The Relationship Between Pyuria and Infection in Patients With Indwelling Urinary Catheters

A Prospective Study of 761 Patients

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Background: Pyuria is universally considered as essential for identifying urinary tract infections in noncatheterized patients. The utility of pyuria in the catheterized patient, to identify catheter-associated urinary tract infection (CAUTI), has not been adequately defined.

Methods: We prospectively studied 761 newly catheterized patients in a university hospital; 82 (10.8%) developed nosocomial CAUTI (>10^5 colony-forming units per milliliter). While catheterized, each patient was seen daily, a quantitative urine culture was obtained, and the urine white blood cell concentration was measured quantitatively using a hemocytometer.

Results: The mean urine leukocyte count in patients with CAUTI was significantly higher than in patients without infections (71 vs 4 per microliter; P = .006). Pyuria was most strongly associated with CAUTI caused by gram-negative bacilli (white blood cell count, 121 vs 4 per microliter; P = .03); infection with coagulase-negative staphylococci and enterococci (white blood cell count, 39 vs 4 per microliter; P = .25) or yeasts (white blood cell count, 25 vs 4 per microliter; P = .15) produced much less pyuria. Pyuria with a white blood cell count greater than 10 per microliter (>5 per high-power field in a conventional urinalysis) had a specificity of 90% for predicting CAUTI with greater than 10^5 colony-forming units per milliliter but a sensitivity of only 37%.

Conclusions: In patients with short-term indwelling urinary catheters, pyuria is less strongly correlated with CAUTI than in noncatheterized patients with urinary tract infection. The strongest association is with CAUTI caused by gram-negative bacilli; the association is far weaker for infections caused by gram-positive cocci or yeasts. Most patients with CAUTI are asymptomatic and do not have associated fever. Pyuria should not be used as the sole criterion to obtain a urine culture in a patient with a catheter.

Arch Intern Med. 2000;160:673-677

Catheter-associated urinary tract infection (CAUTI) is the most common nosocomial infection, accounting for up to 40% of all nosocomial infections and more than 1 million infections in US hospitals each year.1-3 Up to a half of patients requiring an indwelling urethral catheter for 5 days or longer will develop bacteriuria or candiduria.1-3 Silent catheter-associated bacteriuria comprises a huge reservoir of resistant organisms in the hospital, particularly on critical care units.5-13

Pyuria has been shown to have excellent predictive value for identifying urinary tract infections in noncatheterized patients.14-15 Although recently published guidelines16 recommend using pyuria as the criterion for obtaining a urine culture as part of the workup of fever in the hospitalized patient, the utility of pyuria for identifying bacteriuria or candiduria in patients with a short-term catheter has not been clearly defined.

We report the results of a prospective study of the relationship between pyuria and urinary tract infection in 761 hospitalized patients with short-term indwelling urinary catheters.

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RESULTS

A total of 1035 evaluable newly catheterized patients participated in this study. To accurately assess the significance of pyuria in patients with an indwelling urinary catheter, we excluded patients who underwent a kidney or a kidney-pancreas transplantation, who we have found show a burst of sterile leukocyturia immediately after transplantation (P.A.T. and D.G.M., unpublished data, 1998), and analyzed 761 catheterized pa-
PATIENTS AND METHODS

PATIENTS

Patients participating in 2 prospective, randomized, comparative trials of medicated catheters, one a nitrofurazone-impregnated silicone catheter17 and the other a silver-polyurethane hydrogel catheter,18 formed the population studied. Neither medicated catheter was associated with any irritative urinary tract symptoms or with sterile pyuria compared with the control catheters used in each trial.17,18 Participants in both trials were hospitalized patients scheduled to receive an indwelling urethral (Foley) catheter who were expected to be catheterized for more than 24 hours. Patients were excluded if they were younger than 18 years; pregnant; or had a known allergy to silicone, nitrofurazone, or silver. Both studies were approved by the Human Subjects Committee of the University of Wisconsin–Madison Center for Health Sciences, and written informed consent was obtained from all patients.

On enrollment into the study, baseline demographic and clinical data bearing on risk factors for CAUTI19-21 were collected, including age, sex, structural urologic disease, underlying systemic diseases including diabetes mellitus and cancer, immunosuppressive therapy, hospital service, confinement in an intensive care unit, severity of illness using the Acute Physiology and Chronic Health Evaluation II score, recent surgery, and the purpose for catheterization.

On enrollment, and daily thereafter, approximately 3 mL of urine was aspirated from the sampling port of the catheter with a sterile syringe, first disinfecting the port with 10% povidone-iodine. Each specimen was immediately brought to the laboratory and cultured using a technique capable of detecting 1 colony-forming unit (CFUs) per milliliter,20 evenly spreading 1 mL of undiluted urine and serial dilutions on predried sheep blood agar plates. After aerobic incubation at 37°C for 24 to 48 hours, each colony type was enumerated and fully identified using standard techniques and criteria.21

Quantitative urine white blood cell counts were measured daily using a hemocytometer (Hauser Scientific Partnership, Horsham, Pa).21 Every day, in addition to the urine culture, the patient was questioned regarding any discomfort or symptoms associated with the catheter (pain, sense of urgency, or dysuria). Patients’ medical records were reviewed concurrently for fever or other clinical and laboratory data suggesting active infection. Peripheral white blood cell counts were recorded as they were ordered by patients’ physicians.

DEFINITION OF CAUTI

The new appearance of bacteriuria or funguria of greater than 10^3 CFUs per milliliter was considered to represent nosocomial CAUTI. We have previously shown that isolation of greater than 10^3 CFUs per milliliter is highly predictive of CAUTI;22 with greater than 10^3 CFUs per milliliter bacteriuria or candiduria, if intercurrent antimicrobial therapy is not given to the patient, the level of bacteriuria or candiduria uniformly rises to greater than 10^5 CFUs per milliliter within 24 to 48 hours, as confirmed in this study.

STATISTICAL ANALYSIS

The Student unpaired t test was used to determine the significance of differences with continuous variables; and the Fisher exact test, for dichotomous data. Two-tailed tests of significance were used exclusively.

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diagnosis of CAUTI with greater than $10^3$ CFUs per milliliter was only 37%; specificity, 90%; and positive predictive value, 36%; for the diagnosis of CAUTI with greater than $10^4$ CFUs per milliliter, sensitivity was only 47%; specificity, 90%; and positive predictive value, 32% (Table 3).

**COMMENT**

The association between pyuria in a spontaneously voided urine specimen and urinary tract infection in noncatheterized patients is based on the studies of Brumfitt and Little. A urinary leukocyte excretion rate, as measured in a counting chamber, of greater than 400,000 per hour was found by Hutt et al and Gadahløft to be the upper limit of normal and correlated with a quantitative urine white blood cell count of approximately 10 per microliter in a single examination of uncentrifuged urine. In a review of the 5 published studies using counting chamber urine leukocyte determinations, 281 of 291 symptomatic patients with bacteriuria had a white blood cell count greater than 10 per microliter (sensitivity, 97%; specificity, 98%; and positive predictive value, 98%). Since then, pyuria has become universally regarded as an essential criterion for the diagnosis of urinary tract infection. Pyuria has also been recommended as the indication to obtain a urine culture in patients with fever in the intensive care unit in a recent consensus guideline.

In patients with indwelling urinary catheters, the association of pyuria with bacteriuria has been studied primarily in those with spinal cord injury undergoing intermittent catheterization or in those with long-term indwelling catheters. In a study of 32 patients with chronic infections, Peterson and Roth found that 50 white blood cells per high-power field in microscopic examination of urinary sediment separated their cohort into a high pyuria group, 6 of 10 who had fever and symptomatic urinary tract infection, and a low pyuria group, of which only 3 of 22 had fever or other symptoms. However, Gribble et al, studying a population of intermittently catheterized patients with spinal cord injury, reported that pyuria with a white blood cell count greater than 10^9 per liter indicated catheter-associated urinary tract infection; APACHE, Acute Physiology and Chronic Health Evaluation; and ellipses, data not applicable. *Urine culture indicated greater than $10^3$ colony-forming units per milliliter; 71 of the 82 patients ultimately showed greater than $10^3$ colony-forming units per milliliter while catheterized.

### Table 1. Epidemiological Characteristics of 82 Patients With Nosocomial CAUTI Among 761 Catheterized Patients Prospectively Studied

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With CAUTI</th>
<th>Without CAUTI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>82</td>
<td>679</td>
<td>. .</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>60.9 ± 18.7</td>
<td>59.5 ± 16.5</td>
<td>.53</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32 (39)</td>
<td>443 (65)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>50 (61)</td>
<td>236 (35)</td>
<td></td>
</tr>
<tr>
<td>Service, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>40 (49)</td>
<td>543 (80)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Medical</td>
<td>42 (51)</td>
<td>136 (20)</td>
<td></td>
</tr>
<tr>
<td>APACHE II score, mean ± SD</td>
<td>9.2 ± 8.7</td>
<td>7.9 ± 8.0</td>
<td>.25</td>
</tr>
<tr>
<td>Duration of catheterization, mean ± SD</td>
<td>5.2 ± 5.2</td>
<td>3.2 ± 3.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of patients with significant neutropenia (&lt;1.0 x 10^9 per liter)</td>
<td>0</td>
<td>5</td>
<td>. . .</td>
</tr>
<tr>
<td>Peripheral white blood cell count, x10^9 per liter</td>
<td>11.96</td>
<td>11.75</td>
<td>.82</td>
</tr>
</tbody>
</table>

Table 1 indicates catheter-associated urinary tract infection; APACHE, Acute Physiology and Chronic Health Evaluation; and ellipses, data not applicable. *Urine culture indicated greater than $10^3$ colony-forming units per milliliter; 71 of the 82 patients ultimately showed greater than $10^3$ colony-forming units per milliliter while catheterized.

### Table 2. Urine White Blood Cell Counts in Hospitalized Patients With Catheters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Uninfected Patients (n = 679)</th>
<th>All Patients With CAUTIs (n = 92)</th>
<th>Causes of the CAUTI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gram-Negative Bacilli (n = 42)</td>
</tr>
<tr>
<td>First day of infection</td>
<td>5 ± 57†</td>
<td>27 ± 163</td>
<td>34 ± 117</td>
</tr>
<tr>
<td>Mean, throughout infection</td>
<td>4 ± 28</td>
<td>71 ± 245§</td>
<td>121 ± 335§</td>
</tr>
<tr>
<td>Highest value</td>
<td>11 ± 100</td>
<td>309 ± 1065§</td>
<td>497 ± 1408§</td>
</tr>
</tbody>
</table>

*Data are given as the mean ± SD urine white blood cell count per microliter. All comparisons are not significant (P > .05) unless otherwise indicated. CAUTI indicates catheter-associated urinary tract infection.
†First day of catheterization.
‡All patients with CAUTI vs uninfected patients, P = .006.
§Caused by gram-negative bacilli vs uninfected patients, P = .04.
greater than 10 per microliter had a sensitivity of 86% and a specificity of 73% for the diagnosis of CAUTI with greater than $10^3$ CFUs per milliliter; for CAUTI with greater than $10^5$ CFUs per milliliter, the sensitivity was 91% and the specificity was 72%. However, most of their patients were undergoing long-term catheterization, women were not studied, and patients with candiduria were excluded. The utility of pyuria for the identification of CAUTI in hospitalized patients with short-term indwelling urinary catheters has not been adequately defined.

In this large prospective study of hospitalized patients with catheters, with a wide but typical range of underlying conditions, nearly all of the patients with documented CAUTI were asymptomatic for fever or irritative symptoms referable to the urinary tract. Yet, patients with CAUTI did show on average a substantial and significant elevation of the mean urine white blood cell count during the period of active infection (Table 1). However, when infections were analyzed by the organism causing infection, pyuria was most strongly associated with CAUTI caused by gram-negative bacilli ($121 vs 4 per microliter, P = .03$; Table 2); infection caused by coagulase-negative staphylococci and enterococci or yeasts was much less strongly associated with pyuria. On the first day of bacteriuria or candiduria, the mean level of pyuria in patients infected with staphylococci and enterococci or yeasts differed little from that of uninfected patients (8 and 9 per microliter, respectively, vs 5 per microliter). Others have recently reported the frequent absence of pyuria in noncatheterized and catheterized patients with urinary tract infection caused by coagulase-negative staphylococci or yeasts.

The reasons underlying these observations are not entirely clear. While CAUTI caused by staphylococci, enterococci, or yeasts occasionally leads to bloodstream infection, especially if urinary tract obstruction occurs, the degree of urinary tract inflammation elicited by these organisms is clearly not as great as occurs with the gram-negative bacilli. Coagulase-negative staphylococci have been shown in animal models of infection to incite far less cytokine release than gram-negative bacilli. Symptomatic community-acquired urinary tract infections in noncatheterized patients have been associated with more virulent, “pyelonephritogenic” strains of E coli, but most nosocomial gram-negative bacilli for which urovirulence characteristics have yet to be characterized.

The clinical relevance of our findings seems clear. Pyuria cannot and should not be used as the sole criterion for obtaining a urine culture in a catheterized patient. This is especially true in the case of infections caused by yeasts and gram-positive cocci. It is clear that most patients with CAUTI are asymptomatic and do not have fever caused by CAUTI. If a catheterized patient develops fever or signs of sepsis that cannot be linked to another source, such as nosocomial pneumonia, surgical site infection, or vascular catheter-related bloodstream infection, a urine culture should be obtained even if the patient does not have demonstrable pyuria.

In this study of catheter-associated pyuria, we used a counting chamber to determine quantitative urine white blood cell counts. Most clinical laboratories measure pyuria semiquantitatively, reporting the number of white blood cells per microscopic high-power field in a centrifuged urine specimen. Although more than 5 white blood cells per high-power field correlates roughly with a urine white blood cell count greater than 10 per microliter, assessment of pyuria by semiquantitative microscopic examination of the urinary sediment has been shown to have a high degree of interobserver variability and may not be reliable as a diagnostic test. Semi-quantitative pyuria by microscopy may have even poorer predictive value for diagnosing CAUTI.

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*Pyuria is indicated by a white blood cell count greater than 10 per microliter. The sensitivity, specificity, and positive predictive value were obtained using mean values. CAUTI indicates catheter-associated urinary tract infection; CFUs, colony-forming units; and ellipses, data not applicable.

**First day of catheterization.