Advancing age and the risk of nasal carriage of *Staphylococcus aureus* among patients on long-term hospital-based hemodialysis

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Background: Elevated nasal carriage rates of *Staphylococcus aureus* and ensuing complications among the elderly and in those on long-term hemodialysis (HD) are well recognized. The aim of the present study was to determine the extent to which advancing age is associated with the risk of persistent *S. aureus* nasal carriage among end-stage renal disease (ESRD) patients on long-term HD.

Patients and Methods: This prospective study involved 205 ESRD patients enrolled for maintenance HD from July 1997 to July 2000. Persistent nasal carriage was defined by two or more positive cultures for methicillin-susceptible (MSSA) or methicillin-resistant *S. aureus* (MRSA). Five standardized swabs were taken from the anterior nares of all the patients on long-term HD. *S. aureus* nasal carriage rates were estimated and compared among ESRD patients of different age groups.

Results: Overall, a prevalence of 38.05% (78/205) for *S. aureus* nasal carriage was observed, including 27.3% (56/205) for MSSA and 10.7% (22/205) for MRSA. Patients aged 75 to 84 years had the highest (84.6%, 11/13) prevalence of *S. aureus* nasal carriage (RR, 7.000, 95% CI, 4.350-11.763, $P<0.00001$). Those aged 65 to 74 years had the next highest (49.0%, 25/51) nasal carriage rates (RR, 4.083, 95% CI, 2.302-7.658, $P<0.0001$) while patients aged 15 to 24 years (reference group) had the lowest (12.8%, 1/8) prevalence of nasal carriage. The 75 to 84 year age group also had the highest rates of MSSA (46.2%, 6/13), (RR- 3.833, 95% CI, 2.144-7.234, $P<0.0001$) and MRSA (38.5 %, 5/13) (RR, 6.333, 95%CI, 2.767-16.198, $P<0.0001$) nasal carriage compared to the reference group.

Conclusions: Significantly higher persistent MSSA and MRSA nasal carriage rates among ESRD patients >75 years of age are suggestive of an elevated risk of potentially serious *S. aureus*- related complications among the very elderly during long-term HD. These findings might be helpful in the identification of elderly HD patients as a high-risk group for *S. aureus*-linked vascular access-related septicemia (VRS) and to evolve appropriate preventive strategies.

Key words: Hemodialysis, end-stage renal disease, methicillin-resistant *Staphylococcus aureus*, septicemia, Saudi Arabia

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Infection remains one of the most frequent causes of morbidity, mortality and hospitalization among long-term hemodialysis (HD) patients.[1] The United States Renal Data Service (USRDS) data base review (1997) revealed that 15 to 17% of hospitalizations among patients on long-term HD were related to infectious complications of vascular accesses.[2] Gram positive cocci, especially *S. aureus*, are the most frequently associated microorganisms in vascular access-related septicemia (VRS) in HD patients.[3,4] *S. aureus* most often colonize the anterior nares and disseminate to infect other parts of the body, including vascular access sites among ESRD patients on long-term HD.[5]

Persistent nasal carriage of *S. aureus* is a recognised risk factor for the development of VRS. As a result, systemic antibiotics are often started early to prevent complications from such infections.[5,6] The primary risk factor for modification of nasal *S. aureus* flora from methicillin-susceptible to methicillin-resistant (MSSA to MRSA) is the frequent administration of systemic antibiotics.[7]

The need for a vascular access site as well as extracorporeal blood circulation for long-term HD might place the increasingly larger number of elderly ESRD patients at a greater risk of acquisition of nasal carriage of *S. aureus* and ensuing serious complications than younger ESRD patients.[8,9] However, the extent to which age is related to the risk of persistent *S. aureus* nasal carriage during long-term hospital-based HD, which is a high-risk environment for the transmission of nosocomial infections, is not well de-

fined. The present study sought to determine the relationship between the risk of nasal carriage of *S. aureus* (MSSA and MRSA) and advancing age by estimation and comparison of nasal carriage rates among patients of different age groups on long-term HD.

Patients and methods

The present study involved 205 ESRD patients, including 64 (31.2%) patients >65 years of age, enrolled on long-term HD during July 1997 to July 2000, at King Fahad Hospital and tertiary care center in the Eastern Province of Saudi Arabia. These ESRD patients were regularly dialyzed two or three times per week through disposable single-use high-flux dialyzer membranes (polysulphone, Bellco, Mirandola, Italy; polyacrylonitrile, Filtrat 10 AN 69, Hospal, Meyzieu, France.) and bloodlines, in a common space. Nevertheless, male and female patients were dialyzed in separate rooms and hepatitis B positive patients were strictly isolated per CDC recommendations.[10] Screening for HCV, HBV and nasal carriage of *S. aureus* is done routinely for all new patients enrolled on hemodialysis and then once every 3 months.

We used procedures for optimal screening of nasal carriage of *S. aureus* in patients on HD: three cultures at an interval of 1 hour on day 1 with culture four and five taken at subsequent dialysis sessions and with each inter-dialysis interval spanning no less than 48 hours.[11] A swab moistened in sterile 0.9% NaCl solution was rotated in both the anterior nares and placed into a modified Amies charcoal transport medium (Eurotuba, Barcelona). These swabs were processed in the laboratory within 12 hours. Patients who were culture positive for *S. aureus* (either for MSSA or MRSA) on more than two occasions were labeled as persistent *S. aureus* nasal carriers for MSSA or MRSA. The nasal swabs were cultured on blood agar and mannitol salt agar. The culture plates were incubated at 35° C for 48 hours. *S. aureus* was identified on the basis of colony morphology (golden pigmentation of colonies), gram-positive cocci in clusters on microscopic examination and positive results in tube coagulase, mannitol-fermentation, deoxyribonuclease (DNAse) and Staphaurex latex-agglutination tests (Murex Bio Tech, Dartford, UK). MRSA were identified on 1-μg oxacillin discs according to the criteria of National Committee for Clinical Laboratory standards.

Strict adherence to standard precautions for infection control, as recommended by CDC, were practiced routinely for all patients throughout the study and afterwards. These precautions included changing gloves after each patient manipulation and frequent hand washings between each patient. All the staff members taking care of HD patients wore gowns, masks and gloves with protective eye wear while performing procedures and during initiation and termination of dialysis. Meticulous cleaning and disinfection of environmental surfaces at each dialysis station was routinely performed before the beginning of the next HD session.

In the statistical analysis, quantitative variables were expressed as percentages. The estimation and statistical comparison of the *S. aureus* nasal carriage rates among various age groups was carried out using the Web Chi-square Calculator, Georgetown University, Washington DC, USA (http://www.georgetown.edu/faculty/ballc/webtools/web_chi.html). Statistical significance was set at 0.05 level.

Results

An overall prevalence of 38.05% (78/205) of *S. aureus* nasal carriage was observed in this study, including 27.3% (56/205) for MSSA and 10.7% (22/205) for MRSA. None of the isolated strains of *S. aureus* showed borderline oxacillin resistance. Of 205 ESRD patients, 109 (53.2%) were females and 96 (46.8%) were males. Although more males than females (43.8 % vs. 33.9%) were nasal carriers of *S. aureus*, the difference was not statistically significant (RR, 1.325, 95% CI, 0.911-1.926, P=0.152). The mean age of the HD population was 47.8 years (range 15-84 years).

The peak prevalence of nasal carriage of 84.6% was observed in the 75 to 84 year age group (Table 1, Figure 1). The 65 to 74 year age group had the next highest prevalence (49.0%) of nasal carriage while the lowest nasal carriage rate of 12.8% was observed in 15 to 24 year age group (reference group) (Table 1, Figure 1). The highest prevalence of MSSA (46.2%) and MRSA (38.5%) nasal carriage was found in patients aged 75 to 84 years. Patients in the 65 to 74 year age group had the next highest prevalence of MSSA (37.2%) and MRSA (11.8%) while the lowest nasal carriage rates for MSSA (12.5%) and MRSA (0%) was observed in the reference group (Table 2, 3, Figure 2).

Discussion

The global elderly population with ESRD has increased three-fold in the preceding two decades.[8,9] Of the one million patients who require chronic HD worldwide, more than 50% are over 65 years of age.[8] The renal registry report for the United Kingdom for 2002 indicates that the acceptance rate for dialysis for patients over 65 years of age is approaching 300 patients per 1 000 000 population, compared with 72 per 1 000 000 population in those aged 18 to 64 years.[9] The association between nasal carriage of *S. aureus* and ensuing serious complications has been widely established in patients undergoing HD.[5,6]

An overall prevalence of persistent nasal carriage of 38.5% was observed in this study. A relatively lower prevalence of 25.4% for *S. aureus* was reported in hospital personnel in Saudi Arabia.[12] However, the prevalence rate in our study was lower than the 44.0 to 84.0% reported elsewhere.[5,6,13] In the present study, the very elderly (>75 years) represented 6.3% of the total and elderly (65-74 years) patients comprised

Table 1. Persistent nasal carriage of *S. aureus* in ESRD patients on hemodialysis by age group.

Age range (years)	No. patients (% of total)	Persistent nasal carriers (n, %)	Relative risk	95% confidence interval	*P* value
15-24	8 (3.8)	1 (12.8)		Reference group	
25-34	15 (7.2)	3 (20.0)	1.662	0.823-3.465	0.117
35-44	27 (13.2)	7 (25.9)	2.087	1.071-4.201	0.029
45-55	42 (20.1)	11 (26.3)	2.167	1.121-4.347	0.019
55-64	49 (23.5)	20 (40.8)	3.417	1.884-6.552	<0.0001
65-74	51 (24.8)	25 (49.0)	4.083	2.302-7.658	<0.0001
75-84	13 (6.3)	11 (84.6)	7.000	4.350-11.763	<0.0001
Total	205 (100)	78 (38.05)			

Table 2. Nasal carriage of methicillin-sensitive *S. aureus* (MSSA) in ESRD patients on hemodialysis by age group.

Age range (years)	MSSA nasal carriers		Relative risk	95% confidence interval	*P* value
	n	%			
15-24	1/8	12.5		Reference group	
25-34	2/15	13.3	1.083	0.486-2.487	1.000
35-44	5/27	18.5	1.500	0.726-3.169	0.323
45-55	8/42	19.1	1.583	0.774-3.317	0.241
55-64	15/49	30.6	2.500	1.322-4.932	<0.004
65-74	19/51	37.2	3.167	1.729-6.091	<0.0001
75-84	6/13	46.2	3.833	2.144-7.234	<0.0001
Total	56/205	27.3			

ESRD, End-stage renal disease

Table 3. Nasal carriage of methicillin-resistent *S. aureus* (MRSA) in ESRD patients on hemodialysis by age group.

Age range (years)	MRSA nasal carriers		Relative risk	95% confidence interval	*P* value
	n	%			
15-24	0/8	0			
25-34	1/15	6.6		Reference group	
35-44	2/27	7.4	1.333	0.434-4.217	0.782
45-55	3/42	7.2	1.167	0.363-3.812	1.000
55-64	5/49	10.2	1.167	0.580-5.028	0.434
65-74	6/51	11.8	1.833	0.654-5.427	0.311
75-84	5/13	38.5	6.333	2.767-16.198	<0.0001
Total	22/205	10.7			

ESRD, End-stage renal disease

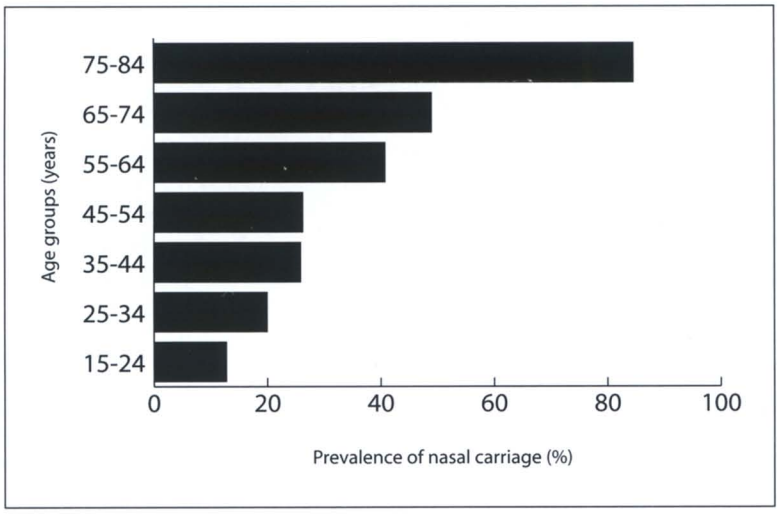

Figure 1. Prevalence of persistent *S. aureus* nasal carriage among ESRD patients on long-term hemodialysis by age group.

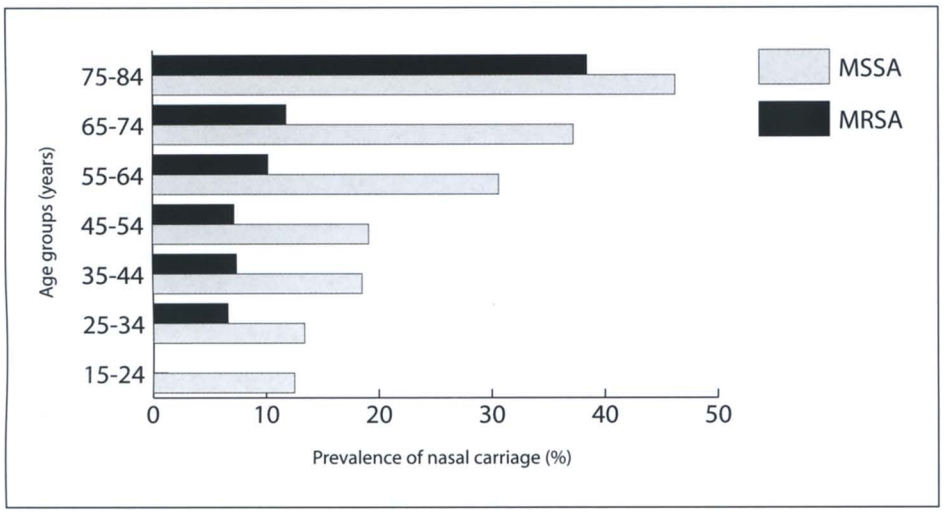

Figure 2. Prevalence of persistent methicillin-sensitive and methicillin-resistent *S. aureus* (MSSA and MRSA) nasal carriage among ESRD patients on long-term hemodialysis by age group.

25.0% of the HD cohort. Patients in very elderly group had a seven-fold greater prevalence of nasal carriage of *S.aureus* than those in the youngest group while the elderly group had a four-fold greater prevalence. Thus, patients >65 years age comprised nearly one-third of the HD cohort and carried an approximately 11 times greater collective risk of *S. aureus* nasal carriage than the youngest group. Peak nasal carriage rates of *S. aureus* among elderly patients have been reported from nursing homes, suggesting frequent and/or prolonged hospitalization as a key factor for an elevated risk for nasal carriage in the elderly.[14]

The difference between MRSA and MSSA is the resistance to β-lactamase-stable β-lactam antibiotics. Often this resistance is associated with resistance to multiple antibiotics, which limits the therapeutic options available in clinical practice. MRSA has become an important pathogen in many hospital-based HD units worldwide. MRSA nasal carriage constitutes a greater risk for the development of *S. aureus* infection than does MSSA carriage. This could be an effect of the resistance itself, of an increased intrinsic virulence of MRSA compared to MSSA, or due to a more vulnerable category of patients being colonized by MRSA, e.g., elderly ESRD patients on long-term HD.[15] In the present study, patients aged 75 to 84 years, showed a significantly higher risk of nasal carriage of MSSA (RR, 3.833, $P<0.0001$) and MRSA (RR, 6.333, $P<0.0001$).

Elderly ESRD patients may have a higher rate of *S. aureus* nasal carriage because they suffer from impaired immune defence mechanisms, attributable to advancing age and concomitant comorbid conditions like diabetes mellitus and malignancies in addition to malnutrition, particularly related to uremia and HD treatment.[16-19] Uremia and inflammation induced by HD filters can cause oxidative stress and activation, apoptosis and reduced numbers of T-lymphocytes leading to defects in cell-mediated immunity.[21,22] Moreover, MHC class II analog protein (Map) expressed by *S. aureus* augments the virulence of the pathogen by attenuating host cell- mediated immunity through reduction in T-cell proliferative response to gram-positive bacterial infections.[22]

Von Eiff et al reported that *S. aureus* blood isolates from septicemic patients were clonally identical to those obtained from a nasal specimen in 82.2% of patients, suggesting that the organisms in the blood stream originated from the patients own nasal flora.[23] *S. aureus* adheres and thrives on the nasal mucosa, particularly in the relative lack of human immunological defences. Specific microbial components known as adhesins mediate adherence of the organism to the host tissues by participating in remarkably sophisticated interactions with host molecules.[24] A class of cell surface adhesins–MSCRAMMs (microbial surface components recognizing adhesive matrix molecules) specifically interacts with extracellular matrix components and plays an important role in host tissue colonization, invasion, and as a key factor for *S. aureus* virulence.[25] *S. aureus* disseminates from the nasal reservoir to the hands and skin that infect vascular access sites. *S. aureus* has a predilection to cause fatal infections among those who have intravascular prosthetic devices such as central venous catheters (CVCs). CVCs become rapidly coated with serum constituents such as fibrinogen, fibronectin and laminin that facilitate the attachment of staphylococci to foreign material through MSCRAMM-mediated mechanisms. Additionally, *S. aureus* elaborates glycocalices, which further promote the bacterial colonization and spread of infection.[26]

Elderly people are less likely to have safe vascular access, such as a native arteriovenous fistula (AVF), which provides an adequate and reliable source of blood flow through the hemodialyzer and has the lowest infection rates. Only 23% of ESRD patients in United States were dialyzed through AVF in 1997.[27] The peak prevalence of persistent nasopharyngeal colonization with *S. aureus* in combination with an impaired immune defense mechanism, places elderly ESRD patients at additional potential risk of developing recurrent episodes of *S. aureus*-related VRS and consequential hospitalizations, especially when they are dialyzed through central venous catheters as an alternative to AVF in a hospital-based HD unit, which creates a high-risk setting for the transmission of nosocomial infections.[28,29]

Efforts to realize the long-term elimination of *S. aureus* from the anterior nares through decolonizing agents such as oral rifampicin and mupirocin nasal applications have been associated with the development of side effects, emergence of resistance and recolonization of *S. aureus* once the drug was discontinued.[30] Of the two types of resistance, the low-level type (MIC 8-256 mg/L) results from modification of the target enzyme and the high-level type (MIC > 500mg/L) is the product of a plasmid-encoded mupirocin-resistant enzyme.[31] It is the transmissible mechanism of the high-level resistance that remains the cause of concern because of the potential spread of mupirocin resistance once the drug is used on a large scale and on a long-term basis, as in chronic HD patients. Thus, at present, most strategies to achieve lasting elimination of the nasal carriage of *S. aureus* for HD patients remain unsatisfactory. Alternatively, the use of a conjugate vaccine has been reported to confer partial immunity against *S. aureus* bacteremia for approximately 40 weeks in patients receiving HD, after which protection wanes as antibody levels decrease.[32] Optimization of AVF prevalence to at least 50%, as recommended by National Kidney Foundation-Dialysis Outcomes and Quality Initiative (NKF-DOQI) had greater potential to reduce *S. aureus* nasal carriage-linked VRS and perhaps the ensuing mortality among the elderly.[33-35] Nevertheless, the necessity to develop novel strategies for the reduction of *S. aureus* nasal carriage rates and the consequential prevention of associated VRS ought to be recognised in this vulnerable group of the elderly HD population.

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