

## NASAL CARRIAGE OF METICILLIN RESISTANT *STAPHYLOCOCCUS AUREUS*: THE PREVALENCE, PATIENTS AT RISK AND THE EFFECT OF ELIMINATION ON OUTCOMES AMONG OUTCLINIC HAEMODIALYSIS PATIENTS

S. R. Lederer, G. Riedelsdorf, H. Schiffel

KfH Nierenzentrum Muenchen-Laim, Munich, Germany

### Abstract

**Objective:** Haemodialysis (HD) patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections face high morbidity and mortality. Nasal carriage of *Staphylococcus aureus* is known to play an important role as an endogenous source for HD-access-related infections that contribute significantly to morbidity, mortality and cost of end-stage renal disease (ESRD) management. This prospective investigation in regular out-clinic haemodialysis patients was undertaken to estimate the prevalence of *S.aureus* nasal carriage, to define patient groups at risk and to evaluate the effect of elimination on outcomes among outclinic haemodialysis patients.

**Methods:** 136 HD patients without signs of overt clinical infection (48 women, 88 men, age 22-88 years) were screened at least twice for the nasal carriage for methicillin-susceptible SA (MSSA) or methicillin-resistant SA (MRSA). Nasal carriage of *S. aureus* was related to demographic (age, gender, duration on HD), comorbidity (diabetes, malignancy) and exposure to health care (dialysis staff, hospitalisation). Nasal carriers for MRSA received standardized mupirocin therapy and were followed up for elimination and infections for 1 year.

**Results:** The prevalence of nasal carriage for *staphylococcus aureus* was 53 % (41 % MSSA, 12 % MRSA). Compared with patients showing no colonization or with MSSA carriers, the 16 patients with nasal carriage for MRSA were older and more likely to have acquired the bacteria while hospitalised. Genotyping of MRSA isolates revealed different strains in patients and care-providers. Mupirocin eliminated MRSA in all patients, none of these patients experienced an infection caused by *staphylococcus aureus*, confirming the known value of MRSA elimination from other studies.

**Conclusions:** Elderly patients hospitalised for surgery constitute a high risk group for nasal carriage for MRSA. Early diagnosis may help prevent clinically relevant infection. Elimination of colonization by mupirocin appears to be an attractive preventive strategy.

**Key words:** Chronic renal failure, colonization, haemodialysis, methicillin-resistant *Staphylococcus aureus*

### INTRODUCTION

End-stage renal disease patients maintained on regular haemodialysis (HD) have a high risk for serious *Staphylococcus aureus* (SA) bacteraemia, primarily arising from the vascular access site. Furthermore, HD patients have higher carriage rates of SA than the healthy population. Other contributors to bloodstream infections include immune dysfunction of uraemic patients, the presence of prosthetic material and frequent breaches of the skin associated with venopuncture [1]. The antimicrobial resistance to this pathogen is rapidly increasing, and the consequences of methicillin-resistance for the outcomes of *S.aureus* infections are drastic. Haemodialysis dependent patients hospitalized with methicillin-resistant SA (MRSA) face an even higher mortality risk, longer hospital stays and higher inpatient costs [2, 3] than do patients with methicillin-sensitive bacteraemia (MSSA).

Since many such infections are potentially preventable, the institution of strategies that reduce infection rates represents an important element in the care of this patient population.

The dominant ecological niche for MRSA carriage is the anterior section of the nose. Organisms may be also found on the skin but elimination of nasal carriage by mupirocin ointment may lead to loss of carriage in other body sites. Moreover, comparison of carriage and infecting MRSA isolates indicates that individuals are commonly infected with their own carriage isolate, an observation that underlines the importance of prevention strategies [1].

The aims of our prospective study were a) to establish the prevalence of MRSA carriers in out-clinic haemodialysis patients and to identify groups of patients at high risk, b) to question whether mupirocin ointment remains effective for eradication of MRSA and c) to test whether eradication of nasal MRSA carriage affects the burden of MRSA blood stream infections.

### SUBJECTS AND METHODS

#### STUDY POPULATION

The study was conducted as an open prospective trial during 6/2004 and 6/2005 at our out-clinic haemodialysis centre. The patients willing to participate after

informed consent represented 100 % of all patients treated over this period. The one year time frame allowed us to obtain an adequate sample size. Each patient was screened at the start of the investigations and at all re-entries to the centre. The number of swabs per patient varied between 2 and 10. Nasal screening cultures were also taken from all employees at the renal unit, i.e. nurses, physicians and others (administration, kitchen, cleaning). The investigations were initiated by an outbreak of MRSA wound infections and performed according to the guidelines of the Robert-Koch-Institut [4] and of the Hygiene Department of the Kuratorium fuer Dialyse und Nieren-transplantation e.V. as well as of the legal authorities (Gesundheitsamt der Landeshauptstadt Muenchen, Munich, Germany).

#### MICROBIOLOGY

Swabs were taken from the anterior nares of the nose by the attending nephrologists as described by Wanten et al. [5]. They were placed on mannitol salt agar, a selective medium for isolation of *S.aureus*. These plates were incubated at 37 °C for 48 hours. Mannitol fermenting colonies were selected from the mannitol salt agar plates and subcultured to trypticase soy agar and 5 % sheep blood agar plates and incubated at 37 °C. Identification of *S.aureus* was based on colony morphology, DNase production and latex agglutination as described in detail by Wanten et al.. *Staphylococcus aureus* isolates were screened for methicillin resistance following the National Committee for Clinical Laboratory Standards (NCCLS) disk-diffusion method. Overnight cultures from sheep blood agar plates were plated on Mueller-Hinton agar and a 1 µg oxacillin disk was placed on the inoculated plate. Zone diameters were measured and recorded after 24 hour incubation at 37 °C as sensitive (greater than 13 mm) or resistant (less than 10 mm).

#### MOLECULAR TYPING

Pulsed-field gel electrophoresis with *Sma*I digestion of chromosomal DNA was used for the genotyping of MRSA isolates (Lehr- und Versuchsanstalt Oberschleissheim der Tierärztlichen Fakultät der LMU Muenchen, Germany) as described by Cuny et al. [6].

#### CLINICAL DATA

Prospective data collection included patient's demographic characteristics, co-morbid conditions, time on haemodialysis, repeated antibiotic therapy and previous hospitalization (within 12 months preceding investigation). We also collected data on response to mupirocin and results of blood cultures taken during the 12 months after documentation of absence of nasal MRSA carriage.

#### DEFINITION OF *S. AUREUS* CARRIER STATUS

*S.aureus* carriage was defined by a positive culture. The MSSA and MRSA positive patients were classified into 3 groups: Persistent carriage was defined by at

least two positive cultures, intermittent carriage by at least one positive and one negative culture in patients receiving no eradication procedures, and non carriage by persistent negative cultures.

#### ERADICATION OF NASAL CARRIERS

Mupirocin ointment was given patients with nasal carriage of MRSA thrice daily over 5 days. Additional swabs of skin areas (forehead, ears, axillae, hands) and throat were taken from patients and employees with documented nasal MRSA carriage.

#### MRSA COLONIZATION

MRSA carriage at other skin areas was treated with antiseptic soaps and fluids. All MRSA carriers were treated in separate rooms (isolated haemodialysis).

Follow-up nasal swabs or swabs from other positive body sites were taken from MRSA carriers three days, one week, one and three months after the end of eradication procedures to confirm eradication.

#### FOLLOW UP OF SCREENED PATIENTS

Patients were clinically followed up for twelve months after documentation of nasal MRSA carriage. End-points were recurrence of nasal MRSA carriage or blood stream MRSA infection.

#### STATISTICS

Data are given as mean  $\pm$  standard deviation. Comparison of continuous demographic variables between groups was conducted with the Mann Whitney test. Discrete categorical demographic variables were compared with the use of the two-sided Fisher's exact test. Statistical significance was set at 0.05 levels.

#### RESULTS

Nasal *S.aureus* carriage was significantly greater in haemodialysis patients than in haemodialysis personnel (53 % vs. 26 %,  $P = 0.009$ ). Nasal carriage of MRSA was present in 16 HD patients (12 % of the cohort), 6 of the patients with positive nasal cultures had additional colonized body sites (predominantly axillae). However, HD patients were not found to have significantly increased nasal MRSA carriage compared to HD personnel. Two out of 16 nurses had positive MRSA cultures. None of the physicians ( $N = 8$ ) or of the other employees ( $N = 7$ ) had nasal colonization with MRSA (Table 1).

Persistent nasal MSSA carriage was noted in 29 HD patients, intercurrent nasal MSSA carriage was found in 27 HD patients. All 16 HD patients with positive nasal MRSA cultures were persistent carriers (two positive cultures at two subsequent cultures). Stratification of our HD patients in the three *S.aureus* carrier states revealed that 33 % of the patients (29 MSSA and 16 MRSA) were persistent nasal *S.aureus* carriers, 20 % of the HD patients had intermittent nasal colonization and 47 % of the patients had repeated and exclusively negative cultures of nasal swabs.

Table 1. Nasal carriage of *S. aureus* in outclinic HD patients and HD staff.

	Number	S.aureus -negative	MSSA	MRSA
HD patients	136	64	56	16
HD personnel	31	23	6	2

Table 2. Demographic characteristics of outclinic HD patients stratified according to the results of nasal SA cultures.

	All patients	MSSA patients	MRSA patients
Number	136	56	16
Age (yr)	63 ( $\pm 15$ )	63 ( $\pm 13$ )	73 ( $\pm 10$ )*
Gender (f/m)	48/88	17/39	4/12
Diabetics	45	15	9*
Number of hospitalized patients	38	15	14*

P < 0.05 vs. MSSA patients

Table 3. Number of nasal MSSA or MRSA carriers stratified according age.

Age	All patients	MSSA (%),	MRSA (%)
20-39 yr	12	7 (58%)	0
40-59 yr	37	17 (46%)	1 (3%)
60-79 yr	74	38 (51%)	9 (12%)
80 and more yr	13	5 (38%)	6 (46%)

Molecular typing of the 18 MRSA isolates by the use of PFGE technique disclosed nosocomial clusters. None of the MRSA isolates was indistinguishable, closely related, or possible related by PFGE typing to another MRSA isolate. The 16 isolates represented different, genetically unrelated MRSA clones.

HD patients with nasal carriage of MRSA were significantly older ( $P < 0.05$ ) than patients with nasal carriage of MSSA (Table 2) and the prevalence of MRSA carriage, but not of MSSA carriage also increased with age. Patients aged 80 years and more had the highest prevalence of nasal carriage of MRSA (Table 3). HD patients with positive MRSA cultures were significantly more often diabetic than patients with nasal MSSA colonization ( $P < 0.05$ ).

The two patient groups differed significantly in the percentage of patients (88% vs. 27 %,  $P = 0.001$ ) who had needed hospitalisations of at least 14 days duration within the 3 months prior to testing.

Neither gender, nor duration on haemodialysis (1-394 months for MSSA patients vs. 1-183 months for MRSA patients), presence of malignancy (11 patients) or immunosuppressive drugs (7 patients) or repeated antibiotic therapy showed a higher prevalence of nasal MRSA carriage.

#### ERADICATION OF NASAL MRSA.

Repeated follow-up swabs demonstrated that mupirocin was an effective agent for the eradication for nasal MRSA. Neither recolonization nor resistance to

mupirocin was a problem in the 16 treated patients. Other colonized body sites were successfully treated with antiseptic soaps and solutions.

During the 12 months none of the patients of the total cohort was hospitalised because of SA blood-stream infection.

#### DISCUSSION

MRSA is a scourge of modern day health care and constitutes a threat to out-patient dialysis facilities. Recommendations for preventing MRSA transmissions among chronic haemodialysis patients have been published [1, 7-12]. Strategies to limit the spread of MRSA include screening and eradication of MRSA carriage, isolation procedures, prompt and accurate diagnosis of infection, optimal anti-microbial use and prevention of transmission. However, there are wide variations in the procedures for the management and control of antimicrobial resistant *S.aureus*. Hand hygiene is the undisputed single most important control measure, but both the practicability of the guidance on MRSA and the clinical benefit of specific infection control measures are subject of an ongoing debate [8, 9].

In our outclinic haemodialysis patients we observed utilizing routine microbiological procedures an overall prevalence of 53 % for *S.aureus* nasal carriage. Not surprisingly, the carriage rate of *S.aureus* was found to be well within rates (37-84 %) reported elsewhere [13-19] and significantly higher in renal patients than in

healthy haemodialysis personnel. Possible explanations for variation of prevalence rates in studies from different dialysis centres include sensitivity of swabbing and microbial culture techniques, the demographic characteristics of the population and geographic differences in the epidemiology of the pathogen.

A substantial number of our haemodialysis patients (12%) were persistently colonized with MRSA. This rate was significantly higher than rates reported by nation wide surveys for Germany [20], USA [21] or Slovenia [22]. However, the rate of nasal carriage in the patients of our renal unit was comparable to prevalence rates observed in US. renal patients [23] admitted to a hospital from different facilities (11 out of 109), in an out-patient dialysis centre in Saudi Arabia (22 out of 208) [17] and in Greek haemodialysis patients receiving chronic haemodialysis either in the clinic or an out-clinic facility (4 out of 16) [14]. The use of nasal cultures alone for the detection of *S.aureus* has a sensitivity of 78 - 85 %. However, we detected colonization with MRSA of other body sites only in patients with MRSA colonization of the nose.

The acknowledged risk factors associated with nasal *S.aureus* carriage among chronic haemodialysis patients include advanced age, insulin-dependent diabetes and preceding antimicrobial therapy. However, it seems unlikely that age per se accounts for these findings. Statistically, elderly patients with diabetic nephropathy represent the majority of current haemodialysis populations. Moreover, a recent survey screening 500 residents of three nursing homes in Germany yielded 36.6 % isolates of *S. aureus* but none of MRSA. Other large-scale studies performed in Germany found nasal MRSA colonization of 4.8% in geriatric rehabilitation and of 2.2 % or 1.1. % in nursing home residents. Furthermore, among diabetics receiving diet alone as therapy [24], the highest prevalence of *S. aureus* colonization was observed. The overwhelming proportion of our patients had undergone a prolonged episode of hospitalisation during the 12 months prior to screening. The importance of preceding stays in hospitals has been also highlighted by a case-control study of nasal surveillance cultures performed at hospital admission on 726 non-renal patients. The multivariate analysis revealed that hospitalisation during the last 12 months had the highest odds ratio [25]. Therefore, it is highly likely that many of our patients acquired MRSA during prior to contact with other health care facilities.

There are three major reservoirs of hospital acquired MRSA: patients, healthcare workers and the inanimate environment. Other hospitalised patients clearly represent the greatest source from which transmission occurs. However colonized health care workers can also transmit the organism. Six percent of all employees of our dialyses centre, but 13 % of our renal nurses were nasal carriers of MRSA in our facility. Few other studies have addressed the issue of colonized personnel. The investigations by Goldblum et al. [26] published 1978 showed that normal HD unit personnel having 40 hours per week exposure to the out-clinic setting had a slight increase in nasal *S. aureus* carriage over normal subjects (22% vs. 12%). The greek report [14] found a prevalence of *S. aureus*

nasal carriage of 17 % among staff (3 out of 18), but only 1 nurse was detected to be a MRSA nasal carrier (6%). Although colonization /infection in haemodialysis patients might be considered community acquired by admitting staff, the organisms may in fact have been nosocomially acquired. Molecular typing of MRSA strains by the use of the PFGE technique revealed that the 16 MRSA strains tested belonged to different clones demonstrating that nasal carriage of our haemodialysis patients is not the result of spread of these bacteria among patients and personnel. The increased mobility of renal patients, together with their access to multiple health institutions may contribute to the dissemination of different strains of MRSA throughout the region.

Preventing transmission of MRSA among chronic haemodialysis patients requires implementation of comprehensive infection control practices. Among these, hand hygiene is the most important. As a result of an outbreak of MRSA infections, our institution routinely screens haemodialysis patients upon first admission, transfer from another dialysis facility or re-admission after hospitalisation. Mupirocin ointment was given to all patients with nasal MRSA carriage. Follow up nasal cultures (up to three months) confirmed eradication of nasal MRSA colonization. Neither resistance nor recolonization was a problem in our study. The efficacy of elimination of nasal MRSA carriage to reduce the incidence of infections among patients undergoing haemodialysis has been demonstrated by several investigations. The application of antiseptics resulted in the elimination of other MRSA colonized body-sites. However, the routine application of mupirocin to the nose of all patients has potentially important implications for the emergence of drug resistance. Individual renal units will be required to develop tailored strategies for mupirocin use. For example, identifying and treating carriers alone will result in lower mupirocin costs and is likely to exert less pressure on MRSA to develop mupirocin resistance.

Strict isolation practices prevented introduction and dissemination of MRSA in hospitals of Scandinavian countries, but were less successful in the USA and Great Britain. Our patients with nasal MRSA carriage were treated in a separate ward until repeated demonstration of MRSA eradication. Osono et al. reported that "isolating haemodialysis" reduced the frequency of patients with MRSA infection from 4.5 % to 2.9 % [12].

The prevalence of nasal carriage of MRSA in out-patient haemodialysis patients has dramatically increased. Additional studies are needed to assess the practicability and the clinical benefit of specific infection control measures - screening, topical administration of mupirocin to carriers or contact precautions such as isolating haemodialysis patients to prevent transmission in out-patient dialysis facilities.

The authors declare no potential conflict or interest.

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*Address for correspondence:*

Priv.-Doz. Dr. med. Stephan Lederer  
 KfH Nierenzentrum Muenchen – Laim  
 Elsenheimerstr. 63  
 80336 Muenchen  
 Germany  
 Phone: +49 89 5472670  
 Fax: +49 89 51739989