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Body Site *Staphylococcus aureus* Colonization among Maintenance Hemodialysis Patients

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Key Words
Staphylococcus aureus · Colonization · Maintenance hemodialysis

Abstract
Background: Patients on maintenance hemodialysis therapy are at high risk for health care-associated infections. *Staphylococcus aureus* is a common cause of health care-associated infections among maintenance hemodialysis patients. It is established that *S. aureus* colonization is associated with an increased risk for subsequent infection in this population. There is an increasing number of reports that extranasal *S. aureus* colonization is more common than previously believed and in certain body sites even more common than nasal colonization. There are few data describing extranasal colonization among maintenance hemodialysis patients. ***Methods:*** We surveyed 100 patients at 3 body sites (anterior nares, oropharynx, and inguinal region) for *S. aureus* colonization. Participants were also administered a standardized survey to assess risk factors for *S. aureus* colonization. ***Results:*** We found that 42% (95% CI 32–52) of patients were *S. aureus* colonized in >1 body site. Extranasal colonization was found among 32% (95% CI 23–41). There were trends suggestive of an association between *S. aureus* colonization and younger age (OR 0.97, 95% CI 0.94–1.001, p = 0.06) and not having been hospitalized in the previous 12 months (OR 0.44, 95% CI 0.19–1.06, p = 0.14). ***Conclusion:*** Extranasal *S. aureus* colonization is common among maintenance hemodialysis patients with a prevalence of approximately one third. Future *S. aureus* decolonization efforts may need to consider not just nasal decolonization but also decolonization of the skin and oropharynx.

Background

Patients on maintenance hemodialysis are at high risk of health care-associated infections, especially those caused by *Staphylococcus aureus*. *S. aureus*, including methicillin-resistant *S. aureus* (MRSA), causes a wide range of community- and health care-associated diseases, ranging from skin and soft-tissue infections to severe sepsis [1]. *S. aureus* is one of the most common pathogens identified in bloodstream infections among hemodialysis patients [2]. Persons receiving maintenance hemodialysis are at very high risk for infection with invasive disease from *S. aureus*

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and MRSA infection compared to the general population. While annual invasive MRSA rates in the general population are 0.2–0.4 infections per 1,000 persons [3], rates among patients on maintenance hemodialysis have been estimated at 37 cases per 1,000 persons [4], a roughly 100-fold higher risk. Of critical concern is that invasive MRSA infection among patients on maintenance hemodialysis is associated with a 17% mortality rate [4].

Asymptomatic *S. aureus* carriage has been an area of great interest due to the risk of subsequent *S. aureus* infection in the colonized individual [5–7]. The ecologic niche for *S. aureus* has traditionally been thought to be the anterior nares [8, 9]. Population-based surveys found that 27–30% of the US population is nasally colonized with *S. aureus* and 1.2–1.8% is nasally colonized with MRSA [10]. The prevalence of nasal *S. aureus* colonization is 30–57% among patients on maintenance hemodialysis [11–13]. MRSA nasal colonization ranges from 5.6 to 12% among maintenance hemodialysis patients [13, 14].

Nasal carriage of *S. aureus* is known to play an important role as an endogenous source for *S. aureus* and MRSA infections that contribute significantly to morbidity, mortality, and cost of end-stage renal disease management [2]. However, recent data suggest that extranasal colonization is more common than previously recognized. Among inpatients with an *S. aureus* infection, MRSA colonization in the nares, axilla, inguinal area, and rectum was 25, 6, 11, and 13%, respectively, and 37% overall were MRSA colonized [15]. A study of households with a history of a recent *S. aureus* skin infection found that up to 50% of household members were *S. aureus* colonized and that a nares-only survey would miss 48% of *S. aureus* colonization and 51% of MRSA colonization [16]. The magnitude of pharyngeal and inguinal colonization has led to a paradigm shift in the understanding of body colonization with *S. aureus* [17]. Older investigations conducted prior to recent increases in MRSA prevalence in patients on maintenance hemodialysis found that 10% of patients (6/59 patients) had *S. aureus* umbilical colonization [18], 8% (3/37 patients) had inguinal *S. aureus* [19], and 7% (2/28 patients) had oropharyngeal *S. aureus* colonization [12]. Because body colonization, especially of extranasal sites, is more widespread than initially believed, interventions to prevent *S. aureus* and MRSA infection may need to consider extranasal decolonization as well as traditional nasal decolonization with agents such as mupirocin [20]. The objective of the present investigation is to identify the frequency and factors associated with extranasal *S. aureus* colonization among maintenance hemodialysis patients.

Methods

This cross-sectional investigation took place at Harbor-UCLA Medical Center-associated outpatient dialysis centers in Torrance, Long Beach, and Hawthorne, Calif., USA, from July 2010 through November 2010. Potential subjects were identified via daily screening of the dialysis centers. All adults receiving dialysis at participating centers were eligible for participation. Interested patients underwent the informed consent process and signed consent forms prior to any research-related samples or surveys being collected. This investigation and the associated consent form were approved by the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center Institutional Review Board.

A standardized survey instrument from a published investigation on risk factors for skin infections was modified and used to assess risk factors for *S. aureus* colonization in this investigation [21]. Subjects were surveyed about past medical history and behavioral risk factors for *S. aureus* colonization. Based on data suggesting that nasal colonization surveillance alone is insensitive for detecting *S. aureus* body colonization [15], we collected nasal, oropharyngeal, and inguinal culture swabs to test for the presence of *S. aureus*.

Culture swabs were transported immediately to the microbiology laboratory and were enriched in trypticase soy broth with 7% sodium chloride overnight at 35°C. The broth was subcultured to BBL CHROMagar *S. aureus* and MRSA plates (BD, Franklin Lakes, N.J., USA) and incubated aerobically for 24 h at 35°C. Isolates were confirmed as *S. aureus* by the catalase test and StaphAureux tests (Remel, Lenexa, Kans., USA). MRSA isolates, confirmed using CHROMagar MRSA plates, were subcultured twice for purity. DNA was extracted, digested with *Sma*I, and subjected to pulsed-field gel electrophoresis (PFGE) as previously described [22]. DNA profiles were analyzed using GelCompar software (Applied Maths, Austin, Tex., USA), and a reference database from the Centers for Disease Control and Prevention (CDC) containing the MRSA USA types strain patterns was used to assign the pulsed-field type (PFT) and determine strain relatedness.

Bivariate analysis was used to compare variables from the risk factor survey hypothesized to be associated with extranasal *S. aureus* colonization. Secondary post hoc bivariate analyses were conducted using different outcomes of (1) any *S. aureus* colonization and (2) extranasal *S. aureus* colonization only. Bivariate analyses were assessed using odds ratios (OR) adjusted for 95% confidence intervals (CI) and the associated p values. All variables were considered significant at the $\alpha = 0.05$ level. Data analyses were performed using SAS (version 9.3; SAS Institute, Cary, N.C., USA).

Results

Among the 100 patients enrolled, the mean age of subjects was 51 years (median 42, range 20–88), 68% were male, 55% were Hispanic, 14% of cases were African-American, 7% were Caucasian, and 24% were of mixed or other race/ethnicity. The mean duration of maintenance hemodialysis was 5 years (median 3.5). Fifty-one percent had been hospitalized in the previous 12 months and 18 had a history of ever having a skin or soft-tissue infection.

Table 1. Baseline characteristics associated with extranasal *S. aureus* colonization among maintenance hemodialysis patients

	All patients (n = 100)	Extranasal colonization (n = 32)	No extranasal colonization (n = 68)	OR	95% CI	p value
Age, years						
Mean ± SD	51±15	47±15	53±15	0.97	0.94, 1.001	0.06
Median (range)	52 (20–88)	46 (23–84)	54 (20–88)			
Male gender	66 (68)	25 (78)	41 (63)	2.09	0.79, 5.56	0.14
Ethnicity						
African-American	14 (14)	5 (16)	9 (13)	0.72	0.10, 5.17	0.74
Hispanic	55 (55)	15 (47)	40 (59)	ref.		
Caucasian	7 (7)	2 (6)	5 (7)	0.68	0.20, 2.34	0.54
Other/unknown	24 (24)	10 (31)	14 (21)	1.29	0.33, 5.02	0.72
History of an *S. aureus* infection	3 (3)	0 (0)	3 (5)	–	–	0.24
History of a skin or soft-tissue infection	18 (19)	7 (23)	11 (16)	1.54	0.53, 4.49	0.42
Close contact with someone who had an *S. aureus* infection in the previous 12 months	2 (2)	0 (0)	2 (3)	–	–	0.47
Method of receipt of dialysis						
Venous catheter	9 (9)	1 (3)	8 (12)	ref.		
Arteriovenous graft or fistula	90 (91)	31 (97)	59 (88)	4.20	0.50, 35.2	0.26
Hospitalization in the previous 12 months	51 (51)	12 (38)	39 (57)	0.44	0.19, 1.06	0.06
Admitted to a long-term care facility in the previous 12 months	6 (6)	2 (6)	4 (6)	1.09	0.19, 6.27	0.99
Years of dialysis						
Mean ± SD	5.0±5.2	5.9±5.2	4.7±5.3	1.04	0.97, 1.13	0.29
Median (range)	3.5 (0.04–31)	4.8 (0.06–25)	3.0 (0.04–31)			
Charlson comorbidity score						
Mean ± SD	3.3±1.7	2.9±1.4	3.4±1.9	0.82	0.60, 1.11	0.19
Median (range)	2.5 (2.0–14.0)	2.0 (2.0–7.0)	3.0 (2.0–14.0)			

Values are n (%) unless otherwise indicated. ref. = Reference group; SD = standard deviation; – = cannot be calculated due to zero cells.

The baseline characteristics of the patients surveyed are summarized in table 1. *S. aureus* colonization results are summarized in table 2. Overall, 42% (95% CI 32–52) of patients were *S. aureus* colonized at >1 body site. Six percent (95% CI 1–11) were colonized with MRSA. Extranasal *S. aureus* colonization was found among 32% (95% CI 23–41) of patients and 4% of patients had extranasal MRSA colonization (95% CI 0–5). The overlap of *S. aureus* colonization among the three body sites surveyed can be found in figure 1.

In our primary bivariate analysis, there were trends of associations between extranasal *S. aureus* colonization and younger age (OR 0.97, 95% CI 0.94–1.001) and not having been hospitalized in the previous 12 months (OR 0.44, 95% CI 0.19–1.06; table 1). In our secondary analysis of factors associated with extranasal *S. aureus* colonization only, we found trends suggestive of an association between extranasal colonization only and more years of dialysis (OR 1.08, 95% CI 0.99–1.18) and lower Charlson comorbidity score (OR 0.57, 95% CI 0.32–1.03). In our secondary analysis of factors associated with overall *S. aureus* colonization, there was an association between any *S. aureus* colonization and younger age (OR 0.97, 95% CI 0.94–0.99).

We recovered 9 MRSA isolates and 64 methicillin-susceptible *S. aureus* (MSSA) isolates for PFGE typing. Of the 20 patients with *S. aureus* cultured from >1 body site, all recovered isolates were indistinguishable from each other, suggesting clonality. The 9 MRSA isolates recovered were all the USA300-MRSA PFT.

Discussion

S. aureus is a common clinical problem resulting in hospitalization, morbidity, and mortality among hemodialysis patients. Our prevalence study found that 42% of maintenance hemodialysis patients were colonized with *S. aureus* when surveyed at the anterior nares, orophar-

Table 2. Body site *S. aureus* colonization results among maintenance hemodialysis patients (n = 100)

	Percentage of colonized patients (95% CI)
Colonization of any body site	
Any *S. aureus*	42 (32, 52)
MSSA	36 (27, 45)
MRSA	6.0 (1.0, 11)
Nasal colonization	
Any *S. aureus*	28 (19, 37)
MSSA	24 (16, 32)
MRSA	4.0 (0.2, 7.8)
Throat colonization	
Any *S. aureus*	27 (18, 35)
MSSA	24 (16, 32)
MRSA	3.0 (0.0, 6.0)
Inguinal-region colonization	
Any *S. aureus*	17 (10, 24)
MSSA	15 (8.0, 22)
MRSA	2.0 (0.0, 5.0)
Extranasal colonization	
Any *S. aureus*	32 (23, 41)
MSSA	28 (19, 37)
MRSA	4.0 (0.2, 7.8)
Colonization at >1 body site	
Any *S. aureus*	19 (11, 27)
MSSA	16 (9, 23)
MRSA	3.0 (0.0, 6.0)
Extranasal colonization only	
Any *S. aureus*	14 (7.0, 21)
MSSA	12 (6.0, 18)
MRSA	2.0 (0.0, 5.0)
Nasal colonization only	
Any *S. aureus*	10 (4.0, 16)
MSSA	9.0 (3.0, 15)
MRSA	1.0 (0.2, 5.0)
Throat colonization only	
Any *S. aureus*	10 (4.0, 16)
MSSA	8.0 (3.0, 13)
MRSA	2.0 (0.0, 5.0)
Inguinal-region colonization only	
Any *S. aureus*	3.0 (0.0, 6.0)
MSSA	3.0 (0.0, 6.0)
MRSA	0.0 (–)

– = Cannot be calculated.

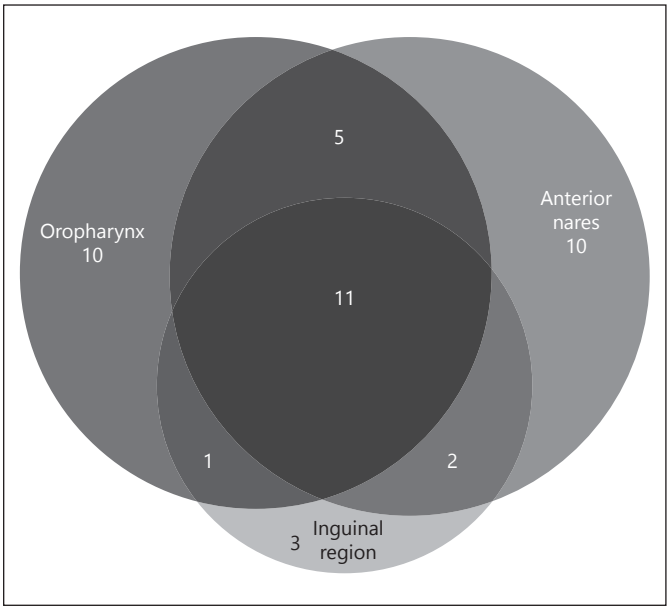

Fig. 1. Overlap of *S. aureus* colonization at the anterior nares, oropharynx, and inguinal region. Each circle size is proportional to the amount of *S. aureus* detected at that given anatomic site.

ynx, and inguinal region with 6% of patients being colonized with MRSA. Extranasal surveillance resulted in 33% additional patients identified with *S. aureus* and MRSA colonization. This is similar to other investigations examining the utility of extranasal *S. aureus* colonization surveillance in populations at high risk for *S. aureus* infection [15, 16, 23].

Trends of association seen between *S. aureus* extranasal colonization and the factors of younger age and not having been hospitalized in the previous 12 months may be a marker that younger and healthier hemodialysis patients are more likely to have *S. aureus* extranasal colonization. The association between younger age and overall *S. aureus* colonization was significant in our post hoc analyses. In an era where community-associated *S. aureus* is common and endemic among younger persons [21], this relationship is unsurprising.

There are limitations to our investigation. First, the patients were enrolled from a single metropolitan area and findings may not be generalizable to other hemodialysis populations. However, the patient population at our institution is similar to that of other large urban US populations and is ethnically diverse. Second, we relied on patients to self-report factors associated with colonization. Patients may not recall health care exposures over the previous 12 months. Third, we did not examine all possible body sites for colonization. However, the increased yield from determining other *S. aureus* colonization sites in addition to nasal, oropharyngeal, and inguinal colonization is not well understood and the sites chosen for surveillance appear to be those of highest yield for nonnasal sites [15, 16, 23]. Fourth, the sample size of our investigation was relatively limited making it difficult to determine factors

associated with colonization. Nevertheless, our investigation is larger than previous surveys of nonnasal *S. aureus* colonization by nearly 2- to 3-fold [12, 18, 19].

In conclusion, we found that extranasal *S. aureus* colonization was common among maintenance hemodialysis patients. Although it is unclear if decolonization efforts targeting MRSA or *S. aureus* in patients on maintenance hemodialysis will reduce subsequent infections [24], future interventional efforts in this field should consider decolonization of skin sites and the throat in addition to nasal decolonization.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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