MAJOR ARTICLE

Isolation of *Staphylococcus aureus* from the Urinary Tract: Association of Isolation with Symptomatic Urinary Tract Infection and Subsequent Staphylococcal Bacteremia

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Background. *Staphylococcus aureus* is frequently isolated from urine samples obtained from long-term care patients. The significance of staphylococcal bacteriuria is uncertain. We hypothesized that *S. aureus* is a urinary pathogen and that colonized urine could be a source of future staphylococcal infection.

Methods. We performed a cohort study of 102 patients at a long-term care Veterans Affairs facility for whom *S. aureus* had been isolated from clinical urine culture. Patients were observed via urine and nasal cultures that were performed every 2 months. We determined the occurrence of (1) symptomatic urinary tract infection concurrent with isolation of *S. aureus* (by predetermined criteria), (2) staphylococcal bacteremia concomitant with isolation of *S. aureus* from urine, and (3) subsequent episodes of staphylococcal infection.

Results. Of 102 patients, 82% had undergone recent urinary catheterization. Thirty-three percent of patients had symptomatic urinary tract infection at the time of initial isolation of *S. aureus,* and 13% were bacteremic. Eight-six percent of the initial urine isolates were methicillin-resistant *S. aureus.* Seventy-one patients had follow-up culture data; 58% of cultures were positive for *S. aureus* at ⩾2 months (median duration of staphylococcal bacteriuria, 4.3 months). Sixteen patients had subsequent staphylococcal infections, occurring up to 12 months after initial isolation of *S. aureus;* 8 late-onset infections were bacteremic. In 5 of 8 patients, the late blood isolate was found to have matched the initial urine isolate by pulsed-field gel electrophoresis typing.

Conclusions. *S. aureus* is a cause of urinary tract infection among patients with urinary tract catheterization. The majority of isolates are methicillin-resistant *S. aureus. S. aureus* bacteriuria can lead to subsequent invasive infection. The efficacy of antistaphylococcal therapy in preventing late-onset staphylococcal infection in patients with persistent staphylococcal bacteriuria should be tested in controlled trials.

Staphylococcus aureus is a relatively uncommon cause of urinary tract infection in the general population [1, 2]. Although isolation of *S. aureus* from urine samples is often secondary to staphylococcal bacteremia arising elsewhere (e.g., in cases of endocarditis) [3], in certain patients, *S. aureus* causes ascending urinary tract colonization and infection. Urinary tract instrumentation and the presence of an indwelling catheter increase the risk of *S. aureus* carriage in the urinary tract [1, 4]. The majority of cases of *S. aureus* bacteriuria are not associated with symptoms of urinary tract infection [1]. Because bacteriuria nearly universally occurs concomitantly with long-term urinary catheterization [5, 6], the clinical significance of isolation of *S. aureus* from the urine is undefined in such patients. Clear differentiation between asymptomatic bacteriuria and clinical urinary tract infection is difficult in the elderly population [7–9]. Although urinary *S. aureus* may be the source of staphylococcal bacteremia [10–12], the proportion of patients with chronic *S. aureus* bacteriuria who subsequently become bacteremic is unknown.

After identifying 2 patients who developed *S. aureus* bacteremia subsequent to staphylococcal colonization of the urinary tract, we undertook a longitudinal study

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of patients identified as having *S. aureus* bacteriuria during the course of routine infection-control surveillance to determine the clinical significance of *S. aureus* bacteriuria, the association between bacteriuria and bacteremia, and the long-term outcome of staphylococcal urinary colonization. We postulated that (1) *S. aureus* urinary tract infection was a true clinical entity, and (2) staphylococcal bacteremia could result from urinary tract colonization with *S. aureus.*

MATERIALS AND METHODS

Patients were identified from microbiology laboratory reports by infection-control practitioners during routine surveillance activities. All patients for whom *S. aureus* was isolated from urine cultures ordered by the patients' physicians for clinical indications were entered into a prospective, observational study. Nares cultures were obtained at entry. Clinical isolates of *S. aureus* were identified by the Vitek system (bioMérieux) using standard criteria. Methicillin resistance was confirmed by plating on Mueller-Hinton agar supplemented with 4% NaCl and oxacillin, 6 μg/mL, followed by incubation at 35°C for 24 h [13]. Nares swab specimens were plated on mannitol salt agar; the methicillin resistance of *S. aureus* isolated in this manner was confirmed as previously described [13]. Clinical data collected included demographic characteristics of the patients, initial location (i.e., long-term care facility, acute care facility, or home), underlying illness(es), and urinary tract catheterization status. Primary site of infection was classified on the basis of Centers for Disease Control and Prevention (CDC) definitions of nosocomial infection [14]. A diagnosis of symptomatic urinary tract infection for the purposes of this study, however, required recovery of 10^5 bacteria/mL from a voided specimen or 10^4 bacteria/mL from a catheter specimen, no clinical evidence of a non–urinary tract site of infection, and at least 2 of the following symptoms: temperature of >38.5°C, change in mental status, gross hematuria, suprapubic discomfort, dysuria, or flank pain. We intentionally chose a strict definition requiring at least 2 symptoms, because fever alone has a low predictive value in localizing infection to the urinary tract in elderly patients with bacteriuria [8].

Nares and urine cultures were repeated every 2 months until culture results were negative for *S. aureus* for 2 consecutive samples or until the patient was lost to follow-up. Other samples were obtained for culture at the discretion of the patients' primary care physicians. Patients were observed for the development of invasive staphylococcal infection for the duration of the follow-up period. Late-onset staphylococcal infection was defined as that which occurred ⩾7 days after the initial positive urine culture result. Antistaphylococcal therapy was defined as vancomycin administered to a patient with methicillin-resistant *S. aureus* (MRSA) bacteriuria and as either vancomycin or a β-lactam antibiotic administered to a patient with methicillin-susceptible staphylococcal bacteriuria.

Isolates of *S. aureus* were characterized by macrorestriction analysis of *Sma*I-digested genomic DNA by PFGE. Agarose plugs of bacterial DNA were digested overnight with 20 U of *Sma*I (New England Biolabs). PFGE was performed using the CHEF-DR-II System (Bio-Rad). The DNA was electrophoresed for 23 h at 14°C in a 1% agarose gel at 6 V/cm with a switch time of 5–40 s. Gels were stained with ethidium bromide and photographed under UV illumination [15]. Strains were classified [15] as identical (0 different bands), closely related (⩽3 different bands), possibly related (4–6 different bands), or unrelated (⩾7 different bands).

Patient data were stripped of identifiers and entered into a computer database. Contingency tables were analyzed using the 2-tailed χ^2 test or Fisher's exact test. The study was deemed to be exempt from review by the local institutional review board.

RESULTS

We identified and entered into the study 102 consecutive patients for whom at least 1 urine culture was positive for *S. aureus;* table 1 presents the patients' characteristics. Eighty-six percent of initial staphylococcal isolates were MRSA. All patients were male, reflecting the Veterans Affairs patient population, with a mean age of 72.8 years. Seventy percent were residents of a long-term care facility, 82% had a urinary catheter of some type in place, and 7% had a recent history of an invasive urinary tract procedure. Only 11% were continent of urine and free of a urinary device. Table 2 shows the clinical findings at the time of the initial positive urine culture result. Thirty-three percent of patients had a symptomatic urinary tract infection, as determined on the basis of study criteria at the time of initial isolation of *S. aureus* from the urine. Forty-eight percent of patients had a diagnosis of urinary tract infection made by a physician. Table 3 shows the frequency of symptoms among those patients with a diagnosis of urinary tract infection based on study criteria. Sixteen (48%) of 33 patients had at least 1 new symptom (hematuria, dysuria, suprapubic pain, or flank pain) specific to the urinary tract; 26 (79%) of 33 had pyuria.

Thirteen patients had *S. aureus* bacteremia identified in association with the first positive urine culture result. Three patients had positive blood culture results before (1–2 days before) urine samples were obtained for culture, 6 had positive blood culture and urine culture results on the same day, and 4 had positive blood culture results subsequent to (1–4 days following) the positive urine culture result. Only 2 patients had received antimicrobial agents ⩽14 days after onset of bacteremia. Table 2 presents the characteristics of patients with and patients without bacteremia. Ten (77%) of 13 patients had a bladder catheter present at the onset of bacteremia. Bacteremic patients

Table 1. Characteristics of 102 patients at the time of their first urine culture positive for *Staphylococcus aureus*.

Characteristic	Value
Age	
Mean years	72.8
Median years	75
Prior residence	
Long-term care facility	71 (70)
Home	28 (27)
Other/unknown	3 (3)
Underlying condition	
Diabetes	43 (42)
Malignancy	29 (28)
Stroke	28 (27)
Other neurologic disease	55 (54)
Peripheral vascular disease	20 (20)
Chronic pulmonary disease	36 (35)
Urinary status	
Bladder catheter	65 (64)
External catheter	15 (15)
Ileostomy/nephrostomy	4 (4)
Continent	11 (11)
Invasive urinary tract procedure	7 (7)
Symptom	
Fever[a]	34 (33)
Change in mental status	22 (22)
Gross hematuria	12 (12)
Suprapubic discomfort	4 (4)
Dysuria	4 (4)
Flank pain	1 (1)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Temperature, >38.5°C.

were significantly more likely to have hematuria, but this occurred in only one-third of bacteremic patients. Patients with MRSA bacteriuria were not significantly more likely to be bacteremic than were those infected with methicillin-susceptible isolates. Initial nares cultures were performed for 76 patients, 57 (75%) of whom had nasal staphylococcal colonization.

Sixteen patients had late-onset staphylococcal infections—that is, infections that occurred after the initial positive urine culture result (range, 7 days to 12 months). Eight patients presented with late-onset *S. aureus* bacteremia that occurred 1–12 months after the initial urine culture. The primary foci of bacteremic infection were the urinary tract in 5 patients; blood and urine samples were obtained for culture on the same day for all 5. Patients with nonbacteremic infections included 5 patients with urinary tract infection. Of the 10 patients with urinary tract infection (including the 5 with bacteremia), 7 had pyuria, and 4 had at least 1 new symptom specific to the urinary tract. All 5 patients with bacteremia had urine and blood samples obtained for culture on the same day.

Thirteen patients died within 30 days after the initial urine culture. Of the survivors, 52% had ⩾2 additional cultures performed, 26% had a single additional culture performed, and 19% were discharged or otherwise lost to follow-up and had no additional cultures performed. Of the 71 patients with at least 1 additional urine culture, 41 (58%) had at least 1 culture positive for *S. aureus*. The mean duration of colonization with *S. aureus* was 4.3 months. Patients with persistent urinary *S. aureus* colonization were more likely to have subsequent infection than those whose urine was free from *S. aureus* (34.6% vs. 10.5%; $P = .086$). Twenty-seven patients had at least 1 follow-up urine culture performed after they received antistaphylococcal antibiotic therapy. Of these, 20 (84%) had cultures that were negative for *S. aureus*.

PFGE typing was performed for the initial urine isolates, as well as for the subsequent blood isolates, from 7 of the 8 patients with late-onset bacteremia. Of these, 5 blood isolates matched the urine isolate, with 3 blood/urine isolate pairs being identical and 2 differing by only 1 band. Three blood isolates were different from the initial urine isolate.

DISCUSSION

S. aureus is a relatively infrequent urinary tract isolate in the general population. In a multicenter, community-based study conducted in Great Britain, *S. aureus* accounted for only 0.5% of isolates [2]. A similar laboratory-based study conducted in France found that *S. aureus* accounted for only 1.3% of isolates from urine specimens submitted from the community [16]. Prior studies suggest that isolation of *S. aureus* from the urine is often secondary to staphylococcal bacteremia originating at another site (e.g., in cases of endocarditis) [17]. Isolation of *S. aureus* from urine samples in the absence of bacteremia is therefore often considered to represent colonization.

In specific patient populations, however, *S. aureus* can be an important primary urinary pathogen. For example, MRSA urinary tract infection occurs in both an endemic and epidemic

Table 2. Symptoms at presentation among 33 patients with urinary tract infection, according to the study definition.

Symptom	No. (%) of patients
Fever[a]	24 (73)
Change in mental status	7 (21)
Hematuria	11 (33)
Dysuria	4 (12)
Suprapubic pain	4 (12)
Flank pain	1 (3)

[a] Temperature, >38.5°C.

Table 3. Risk factors for bacteremia at time of the initial urine culture positive for *Staphylococcus aureus*.

Factor	Blood culture result, no. of patients		*P*
	Positive	Negative	
S. aureus susceptibility			
MRSA	10	78	>.2
MSSA	3	11	
Diabetes			
Present	7	36	>.2
Not present	6	53	
Bladder catheter			
Present	10	44	.064
Not present	3	45	
Gross hematuria			
Present	4	8	.045
Not present	9	81	
Physician diagnosis of UTI			
Present	9	39	.086
Not present	4	50	
Criteria-based diagnosis of UTI			
Present	7	26	.11
Not present	6	63	

NOTE. MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-susceptible *S. aureus;* UTI, urinary tract infection.

fashion among patients undergoing urologic surgical procedures [18–20]. MRSA bacteriuria occurs among long-term care patients as well, and it is significantly associated with urinary catheterization and antibiotic use [4]. It is problematic to define the exact role of *S. aureus* as a cause of symptomatic urinary tract infection, as opposed to colonization, in this population. Long-term care patients have a high frequency of asymptomatic bacteriuria [5, 6]. There is evidence to suggest that the majority of febrile episodes in long-term care patients with bacteriuria are not, in fact, due to urinary tract infection [7, 8]. Furthermore, long-term care patients may have atypical symptoms in response to true infection [19]. Thus, a significant problem with interpreting prior studies lies in the inherent difficulty in making a definitive diagnosis of urinary tract infection in the long-term care population.

For example, Capitano et al. [21] identified 90 *S. aureus* infections during a retrospective cohort study in a single nursing home. Of these, 48% were classified as urinary tract infection using a definition of fever (temperature, >37.5°C) in association with staphylococcal bacteriuria. As noted above, this definition of urinary tract infection has poor specificity in the long-term care population. In an observational cohort study, Pacio et al. [22] reported that 13% of long-term care patients colonized with MRSA at any site developed symptomatic urinary tract infection. No definition of urinary tract infection was given, and molecular typing to confirm identity of the initial colonizing and subsequent infecting strains was not performed.

There is evidence that *S. aureus* is a primary urinary tract pathogen in this population. Using the CDC criteria for nosocomial infection to define urinary tract infection, we found that 4% of cases of bacteremia of urinary tract origin among long-term care patients were due to *S. aureus* [10]. In a subsequent study of hospitalized nursing home patients, Mylotte et al. [12] reported that 11% of bacteremic episodes with urinary tract infection as the putative source were cause by MRSA, as determined on the basis of symptoms and concomitant isolation of MRSA from urine samples. The specific urinary tract symptoms supporting a diagnosis of urinary tract infection were not given.

In our prospective study of 102 patients with *S. aureus* bacteriuria, we used an a priori definition of urinary tract infection that required the presence of at least 2 clinical indicators of infection. We intentionally used a more restrictive definition of infection than that used in reporting nosocomial infection because of the difficulty in differentiating asymptomatic bacteriuria from urinary tract infection in elderly persons and in persons with indwelling catheters in place. Even with a highly restrictive definition, we found that one-third of patients (33 of 102) with *S. aureus* bacteriuria had evidence of primary urinary tract infection, and one-third (13 of 33) of these patients were bacteremic at presentation. Furthermore, we found that, of the patients who had persistent staphylococcal bacteriuria, 14 (34%) of 41 had subsequent staphylococcal infection. Of these, 12 had cases that were classified as urinary tract infection on the basis of our a priori definition. Six late-onset infections (43%) in these patients were associated with bacteremia. PFGE typing of the initial isolates and subsequent isolates associated with infection showed that the initial and subsequent isolates were identical or closely related in 5 of 7 patients whose isolates were typed. Thus, we document that, in the long-term care population, a urinary tract that is persistently colonized with *S. aureus* can be an important focus for the subsequent occurrence of staphylococcal infection. This risk appears to be greater than the risk associated with nares colonization alone. In a previous study from the same health care center, we noted that the incidence of infection associated with persistent MRSA nares colonization was 25% [23].

These findings have important implications for patient care. Because urinary catheterization is a major risk factor for *S. aureus* bacteriuria, reducing the prevalence of catheterization should be beneficial. Efforts to limit the acquisition of MRSA by catheterized patients through appropriate infection-control measures and limitation of unnecessary antibiotic administration are warranted in long-term care facilities.

Given the high risk of subsequent infection in patients whose urine is persistently colonized with *S. aureus,* it is appropriate to

question whether elimination of MRSA colonization in these patients may be beneficial. In a general population of long-term care patients with MRSA colonization of the nares, application of mupirocin to the nares has not been shown to significantly reduce the risk of MRSA infection [24]. It is unlikely that intranasal mupirocin would have any effect on urinary colonization in any event. Systemic therapy with antimicrobial agents that are excreted in the urine is a possible approach, but the results of the limited clinical trials involving this patient population have been disappointing. For example, the combination of rifampin and minocycline had a high failure rate with regard to eradicating MRSA in long-term care patients; resistance to both rifampin and minocycline occurred [25].

Our study has some potential limitations. The first is that the initial identification of staphylococcal bacteriuria required that a urine sample be obtained by a clinician's order. Thus, the patient population identified may have differed from that identified by systematic surveillance of all patients for *S. aureus* in the urine. The second is that concomitant blood cultures were not performed for all patients with staphylococcal bacteriuria; some cases of bacteremia may have been missed. We note that this would cause underestimation of the importance of the urinary tract as the source for *S. aureus* bacteremia.

In summary, our study demonstrates that *S. aureus*—and MRSA in particular—is a primary urinary pathogen among long-term care patients. One-third of patients with MRSA bacteriuria have symptomatic urinary tract infection at presentation, and one-third of these patients have concomitant bacteremia. Persistent urinary colonization carries with it a high risk of subsequent infection and bacteremia. In patients who present with fever or sepsis, previous identification of *S. aureus* colonization of the urinary tract may be useful in selecting empirical antimicrobial therapy. This study demonstrates that focusing on the urine as a potential reservoir for infection may be an effective strategy for prevention.

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