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Molecular Epidemiology of Catheter-Associated Bacteriuria in Nursing Home Patients

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Urine samples from 19 nursing home patients with long-term urinary catheters were cultured every 3 months for 18 months. *Providencia stuartii*, present in 74% of the elderly and in 59% of urine specimens, was the most frequently isolated bacteria. The persistence of *P. stuartii* was significantly higher among females than among males. In order to study the epidemiology of bacteriuria in this nursing home, bacteria were characterized by biochemical tests, antibiotic susceptibility patterns, and restriction fragment length polymorphism (RFLP) analysis. The antibiotic susceptibility pattern indicated that each patient had two to three different strains of *P. stuartii* during the 18 months of follow-up. In contrast, the RFLP analysis revealed that a specific strain had persisted in the urinary tract of the patient during the entire follow-up period. According to the biochemical profile, 74% of the patients had the same bacteria in urine cultures, pointing to a common source of transmission. RFLP analysis, however, demonstrated different patterns of RFLP, suggesting concomitant multiple sources of infection.

Bacteriuria associated with long-term urinary catheterization is the most common nosocomial infection in the United States (30). It is also the most commonly acquired infection in nursing homes (8). Most cases of bacteriuria in nursing home patients are associated with indwelling urethral catheters, and virtually all long-term urethral catheters are associated with bacteriuria. Between 35 and 50% of nursing home patients are incontinent (21), and long-term indwelling urethral catheters are frequently used in managing these patients. Complications of bacteriuria associated with long-term catheterization may be severe and include fever, obstructed catheters, acute pyelonephritis, bacteremia, periurethral purulent infections, vesiculoureteral reflux, chronic tubulointerstitial nephritis, chronic renal failure, and death (32). Most studies of infections associated with bladder catheterization have been conducted in acute-care hospitals, and their results are probably not applicable to nursing home patients, who are a growing part of the population in industrial countries.

Catheter-associated bacteriuria is usually of polymicrobial etiology (2, 33). The most common isolates are *Proteus mirabilis*, *Escherichia coli*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa* (2, 31). *Providencia stuartii* is an unusual pathogen in acute and community-acquired bacteriuria. However, this pathogen has been isolated from 0 to 61% of urine samples collected from patients with urinary catheters in nursing homes (1, 2, 8, 31, 33). Change in the etiological agent of bacteriuria over time is the rule (2). Evaluation of the dynamics of bacteriuria is dependent on the precise identification of all isolated bacterial strains. Techniques based on antibiotic susceptibility (20), biochemical characteristics (6), and antigenic characterization (29) rely on phenotypic characteristics that may not be stably expressed or may not be refined enough to differentiate between strains. Methods relying on the study of genotypes may be more accurate in discriminating between strains of the same species. Hybridization of *E. coli* rRNA to digests of bacterial chromosomal DNA identifies in the family *Enterobacteriaceae* several fragments containing rRNA coding sequences; the length distribution of such fragments varies within species, providing a useful restriction fragment length polymorphism (RFLP) for strain differentiation (26). RFLP of bacterial chromosomal DNA has recently been employed as a tool in the molecular epidemiology of various infections (12, 26). We performed a long-term prospective microbiological study of bacteriuria in patients with chronic indwelling catheters. The prevalence, the incidence, and the dynamics of bacteriuria were studied. The molecular typing of species (RFLP) causing bacteriuria was performed to understand the epidemiology of bacteriuria in nursing home patients.

MATERIALS AND METHODS

Characteristics of the studied population and urine sampling. Patients residing at a chronic-care facility in Jerusalem, Israel, were eligible for participation in the study if they had an indwelling or condom catheter in place for more than 1 month. All patients were bedridden and were unable to care for themselves. Latex catheters were changed monthly and bags were changed weekly. A periurethral wash was done once a day with soap. Each patient was to be sampled every 3 months for an 18-month period. All patients were monitored prospectively by the same physician. Antibiotics were not administered during the study period, except to one patient who was treated for a documented pulmonary infection 1 month before the first urine specimen was obtained. The urine specimens were obtained by a trained nurse or physician by needle aspiration of the distal catheter after disinfection with chlorhexidine. In patients with condom catheters, the device was removed, the penis was washed carefully, and a clean-voided specimen was obtained. Urine specimens were immediately transported to the laboratory at the Hadassah Medical Center.

Bacterial characterization. The urine was plated by a loop quantification method (10) on blood-based agar and on MacConkey agar, and plates were incubated aerobically only. Colonies with distinct morphology were isolated from samples containing at least 100,000 CFU per ml of urine and were

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identified by using the API-20E system (Ayerst Laboratories, Plainview, N.Y.). Antibiotic susceptibility was determined by a disk diffusion test (20). Whole chromosomal DNA was purified from bacterial cells as described by Marmur (13). Bacteria grown in 250 ml of tryptic soy broth overnight at 37°C were centrifuged, and the pelleted bacteria were washed and resuspended in Tris-EDTA buffer (pH 8.0). Bacterial cells were lysed by the sequential addition of sodium dodecyl sulfate (0.5%)-pronase B (75 μg/ml). The mixture was incubated overnight at 37°C. The cell lysate was extracted with phenol-chloroform. Chromosomal DNA was precipitated with ethanol, recovered by centrifugation, dried, and resuspended in Tris-EDTA. The DNA of plasmid pKK3535, carrying the *E. coli rrnB* operon (3), was extracted by alkaline lysis and purified by ultracentrifugation on a cesium chloride-ethidium bromide equilibrium density gradient (24). The 2.5-kb *Eco*RI-*Hin*dIII restriction fragment encoding 16S rRNA and part of 23S rRNA, used as a probe, was separated by low-melting-temperature agarose gel electrophoresis and was labeled with ^{32}P-CTP by a multiprime labeling system (Amersham). The specific activity of the probe was 10^7 to 10^8 cpm/μg of DNA. About 6 μg of purified chromosomal DNA from the isolated bacteria was digested separately with *Eco*RI, *Bam*HI, and *Hin*dIII (International Biotechnologies Inc., New Haven, Conn.) according to the manufacturer's instructions. The restriction fragments were separated in 0.8% agarose and transferred to a nitrocellulose membrane by the method of Southern (25). The membrane was hybridized at 67°C for 16 h with ^{32}P-labeled rDNA, washed, and exposed to X-ray film. In order to verify that DNAs were completely digested by the various enzymes used, an additional probe, pTUB1, encoding the *E. coli tufB* gene (17) present in a single copy in chromosomal DNA from members of the family *Enterobacteriaceae*, was hybridized separately to the membranes. Bacteria isolated from the same patient on different occasions were assumed to be the same strain if their API system biotype, as well as their banding patterns on RFLP analysis, was the same. Statistical analyses were performed with JMP (SAS Institute, Cary, N.C.) and StatXact (Cytel Software, Cambridge, Mass.) software. The persistence of bacteria in the urinary catheter or in the urinary tract was determined for each patient by calculating the percentage of positive cultures for a specific pathogen in the total number of urinary cultures taken for that patient. The difference between the persistence of the different bacteria was analyzed by using a mixed-model analysis of variance. The response variable was calculated by using the arcsin transformation ($2 \cdot \arcsin \sqrt{P}$) on persistence. Sex and bacteria were taken as fixed effects, and person nested within sex was taken as a random effect. The observations were weighted by the number of cultures taken from each patient.

RESULTS

The long-term care department of the retirement home investigated included 49 patients. All 19 long-term residents with catheters were evaluated: 13 patients with an indwelling urinary catheter and 6 patients with a condom catheter. The patient population included 11 women and 8 men. Two males had urinary catheters and six had condom catheters. The ages of the individuals studied ranged from 69 to 107 years (mean age, 82.6 ± 7.9 years). The mean age of the males was 82.9 ± 10.9 years, and that of the females was 82.4 ± 5.4 years. Seventeen patients (90%) had underlying neurologic disease. Six (31%) had fractures of the neck of the femur, six had ischemic heart disease with congestive heart failure, and four patients had diabetes mellitus. Eight patients (42%) had recurrent symptomatic urinary tract infections. Due to death or hospitalization of some patients, the mean number of urinary specimens taken from patients was only 4.1 ± 1.2 (females, 4.4 ± 1.4; males, 3.8 ± 0.9; difference not significant with the Wilcoxon/Kruskal-Wallis test).

A single pathogen was isolated from 34 of the 78 urinary specimens (43.6%). Polymicrobial bacteriuria was found in 43 urinary cultures: two pathogens were isolated from each of 26 specimens (33.3%), three pathogens were isolated from 13 specimens (16.7%), and four pathogens were isolated from 4 specimens (5.1%). Only 1 of the 78 urine specimens was found to be sterile. One hundred forty-two organisms were isolated (mean, 1.8 ± 0.9 organisms per urinary specimen). The number of pathogens was higher in males (2.1 ± 0.8) than in females (1.6 ± 0.9) (Wilcoxon test; $P = 0.01$). By far the most prevalent organism was *P. stuartii*, which was found in 59% (46 of 78) of the specimens. The next most prevalent species was *E. coli*, which was found in 32% of the specimens; *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Acinetobacter calcoaceticus* var. *anitratus* were each found in 16.7%, and *Pseudomonas aeruginosa* was found in 12.8%. Few isolates of *Proteus vulgaris*, *Providencia rettgeri*, *Morganella morganii*, *Proteus penneri*, *Pseudomonas cepacia*, and *Moraxella* spp. were found. No gram-positive cocci or yeasts were isolated. With the initial urine specimens as a baseline, of 78 examinations, 18 new episodes of bacteriuria were defined (23%). The ability of the bacteria to persist in the urinary tract varied considerably. Only 3 of the 46 positive urinary cultures with *P. stuartii* (6.4%) were single episodes. Among *E. coli*, *K. pneumoniae* and *A. anitratus*, 7 to 15% of the episodes were identified only in a single culture and not in subsequent specimens; 50% of the episodes with *Pseudomonas aeruginosa* and 23% of the episodes with *Proteus mirabilis* were identified only in a single urinary culture.

The persistence of bacteria in the urinary tract was analyzed by using a mixed-model analysis of variance, as described in Materials and Methods. Rsquare for the model was 0.61, meaning that 61% of the variation in the model was explained. None of the effects in the model were significant: the *P* value for bacterial effect was 0.50, the *P* value for the effect of sex was 0.12, and the *P* value for the effect of person (sex) was 0.22.

A significant difference in the persistence pattern of bacteriuria with *P. stuartii* was found among males and females: bacteriuria persisted in 88.25% of the females but in only 50.5% of the males. We used a weighted analysis of variance in order to examine the difference in the persistence of *P. stuartii* between males and females. The response variable, as before, was $2 \cdot \arcsin \sqrt{P}$. The single fixed effect was sex, and the analysis was again weighted by the number of cultures taken for each patient. (The mixed model was not necessary in this case, as each person had only one associated observation.) Rsquare for the model was 0.35. The sex effect was significant ($P = 0.02$). No difference in the persistence pattern was found between males and females concerning other pathogens.

P. stuartii isolates were resistant to most of the antibiotics tested, as follows (in percent resistance): tetracycline, 100; nitrofurantoin, 98; ampicillin, 96; cephalothin, 96; cotrimoxazole, 72; ciprofloxacin, 33; mezlocillin, 16; gentamicin, 11; cefuroxime, 7; amikacin, 0.

The antibiotic susceptibility and the RFLP patterns of *P. stuartii* were determined in successive strains isolated from nine patients, eight females and one male, all with indwelling catheters. Successive isolates from the same patient had two to three different antibiotic susceptibility patterns over the 18 months of follow-up. The change in the antibiotic susceptibility pattern was due to the acquisition of resistance to ciprofloxacin (four patients), mezlocillin, nitrofurantoin, and gentamicin

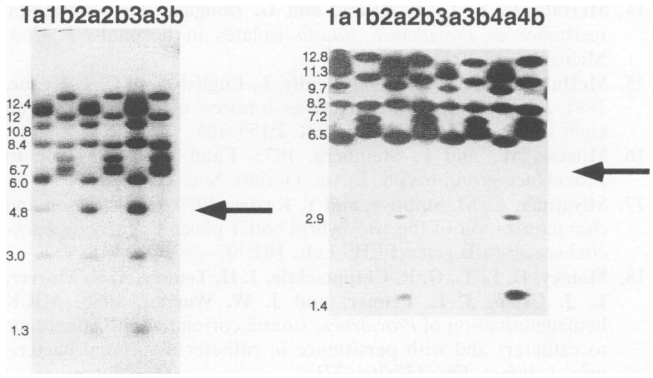

FIG. 1. RFLP patterns of *P. stuartii* isolates from two patients after digestion with *Eco*RI (a) and *Hin*dIII (b).

(three patients each), cefuroxime, ampicillin, and cotrimoxazole (two patients each), and cephalothin (one patient). On the other hand, the RFLP pattern of the successive isolates from the same patient did not change over time (Fig. 1), although two different RFLP patterns were noted overall in the strains isolated in the institution. *Eco*RI provided the highest degree of polymorphism with a unique 4.8-kb restriction fragment on the left pattern only (Fig. 1). Hybridization of the membrane with the *tufB* probe revealed two bands constantly, while the rRNA probe revealed eight to nine bands. The Wilcoxon signed rank test was used to determine differences between number of patterns in antibiotic susceptibility and RFLP methods. The results were highly significant ($P = 0.004$).

DISCUSSION

Thirty-nine percent of the patients residing in a chronic-care facility who participated in this study had a urinary or a condom catheter. The high frequency of background neurological problems emphasizes the severity of the general conditions of these patients.

A single isolate was found in 43.6% of the urine specimens, whereas polymicrobial bacteriuria was found in 55.1%, a number slightly smaller than that reported in other studies (77 to 86%) (2, 33). The mean number of pathogens isolated was 1.8 ± 0.9, comparable to the numbers reported (2.4 to 2.6 species per patient) in other studies (2, 33). However, in contrast to the observation of Bergqvist et al. (1), in our study the number of pathogens was significantly higher in males than in females (2.1 ± 0.8 and 1.6 ± 0.9, respectively). This difference may be related to the type of catheters used (condom catheters in this study).

P. stuartii bacteriuria is clinically significant, as it has been complicated by bacteremia and death (15, 16, 19). Although bacteriuria due to *P. stuartii* in patients in acute-care hospitals (4) is relatively rare (0.3 to 1%), it is frequently present in the catheterized urinary tract and also in patients with intermittent and condom catheters (7, 11, 15). In this study, *P. stuartii* was found in 59% of the urinary specimens. The bacterial species causing catheter-associated bacteriuria varies from institution to institution. *Proteus mirabilis*, *E. coli*, and *P. stuartii* were each found in about 40% of urine specimens from patients with indwelling urinary catheters, enterococci were found in 20%, and *Pseudomonas aeruginosa* was found in 28% (1, 8, 31, 33). The high frequency of isolation of *P. stuartii* from urine of patients with chronic indwelling catheters is probably due to the tendency of this organism to persist in the catheterized urinary tract once having gained access. Warren et al. found that the duration of bacteriuria episodes caused by *P. stuartii* was significantly longer than that of episodes caused by all other species, except *E. coli* (33). In the present study, a mixed-model analysis of variance did not find a difference in the persistence of different bacteria, but the most prevalent organisms (*P. stuartii*, *E. coli*, *K. pneumoniae*, and *A. anitratus*) appeared in consecutive cultures, and only 6.4 to 15% were single episodes. In contrast, 50% of the episodes with *Pseudomonas aeruginosa* and 23% of the episodes with *Proteus mirabilis* were identified only in a single urinary culture. The median duration of episodes due to *P. stuartii* was 6.4 months. A significant difference in the persistence pattern of bacteriuria with *P. stuartii* was found among males and females, an interesting finding that may be due to the presence of different receptors to the bacteria in the urinary tracts of males and females or to differences in the adhesive properties of indwelling and condom catheters. The MR/K hemagglutinin (mannose-resistant, klebsiella-like fimbriae) of *P. stuartii* probably plays an important role in the ability of the bacteria to persist and to adhere to the urinary catheter (18).

Strains of *P. stuartii* are commonly resistant to many drugs (9, 14, 27, 28). The finding in the present study that 32.6% of the strains were resistant to ciprofloxacin, which has not been reported previously, is probably due to the frequent use of this antibiotic in nursing homes.

Interpretation of the epidemiology of bacteriuria in catheterized patients is limited by the dynamics of the bacteriuria. In order to define precisely the pathogens causing the bacteriuria, a system that identifies differences among strains should be used. The possible techniques to identify isolates of *P. stuartii* are biochemical profiles (6), serotyping (15, 23), and antibiotic susceptibility patterns (9). These methods, however, rely on phenotypic characteristics that may not be stably expressed. Polyacrylamide gel electrophoresis of proteins was also suggested for bacterial typing (5). RFLP analysis of bacterial chromosomal DNA does not present the above-mentioned disadvantages, and "ribotyping" especially has been employed to investigate the epidemiology of various infectious diseases (12, 26). Owen and colleagues (22), using a similar DNA probe, found 11 different *Eco*RI patterns among 26 clinical isolates of *P. stuartii* from different hospitals in the United Kingdom. Bands in the 5- to 6-kb, 13- to 14-kb, and 19- to 20-kb regions were common features of most of the *P. stuartii* fingerprints, with a band of 6 kb present in almost all of them (22). The *P. stuartii* isolates in this study did not have the 19- to 20-kb band, but they had a distinctive band at 3 to 4 kb. The differences in patterns indicate that the *P. stuartii* strains isolated in Israel were different from the one isolated in the United Kingdom.

In the present study, antibiotic susceptibility patterns suggested that each patient had two to three different strains of *P. stuartii* during the 18 months of follow-up. In contrast, RFLP analysis revealed that a specific strain persisted in the urinary tract or in the urinary catheter of the patient involved during the entire follow-up period.

According to the biochemical profile, 14 of 19 (74%) patients residing in the same nursing home had the same bacteria in urine cultures, pointing to a common source of transmission, most probably the personnel treating the patients. RFLP analysis, however, demonstrated two different patterns of RFLP among the patients, indicating that the high prevalence of *P. stuartii* among catheterized patients in the nursing home was probably due to the adherence properties of

the bacteria and not to the transmission of the bacteria among patients by the attending staff.

In conclusion, our findings indicate that RFLP analysis of *P. stuartii* strains appears to be a powerful epidemiologic tool in the investigation of outbreaks due to this bacterium: the RFLP reveals that the same strain had persisted in the urinary tract of the same patient during the entire follow-up period, in spite of changes in the antibiotic susceptibility patterns. Furthermore, the different RFLP patterns among residents of the nursing home allowed us to conclude that multiple sources of infection were responsible for the high frequency of this bacterium in the urinary tract.

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