with bacterial counts between 50,000 and 99,000 CFU/ml, and from 92 (95%) of 97 cultures with bacterial counts ≥100,000 CFU/ml.

A receiver-operating characteristic curve for leukocyte counts (Fig. 2) was constructed to determine the most appropriate cutoff point for identification of urine cultures with ≥50,000 CFU/ml. The presence of ≥10 leukocytes/mm^3 appeared to be the most useful value because of its high sensitivity (91%) and low false-positive rate (3.4%). A lower cutoff point (5 leukocytes/mm^3) had higher sensitivity (96%) but also had a higher false-positive rate (13%). Conversely, a higher cutoff point (15 leukocytes/mm^3) had lower sensitivity (89%) and a similar false-positive rate (2.4%). The relation of the degree of pyuria to the bacterial colony counts is shown in Fig. 3. The presence of fewer than 10 leukocytes/mm^3 was almost invariably associated (1953/1978; 98.7%) with a sterile urine culture. In contrast, the presence of at least 10 leukocytes/mm^3 was found in 93 (91%) of 102 patients with at least 50,000 CFU/ml of a single organism. Fifty-nine patients with ≥10 leukocytes/mm^3 had sterile urine cultures and various diagnoses: fever of unknown origin (13 patients), otitis media (10), viral syndrome (7), pneumonia (6), gastroenteritis (5), bronchopul-

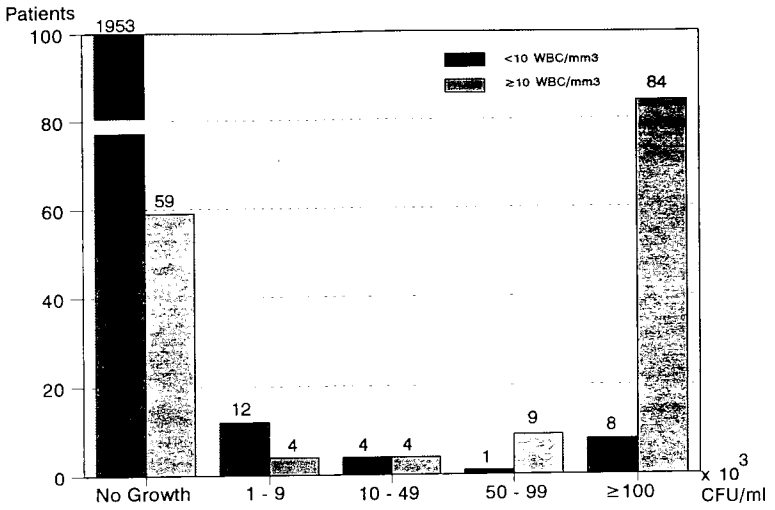

Fig. 3. Frequency distribution of amount of pyuria according to bacterial colony counts in cultures of urine obtained by catheter from young children with fever *WBC*, white blood cells.

Table. Sensitivity, specificity, positive predictive value, and negative predictive value of ≥10 leukocytes/mm³, presence of bacteria in a gram-stained smear, and their combination in identifying positive urine cultures (≥50,000 CFU/ml)

Criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥10 WBC/mm³	91.2	96.5	56.4	99.6
Any bacteria	93.1	96.6	57.2	99.7
≥10 WBC/mm³ and any bacteria	89.2	99.4	88.3	99.5

PPV, Positive predictive value; *NPV*, negative predictive value; *WBC*, white blood cells.
N = 2181.

monary dysplasia (3), pyloric stenosis (2), upper respiratory tract infection (2), and bronchiolitis, herpangina, Kawasaki syndrome, bacteremia, scarlet fever, aseptic meningitis, perirectal abscess, impetigo, vulvovaginitis, burn, and conjunctivitis in one patient each. Mixed organisms or Gram-positive cocci (excluding enterococci), regarded as contaminants, were isolated from a significantly higher proportion of urine specimens with <10 leukocytes/mm³ (38/63, 60%) compared with specimens with ≥10 leukocytes/mm³ (5/106, 4.7%) (p <0.001).

Validity of microscopic urinalysis. Sensitivities, specificities, positive predictive values, and negative predictive values of (1) ≥10 leukocytes/mm³, (2) presence of any bacteria in a Gram-stained smear, and (3) ≥10 leukocytes/mm³ and presence of any bacteria, in detecting urine cultures with ≥50,000 CFU/ml, are presented in the Table. The presence of each of the two components of the microscopic urinalysis used in this study—≥10 leukocytes/mm³ or any bacteria in a Gram-stained smear—had both high sensitivity and high specificity in detecting urine cultures with positive results. However, each of these components alone had limited usefulness in guiding management because of the relatively low positive predictive value. However, when combined, determinations of pyuria and bacteriuria constituted the most accurate screening test in detecting urine cultures with ≥50,000 CFU/ml. Results of the initial 698 and the additional 1483 specimens were almost identical.

Dipstick leukocyte esterase and nitrite tests. Urine specimens obtained by catheter from 1230 infants and young children were assessed for dipstick leukocyte esterase. A positive test result had a sensitivity of 52.9% in detecting the presence of ≥10 leukocytes/mm³ and a positive predictive value of 82.1%. When the validating standard value was doubled to ≥20 leukocytes/mm³, the sensitivity increased to 66.7% and the positive predictive value decreased to 75%. Dipstick determination of nitrite in 1241 specimens showed a sensitivity of 31.4% in identifying young children with urine cultures that contained ≥50,000 CFU/ml.

Pyuria as an indicator of urinary tract infection. The method and criteria for urinalysis described in this report resulted in 11 (of 2181) false-negative UTI identifications, that is, identifications of children with negative urinalysis results (no bacteria and/or fewer than 10 leukocytes/mm³) and a urine culture with ≥50,000 CFU/ml. Nine of the

eleven children had either no pyuria or fewer than 10 leukocytes/mm^3 but cultures with ≥50,000 CFU/ml. Of these nine children, six had renal scintigraphy performed. At the time of the scan, pyuria had developed in one child (>100 leukocytes/mm^3); the others did not have pyuria. Scans of the five patients without pyuria were compared with scans of 65 patients who had both a positive urine culture result and pyuria of at least 10 leukocytes/mm^3. All 5 patients without pyuria had normal scans compared with 50 (77%) of the 65 patients with ≥10 leukocytes/mm^3, whose DMSA scan findings were consistent with the presence of acute pyelonephritis (p <0.01).

DISCUSSION

Bacteriuria can arise from contamination of a urine specimen, colonization of the urinary tract (asymptomatic bacteriuria), or UTI. On the basis of quantitative cultures of urine specimens obtained by catheter from women with symptoms compatible with acute pyelonephritis (chills, flank pain, and dysuria) and from randomly selected, symptom-free women, Kass[10] reported that bacterial colony counts divided women into two groups: women with acute pyelonephritis had cultures with bacterial counts primarily ≥100,000 CFU/ml (almost always common urinary tract pathogens), and symptom-free women had bacterial counts primarily between 0 and 10,000 CFU/ml (usually common saprophytes of the urinary tract and occasionally common urinary tract pathogens). Only small numbers (1%) of women in the groups with and those without symptoms had cultures with bacterial counts between 10,000 and 100,000 CFU/ml. When the counts were repeated with the use of a first morning specimen of urine, the distinction between contamination and bacteriuria was readily made. On the basis of these data, Kass designated a bacterial culture count of ≥100,000 CFU/ml as the dividing line between true bacteriuria and contamination.

In febrile infants and children the growth of a single organism at a concentration of at least 10,000 CFU/ml from a urine specimen obtained by catheter has been considered diagnostic of UTI.[11] However, the frequency distribution of bacterial colony counts and the prevalence and significance of low colony bacterial counts (1,000 to 49,000 CFU/ml) have not been reported. In this study, among the 110 febrile children aged less than 24 months with growth of single organisms at a concentration ≥10,000 CFU/ml, 102 (93%) had ≥50,000 CFU/ml and 92 (84%) had ≥100,000 CFU/ml. These results in young children are similar to observations made in adult women with acute pyelonephritis by Kass[10] 30 years ago (i.e., that low colony bacterial counts are uncommon). In addition, the change in the proportion of "false" positive cultures (most commonly mixed organisms, and less commonly saprophytes) to "true" positive cultures (common urinary tract pathogens) occurred at 50,000 CFU/ml. Mixed organisms and Gram-positive organisms (excluding enterococci) were isolated from 65% of urine cultures with growth of 10,000 to 49,000 CFU/ml, 17% of cultures with 50,000 to 99,000 CFU/ml, and 5% of cultures with ≥100,000 CFU/ml. These findings form the basis for our conclusion that bacterial colony counts of ≥50,000 CFU/ml best identify "significant" bacteriuria in evaluations of urine specimens obtained by catheter from young febrile children. Counts less than 50,000 CFU/ml are likely to represent contamination in the majority of instances. Bacterial colony counts may fall below the range that is most characteristic of infections when (1) an antimicrobial agent is present in the urine, (2) there is a rapid rate of urine flow and reduced bladder incubation time, and (3) obstruction of the ureter interferes with discharge of bacteria into the bladder. Accordingly, when patients with bacterial colony counts between 10,000 and 49,000 CFU/ml have persistent symptoms, the urine culture should be repeated and management individualized.

The diagnostic accuracy and the interpretation of microscopic urinalysis are influenced by the preparation of the specimen (centrifuged vs uncentrifuged, stained vs unstained), the method of quantifying and reporting leukocytes and bacteria (per microscopic high-power field vs per cubic millimeter), and the criteria used to define pyuria and bacteriuria. Stamm[12] defined pyuria as the presence of ≥10 leukocytes/mm^3 in uncentrifuged urine. This definition proved to be very sensitive in adults, identifying 96% of patients with bacterial colony counts of >1000 CFU/ml. In our study of urine specimens obtained by catheter from young febrile children, patients with pyuria <10 leukocytes/mm^3 almost invariably had sterile urine cultures, and patients with pyuria of at least 10 leukocytes/mm^3 had either sterile cultures—pyuria representing a nonspecific finding in febrile children—or positive culture results, usually with bacterial colony counts of ≥50,000 CFU/ml. The combination of hemocytometer leukocyte counts and bacteria in a Gram-stained smear provided specificity and high positive predictive value for identifying patients with UTI.

Dipstick leukocyte esterase and nitrite tests are commonly used to identify pediatric patients with positive urine culture results. Some studies have suggested that the routine use of dipstick tests could result in substantial cost savings by decreasing the need for the more expensive microscopic urinalysis and culture.[13-16] However, other studies have found dipstick tests less accurate than microscopic examination in identifying patients with positive urine culture results.[17-20]. Our finding of low sensitivity of the dipstick leukocyte esterase test for pyuria in young febrile children differs from reports in adult women. Kunin et al.[20a] recently demonstrated sensitivities for the leukocyte esterase test of

79.7% and 92.5% for hemocytometer counts of ≥10 leukocytes/mm^3 and ≥20 leukocytes/mm^3, respectively. The differences between findings in adult women and in young children may be related to the degree of pyuria, the enzyme content of immature leukocytes, or both. The finding of low sensitivity of dipstick nitrite testing among young febrile children, contrary to findings in adults, may be the result of the use of random urine specimens obtained by catheter rather than first morning voids, which are usually recommended for adults. Bacteria must be in the bladder for a sufficient time to produce the nitrite that yields a positive test result. The low sensitivity of the dipstick leukocyte esterase and nitrite tests in identification of young febrile children with pyuria and positive urine culture findings, respectively, underscores the need to perform the more labor-intensive but significantly more accurate microscopic urinalysis and urine culture to diagnose UTI. Among the patients whom we studied, use of a sequential approach in which only leukocyte esterase–positive specimens were examined microscopically and subsequently cultured would have resulted in missing 78 of 165 patients with pyuria of at least 10 leukocytes/mm^3.

The DMSA renal scans are currently considered the most sensitive measure of upper urinary tract inflammation. In animals, DMSA scans performed immediately before the animals were killed had a sensitivity of 87% and a specificity of 100% in the detection of experimentally induced acute pyelonephritis.[21] In children Jakobsson et al.[22] reported a sensitivity of 92% for DMSA scans during acute UTI, and Rushton et al.[23] reported that of 94 children hospitalized with a diagnosis of febrile UTI, 62 patients (66%) had initial DMSA scan findings of acute pyelonephritis. Our use of a pinhole collimator and a computer with a high-resolution video screen for performing DMSA scans is likely to enhance the sensitivity of the test. However, DMSA scans do not identify infection limited to the lower urinary tract (cystitis). Accordingly, febrile young children with pyuria and a positive urine culture finding but normal DMSA renal scans may have lower UTIs.

We found 11 children to have a negative urinalysis result (<10 leukocytes/mm^3 and/or no bacteria on Gram-stained smears), but a positive urine culture finding (≥50,000 CFU/ml). These children have either false-negative laboratory data or asymptomatic bacteriuria and fever from another source. The absence or low level of pyuria in 9 of 11 patients was consistent with the absence of inflammatory response in colonized (rather than infected) individuals. The negative DMSA scan findings in the five patients without pyuria for whom scans were available also are most consistent with minimal or absent inflammation of the upper urinary tract. Accordingly, our finding that most (77%) of the patients with positive culture findings and positive urinalysis results had DMSA scan findings consistent with acute pyelonephritis, whereas all five patients with positive culture findings and negative urinalysis results had normal scan findings, suggests that these two groups probably represent different conditions. If the point prevalence of asymptomatic bacteriuria of 0.6%, reported by Wettergreen et al.[24] in a survey of 3581 infants, prevailed in the 2181 children in our study, asymptomatic bacteriuria incidental to—but not the cause of—febrile illness would have been present in 13 patients.

The management of children with asymptomatic bacteriuria is controversial. Antimicrobial treatment may have no effect on the emergence of symptoms or on kidney function, kidney growth, or the progression of scarring. Furthermore, eradication of low-virulence organisms may be followed by recolonization with more virulent bacterial species and may precipitate acute pyelonephritis.[25, 26] Drug side effects and nosocomial infections may represent further risks for patients with asymptomatic bacteriuria.

We conclude that when urinalysis of specimens obtained by catheter from young febrile children is performed with hemocytometer counts and Gram-stained smears, UTI is best defined by the presence of ≥10 leukocytes/mm^3 and cultures with growth of ≥50,000 CFU/ml. This definition almost invariably discriminates true UTI from bacteriuria resulting from contamination or colonization. The high positive predictive value (88.3%) of a positive urinalysis result should encourage prompt institution of therapy with antimicrobial agents. In febrile children in whom bacteriuria is not associated with pyuria, the source of the fever is not likely to be UTI.

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