Recurrent Urinary Tract Infections in Men: a Role for Aberrant Bacterial Forms?

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We studied 11 infected, asymptomatic elderly men who had experienced recurrent urinary tract infections classified as bacterial relapse. These men did not have ileal loop bladders, urethral catheters, suprapubic catheters, or condom drainage. We had to process more than 1,000 urines from men attending the urology clinic to identify the 11 study patients. A positive antibody-coated bacteria immunofluorescence test was detected on the urinary sediments of each of these men. This selective study group was subjected to excretory urography and a 2-week course of antibiotics, in accordance with the results of in vitro susceptibility tests. Two patients experienced a “cure.” Recurrences developed in eight patients (six relapses, two reinfections), and in one patient a superinfection emerged. No pathogenic role could be attributed to aberrant bacterial forms in this elderly population of asymptomatic men with recurrent, invasive urinary tract infections.

Antibiotic treatment of men with urinary tract infections often fails to achieve the therapeutic goal, namely, prolonged sterility of the urine (4, 10, 13). A number of anatomical abnormalities, including infection stones, prostatic calculi, reflux nephropathy, papillary necrosis, and obstructive uropathy, adequately explain many treatment failures (2, 12). We performed a prospective study of men with recurrent, invasive urinary tract infections to determine the impact provided by aberrant bacterial forms. Our study failed to implicate these organisms as a cause of recurrent, invasive urinary tract infections in elderly men.

MATERIALS AND METHODS

Selection of patients. The study group consisted of 11 asymptomatic, adult males, previously identified by a screening procedure to detect bacteriuria, who attended the urology outpatient clinic of the Boston Veterans Administration Medical Center. To identify these men, we had to process more than 1,000 urines. Three criteria had to be fulfilled for a patient to be studied. Documentation had to exist in the patient’s medical record that he had experienced recurrent urinary tract infections, characterized as bacterial relapse, during the preceding 3 years. There had to be significant bacteriuria with a pure culture of Pseudomonas aeruginosa or a member of the Enterobacteriaceae family that was susceptible, in vitro, to the antibiotic prescribed. Significant bacteriuria was defined as the presence of >100,000 colony-forming units per ml of urine of the identical organism in two consecutive, clean-catch, midstream urine samples collected within 5 days before entering the study. Lastly, the urinary sediment from the patient had to demonstrate a positive antibody-coated bacteria immunofluorescence test.

The following patients were excluded from entrance into the investigation: patients with ileal loop bladder, urethral catheter, suprapubic catheter, condom drainage, infection stones, known vesico-ureteric reflex, or a serum creatinine that exceeded 3 mg/dl. No concomitant antimicrobial therapy was administered or invasive urological procedure performed during the study period.

After informed consent was obtained, the patients received a 2-week course of oral antibiotic therapy in accordance with identification and susceptibility testing of the urinary isolate and the patients’ drug allergy history. No patient refused to participate in the investigation. The study was completed for a patient when drug intolerance, continuous bacteriuria, superinfection, reinfection, or relapse occurred, or successful microbiological response was achieved for a minimum of 6 weeks after the termination of the course of medication. The study received the approval of the Institutional Review Committee for Human Research at the Boston Veterans Administration Medical Center.

Each patient was subjected to excretory urography. Cultures of the urine were performed 1, 2, 4, 6, and 8 weeks after the onset of drug therapy. Urine samples were clean-catch, midstream voided samples. All specimens were inoculated onto 5% tryptic soy sheep blood agar (Scott Laboratory) and Levine eosin methylene blue agar (Scott Laboratory) plates by a Jorgensen tungsten alloy 4-mm calibrated wire loop, calculated to deliver 0.01 ml of urine, and then incubated aerobically at 37°C. Cultures were observed for growth for
been developed by Thomas and co-workers. This technique has become a preferred noninvasive method for the identification of urinary tract pathogens. With the Dienes method (11), all cultures were examined daily for 4 days and again on day 10 before discarding. Examination of the plates was made with a magnifying hand lens and microscopically by the Dienes method of stained agar cultures (11). Subcultures of suspected colonies were made to L-form media and to conventional media for definitive identification. With the development of turbidity in broth, subcultures, both aerobic and anaerobic, were made to L-form media and examined for growth as above. All broths were evaluated at 10 days, before discarding.

Immunological tests. The antibody-coated bacterial immunofluorescence test was performed by the method developed by Thomas and co-workers (3, 14). This technique has become established as the preferred noninvasive procedure to identify the site of a urinary tract infection, and the validity of this determination has been confirmed in men with recurrent urinary tract infections (8–10). A specimen was arbitrarily designated as positive when more than five uniformly fluorescent bacteria of at least grade 2+ intensity were seen after viewing the sediment for a minimum of 5 min (7).

Serological typing of determination of the somatic O antigen were performed on Escherichia coli isolates in the laboratory of Marvin Turck, Seattle, Wash. The technique of this serotyping procedure has previously been published (15). Pyocin typing of P. aeruginosa was performed in the laboratory of Ruth Kundsin, Boston, Mass.

Evaluation. No absolute standards currently exist to appraise drug therapy of recurrent urinary tract infections. We, therefore, elected to adhere to the Food and Drug Administration protocol guidelines issued in 1975 and accepted the following definitions (3). Reinfection occurs after medication has been discontinued and represents a recurrent bacterial infection produced by an organism different from that causing the original infection. Bacterial persistence, also known as relapse, defines that situation in which the pretreatment pathogen, having been temporarily eliminated from the urine in response to therapy, survived within the urinary tract and subsequently initiated a recurrent infection. Colonial morphology, biochemical tests, antimicrobial susceptibility testing, and serotyping of the E. coli isolates and pyocin typing of P. aeruginosa were the methods used to differentiate bacterial persistence from reinfection. Therapeutic success, "cure," consisted of finding <10³ organisms per ml of urine for a minimum of 6 weeks after cessation of therapy. Superinfection was defined as an infection characterized by consistent urine colony counts exceeding 10⁴ organisms per ml occurring during chemotherapy and caused by an organism different from the pretreatment organism.

RESULTS

The patients were eight Caucasian and three black men. The ages of these patients ranged from 50 to 84 years, with a median of 72. Two patients experienced a cure. Recurrence developed in eight patients (six relapses, two reinfections), and in one patient a superinfection emerged. Each time bacterial relapse occurred, the organism remained susceptible to the antibiotic prescribed. Tables 1 and 2 outline the

### Table 1. Patient profile

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Race</th>
<th>IVP</th>
<th>Pretreatment organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>Caucasian</td>
<td>Normal</td>
<td>E. coli</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>Black</td>
<td>Normal</td>
<td>Klebsiella species</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>Caucasian</td>
<td>Normal</td>
<td>Citrobacter diversus</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>Caucasian</td>
<td>Normal</td>
<td>E. coli</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>Caucasian</td>
<td>Prostatic calcification</td>
<td>P. aeruginosa</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>Caucasian</td>
<td>Prostatic calcification</td>
<td>E. coli</td>
</tr>
<tr>
<td>7</td>
<td>75</td>
<td>Caucasian</td>
<td>Normal</td>
<td>Klebsiella species</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>Black</td>
<td>Normal</td>
<td>E. coli</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>Black</td>
<td>Bilateral small kidneys</td>
<td>E. coli</td>
</tr>
<tr>
<td>10</td>
<td>72</td>
<td>Caucasian</td>
<td>Moderate post-void residual</td>
<td>E. coli</td>
</tr>
<tr>
<td>11</td>
<td>76</td>
<td>Caucasian</td>
<td>Normal</td>
<td>Proteus mirabilis</td>
</tr>
</tbody>
</table>
TABLE 2. Therapeutic results

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Therapy</th>
<th>Treatment results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cephalexin, 500 mg every 6 h</td>
<td>Cure</td>
<td>Normal cystoscopy; normal renal ultrasound</td>
</tr>
<tr>
<td>2</td>
<td>Trimethoprim-sulfamethoxazole, 2 tablets every 12 h</td>
<td>Cure</td>
<td>Extensive squamous metaplasia of bladder associated with acute and chronic inflammation; diabetes mellitus</td>
</tr>
<tr>
<td>3</td>
<td>Cephalexin, 500 mg every 6 h</td>
<td>Relapse</td>
<td>Urethral stricture</td>
</tr>
<tr>
<td>4</td>
<td>Ampicillin, 500 mg every 6 h</td>
<td>Relapse</td>
<td>Spondylolisthesis</td>
</tr>
<tr>
<td>5</td>
<td>Carbenicillin indanyl sodium, 382 mg every 6 h</td>
<td>Relapse</td>
<td>Urethral diverticulum</td>
</tr>
<tr>
<td>6</td>
<td>Ampicillin, 500 mg every 6 h</td>
<td>Relapse</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>7</td>
<td>Cephalexin, 500 mg every 6 h</td>
<td>Relapse</td>
<td>Recurrent epididymitis</td>
</tr>
<tr>
<td>8</td>
<td>Tetracycline, 500 mg every 6 h</td>
<td>Relapse</td>
<td>Urethral stricture</td>
</tr>
<tr>
<td>9</td>
<td>Ampicillin, 500 mg every 6 h</td>
<td>Reinfecion</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Ampicillin, 500 mg every 6 h</td>
<td>Reinfecion</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Ampicillin, 500 mg every 6 h</td>
<td>Superinfection (Morganella morganii)</td>
<td></td>
</tr>
</tbody>
</table>

excretory urography findings, pretreatment urinary pathogen, antibiotic therapy, treatment outcome, and results of processing urine to recover aberrant bacterial forms. We were unable to establish any causative role for aberrant bacterial forms in these elderly men with recurrent, invasive urinary tract infections.

DISCUSSION

This study underscores the observation that the conventional 2-week course of chemotherapy for men with recurrent invasive urinary tract infections has not been highly successful (4, 10, 13). Invasion was manifest as a positive antibody-coated bacteria determination, a measure of deep-seated infection of the "uroepithelium," and a reliable indicator of tissue invasion in men with recurrent urinary tract infections (8-9).

Investigators have suggested that cell wall-defective bacteria contribute to chronic pyelonephritis and provide an explanation for the bacterial relapses that develop so frequently after chemotherapy has been discontinued. Data have emerged to support (6) and refute (5) this theory. Other researchers assume a more cautious posture and express the opinion that the importance attached to the recovery of these aberrant bacterial forms has been exaggerated (16). With the techniques we employed, no cell wall-defective bacteria were isolated from the urine, although patients received antibiotics capable of inducing aberrant bacterial forms, and this research laboratory, specializing in the study of cell wall-defective bacteria, has had considerable experience in the isolation of these organisms (11). The use of media containing osmotic stabilizers did not detect L-forms or other aberrant bacterial forms from multiple specimens obtained during the 6-week posttreatment period. After drug therapy, no patient experienced a sequence in which the cell wall-defective form was isolated from the urine before the development of a recurrent urinary tract infection. Patients were not cautioned to restrict fluids before voiding, however, and the possibility exists that the inability to insure a high urinary osmolality precluded survival or recovery of aberrant bacterial forms.

In our limited number of study patients, we failed to isolate aberrant bacterial forms. These findings apply exclusively to a small, selective population of elderly, asymptomatic men who experienced recurrent, invasive urinary tract infections. Investigations performed on younger men, patients with irritative voiding symptoms, or a larger number of men with recurrent, invasive urinary tract infections characterized by bacterial relapse could provide different results. Our study suggests that aberrant bacterial forms often fail to provide an explanation for the observation that urinary pathogens are able both to persist during therapy and to cause relapsing infections in the male urinary tract (4).

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LITERATURE CITED