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Staphylococcus aureus nasal carriage among the diabetic and non-diabetic haemodialysis patients

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SUMMARY

Staphylococcus aureus is the most common cause of serious infections in patients undergoing long-term haemodialysis (HD). *S. aureus* infections in HD patients are associated with considerable morbidity and mortality. Especially, methicillin-resistant *S. aureus* (MRSA) strains are becoming increasingly multidrug-resistant and have recently developed resistance to vancomycin, used successfully to treat MRSA for more than 30 years. *In vitro* determination of resistance patterns of *S. aureus* is critical in terms of administering suitable antimicrobial treatment. The objective of this study was to identify the frequency of *S. aureus* among diabetic and non-diabetic HD patients and to investigate resistance patterns against various antibiotics used broadly for treatment. This study was carried out between January 2004 and December 2004. In the present survey, 261 patients undergoing HD treatment from three HD units in Hatay were examined. A total of 148 *Staphylococcus aureus* strains were processed to assess their occurrence rates and antimicrobial susceptibility profiles. *S. aureus* positivity was determined in 148 (56.7%) of the 261 HD patients and 26 (16.2%) of the 160 individuals in the control group. The difference was significant ($p < 0.001$). HD length was found to be 38.4 ± 24.3 months in the patients of *S. aureus* carrier and 27.3 ± 18.5 months in non-carrier patients. Significant correlation was also identified between durations those on HD and the isolation of *S. aureus* ($p < 0.001$). However, the carrier state was unrelated to the presence of diabetes mellitus (DM), age or sex. In conclusion, nasal carriage of *S. aureus* was found to be more prevalent in HD patients than that in those in the control group. Also, it is concluded that DM was not a risk factor for the nasal carriage of *S. aureus*. In addition, the rates of antibiotic resistance of *S. aureus* strains were found to be quite higher in HD patients than in the control group ($p < 0.05$).

Keywords: *Staphylococcus aureus*; nasal carriage; MRSA; haemodialysis; susceptibility

INTRODUCTION

Staphylococcus aureus has long been recognised as an important pathogen in humans. The nasal carriage of *S. aureus* represents a risk factor for subsequent invasive infection of patients and also for interpatient transmission. It is described that a nasal carrier state seems to be the origin for the development of staphylococcal infections in haemodialysis (HD) patients (1,2). In addition, the nasal carriage of *S. aureus* appears to play some role in the epidemiology and pathogenesis of staphylococcal skin infections (3).

Infection is a major cause of morbidity and the second most common cause of death in HD patients (4). Nasal carriage of *S. aureus* plays a key role in the development of *S. aureus* infections. It is a major risk factor for the development of infection in patients undergoing HD (5). HD patients are more prone to staphylococcal infections because of their decreased immunity, increased skin colonisation by staphylococci and the multiple needle punctures required for dialysis. The source of the staphylococci is the anterior nares. Elimination of staphylococcal nasal carriage results in a significantly lower infection rate (6).

Long-term stay in hospital, repeated antibiotic treatment, diabetes mellitus (DM) and a compromised immune system all increase the risk of the development of a serious nosocomial infection (5). Several reports highlight the importance of *S. aureus* carriage in endogenous infection of patients on HD (5–7). It is reported that the percentage of *S. aureus* nasal carriers ranges from 59.5 to 76% in different dialysis centres (5,8,9). A direct link between such a high nasal carriage of *S. aureus* in HD patients and subsequent infection by the same organism has been found in numerous studies (4,7,10,11). Moreover, infections cause considerable morbidity and

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mortality in patients with DM. Previous studies have reported nasal carrier rates for *S. aureus* ranging from 11 to 46.5% in diabetic subjects (12,13). Several aspects of immunity are altered in patients with diabetes. Polymorphonuclear leucocyte function is depressed, particularly when acidosis is also present. Leucocyte adherence, chemotaxis and phagocytosis may be affected (14,15).

Staphylococcal infections occur regularly in hospitalised patients and have severe consequences, despite antibiotic therapy (16). Due to an increasing number of infections caused by methicillin-resistant *S. aureus* (MRSA) strains, which are now most often multidrug-resistant, therapy has become problematic (17).

Determination of *in vitro* resistance of *S. aureus*, which causes hospital-originated infection, is crucial to apply appropriate antibiotics (18,19). Despite rapid development in antimicrobial treatment, there are still great difficulties in the treatment of staphylococcal infections. It has been reported that methicillin-resistant and susceptible staphylococci also exhibit resistance to β-lactam antibiotics as well as other antibiotics. As staphylococci may cause hospital epidemics, they are considered as potentially important health problems all over the world (20).

This study has been performed to determine the nasal carriage of *S. aureus* among diabetic and non-diabetic HD patients and to investigate resistance patterns against various antibiotics used broadly for treatment.

PATIENTS AND METHODS

Clinical samples were obtained from January 2004 to December 2004 at three different HD centres (consisting of 54 patients at the haemodialysis centre of Antakya State Hospital, 119 patients at Antakya haemodialysis centre and 88 patients at Emir haemodialysis centre) in Antakya, Turkey.

Of the 261 patients, 67 (25.7%) had type 2 DM and 194 (74.3%) were with diverse aetiology for end-stage renal disease, forming the non-diabetic cohort. Of 67 patients with type 2 DM, 91.0% (61/67) did not require insulin, whereas 9.0% (6/67) required it.

The control group consisted of 80 healthy individuals and 80 diabetic patients. The control group, matched according to their sex and age, were recruited from the same clinics regions.

All patients undergoing regular haemodialysis in the Hatay region (Turkey) were included in this study. Conventional haemodialysis techniques were performed, for 3–5 h per treatment 2–3 times a week. Polysulfone dialysers and bicarbonate dialysis were used for all patients. All HD patients were under treatment for at least 12 months, and the patients who had undergone haemodialysis for <12 months were excluded from this study. The time of dialysis (time span since initiation of HD therapy) was recorded. The main characteristics of these patients are summarised in Table 1. Formal consent to participate was obtained from all patients.

Bacteriological Specimens

Nasal specimens were collected from the 261 long-term HD patients using two sterile dry cotton-wool swabs for each patient. The swab was circled through both nostrils consecutively while applying an even pressure. The swabs were immediately placed in transport medium. The nasal swabs were inoculated onto sheep blood-agar plates and phenol-red mannitol salt agar (Difco Laboratories, Detroit, USA) plates. The plates were incubated at 37 °C for 48 h. The identification of *S. aureus* was based on colony morphology, biochemical activities and coagulase test (21). API Staph (bioMerieux, Lyon, France) strips were used for the identification of Staphylococcus species.

Antimicrobial Susceptibility Tests

All isolated *S. aureus* strains were identified using standard procedures (21), and antimicrobial susceptibility testing was performed in accordance with the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) by using Kirby-Bauer disc diffusion method (22).

The susceptibilities of isolated *S. aureus* strains against methicillin (10 μg/disc), penicillin (10 μg/disc), gentamicin (10 μg/disc), amoxicillin (20 μg/disc) + clavulanic acid (10 μg/disc), trimethoprim–sulfamethoxazole (1.25/23.75 μg/ml), erythromycin (15 μg/disc), rifampicin (5 μg/disc), clindamycin (2 μg/disc), teicoplanin (30 μg/disc), ciprofloxacin (5 μg/disc) and vancomycin (30 μg/disc) were tested. All antibiotics discs were obtained from Oxoid firm (Oxoid, Hampshire, England).

As a control strain, *S. aureus* ATCC 33591 (methicillin resistance) and *S. aureus* ATCC 25923 (methicillin susceptible) were used for identification and susceptibility tests.

Ascertainment of Diabetes

DM was diagnosed after two consecutive fasting (minimum of 8 h) glycaemia values of $\geq$126 mg/dl, collected during ambulatory appointments (23).

Statistical Analysis

Data were analysed by using a commercially available statistic software package (SPSS® for Windows V. 11.5, Chicago, IL, USA). One-way ANOVA test was performed, and post hoc multiple comparisons were performed with LSD. Results were presented as mean ± SD. The p-values of <0.05 were regarded as statistically significant.

RESULTS

In this study, the average age of the patients was 53.3 ± 20.7 years; 176 of them were males (67.4%) and 85 were females (32.6%). The average age of the healthy control group was 52.6 ± 18.2 years; 64 of them were males and 56 were

Table 1 The characteristics of the haemodialysis (HD) patients and control group

	HD patients	*Control group*
Total age (years), mean ± SD	53.3 ± 20.7	52.6 ± 18.2
Male, total (%)	67.4 (176/261)	54.4 (87/160)
Female, total (%)	32.6 (85/261)	45.6 (73/160)
Diabetic patients (%)	25.7 (67/261)	50 (80/160)
Period on HD in all patients (months), mean ± SD	33.6 ± 16.9	
Period on HD in patients with *Staphylococcus aureus* (months), mean ± SD	38.4 ± 24.3	
Period on HD in patients without *S. aureus* (months), mean ± SD	27.3 ± 18.5	

females. The mean period on haemodialysis was calculated as 33.6 ± 16.9 months (range 12–168 months) for 261 patients on HD. The HD patients and the control group demonstrated similar sex and age distributions (Table 1).

S. aureus positivity was determined in 148 (56.7%) of the 261 HD patients and 26 (16.2%) of the 160 individuals in the control group [12 (15%) of the 80 individuals in the healthy control group and 14 (17.5%) of the 80 individuals in the diabetic control group]. The difference between HD patients and control group was significant ($p < 0.001$).

Whereas the rate of *S. aureus* was found to be 55.7% (98/176) in the male patients, this ratio was 58.8% (50/85) in the female patients included in this study. In the healthy control group, the rate of *S. aureus* positivity was detected as 15.6% (7/45) in the male and 14.3% (5/35) in the female of the healthy control group, and in the diabetic control group, these rates were 16.7% (7/42) for males and 18.4% (7/38) for females. The positivity rate of *S. aureus* was not significantly different between HD patients and healthy group or males and females ($p > 0.05$).

The relativity between the HD duration and isolation rate of *S. aureus* was also examined in this study. HD length was found to be 38.4 ± 24.3 months in the patients with *S. aureus* and 27.3 ± 18.5 months in non-isolated group. Significant correlation was also found between the length of period on HD and the isolation rate of *S. aureus*. With regard to diabetic HD patients, HD length was found to be 43.2 ± 28.4 months in *S. aureus* carriers and 34.6 ± 23.9 months in non-carriers. Similarly, significant correlation was found between these two groups ($p < 0.001$, Figure 1).

A total of 25.7% (67/261) of HD patients and 50% (80/160) of the control group were diabetic (Table 1). While *S. aureus* isolation rate was 16.4% (11/67) in diabetic HD patients, it was determined as 15% (12/80) and 17.5% (14/80) in diabetic and healthy control groups, respectively. Nasal carriage rates of *S. aureus* in the haemodialysis patients and control group are presented in Table 2.

In this study, *S. aureus* was present in 56.7% of patients' nostrils (36.0% MSSA and 20.7% MRSA). Methicillin-resistance rate was 36% among the *S. aureus* strains, while it was not isolated among healthy control group ($p < 0.001$). The most effective antibiotics were glycopeptides, and of 148 *S. aureus* strains, no resistance was acquired against vancomycin.

The resistance of *S. aureus* in HD patients and control group was: penicillin (100%, 54%), clindamycin (48%, 13%), gentamicin (66%, 36%), erythromycin (76%, 34%), ciprofloxacin (51%, 8%), amoxicillin + clavulanic acid (56%, 25%), trimethoprim + sulfamethoxazole (35%, 176%), rifampicin (64%, 14%) and teicoplanin (12%, 0%), while vancomycin showed no resistance (Figure 2).

DISCUSSION

Serious *S. aureus* infections in hospitalised patients are caused by autoinoculation from a common carriage site, usually the anterior nares, or by transfer from another carrier such as a patient (24). *S. aureus* carriage in the nose and on the skin has been shown to be more common in patients receiving chronic HD than in the general population (7,25,26). *S. aureus* has been found to be a major pathogen in this population (4). *S. aureus*, especially MRSA, are very dangerous organisms that cause hospital outbreaks which are difficult to control, costly and very dangerous for high-risk patients (27). MRSA prevalence has been increasing all over the world from the first

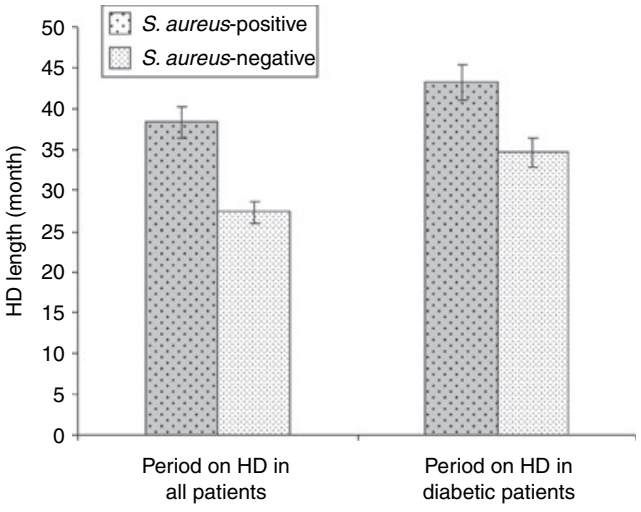

Figure 1 The relativity between the haemodialysis (HD) duration and isolation rates of *Staphylococcus aureus*

Table 2 The nasal carriage rates of *Staphylococcus aureus* in the haemodialysis (HD) patients and control group ($n = 261$)

Patients, total (%)	*S. aureus* positivity	*p-value*	
I HD patients	56.7% (148/261)	I–II	0.000
II Healthy control	15% (12/80)	I–III	0.000
III Diabetic control	17.5% 14/80)	II–III	Not significant
Male (%)			
I HD patients	55.7% (98/176)	I–II	0.000
II Healthy control	15.6% (7/45)	I–III	0.000
III Diabetic control	16.7% (7/42)	II–III	Not significant
Female (%)			0.000
I HD patients	58.8% (50/85)	I–II	0.000
II Healthy control	14.3% (5/35)	I–III	0.000
III Diabetic control	18.4% (7/38)	II–III	Not significant

day it was identified. Although MRSA was rarely reported in the beginning, it has become mostly resistant not only to all β-lactams but also to a wide range of other antibiotics and has emerged as major nosocomial pathogen during the past two decades. Furthermore, multidrug-resistant MRSA has become a major problem (28).

In this study, the nasal carriage rate of *S. aureus* was found to be 56.7% in 261 HD patients and 16.2% in 160 control patients ($p < 0.05$). While MRSA rate was 20.6% in HD patients, no methicillin-resistant strain was detected in the control group ($p < 0.05$). According to the *in vitro* sensitivity test results, resistance rates of *S. aureus* strains isolated from HD patients to methicillin, teicoplanin and vancomycin were as 36, 12 and 0%, respectively. There were no strains resistant to these antibiotics among the control group, isolated from control group. In terms of acquiring resistance against all antibiotics (gentamicin, amoxicillin + clavulanic acid, erythromycin, trimethoprim–sulfamethoxazole, teicoplanin, rifampicin, clindamycin, ciprofloxacin and penicillin), there was significant difference between HD patients and control group ($p < 0.05$).

Numerous studies performed in different countries and in different populations of patients on HD have consistently documented that a large proportion of such patients carry *S. aureus* in their nares and that the risk of their becoming infected with their own strains is quite high. Furthermore, *S. aureus* infections can cause considerable morbidity and mortality in these patients. Decolonisation of the nares may prevent *S. aureus* infections and accompanying complications (29).

With regard to studies from other countries on the nasal carriage of *S. aureus* in HD patients, Yu et al. (10) performed a 5-year prospective controlled study of prophylaxis of *S. aureus* nasal carriage and infection among patients in an HD unit and they determined that *S. aureus* infections occurred significantly more frequent in carriers than in non-carriers. Moreover, they concluded in their study that the incidence of infection at the dialysis access site, skin and soft tissue of patients on HD could be decreased by interventions directed at nasal carriage of *S. aureus* (10).

Piraino et al. (30) investigated the relationship between *S. aureus* infections and nasal carriage in 138 patients on peritoneal dialysis. They established that approximately 50% of the patients were carriers. This value is similar to the rates

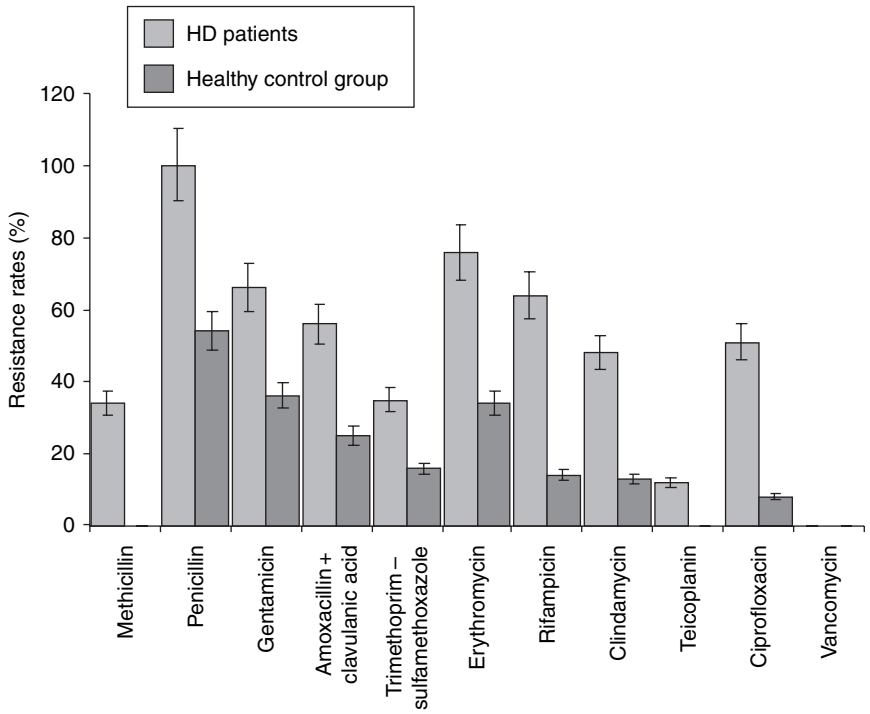

Figure 2 Antibiotic resistance patterns of *Staphylococcus aureus* isolated from haemodialysis (HD) patients and healthy control group

of nasal carriage we have determined in HD patients (55.7%). In their study, they determined that the rates of *S. aureus* exit-site infections and peritonitis were lower in the non-carriers than in carriers (30).

It is reported that elimination of staphylococcal nasal carriage resulted in a significantly lower infection rate (7), assuming that 75% of *S. aureus* infections are attributable to nasal carriage in HD patients (31). Multidrug-resistant organisms are becoming more prevalent in hospitalised patients, as well (32).

In a study performed by Boelaert (33), *S. aureus* isolation rate was detected as 42% in HD patients. It is indicated that nasal carriage of *S. aureus* is of pivotal importance in determining the risk of subsequent infections by this microorganism in HD patients. In his study, it is found that there was a significant relationship between nasal and hand carriage of the organisms (33). In another study, it was maintained that the rate of nasal carriage was 42% in HD patients (34). It can be concluded that patients on HD have an increased *S. aureus* carriage rate and that most *S. aureus* infections in this setting are of endogenous origin.

In our study, the 55.7% of nasal carriage of *S. aureus* found in the HD patients is almost as high as that of the carriage of *S. aureus* reported by Boelaert (33). That reported by Piraino et al., however, is similar (30).

In the present study, no statistical relationship was found between the patients who were carrying *S. aureus* and age and gender ($p > 0.05$). However, a statistical difference was detected between *S. aureus* carriers and patients not having *S.aureus* for the intervals of patient's admission to the dialyses ($p < 0.001$). Its explanation is that patients who are admitted for HD for long time have high possibility to get infected with *S. aureus* from other patients or healthy personnel carrying this bacterium.

S. aureus nasal carriage is a major risk factor for *S. aureus* infections; in addition, environmental factors are recognised as determinants of the *S. aureus* nasal carrier state (35). It is generally believed that infection is more common in people with diabetes. Although there are no good epidemiological studies in the literature to support or dispute this fact, numerous reports demonstrate that diabetics present with an increased susceptibility to infection. The mechanisms for this remain unclear. Few pathological features have been described in both type 1 and type 2 DM (36). In this study, it was determined that no significant correlation was found about the nasal carriage of *S. aureus* between diabetic HD patients and the diabetic persons in the control group; also, no statistical difference were found for the length of time on HD between the diabetic patients carrying *S. aureus* and non-diabetic *S. aureus* carriers ($p > 0.05$, significance: 0.53). In conclusion, DM was not a risk factor for the nasal carriage of *S. aureus.*

It is concluded that while the length of admission to HD is an important risk factor for *S. aureus* carriers, DM is not a threat for *S. aureus* carriers in the HD patients. Furthermore, it is determined that age and gender were not important risk factors for *S. aureus* carriers. Additionally, it was shown that *S. aureus* strains isolated from the HD patients have developed high resistance to many of the known antibiotics. The colonisation of the resistant strains rather than the frequency of *S. aureus* colonisation is more important in the HD patients.

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