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Uropathogens and Host Characteristics▽

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Uropathogens other than *Escherichia coli* occur with greater frequency in patients with risk factors for urinary tract infection (UTI). However, little is known about associations between uropathogen species and host characteristics. Three hundred nineteen urine specimens containing a balanced distribution of uropathogen species were selected from inpatients and outpatients at a university hospital clinical microbiology laboratory. Information on host characteristics was retrospectively collected by chart review. Differences in the frequencies of host characteristics in UTI groups, as defined by the causative uropathogen, were compared by chi-square/Fisher analysis. Multivariate classification and regression tree analysis were used to identify host characteristic subsets that distinguish among uropathogen groups. In this exploratory study, several uropathogen species were found to be strongly linked to host characteristics relevant to UTI. Patients with *Pseudomonas aeruginosa* UTIs were more likely to have undergone urinary tract procedures (43% versus 15% overall), to have a neurogenic bladder (29% versus 12% overall), to have received recent antibiotic therapy (52% versus 24% overall), and to be male (76% versus 28% overall). Patients with *Proteus mirabilis* UTIs were more likely to have a foreign body in the lower urinary tract (48% versus 30% overall). The classification tree identified males over the age of 27 years who had undergone a prior urinary tract procedure as belonging to a host characteristic profile associated with *P. aeruginosa* UTI: 38% of patients with *P. aeruginosa* UTIs fit this profile. These data may be useful for planning future targeted prophylaxis studies.

Urinary tract infections (UTIs) account for more than 8 million visits to physicians' offices, 1.5 million emergency room visits, and 300,000 hospital admissions in the United States annually (2, 4, 9). UTIs are the second most common infection of any organ system and the most common urological disease in the United States, with a total annual cost of more than $3.5 billion (4).

In general, *Escherichia coli* is the most common uropathogen, responsible for approximately 80% of UTIs (2, 7, 12). Non-*E. coli* infection is considerably more common (44% to 72%) in the subset of patients with complicated UTIs (7). UTIs are defined as complicated when they occur in patients with immunosuppression, including diabetes, or in the context of structural or functional abnormalities of the urinary tract.

Complicated UTIs, due to either intrinsic or extrinsic urinary tract abnormalities, are becoming increasingly common due, in part, to increases in the elderly population. For example, benign prostatic hyperplasia is an intrinsic obstructive abnormality affecting >50% of the male population over 60, and 40% of benign prostatic hyperplasia patients will develop sufficient obstruction to require a prostatic tissue-ablative intervention, amounting to nearly 400,000 prostate procedures per year (5). Other intrinsic abnormalities potentially increasing the risk of UTI include congenital anomalies, a neurogenic bladder, and fistulae involving the urinary tract. Extrinsic abnormalities, such as stents and catheters, are also important risk factors for UTI. Catheter-associated UTI is responsible for 40% of nosocomial infections, making it the most common cause of nosocomial infection. Catheter-associated UTIs account for more than 1 million cases in hospitals and nursing homes annually and often involve uropathogens other than *E. coli* (2). While the epidemiology and pathogenic mechanisms of uropathogenic *E. coli* have been extensively studied, little is known about the associations between other uropathogens and the risk factors for their acquisition.

Uropathogens differ in terms of the virulence factors and pathogenic mechanisms that allow them to colonize and infect the urinary tract. For example, some uropathogens, especially *Proteus* spp., make the enzyme urease, which hydrolyzes urea to ammonia and carbon dioxide. The release of ammonia raises the urinary pH, which favors the precipitation of urinary salts in the form of kidney or bladder stones, which frequently serve as a nidus for recurrent *P. mirabilis* infection. Another mechanism for colonization of the urinary tract, particularly relevant to stones and other foreign bodies, is biofilm formation. *Pseudomonas aeruginosa* is well known to be adept at biofilm formation because of genes, such as alginase, that are involved in the formation of the exopolysaccharide matrix of the biofilm. Nosocomial UTIs frequently involve organisms selected for by their antibiotic resistance mechanisms, such as vancomycin-resistant enterococci and extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* (3, 10). The emergence of antibiotic resistance in the hospital setting has frequently been associated with UTIs (11). However, comparatively little is known about the associations between specific uropathogen species and patient populations with risk factors for UTI (1, 6, 8, 13, 14).

We conducted an exploratory case-case comparison study

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using a novel microbiological approach: we started with the urine isolate and then asked which host characteristics were negatively or positively associated with a particular uropathogen species. Urine specimens containing a diverse set of uropathogen species were prospectively collected, and host characteristics of the corresponding patients were then obtained by chart review. We found that certain uropathogens, especially *P. aeruginosa*, were strongly associated with particular host characteristics, including the male gender, recent antibiotic therapy, prior urinary tract procedures, and a neurogenic bladder. This is the first study we are aware of to examine the relationship between particular uropathogen species and host characteristics.

MATERIALS AND METHODS

Uropathogen isolates and clinical urine specimens. Consecutive uropathogen isolates were obtained from the UCLA Clinical Microbiology Laboratory with approval from the UCLA Institutional Review Board and an appropriate Health Insurance Portability and Accountability Act exemption. To obtain a balanced distribution of uropathogen species, the numbers of specimens were limited to 80 for *Escherichia coli*, 40 for *Klebsiella pneumoniae*, 40 for *Enterobacter* spp., 40 for *P. aeruginosa*, 40 for *Proteus mirabilis*, 80 for *Enterococcus* spp., and 80 for miscellaneous uropathogens. Half of the specimens provided from each category were from inpatients, and the other half were from outpatients. Only the initial specimen from a patient was included (i.e., subsequent isolates from the same patient were excluded), and isolates from specimens containing less than 10^5 CFU per milliliter were excluded.

Data collection. A review of medical records was performed to acquire information on 15 different characteristics of the patients from whom the specimens were obtained. These consisted of (i) gender, (ii) age, (iii) prior UTI within the last year with a culture density greater than 10^5 CFU/ml, (iv) prior antibiotic therapy within the past month, (v) prior procedures (surgical procedures at any time and nonsurgical procedures within the past year), (vi) prior urinary tract procedures (surgical procedures at any time and nonsurgical procedures within the past year), (vii) upper urinary tract obstruction (e.g., hydronephrosis, hydroureter, kidney or ureteral stone, vesicoureteral reflux, ureteropelvic junction obstruction) within the past year, (viii) lower urinary tract obstruction (e.g., bladder stone, enlarged prostate, urethral stone or stricture) within the past year, (ix) upper urinary tract foreign body (e.g., ureteral stent, nephrostomy tube) within the past year, (x) lower urinary tract foreign body (e.g., intermittent or indwelling catheterization, suprapubic catheter) within the past year, (xi) diabetes at the time of infection, (xii) immunocompromised state (e.g., bone marrow or solid-organ transplantation, immunosuppressant therapy, human immunodeficiency virus, liver failure, bed-bound nursing home patient) at the time of infection, (xiii) history of neurogenic bladder, (xiv) pregnancy at the time of infection, and (xv) urinary tract reconstruction (e.g., renal transplant, prostatectomy, appendicovesicostomy, ureteroneocystostomy) at any time. If there was no mention of a particular host characteristic in the medical record, it was assumed that the patient did not have that host characteristic. The medical record of each isolate was also reviewed for antibiotic susceptibility data.

Data analysis. (i) Bivariate. Each host characteristic was compared one at a time across uropathogen groups. The exact overall (omnibus) chi-square *P* value across groups was computed using specialized software (Stat Xact, version 8, 2007, Cytel Inc., Cambridge MA). Under the Fisher least-significant-difference criterion, for host characteristics that were significant overall across groups, exact *P* values were computed by using Fisher's exact test for pairwise comparisons between the uropathogen group with the lowest percentage and each of the other uropathogen groups. To further explore these findings, chi-square test comparisons were also made to see if there were significant differences between host characteristics in patients with *E. coli* versus *P. aeruginosa* infections.

For descriptive purposes only, the log of the relative ratio was reported where the relative ratio is defined as the proportion with the given host characteristic in each uropathogen group divided by the overall sample proportion with that host characteristic. The group proportions were divided by the overall proportion in order to make standardized, qualitative comparisons across host characteristics. If the proportion with a given host characteristic was the same across groups, the relative ratio would be 1 and its log would be zero. For age, the relative ratio was defined as the mean age in each uropathogen group divided by the overall mean.

In addition to chi square tests, the corresponding 95% confidence intervals were reported for selected important host characteristic proportions by uropathogen group.

(ii) Multivariate. A classification and regression tree (CART) model (Answer Tree, version 3.0; SPSS Inc., Chicago, IL) was used to simultaneously identify host characteristic profiles that distinguish among *E. coli*, *P. aeruginosa*, other gram-negative bacteria, and gram-positive bacteria. Equal prior probabilities were assumed for the four bacterial groups in this model so that a terminal node's predictive classification would be assigned to the bacterial group whose proportion exceeded its overall proportion. A 1,000-fold resampling cross-validation of the tree was performed to test whether the tree nodes were significant. The overall absolute proportions of these four bacterial groups were not necessarily representative of the true absolute risks of infection for the population.

RESULTS

Between 16 December 2002 and 16 May 2003, 453 urine specimens with positive cultures were selected. Of these, 134 were excluded: 91 for not being a patient's initial specimen and 43 for containing less than 10^5 CFU/ml. Of the remaining 319 specimens, 149 were from outpatients and 170 were from inpatients. The 319 urine specimens contained isolates representing 24 different bacterial species. The specimens were organized into 10 groups, each group containing a minimum of 10 specimens (Table 1). The *Enterobacter* genus was divided into the *Enterobacter aerogenes* and *Enterobacter cloacae* species, because each had more than 10 samples. Specimens containing two or three organisms were placed in the polymicrobial group.

The medical record of each patient corresponding to the 319 specimens was reviewed for 17 host characteristics predisposing to UTI. The mean age of the total patient sample was 55 years, 27.9% were male, and 79.9% were positive for at least one host characteristic. Whereas there was no significant age difference among bacterial groups, chi-square omnibus screening comparison revealed significant *P* values for gender (<0.0001), prior UTI (0.0583), prior antibiotics (0.0199), urinary tract procedures (0.0098), a lower foreign body (0.0647), a neurogenic bladder (0.0179), and no risk factors (0.0001). *P* values for the other 10 host characteristics were >0.1. Given the importance of gender for UTI, it is not surprising that there were highly significant differences in gender between UTIs caused by *E. coli* and several uropathogen groups including *Citrobacter* spp., *E. cloacae*, *P. mirabilis*, and *P. aeruginosa*. Aside from male gender, patients with *P. aeruginosia* infections were also significantly more likely to have had prior antibiotics, prior urinary tract procedures, and a neurogenic bladder. Other significant associations were found between a prior UTI and *E. cloacae* infection and between a foreign body in the urinary tract and *P. mirabilis* infection. Indicators of pyelonephritis (elevated white blood cell count, fever, flank pain, or upper urinary tract obstruction) were found in 32.9% of patients but were not associated with any particular bacterial group. Interestingly, none of the 50 patients with enterococcal infections were free of UTI risk factors.

Comparison of patients with *E. coli* and *P. aeruginosa* infections revealed statistically significant differences in the proportion with recent antibiotic therapy, as well as in six of the host characteristics directly relevant to the urinary tract, including urinary tract procedures, a neurogenic bladder, and obstruction of, and a foreign body in, the upper and/or lower urinary tract (Table 2). The only host characteristics relevant to the urinary tract in which patients with *E. coli* and *P. aeruginosa*

TABLE 1. Host characteristics of patients with UTIs due to various bacterial groups

Host characteristic[a]	Value for the indicated characteristic[b] in the following bacterial group[c] (no. of samples):									
	Citrobacter spp. (18)	*Enterococcus* spp. (50)	*Enterobacter aerogenes* (11)	*Escherichia coli* (66)	*Enterobacter cloacae* (21)	*Klebsiella pneumoniae* (26)	Miscellaneous *Enterobacteriaceae* (22)	*Pseudomonas aeruginosa* (21)	*Proteus mirabilis* (23)	Polymicrobial specimens (61)	Total (319)
Male	44.4**	20.0	27.3	10.6	38.1**	23.1	40.9**	76.2**	34.8**	23.0*	27.9
Age (mean)	49.3	55.9	37.4	57.4	55.3	63.2	55.7	56.2	62.4	55.2	55.2
Prior UTI	27.8	30.0	27.3	28.8	66.7*	53.8	36.4	42.9	47.8	41.0	38.6
Prior Abx	22.2	32	9.1	10.6	28.6	23.1	18.2	52.4**	21.7	27.9	24.1
Procedures	44.4	18.0	54.5	34.8	37.6	38.5	45.5	52.4	43.5	34.4	37.0
UT procedures	5.6	8.0	27.3*	12.1	9.5	19.2	18.2	42.9**	4.3	16.4	14.7
Upper obstruction	0.0	10.0	9.1	1.5	19°	3.8	9.1	14.3	8.7	14.8°	8.8
Lower obstruction	0.0	4.0	9.1	4.5	0.0	7.7	9.1	19.0	8.7	6.6	6.3
Upper foreign body	0.0	6.0	0.0	0.0	4.8	0.0	9.1	9.5	4.3	3.3	3.4
Lower foreign body	27.8	20.0	36.4	21.2	23.8	26.9	45.5**	42.9*	47.8**	36.1*	30.4
Diabetes	11.1	12.0	9.1	12.1	14.3	23.1	9.1	14.3	30.4	16.4	15.0
Immunocompromised	22.0	18.0	27.3	10.6	19.0	7.7	18.2	19.0	8.7	13.3	14.7
Neurogenic bladder	0.0	8.0	18.2	1.5	19.0	19.2*	18.2	28.6**	21.7*	11.5	11.9
Pregnant	0.0	10.0	0.0	6.1	4.8	3.8	0.0	0.0	0.0	8.2	5.0
UT reconstruction	0°	2.0	18.2	9.1	4.8	7.7	13.6	23.8	8.7	11.5	9.1
Pyelonephritis	27.8	40.0	45.5	24.2	38.1	26.9	31.8	38.1	39.1	32.8	32.9
No risk factors	16.7**	0.0	36.4**	36.4**	4.8	11.5**	13.6**	9.5*	17.4**	19.7**	20.1

[a] UT, urinary tract; Abx, antibiotic therapy.
[b] Unless indicated otherwise, the value is the percentage of patients with the characteristic in each group. *, pairwise difference ($P < 0.1$) among the indicated percentages compared to lowest percentage (underlined). **, significant pairwise difference ($P < 0.05$) among the indicated percentages compared to the lowest percentage (underlined).
[c] Miscellaneous *Enterobacteriaceae* comprise *Aerococcus urinae*, *Hafnia alvei*, undifferentiated *Klebsiella* spp., *Klebsiella oxytoca*, *Morganella morganii*, *Providencia alcalifaciens*, *Providencia stuartii*, and *Serratia marcescens*. Polymicrobial specimens have a combination of any of the species given in the table or included under miscellaneous *Enterobacteriaceae* as well as any of the following: *Acinetobacter baumanii*, *Alcaligenes xylosoxidans*, *Pseudomonas fluorescens*, *Chryseobacterium indologenes*, viridans streptococci, *Staphylococcus aureus*, or lactose-positive, gram-positive rods.

TABLE 2. Comparison of host characteristics in *E. coli* versus *P. aeruginosa* UTIs[a]

Host characteristic[b]	Value for the indicated characteristic[c] in UTI with:		*P* value
	E. coli	*P. aeruginosa*	
Male	10.6	76.2	<0.00001
Age (mean)	57.4	56.2	0.86
Prior UTI	28.8	42.9	0.23
Prior Abx	10.6	52.4	0.00004
Procedures	34.8	52.4	0.78
UT procedures	12.1	42.9	0.002
Upper obstruction	1.5	14.3	0.015
Lower obstruction	4.5	19.0	0.033
Upper foreign body	0.0	9.5	0.011
Lower foreign body	21.2	42.9	0.05
Diabetes	12.1	14.3	0.79
Immune compromise	10.6	19.0	0.31
Neurogenic bladder	1.5	28.6	0.00007
Pregnancy	6.1	0.0	0.25
UT reconstruction	9.1	23.8	0.077
Pyelonephritis	24.2	38.1	0.21
No risk factors	36.4	9.5	0.019

[a] Differences in percentages of host characteristics were compared by chi-square analysis.
[b] Abx, antibiotic therapy; UT, urinary tract.
[c] Except where indicated otherwise, the value is the percentage of patients with the indicated characteristic.

infections did not differ were a prior history of UTI and urinary tract reconstruction.

Figure 1 illustrates the variation in relative ratios of host characteristics for patients with four types of common uropathogens. Mean age was the least variable host characteristic, followed by a history of prior surgical or nonsurgical procedures, suggesting that

FIG. 1. Log relative ratio of host characteristics in UTIs due to four uropathogens. The relative ratio, defined as the proportion with the given host characteristic divided by the overall sample proportion with that characteristic, is compared descriptively across characteristics for four uropathogens: *Escherichia coli* (*Ec*), *Klebsiella pneumoniae* (*Kp*), *Pseudomonas aeruginosa* (*Pa*), and *Proteus mirabilis* (*Pm*). A log relative ratio of zero results from a relative ratio of 1, indicating no difference in the proportion with a host characteristic compared with the overall patient population. Host characteristics are arranged from lowest (left) to highest (right) cumulative deviations of the log relative ratio from zero. For example, patient age was similar in UTIs due to all four uropathogens. In contrast, there were strong positive (*P. aeruginosa*) and negative (*E. coli* and *K. pneumoniae*) associations with a foreign body in the upper urinary tract. One or two asterisks indicate host characteristics with significant ($P < 0.1$) or highly significant ($P < 0.05$) differences among uropathogen groups. Abx, antibiotic therapy.

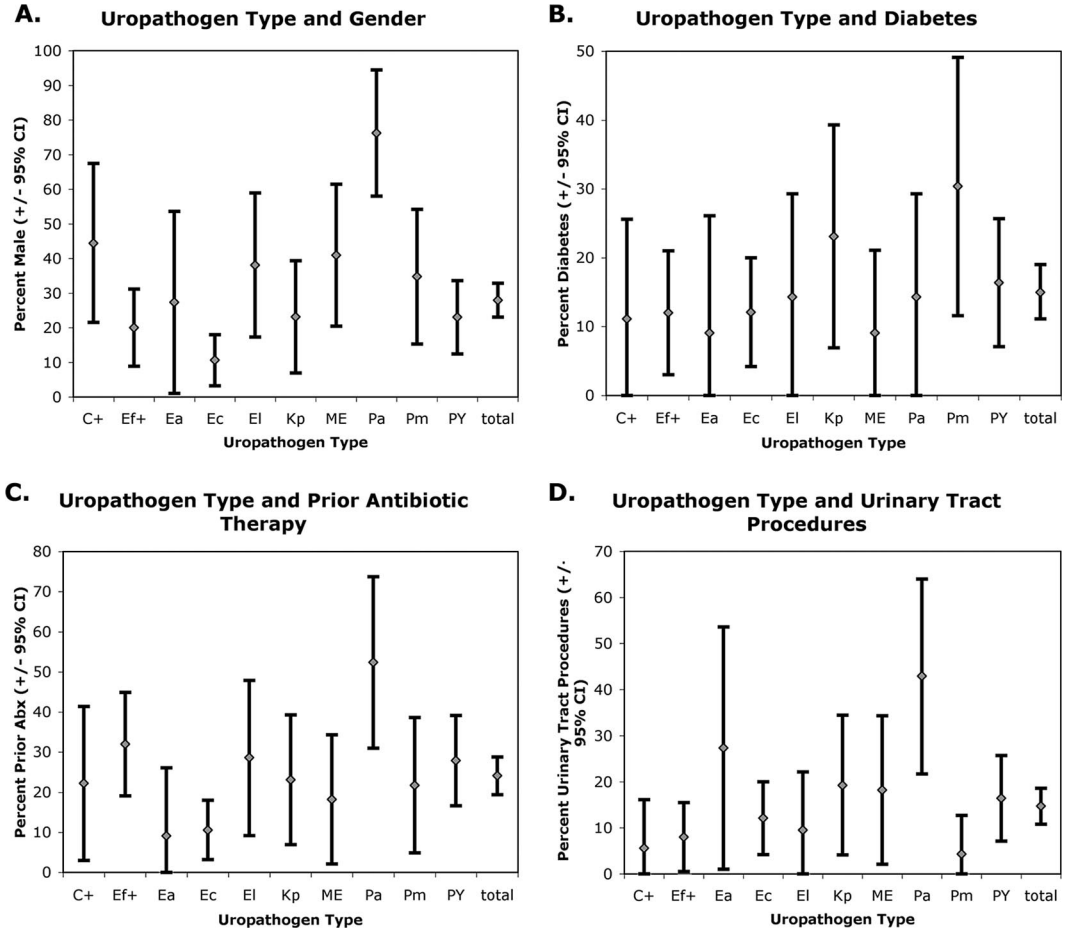

FIG. 2. Host characteristics and uropathogen types. Percentages (±95% confidence intervals) of patients with four host characteristics were compared for patient groups with UTIs due to various uropathogens (C+, *Citrobacter* spp.; Ef+, *Enterococcus* spp., Ea, *Enterobacter aerogenes*; Ec, *Escherichia coli*; El, *Enterobacter cloacae*; Kp, *Klebsiella pneumoniae*; ME, miscellaneous *Enterobacteriaceae* [*Aerococcus urinae*, *Hafnia alvei*, undifferentiated *Klebsiella* spp., *Klebsiella oxytoca*, *Morganella morganii*, *Providencia alcalifaciens*, *Providencia stuartii*, and *Serratia marcescens*]; Pa, *Pseudomonas aeruginosa*; Pm, *Proteus mirabilis*; PY, polymicrobial specimens [a combination of any of the aforementioned 16 isolates as well as any of the following: *Acinetobacter baumanii*, *Alcaligenes xylosoxidans*, *Pseudomonas fluorescens*, *Chryseobacterium indologenes*, viridans streptococci, *Staphylococcus aureus*, or lactose-positive, gram-positive rods]). Associations with *P. aeruginosa* UTI were found for gender (A), prior antibiotic therapy (C), and urinary tract procedures (D). An association was also found between *P. mirabilis* UTI and diabetes (B).

these host characteristics either were not associated with infection or were equally associated with all uropathogen types. In contrast, considerable differences among patients with different types of UTIs were observed for host characteristics such as pregnancy and an upper foreign body. Although these host characteristics did not occur frequently enough for the differences to be statistically significant at a P value of <0.05, it is notable that no *P. aeruginosa* or *P. mirabilis* infections occurred among pregnant women (compared to 5% of total infections), while no *E. coli* or *K. pneumoniae* infections occurred among patients with upper foreign bodies (compared to 3.4% of total infections).

Patients with *P. aeruginosa* infection differed in a number of respects from those with infections due to other types of uropathogens. Of the host characteristics illustrated in Fig. 2, differences in gender were the most striking, where 95% confidence intervals for *P. aeruginosa* infection do not overlap with those of any of the other bacterial groups except *Citrobacter* spp., *E. cloacae*, and the miscellaneous uropathogen group. The percentages of patients with recent antibiotic therapy, prior urinary tract procedures, and a history of neurogenic bladder were numerically higher for patients with *P. aeruginosa* infections than for patients with any other uropathogen species and were significantly greater than those in the total sample (Table 1). In contrast, patients with *P. aeruginosa* infections were similar to the overall patient population in the frequency of diabetes, which occurred more frequently in patients with *P. mirabilis* infection (Fig. 1B).

A multivariate CART analysis was carried out to identify host characteristics simultaneously associated with particular bacterial uropathogen groups. Patients' infections were divided into four simplified categories: UTI due to *E. coli*, *P. aeruginosa*, other gram-negative bacteria, and gram-positive bacteria (excluding polymicrobial specimens). As shown in Fig. 3, gender was found to be the host characteristic most strongly associated with a uropathogen category. Although mean age was not a significant host characteristic in any bacterial group in the bivariate analysis, the CART analysis identified an association between age and uropathogen category. For example, all the

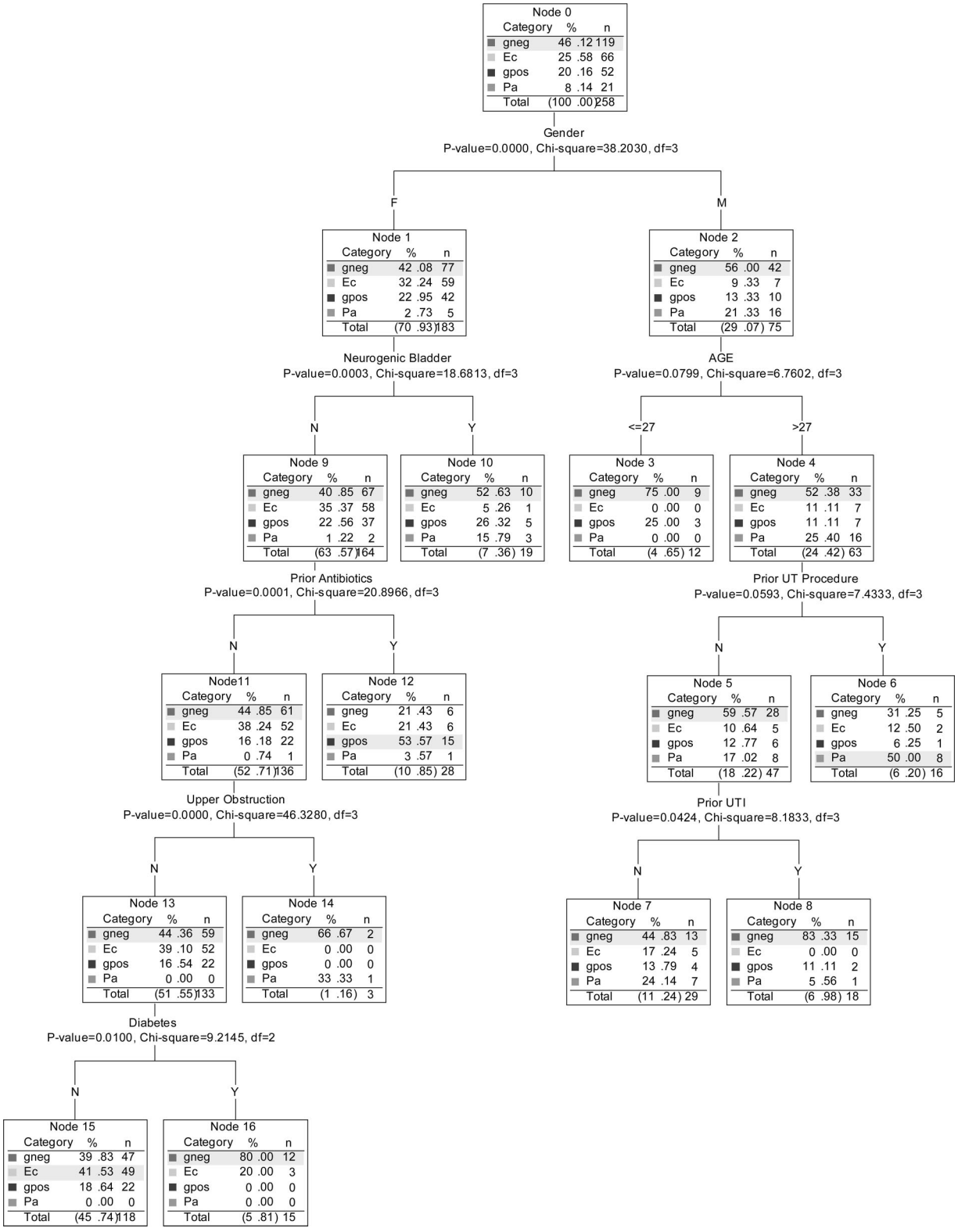

FIG. 3. Classification tree showing host characteristics most strongly associated with categories of uropathogens. A multivariate CART analysis was performed to identify the host characteristics most strongly associated with uropathogen groups. The tree follows an equal-prior-probabilities rule, in that predictions are relative to the proportions in the root node and thus are not biased by initial group sizes. The shaded band in each node indicates the predicted (most likely) bacterial group based on equal prior probabilities. Polybacterial specimens were not included in this analysis. Uropathogen group abbreviations: gneg, gram-negative bacteria; gpos, gram-positive bacteria; Ec, *E. coli*; Pa, *P. aeruginosa*.

male patients with *P. aeruginosa* infections were over 27, and half of them (8/16) had undergone a urinary tract procedure. The shaded band in each node in Fig. 3 indicates the predicted (most likely) bacterial group based on equal prior probabilities. For example, in "node 6," *P. aeruginosa* is the predicted bacterial group, since its prevalence of 8/16 (50.00%) in this node is higher than its overall prevalence of 8.14% (node 0), making *P. aeruginosa* "more likely than average," whereas the prevalences of the other three groups are lower than their overall prevalences (less likely than average). The typical patient with a UTI due to *P. aeruginosa* was a male older than 27 who had undergone a urinary tract procedure. In contrast, the typical patient with a UTI due to *E. coli* was a female without the host characteristics of neurogenic bladder, prior antibiotic therapy, upper urinary tract obstruction, or diabetes. By using all eight variables (tree nodes), the accuracy of patient categorization was 56%. A 1,000-fold resampling cross-validation showed that the same tree nodes are significant except for the upper-obstruction node, which had only three patients. The average accuracy after the 1,000-fold cross-validation was reduced only slightly, from 56% to 53%.

Antibiotic susceptibility results were available for 99% (255/258) of the uropathogens obtained from single-isolate specimens examined in this study (Table 1). We considered the possibility that some of the strength of negative (in the case of *E. coli*) and positive (in the case of *P. aeruginosa*) associations between causes of UTI and host characteristics may be due to antibiotic susceptibility and resistance, respectively. To control for the role of antibiotic resistance in host characteristics, an additional analysis was performed using only infections due to antibiotic-susceptible bacteria. The antibiotics chosen for analysis were those that spanned a broad range of mechanistic groups and had sufficient laboratory information to produce reasonably large sample sizes. Trimethoprim-sulfomethoxazole was not included in this analysis, because *P. aeruginosa* is intrinsically resistant to this antibiotic combination. As shown in Fig. 4, when only organisms susceptible to cefepime, ciprofloxacin, piperacillin-tazobactam, or tobramycin were examined, the associations between *E. coli* and *P. aeruginosa* infections with regard to male gender, prior antibiotic therapy, and urinary tract procedures were largely preserved.

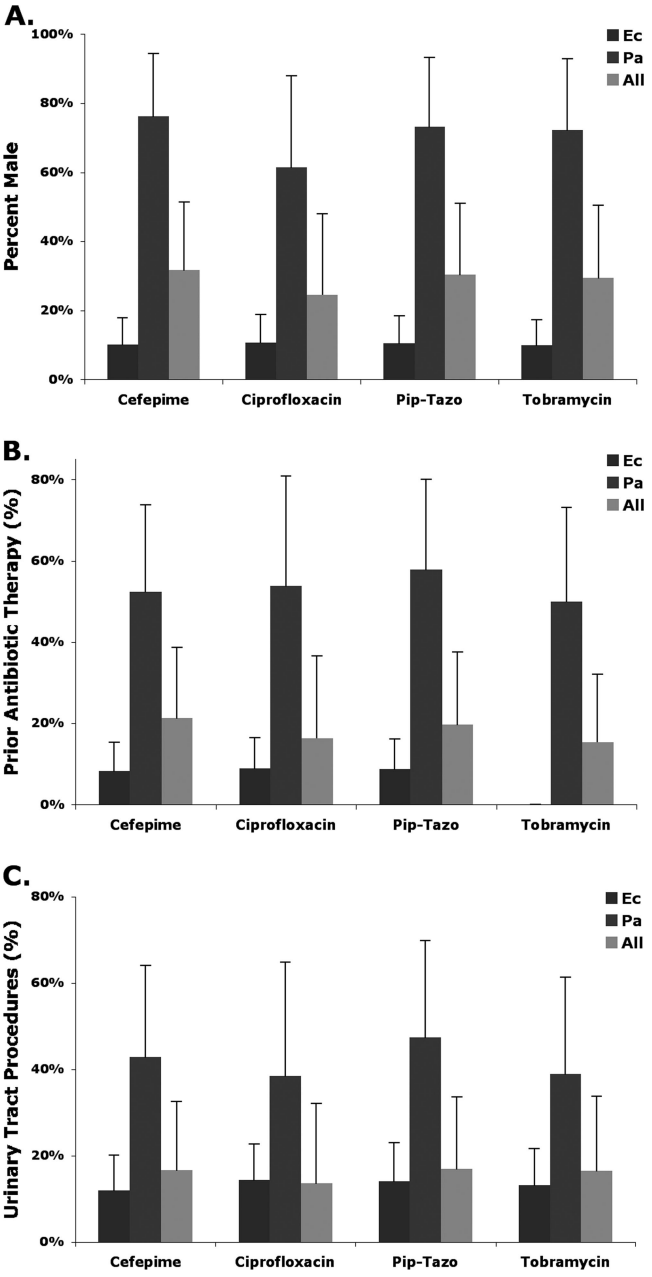

FIG. 4. Associations between antibiotic-susceptible uropathogens and host characteristics. The percentages of samples from patients who were male (A), received antibiotic therapy within the past month (B), or had a history of urinary tract procedures (C) among urine specimens containing antibiotic-susceptible uropathogens (*E. coli*, *P. aeruginosa*, and all bacteria) are shown. Differences between *E. coli* and *P. aeruginosa* were significant ($P < 0.05$) in all cases except for cefepime susceptibility in patients with prior antibiotic therapy (B). The higher percentage of host characteristics in UTIs due to *P. aeruginosa* persisted despite the inclusion of antibiotic-susceptible organisms only in the analysis, indicating that the association with host characteristics is independent of antibiotic susceptibility. Ec, *E. coli*; Pa, *P. aeruginosa*; Pip-Tazo, piperacillin-tazobactam.

DISCUSSION

In this study, we utilized a novel, microbiology-oriented approach to identify host characteristics associated with UTIs due to a variety of uropathogen species. To obtain a data set containing a broad range of uropathogens, we limited the number of specimens containing any one uropathogen species, thereby avoiding dominance of the study by specimens containing common uropathogens such as *E. coli*. Specimens containing various uropathogen species were collected prospectively, followed by data extraction from the medical records of patients from whom the specimens were collected. As expected, specimens containing *E. coli* were typically from patients with uncomplicated UTIs. In contrast, specimens containing organisms other than *E. coli* were more commonly isolated from patients with complicated UTIs. The organism that stood out most strikingly in this regard was *P. aeruginosa*. Patients with *P. aeruoginosa* UTIs were more likely to have undergone urinary tract procedures (43% versus 15% overall), to have a neurogenic bladder (29% versus 12% overall), to have received recent antibiotic therapy (52% versus 24% overall), and to be male (76% versus 28% overall). These results

implicate *P. aeruginosa* as an opportunistic pathogen in patients with susceptibility to UTI.

The association with antibiotic therapy within the past month in patients with *P. aeruginosa* infections might suggest that selection for antibiotic-resistant uropathogens was an important factor in determining why patients at risk for UTI acquire particular uropathogens. Medical records indicated that 24% of patients had received antibiotics within 1 month of specimen collection, and we acknowledge that this may be an underestimate resulting from our method of data collection. One explanation for this association is that *P. aeruginosa* is intrinsically resistant to many of the antibiotics these patients received. However, two lines of evidence suggest that antibiotic resistance is only a partial explanation for our results. First, the associations between *P. aeruginosa* infection and gender, recent antibiotic therapy, and prior urinary tract procedures persisted even after data were analyzed using only antibiotic-susceptible organisms (Fig. 4). Second, CART analysis revealed that the male gender, an age of >27 years, and a prior urinary tract procedure were more strongly associated with *P. aeruginosa* infection than recent antibiotic therapy (Fig. 3). An alternative explanation for the relationship between *P. aeruginosa* UTIs and antibiotic therapy is that the latter leads to an alteration in the resident microflora, facilitating colonization with *P. aeruginosa* prior to UTI.

Some of the UTIs in the study sample were probably related to an indwelling bladder catheter. Thirty percent of patients had a foreign body in the lower urinary tract, the most common being a bladder catheter. Catheters and other foreign bodies in the urinary tract predispose to UTI by violating natural barriers to infection (urethral sphincter) and providing a nidus for infection by serving as a substrate for biofilm formation. Most uropathogens are able to form biofilms, which is reflected in the fact that no single bacterial type was significantly associated with a lower foreign body (Table 1). Comparatively little was known about the prevalence of non-*E. coli* uropathogens in patients with complicated UTIs (1, 6, 8, 13, 14). In a prospective study of bacteriuria in patients with chronic indwelling urethral catheters, the most common isolates were enterococci, *P. aeruginosa*, and coagulase-negative staphylococci (14). In the same study, the organism that caused infections of the longest duration was *Providencia stuartii*. *P. stuartii* was also the most common bacterial species isolated in a prospective study of 47 chronically catheterized women who underwent weekly urine culture (13). In a study of 54 patients with spinal cord injuries who were undergoing intermittent catheterization, a variety of uropathogens were associated with UTIs in males; of these, *E. coli* composed only 18% (1). This contrasts with the UTIs of females, where *E. coli* accounted for 53% of cases, the rest being due to *Klebsiella*, *Enterococcus*, and other species (1). Our study complements and extends previously published studies of the microbiology of complicated UTIs.

This case-case comparison study does not address whether certain host characteristics predispose to infection with particular uropathogens. A population-based study would be required in order to determine which host characteristics are predictive of specific uropathogens. Although the only basis for specimen selection was the uropathogen species in the specimen, different results might be observed in other patient populations. Our study sample was predominantly an older group (mean age, 55), with only 8.2% of patients under the age of 18 years. Furthermore, the UCLA Medical Center is a tertiary referral center, so patients with urological disorders may be overrepresented in this study, as evidenced by the relatively high percentage of patients who had undergone surgery or another procedure (37%).

This is the first study we are aware of to systematically examine the association between uropathogen species and host characteristics. The current study should be considered exploratory in nature but is sufficient to allow hypotheses to be generated regarding the relationship between particular uropathogen species and characteristics of the host that predispose to infection. Additional studies involving larger numbers of patients will be needed to confirm these data, examine the hypotheses, and improve the classification accuracy.

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