An Unusual Case of Acute Cystitis Associated with Mixed Flora in Voided Urine in an Adult Male

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This report describes two episodes of acute cystitis associated with “mixed flora” in an elderly male following a cystoscopy. The initial episode was accompanied by pyuria and a positive nitrite test. Both episodes responded to treatment with nitrofurantoin. Urine cultures were negative prior to the episodes and at a 1-year follow-up.

CASE REPORT

The patient was an otherwise healthy, circumcised 83-year-old retired physician. He was referred to a urologist for evaluation of several episodes of asymptomatic gross hematuria. His urologic history consisted of an uncomplicated prostate biopsy specimen collected 13 years previously. On examination, he was found to have a large, soft prostate and 100 ml of residual urine by bladder ultrasound. Leukocyte esterase and nitrite tests and a urine culture were negative (Table 1). An abdominal and pelvic computerized tomography scan showed normal kidneys and ureters, a large volume of residual bladder urine, and a possible bladder mass. A clot was noted on the bladder wall on cystoscopy. He was referred to a urinary bladder specialist for a second cystoscopy. This revealed a normal bladder wall. Antimicrobial prophylaxis was not given. The gross hematuria was attributed to bleeding from large prostatic veins and straining on urination. It did not recur following treatment with tamsulosin.

About 3 weeks following the second cystoscopy, the patient noted burning upon urination, frequent urination, and prostatic discomfort without fever, chills, or flank pain. Leukocyte esterase and nitrite tests were strongly positive. Urine microscopy revealed >50 white blood cells and the presence of bacteria. On the basis of these findings, he was treated with a 5-day course of nitrofurantoin. The symptoms resolved within a few days. The microbiology laboratory provided the following report. “Mixed skin/urogenital flora. 50,000 to 100,000 CFU/ml; suspect contamination during collection; suggest recollection.” “Mixed flora” was defined as 3 or more different species on a split plates containing Columbia CNA and MacConkey agar. Further microbial studies were not done. The urinary symptoms recurred about 3 weeks later. The leukocyte esterase test was strongly positive, but this time the nitrite test was negative. The urine culture again revealed 50,000 to 100,000 CFU/ml of mixed skin and urogenital flora. No further work-up was done. The symptoms resolved in association with a 10-day course of nitrofurantoin. The patient remained symptom free during the following year. At a 1-year follow-up, the leukocyte esterase and nitrite tests were negative and the urine bacterial count was <1,000 CFU/ml.

The occurrence of acute bacterial cystitis in an elderly male associated with mixed flora in his voided urine was unexpected. The current bacteriologic criteria for the diagnosis of significant bacteriuria in males are based on the classic studies of Lipsky and coworkers (1–3). They found that cultures from bladder specimens obtained by suprapubic aspiration or urethral catheterization showed excellent agreement with those of clean-catch midstream-void and uncleansed first-void specimens. The criterion that best differentiated sterile from infected bladder urine was growth of ≥10^5 CFU/ml of one predominant species at either 100% or >50% of total growth. A single predominant microbial species constituted ≥99% of growth on all first specimens. Mixed flora was encountered in a second bladder culture in only one patient. They also found that the Gram stain of uncentrifuged male voided urine accurately predicted the predominant species on culture. Gram-positive cocci were isolated as often as Gram-negative rods. Escherichia coli was the single predominant isolate in only 14% of cases. Enterococcus faecalis was the single most commonly identified species (22.5%).

The most likely causative agent in this case appears to have been a Gram-negative enteric uropathogen masked by commensal bacteria growing in a large volume of residual urine. This notion is supported by the following evidence. The patient had no history of a urinary tract infection, sexually transmitted disease, or irritative prostatic symptoms. A culture of voided urine obtained 10 weeks prior to the first episode revealed <1,000 CFU/ml. The first symptomatic episode occurred three weeks following an invasive urological procedure, cystoscopy. Both the leukocyte esterase and nitrite tests were positive. The symptoms resolved following treatment with nitrofurantoin. The second episode occurred a few weeks later. The leukocyte esterase test was positive. The symptoms again resolved within a 10-day course of nitrofurantoin. The urine specimens were sent to the laboratory in transport medium. The same bacterial counts of 50,000 to 100,000 CFU/ml of mixed flora were noted with each episode. These counts are well above the range required for urinary tract infections in males. A catheterized specimen was not needed since voided urine has been shown to be adequate in males. It is doubtful that the laboratory misinterpreted the growth on the plates on...
two separate occasions. The episodes were book-ended by negative leukocyte esterase and nitrite tests and urine cultures of <1,000 CFU/ml prior to the episodes, at 1 year later, and on several occasions thereafter. This is strong evidence that his urine was not contaminated. The nitrite test is highly specific for urinary tract infections caused by *Enterobacteriaceae*.

The specificity of the nitrite test ranges from 97% to 98%, with bacterial counts of ≥10⁴ CFU/ml (4). Most studies have been conducted in females, but there is no reason to question the validity of a positive test in males. The test is most sensitive in first morning urine. Overnight incubation in the bladder allows sufficient time for the bacteria to reduce dietary nitrate to nitrite. It is possible that the large volume of residual urine in this case may have allowed sufficient time for incubation during the first episode. Treatment with tamsulosin may have reduced the level of residual urine prior to the second episode and not allowed sufficient time for nitrate to be reduced to nitrite. The positive nitrite test favors the concept that the primary causal agent(s) was one or more enteric Gram-negative bacterial species perhaps masked by a Gram-positive bacterial species capable of growing in urine or a Gram-negative species that does not produce nitrate reductase. *Enterococcus faecalis*, *Staphylococcus saprophyticus*, and *Pseudomonas* spp. do not reduce nitrate to nitrite.

Urine specimens account for 24% to 40% of cultures, and as many as 80% are from outpatients in hospital-based clinical microbiology laboratories (5). In order to provide meaningful species identification and susceptibility tests, the laboratory must be able to distinguish infection from contaminants in voided urine and mixed flora in patients with long-term indwelling urinary catheters. Laboratory guidelines for specimen work-up and interpretation are based on the method of collection, bacterial counts, and number of colonial types. Some incorporate partial clinical information (4, 6), while others do not consider patient gender (5). A key point listed in a recent guide to utilization of the microbiology laboratory for the diagnosis of infectious diseases states that “Three or more species of bacteria in a urine specimen usually indicates contamination at the time of collection and interpretation is fraught with error” but does not separate males from females (6). A Canadian guideline (7) provides exceptions for low counts and mixed growth, symptomatic males, adult females with mixed flora in male voided urine are usually reported as “suspect contamination” but does not separate males from females. Some incorporate partial clinical information. It might be helpful to add to the laboratory reports some of the exceptions provided in the Canadian guideline. This would help the referring physician to evaluate the laboratory findings in relation to the clinical setting.

It is not known whether the current case is exceptional or whether similar cases may have been missed because cultures of mixed flora in male voided urine are usually reported as “suspect contamination during collection.” It is often too late to obtain a repeat culture because patients with acute symptomatic urinary tract infections are usually treated well before culture results are available. In the current case, dip sticks for leukocyte esterase and nitrite tests provided useful information.

**ACKNOWLEDGMENTS**

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**REFERENCES**


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**TABLE 1 Clinical course of an 83-year-old man with acute bacterial cystitis associated with mixed flora in his voided urine**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>LE/nitrite results</th>
<th>Culture result</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/15/2012</td>
<td>Gross hematuria</td>
<td>Negative/negative</td>
<td>&lt;1,000 CFU/ml</td>
<td>Ciprofloxacin, single dose</td>
</tr>
<tr>
<td>6/26/2012</td>
<td>Cystoscopy 1</td>
<td>Negative/negative</td>
<td>50,000–100,000 CFU/ml</td>
<td>Nitrofurantoin, 100 mg b.i.d. × 5 days</td>
</tr>
<tr>
<td>7/3/2012</td>
<td>Cystoscopy 2</td>
<td>Negative/negative</td>
<td>Mixed skin, urogenital flora</td>
<td></td>
</tr>
<tr>
<td>8/21/2012</td>
<td>Frequency of urination, burning</td>
<td>Strongly positive/positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/15/2012</td>
<td>Frequency of urination, burning</td>
<td>Positive/negative</td>
<td>50,000–100,000 CFU/ml</td>
<td>Nitrofurantoin, 100 mg b.i.d. × 10 days</td>
</tr>
<tr>
<td>9/18/2012</td>
<td>Symptoms resolved</td>
<td>Positive/negative</td>
<td>Mixed skin, urogenital flora</td>
<td></td>
</tr>
<tr>
<td>10/5/2012</td>
<td>Frequency of urination, burning</td>
<td>Positive/negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/8/2012</td>
<td>Symptoms resolved</td>
<td>Positive/negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/25/2013</td>
<td>No recurrences</td>
<td>Negative/negative</td>
<td>&lt;1,000 CFU/ml</td>
<td></td>
</tr>
</tbody>
</table>

* Cystoscopy 1 revealed a blood clot; cystoscopy 2 revealed a normal bladder with large prostatic veins. LE, leukocyte esterase; b.i.d., twice a day.