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Proteus bacteriuria is associated with significant morbidity in spinal cord injury

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Abstract

Study Design—Retrospective chart review.

Objectives—We investigated the morbidity associated with *Proteus* bacteriuria in a spinal cord injured (SCI) population.

Setting—Michael E DeBakey Veterans Affairs Medical Center in Houston, Texas, USA.

Methods—We reviewed the medical records of all veterans with SCI who received care in our medical center during the past 3 years. *Proteus* bacteriuria was defined as the growth of *Proteus* species in any urine culture during the study period. Urinary stones were defined as either renal or bladder calculi.

Results—During the study period, 71 of the 501 subjects (14%) had *Proteus* and 90 (18%) had urinary stones. Twenty-seven percent of the subjects with *Proteus* had stones, and the association of *Proteus* with stones was significant ($P<0.05$). *Proteus* bacteriuria was likewise associated with complete injury, hospitalization, decubitus ulcers, and history of stones ($P<0.001$). Subjects using indwelling catheters, either transurethral or suprapubic, were significantly more likely to have *Proteus*, whereas subjects practising spontaneous voiding and clean intermittent catheterization were significantly less likely to have *Proteus*. In the 90 patients with stones, *Proteus* was associated with requiring treatment for stones and having multiple stones ($P<0.01$). Twenty-five of the 90 patients with stones (28%) required treatment, most often with lithotripsy, and 6 (7%) developed urosepsis.

Conclusions—In persons with SCI, *Proteus* was found in subjects with a greater degree of impairment who were more likely to be hospitalized, to have decubiti, and to use indwelling catheters. Bacteriuria with *Proteus* predicted urologic complications in persons with SCI.

Statement of Ethics—All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

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Keywords

spinal cord injury; bacteriuria; *Proteus*; urinary stones

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Introduction

Patients with spinal cord injury (SCI) and neurogenic bladders are at high risk for recurrent urinary tract infections. Predisposing factors include impaired bladder emptying, repeated instrumentation, vesicuoureteral reflux, and indwelling urinary catheters.1 Patients with SCI are also prone to the development of bladder and renal stones.2,3 One link between chronic bacteriuria and the formation of stones is infection of the urinary tract with urease-producing organisms.4 Urease splits the urea present in urine to form ammonia and carbon dioxide, thus raising urinary pH and causing normally soluble ions to precipitate and form stones.5 Several bacterial species that commonly infect neurogenic bladders can split urease, including *Klebsiella*, *Providencia*, *Morganella*, *Pseudomonas*, and *Proteus*. As the *Proteus* urease has the fastest rate of urea hydrolysis,4,6 *Proteus* is the organism most commonly implicated in catheter encrustation, catheter blockage, and stone formation in the urinary tracts of individuals with indwelling catheters. Antimicrobial therapy often fails to eradicate *Proteus* and other organisms embedded in the crevices of stones.7

Infectious complications of *Proteus* bacteriuria have been well documented in the general population of persons with indwelling catheters or abnormal urinary tracts.7 However, the outcomes of *Proteus* bacteriuria specifically in persons with SCI have not been described. Accordingly, we sought to define the relationship in the SCI population between *Proteus* bacteriuria and the presence of urinary complications, including stones.

Methods

Study design

A retrospective chart review of the electronic medical record was performed on all veterans with SCI who had received care at the Michael E DeBakey Veterans Affairs Medical Center over the 3 previous years, from 1 January 2003 to 2 January 2006. Patients who had undergone urinary diversion/ileostomy were excluded. Demographic information collected included age, time since injury, ethnicity, level of SCI, complete *versus* incomplete injury, substance abuse (alcohol, illicit drugs, and tobacco), and type of bladder management. In subjects who had more than one type of bladder management during the study period, all methods used were recorded. Thus, each subject could have several types of bladder management. Medical information collected included whether the subject was hospitalized, treated for a decubitus ulcer, treated for diabetes, developed urosepsis, had a prior history of stones, or required treatment for stones during the study period.

Microbiology

All urine cultures collected from subjects during the study period were reviewed. Any organism identified to the genus level was recorded. *Proteus* bacteriuria was defined as the growth of *Proteus* species in any urine culture during the study period. Urinalysis data were collected from all urine specimens corresponding to a documented episode of *Proteus* bacteriuria.

Definitions of stones

Stones were defined as either renal or bladder calculi during the 3-year time frame of the study. Multiple stones was defined as the presence of >1 stone during the time period, regardless of whether the multiple stones were present at the same time or separated in time. Treatments for stones included nephrostomy tube placement, lithotripsy, and surgical removal.

Statistical analysis

Data were compared using SAS (Release 8.2). The Fisher exact test was used for all pairwise comparisons, and logistic regression was used for multivariate analysis.

Results

Demographics

Our medical center currently serves 596 veterans with SCI. We excluded a total of 95 patients for not being seen at our medical center during the study period (71 patients) or for having had urinary diversion (24 patients). Demographic information on the remaining 501 subjects is shown in Table 1. The median age was 57.5 years (interquartile range 50–63 years) and the median time since injury was 15 years (interquartile range 5–26 years). Only 4 subjects had bladder stones, and 1 of these 4 had both bladder and renal stones. The type of bladder management from the most common to the least common was clean intermittent catheterization ($N = 230$), spontaneous voiding ($N = 136$), indwelling Foley catheter ($N = 99$), external condom catheter ($N = 98$), and suprapubic tube ($N = 56$).

Medical conditions

The following conditions were associated with having *Proteus* bacteriuria: complete injury, hospitalization, decubitus ulcer, and a history of stones (Table 2). Veterans with tobacco abuse were less likely to have *Proteus* in the urine. Complete injury, hospitalization, decubitus ulcer, and tobacco abuse remained significant predictors in multivariate analysis ($P<0.02$). Only hospitalization, decubitus ulcer, and a history of stones were associated with having stones (Table 2), and in the multivariate analysis only decubitus ulcer and a history of stones remained significant predictors of stones ($P<0.03$). Not surprisingly, hospitalization was significantly associated with decubitus ulcer ($P<0.0001$). Time since SCI did not prove to be significantly related to *Proteus* bacteriuria, decubitus ulcer, stones, or type of bladder management.

Microbiology

Many of the bacterial species cultured from subjects' urine were strongly associated with having *Proteus* bacteriuria during the study period. These organisms included *Staphylococcus aureus, Enterococcus, Escherichia coli, Pseudomonas, Morganella,* group B *Streptococcus, Providencia,* and *Candida* ($P<0.001$). *Serratia* was also significantly associated with *Proteus* bacteriuria ($P<0.04$). A statistically insignificant trend was noted between *Acinetobacter* and *Proteus* bacteriuria ($P = 0.06$). Organisms not significantly associated with *Proteus* bacteriuria included *Enterobacter, Klebsiella, Citrobacter,* and *Alcaligenes.* Of the 71 subjects diagnosed with *Proteus* in their urine at some point during the study period, 19 (27%) were also diagnosed with stones ($P = 0.045$). Other organisms associated with the presence of stones included *Enterococcus, Klebsiella, Pseudomonas, Morganella,* and *Providencia* ($P<0.05$).

Bladder management

Subjects using indwelling catheters, either transurethral or suprapubic, were significantly more likely to have *Proteus* bacteriuria ($P<0.001$), whereas subjects practising spontaneous voiding and clean intermittent catheterization were significantly less likely to have *Proteus* bacteriuria ($P<0.01$) (Table 3). The association between external catheter use and *Proteus* was not significant in either direction. Of these types of bladder management, only suprapubic catheters were significantly associated with stones ($P = 0.04$). The association of indwelling catheters with stones nearly reached significance ($P = 0.08$), and spontaneous voiding was nearly significantly protective against having stones ($P = 0.07$). Indwelling

Foley catheters, external catheters, and suprapubic catheters were also significantly associated with having decubitus ulcer ($P<0.02$).

Analysis of subjects with stones

During the study period, 90 SCI patients were diagnosed with either bladder or renal stones. In these subjects, having *Proteus* bacteriuria was associated with requiring treatment for stones and having multiple stones ($P<0.01$). Of the 90 patients with stones, 25 (28%) required treatment, most often with lithotripsy (22/25, 88%). Six of the 90 (7%) patients with stones developed urosepsis.

Urinalysis data

When available, urinalysis data were recorded during each episode of *Proteus* bacteriuria. These results appear in Table 4. Means differ considerably from medians owing to the presence of outliers in each category. For example, one urine sample had 15 429 wbc/hpf, whereas another urine sample had 5100 rbc/hpf. Of note, the urinary pH was slightly basic, as expected. Also, 66% of such urines had large leukocyte esterase and 43% had a positive nitrite test.

Conclusions

Our study confirms that bacteriuria with *Proteus* predicts urologic complications in persons with SCI. *Proteus* bacteriuria was more common in persons who had a greater degree of spinal cord impairment, were hospitalized, had decubitus ulcers, and used indwelling catheters. *Proteus* bacteriuria was associated with having stones, and subjects with both *Proteus* and stones were more likely to require treatment for stones or have multiple stones. Thus, the presence of *Proteus* in the bladder is not a benign condition and may be a marker for poor urinary tract health overall.

The association between *Proteus* bacteriuria and other nosocomial urinary pathogens was not surprising. Several of the less common nosocomial pathogens were not significantly associated with *Proteus*, such as Alcaligenes, but the very few infections caused by these organisms during our study were unlikely to achieve statistical significance. The lack of association of *Enterobacter*, *Klebsiella*, and *Citrobacter* with *Proteus* cannot be attributed to low numbers of infections, as these organisms are relatively common. Perhaps these organisms, unlike *Proteus*, have an equal propensity to infect healthy and diseased urinary tracts. Of the organisms found to be associated with stones, one of these, *Enterococcus*, does not make urease. We suspect that the strong association of this nosocomial pathogen with *Proteus* bacteriuria accounts for its association with stones.

Proteus has previously been reported as a common cause of bacteriuria in chronically catheterized residents of long-term care facilities.8 Furthermore, the relationship between *Proteus* bacteriuria and urinary catheter encrustation and blockage is well documented.9,10 *Proteus* bacteriuria has likewise been documented in persons with SCI,1,11,12 but not specifically in association with stones. Two retrospective reports published two decades ago of almost 6000 patients with SCI found that bladder calculi were associated with the complete injuries and with *Klebsiella* bacteriuria.2,3 In these studies, *Proteus* bacteriuria was nearly significantly associated with development of bladder stones within 2 years of hospital discharge for initial injury ($P = 0.06$). Renal stones were likewise associated with neurologically complete lesions, and having an indwelling catheter showed a trend toward an association with stones. Thus, our results confirm and expand upon these earlier studies. Our Veterans Affairs Medical Center serves a large and diverse population of SCI patients, so we suspect that our results would also be applicable to other predominantly male SCI

populations. As only 2% of our SCI subjects were female, we cannot presume that our results can be generalized to women with SCI.

Our study has several limitations. Like all retrospective studies, we relied on data reported in the medical record. We looked at all urine culture results on SCI subjects during the study period, but we do not know the reason why urine was cultured at a given time. The computerized medical record did not adequately capture data about catheter blockage; hence we were unable to study that outcome. Dates at which catheter management strategies changed were likewise not recorded; therefore, we cannot report a temporal relationship between bladder management strategies and *Proteus* bacteriuria or stones. We also suspect that the data on substance abuse were unreliable, both because physicians may not always record this information and because patients may not disclose the extent of their substance use. The apparent protective effect of tobacco use on *Proteus* bladder infection could be attributed to the fact that subjects with lesser degrees of neurological impairment, and thus less likely to have *Proteus* bacteriuria, had greater opportunities to acquire and smoke cigarettes. As with all observational studies, we can demonstrate associations of various outcomes with *Proteus* bacteriuria, but we cannot prove causality.

Proteus is extremely diKcult to eradicate from the catheterized urinary tract. In a study that investigated the molecular epidemiology of catheter-associated bladder infections with *Proteus*, the same strain of *Proteus* persisted in one patient over 121 days despite eight catheter changes, a 20-day period without catheterization, and an 8-day course of antibiotics.9 In our own study of bladder colonization with benign E. coli in patients with SCI and indwelling urinary catheters, we were unable to eradicate *Proteus* bacteriuria in four of four subjects despite a week of targeted antibiotics accompanied by catheter change during the course of antibiotics.13 Two of these subjects developed catheter encrustation and blockage within <3 weeks. As we have confirmed that the same SCI patients who are infected with *Proteus* are likely to experience complications such as stones and catheter encrustation, a more effective approach to clearing this organism from the urinary tract is needed. Urinary catheters inflated with triclosan prevented catheter colonization and biofilm formation by *Proteus in vitro*.14 Microbicins, or natural antibiotics produced by bacteria, may offer another defensive strategy against *Proteus*, but as yet we have only used microbicins against *E. coli in vitro*.15 The data that we have collected on the conditions associated with *Proteus* bacteriuria in SCI patients indicate that bladder colonization with *Proteus* is harmful, and we anticipate using this information to design future clinical studies targeting this pathogen.

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Table 1

Demographic information

	Frequency (*N* = 501)	%
Gender		
Male	491	98
Female	10	2
Ethnicity[a]		
African-American	172	35
Latino	22	4.5
Caucasian	297	60
Other	3	0.6
Hospitalized	279	56
Diabetes mellitus	109	22
Decubitus ulcer	209	42
Drug abuse	61	12
Alcohol abuse	85	17
Tobacco abuse	184	37
History of stones	91	18
Stones during study	90	18
Proteus bacteriuria	71	14

[a] *N* = 494 as no racial information was noted in 7 patients

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Table 2

Association of medical conditions with *Proteus* bacteriuria or stones

Condition	N	*Proteus* N (%)	P *for Proteus comparison*[a]	*Stones* N (%)	P *for stone comparison*[a]
Completeness of injury					
Complete	181	41 (22.7)		38 (21)	
Incomplete	320	30 (9.4)	<0.0001	52 (16.3)	0.19
Level of injury					
Paraplegia	256	32 (12.5)		46 (18)	
Quadriplegia	244	38 (15.6)	0.37	43 (17.6)	1.0
Hospitalization					
Yes	279	58 (21)		59 (21.2)	
No	222	13 (5.9)	<0.0001	31 (14)	0.046
Diabetes mellitus					
Yes	109	21 (19.2)		24 (22)	
No	392	50 (12.8)	0.09	66 (16.8)	0.21
Decubitus ulcer					
Yes	209	54 (25.8)		47 (22.5)	
No	292	17 (5.8)	<0.0001	43 (14.7)	0.03
History of stones					
Yes	91	19 (20.9)		39 (42.9)	
No	410	52 (12.7)	0.047	51 (12.4)	<0.0001
Drug abuse					
Yes	61	12 (19.7)		6 (9.8)	
No	440	59 (13.4)	0.24	84 (19.1)	0.11
Alcohol abuse					
Yes	85	12 (14.1)		16 (18.8)	
No	416	59 (14.2)	1.00	74 (17.8)	0.88
Tobacco abuse					
Yes	184	16 (8.7)		35 (19)	
No	317	55 (17.4)	0.008	55 (17.4)	0.63

[a]All comparisons were carried out using the Fisher exact test

Table 3

Association of bladder management strategy with *Proteus* or stones

Bladder management	**N**	***Proteus* N (%)**	**P *for Proteus comparison*[a]**	***Stones* N (%)**	**P *for stone comparison*[a]**
Spontaneous voiding					
Yes	136	5 (3.7)		17 (12.5)	
No	365	66 (18.1)	<0.0001	73 (20)	0.07
Suprapubic catheter					
Yes	56	18 (32.1)		16 (28.6)	
No	445	53 (11.9)	0.0003	74 (16.6)	0.04
Indwelling foley					
Yes	99	26 (26.3)		24 (24.2)	
No	402	45 (11.2)	0.0003	66 (16.4)	0.08
External catheter					
Yes	98	17 (17.4)		15 (15.3)	
No	403	54 (13.4)	0.33	75 (18.6)	0.56
Clean intermittent catheterization					
Yes	230	22 (9.6)		43 (18.7)	
No	271	49 (18.1)	0.007	47 (17.3)	0.73

[a]All comparisons were carried out using the Fisher exact test

Table 4

Urinalysis data during episodes of *Proteus* bacteriuria

Urinary findings	Median	IQR[a]	Mean
White blood cells/hpf	34	11–112	351
Red blood cells/hpf	6	1–35	102
pH	7.5	6.5–8.0	7.35

[a] Interquartile range