Nosocomial *Staphylococcus aureus* Bacteremia among Nasal Carriers of Methicillin-resistant and Methicillin-susceptible Strains

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OBJECTIVES: To determine the relevance of nasal carriage of *Staphylococcus aureus*, either methicillin-sensitive (MSSA) or methicillin-resistant (MRSA), as a risk factor for the development of nosocomial *S aureus* bacteremia during an MRSA outbreak.

PATIENTS AND METHODS: In this prospective cohort study, 488 patients admitted to an intensive care unit (ICU) during a 1-year period were screened with nasal swabs within 48 hours of admission and weekly thereafter in order to identify nasal *S aureus* carriage. Nasal staphylococcal carriers were observed until development of *S aureus* bacteremia, ICU discharge, or death.

RESULTS: One hundred forty-seven (30.1%) of 488 patients were nasal *S aureus* carriers; 84 patients (17.2%) harbored methicillin-sensitive *S aureus*; and 63 patients (12.9%) methicillin-resistant *S aureus*. Nosocomial *S aureus* bacteremia was diagnosed in 38 (7.7%) of 488 patients. Rates of bacteremia were 24 (38%) of the MRSA carriers, eight (9.5%) of the MSSA carriers, and six (1.7%) of noncarriers. After adjusting for other predictors of bacteremia by means of a Cox proportional hazard regression model, the relative risk for *S aureus* bacteremia was 3.9 (95% confidence interval, 1.6–9.8; $P = 0.002$) for MRSA carriers compared with MSSA carriers.

CONCLUSIONS: Among ICU patients, nasal carriers of *S aureus* are at higher risk for *S aureus* bacteremia than are noncarriers; in the setting of an MRSA outbreak, colonization by methicillin-resistant strains represents a greater risk than does colonization by MSSA and strongly predicts the occurrence of MRSA bacteremia. *Am J Med.* 1996;100:509–516.

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This paper was presented in part at the 33nd meeting of the ICAAC, New Orleans, Louisiana, October 1993.

This work was supported in part by grant (Fis 94/1112) from Fondo de Investigaciones Sanitarias, National Health Service, Madrid, Spain.

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Manuscript submitted July 28, 1995 and accepted in revised form January 5, 1996.

Although *Staphylococcus aureus* has maintained its role as one of the most common nosocomial pathogens since the 1950s, a renewed interest in nosocomial staphylococcal infections has emerged in recent years, since methicillin-resistant *S aureus* (MRSA) has been reported with increasing frequency worldwide.[1–4] In large tertiary hospitals, outbreaks of MRSA are commonly encountered in critical care areas,[5] where colonized and infected patients constitute a significant reservoir and a source of spreading to other hospitalized patients.

During these outbreaks, MRSA does not simply replace methicillin-sensitive strains but seems to emerge as a distinct microorganism, increasing the overall number of staphylococcal infections.[6] During the outbreak of MRSA infections detected at our institution at the end of 1989, we observed a high incidence of MRSA bacteremia among nasal *S aureus* carriers admitted to the intensive care unit (ICU) with nasal staphylococcal carriage, while the incidence of nosocomial bacteremia due to methicillin-sensitive strains has remained unchanged.[7] Stable nasal staphylococcal carriage has been considered to play an important role in the pathogenesis of surgical staphylococcal wound infections,[8–10] as well as in patients on hemodialysis with *S aureus* bacteremia.[11–13] However, its role in the subsequent development of nosocomial bloodstream infections in critically ill patients admitted to the ICU, where cross infections may be frequent, is uncertain.

We therefore undertook a prospective study among ICU patients to evaluate the relevance of nasal carriage of *S aureus*, either methicillin-sensitive or methicillin-resistant, as a risk factor for the development of nosocomial *S aureus* bacteremia in the setting of an MRSA outbreak.

PATIENTS AND METHODS

The study was carried out in the Hospital de Bellvitge, a 1,000-bed teaching hospital for adult patients in Barcelona. Our hospital has three medical-

surgical ICUs with a total of 36 beds, and an annual admittance rate of 600–700 patients.

Infection Control Policy

Nosocomial infection surveillance has been carried out in our hospital over the past 15 years. All patients with bacteremia identified daily at our microbiology laboratory are visited by an infectious disease physician who fills out a computer-assisted protocol and provides medical advice when indicated.

The MRSA Infection Control Program was introduced in 1990, when the initial MRSA isolates were detected, as has previously been reported.[7] The MRSA patients were daily identified by laboratory surveillance. The control measures applied were as described below.

In surgical and medical wards the program includes identification and isolation of all patients with MRSA colonization or infection, use of nasal mupirocine for nasal carriers among health care workers and colonized patients,[14] reinforcement of careful handwashing, and educational programs. In the ICU the program includes screening of patients with nasal swabs for early MRSA detection and isolation purposes. Treatment with nasal mupirocine ointment was not considered for MRSA-colonized patients due to the potential risk of developing mupirocine resistance among critically ill patients with nasogastric tubes, endotracheal intubation, or tracheostomy.[14,15] Health-care workers colonized with MRSA were treated with a 5-day course of intranasal mupirocine as has been recommended.[14] Treatment with nasal mupirocine was not administrated to patients or health-care workers colonized with MSSA strains.

Patients and Definitions

All patients admitted to ICUs from March 1991 to April 1992 for more than 48 hours were included in the study. Patients were weekly screened with nasal swabs in order to identify nasal staphylococcal carriage. Blood cultures were performed when bacteremia was suspected by the attending physician. All nasal staphylococcal carriers were prospectively surveyed until progression to one of the following situations: *S aureus* bacteremia, ICU discharge, or death. Significant clinical and epidemiological features of all nasal carriers occurring during their stay in the ICU were included in a computer-assisted protocol.

Nasal staphylococcal carriage was defined as the presence of *S aureus* in nares culture at any period during ICU hospitalization. Patients with transient carriage or low level carriers (one or more negative cultures after initial positive detection) were also considered staphylococcal colonized patients.

Patients were considered to have *S aureus* bacteremia when one or more blood cultures were positive for *S aureus* in a clinical setting of infection. The episode of bacteremia was considered acquired in the ICU if it appeared 72 hours after admission to this area and no evidence of staphylococcal infection was present at admission.

Primary bacteremia was defined according to CDC criteria[18] as those episodes of bacteremia of unknown source and those with bacteremia due to intravascular catheter infection. Secondary bacteremia was considered when a portal of entry was clinically evident. Length of nasal *S aureus* carriage was defined as the number of days of nasal staphylococcal carriage from the day of the first nasal swab positive for *S aureus* to the day of *S aureus* bacteremia, ICU discharge, or death.

Underlying diseases were classified into three groups according to the McCabe classification:[16] group 1 includes chronic or curable disease; group 2 includes malignancy or any other disease with a life expectancy of less than 5 years; and group 3 includes diseases with life expectancy of less than 1 year. Severity of illness was calculated by means of evaluation of the Simplified Acute Physiologic Score (SAPS)[17] measured at ICU admission and also measured on the day of detection of nasal colonization.

Antibiotic therapy was considered when the patient received one or more antimicrobial agents for more than 48 hours during the ICU stay. Antibiotic therapy was divided into two periods: those administered during ICU stay before the day that staphylococcal colonization was detected and those received after staphylococcal colonization and up to bacteremia, discharge, or death. Intravascular catheterization, urinary catheter, mechanical ventilation, or tracheostomy were considered if they were in place for more than 48 hours during the ICU stay.

Microbiological Studies and Molecular Typing

Screening swabs collected from the anterior nares of ICU patients submitted to the laboratory for MRSA screening were inoculated onto mannitol-salt agar plates. All cultures were incubated at 35°C for 2 days and examined daily for evidence of growth. Blood cultures were performed by inoculating 5–10 mL of blood into a commercial two-bottle system (BACTEC system; Becton Dickinson, Diagnostic Instrument System, Sparks, MI). Gram-positive, catalase-positive cocci were identified as *S aureus* in accordance with their growth characteristics on mannitol-salt agar, DNA hydrolysis, latex agglutination (Slidex StaphKit; Biomerieux, France) and the coagulase reaction. Susceptibility of oxacillin was

tested by disk diffusion using a 1-μg oxacillin disk and standard zone size criteria.[19] The minimum inhibitory concentration (MIC) was determined in a representative sample of MRSA strains by commercial plates (Pos Combo Panel 4I, MicroScan R, West Sacramento, CA), with two oxacillin dilutions wells of 1 and 2 μg/mL, supplemented with 2% sodium chloride. The microdilutions trays were inoculated with an inoculum of 10^5 cfu/mL and incubated at 35°C for 24 hours. Following the NCCLS criteria, the organism was considered resistant to oxacillin if the MIC was greater than 2 μg/mL.

The molecular epidemiology of the MRSA outbreak in Hospital de Bellvitge has been recently described.[20] For the current study, similar techniques (pulsed-field gel electrophoresis and *mecA* polymorphism analysis) were applied to assess the identity among colonizing and bacteremic strains of MRSA and MSSA.

Statistical Analysis

For purpose of data analysis, patients with MRSA carriage and with prior ICU MSSA nasal colonization (MRSA recolonization) were considered only as MRSA carriage. Patient characteristics and several other clinically relevant variables present before nasal carriage were analyzed in MRSA carriers and compared with MSSA carriers.

Rates of nosocomial *S aureus* bacteremia were determined in noncarriers, MRSA carriers, and MSSA carriers. Risk factors for nosocomial *S aureus* bacteremia among nasal carriers were analyzed using univariate and multivariate analyses. The Chi-square or Fisher's exact tests were used to compare proportions and the Student *t*-test to compare means. Cumulative Kaplan-Meier plots were constructed with day of nasal *S aureus* carriage as the starting point and the first episode of bacteremia as the end point, and curves were compared by means of the log rank test. To determine the independent predictors of bacteremia, we performed a Cox proportional-hazards regression analysis, including the following covariates: type of nasal carriage (MRSA versus MSSA), SAPS at time of colonization, antibiotic therapy from day of colonization to bacteremia (in cases) or discharge (in controls), and three or more intravascular catheters in place.

A *P* value less than 0.05 was considered statistically significant, and all reported *P* values were two-sided. The statistical analysis was performed using SPSS/PC and BMDP statistical packages.

RESULTS

Nasal Staphylococcal Carriage

From March 1991 to April 1992, 488 patients admitted to our ICU for more than 48 hours were included in the study. Of them, 147 (30.1%) were nasal staphylococcal carriers; 63 (12.9%) were MRSA, and 84 (17.2%) MSSA carriers. Sixteen (25%) of the MRSA carriers had prior MSSA colonization detected during the ICU stay, but on the contrary, no case turned to MSSA after MRSA colonization. Among MSSA nasal carriers, 77 (92%) were positive for MSSA at admission to ICU, whereas the other 7 patients developed MSSA nasal colonization after the first week of ICU stay. Among MRSA carriers, 56 (89%) developed nasal carriage after the first week of ICU stay; patients with positive MRSA nasal swab culture at admission were colonized in other areas before ICU admittance (four patients), or had early ICU-acquired MRSA nasal colonization (three patients). Fifty-six (88.8%) of 63 MRSA carriers had two or more positive nasal swab cultures during ICU stay and were considered patients with stable nasal colonization, one (1.6%) patient had a negative nasal swab control after an MRSA positive culture and was considered transient colonization, and six (9.5%) patients had a positive MRSA nasal swab culture without further controls because of ICU discharge within a week of positive MRSA cultures. Among MSSA patients, 44 (52.3%) had stable colonization with two or more positive nasal swab cultures, 12 (14.2%) had transient colonization, and 28 (33.3%) had a positive nasal swab culture without subsequent controls because of ICU discharge within a week.

A comparison of clinical and epidemiological features between MRSA and MSSA carriers is shown in **Table I**. Patients with MRSA carriage, compared with MSSA carriers, had higher SAPS at ICU admission, longer length of ICU stay, surgery, and greater intravascular device use, mechanical ventilation, antibiotic therapy, tracheostomy, and pressure ulcers. In addition, length of nasal carriage was longer in MRSA than in MSSA cases. However, no differences were observed in the mortality rate during ICU stay between both groups (28.5% for MRSA and 23.8% for MSSA carriers; *P* = nonsignificant). Besides clinical findings, characterization of MRSA isolates by chromosomal DNA fingerprinting showed a dominant clone during the study period, whereas great molecular variability was observed among MSSA isolates (**Figure 1**).

Nosocomial *S aureus* Bacteremia

Nosocomial *S aureus* bacteremia was diagnosed in 38 (7.7%) of the 488 patients included in the study; 32 (84%) of these patients had prior nasal staphylococcal carriage, whereas the other six patients (16%) had negative nasal swabs performed prior to bacteremia. Among bacteremic patients with prior negative nasal swab cultures, three (one MSSA and two MRSA) remained free of nasal staphylococcal car-

TABLE I
Comparison of Clinical and Epidemiological Features between MRSA and MSSA Nasal Carriers (Univariate Analysis)

	MRSA (n = 63)	MSSA (n = 84)	*P* Value
Age (yrs) (mean ± SD)	47.2 (±20.7)	42.6 (±18.1)	0.166
Sex: male/female (%)	46 (73)/17 (27)	61 (73)/23 (27)	0.957
Severity of underlying disease:			
McCabe, Group 1 (%)	42 (66.7)	61 (72.6)	0.435
SAPS (±SD)	11.5 (±3.5)	10.2 (±3.3)	0.045
Primary diagnosis:			
COPD (%)	8 (12.7)	4 (4.8)	0.086
Polytrauma (%)	30 (47.6)	38 (45.2)	0.774
Malignancy (%)	8 (12.7)	8 (9.5)	0.540
Liver disease	2 (3.2)	12 (14.5)	0.021
Prior to staphylococcal colonization			
ICU stay: mean days (±SD)	15.0 (±10.5)	2.7 (±4.5)	<0.01
Surgery (%)	38 (60.3)	31 (36.9)	<0.01
≥3 Intravascular catheters	39 (61.9)	30 (35.7)	<0.01
Mechanical ventilation (%)	59 (93.7)	69 (82.1)	0.039
Urinary catheter (%)	61 (96.8)	81 (96.4)	0.895
Tracheostomy (%)	11 (17.5)	2 (2.4)	<0.01
Pressure ulcers (%)	6 (9.5)	0	0.013
Antibiotic Rx (%)	60 (95.2)	10 (11.9)	<0.01
Source of bacteremia			
Bacteremia (%)	24 (38.1)	8 (9.5)	<0.01
Intravascular catheter (%)	14 (58.3)	5 (62.5)	
Unknown (%)	9 (37.5)	2 (25)	
Secondary source	1 (4.1)	1 (12.5)	
Outcome			
Overall ICU mortality (%)	18 (28.5)	20 (23.8)	0.643

riage during their ICU stay, while the other three patients with MRSA bacteremia had nasal staphylococcal carriage detected after MRSA bacteremia. All bacteremic patients with nasal staphylococcal carriage had the same susceptibility pattern in nasal swabs as in blood cultures; in addition, pairs of isolates had clonal similarity by molecular typing (Figure 1). Twenty-four (38%) of 63 MRSA carriers, eight (9.5%) of 84 MSSA carriers, and six (1.7%) of 341 noncarriers developed nosocomial *S aureus* bacteremia during the study period ($P \ll 0.001$). Mean days (±SD) from nasal staphylococcal colonization to bacteremia were 11.1 (±13.4) for MRSA carriers compared with 6.1 (±5.2) for MSSA carriers ($P = 0.14$). Primary bacteremia was the most common source of bacteremia among MRSA and MSSA carriers (Table I), as well as in noncarriers (six of six episodes). Patients with MRSA colonization and with initial MSSA colonization had similar clinical and epidemiological characteristics as well as similar risk of developing *S aureus* bacteremia as patients with MRSA carriage but without initial MSSA colonization: six of 16 (37.5%) MSSA/MRSA carriers, compared with 18 of 47 (38.3%) MRSA carriers. Overall mortality from bacteremia was eight of 24 (33.3%) for MRSA cases and three of eight (37.5%) for MSSA cases (P = NS).

Nosocomial *S aureus* Bacteremia Risk Factors among Nasal Carriers

The univariate analysis comparing 32 bacteremic nasal carriers with 115 nonbacteremic nasal carriers is shown in **Table II**. There were no significant differences between the two groups in terms of age, SAPS at ICU admission, McCabe classification, and surgery. Significant differences were found in the following variables for bacteremic versus nonbacteremic carriers: SAPS measured on the day of staphylococcal colonization (11.1 ± 3.1 versus 9.9 ± 3.5, respectively), rates of nasal MRSA carriage (75% versus 33.9%), use of antibiotic therapy after staphylococcal colonization (65.6% versus 92.2%), and use of ≥3 intravascular catheters (62.5% versus 43.5%). **Figure 2** shows the Kaplan-Meier estimated probability of developing *S aureus* bacteremia after nasal colonization among both groups of carriers. The probability of developing *S aureus* bacteremia was higher in MRSA than in MSSA carriers. On the contrary, the probability of developing *S aureus* bacteremia was lower in patients who received antibiotic therapy than in those who did not (**Figure 3**). A detailed analysis of antibiotic therapy after staphylococcal colonization among bacteremic and nonbacteremic patients is shown in **Table III**. The administration of vancomycin among MRSA carriers

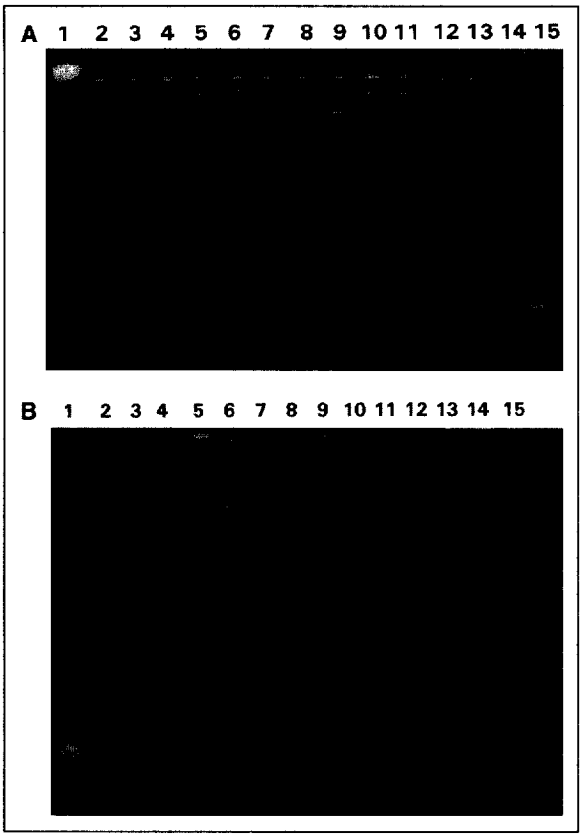

Figure 1. *Sma*I restriction patterns generated from chromosomal DNA of *S aureus* isolates after PFGE. **A.** The methicillin-resistant *S aureus* dominant clone is shown, excepting lanes 6 and 9, containing PFGE subtypes from the epidemic strain, and lane 12, with a representative from a distinct clone (lanes 1 and 15, molecular weight markers). **B.** The methicillin-susceptible *S aureus* chromosomal variety is shown on lanes 2–14. Isolates from the same patient were compared side by side; lanes 2, 6, 8, 11, and 13 contain nasal swabs from five patients included in the study; lanes 3, 7, 9, 12, and 14 contain the methicillin-susceptible *S aureus* isolated from blood cultures in the same five patients (lanes 1 and 15, molecular weight markers).

and the administration of betalactams with activity against methicillin-susceptible strains among MSSA carriers was associated with a significantly lower risk of bacteremia.

After adjustment for severity of illness measured by SAPS (day of staphylococcal colonization) and the presence of ≥3 intravascular catheters, the relative risks for *S aureus* bacteremia were 3.9 (95% confidence interval [CI], 1.6–9.8; $P = 0.002$) for MRSA carriers compared with MSSA carriers and 0.04 (95% CI, 0.01–0.1; $P \ll 0.001$) for patients who had been receiving antibiotics compared with those without antibiotics.

DISCUSSION

The epidemiology of nasal staphylococcal carriage in ICU patients, as well as its subsequent clinical consequences, are still poorly understood because few detailed investigations have been carried out in this setting. Our study, performed during an extended MRSA outbreak, documents the association between nasal *S aureus* colonization and development of bacteremia.

It has been reported that up to 25% of patients admitted to hospitals will become nasal staphylococcal carriers, often with prevalent hospital strains[21]; this figure may be higher for some populations such as diabetic patients, HIV patients, and patients on chronic hemodialysis, ranging from 40% to 60%.[13,21–23] In ICU patients, rates of carriage may vary from the 30% found in this study to 33–41% observed in other recent reports.[24,25] Our results showed that MSSA carriage was predominantly community acquired and more prevalent than MRSA carriage. Thirteen percent of our patients were colonized by the epidemic MRSA strain. Molecular epidemiology of the outbreak[20] revealed that the majority of MRSA cases were due to a single clone that appeared at the beginning of the outbreak, colonizing patients and sanitary personnel and spreading rapidly throughout the hospital.

It is noteworthy that 25% of MRSA carriers were patients with prior MSSA nasal colonization, suggesting that some individuals are more prone to colonization than others. This group of patients was included in the study because they had similar clinical and epidemiological characteristics than those with MRSA carriage alone.

Studies comparing both methicillin-sensitive and methicillin-resistant strains had shown no differences in their ability to adhere to nasal epithelial cells.[26] It is possible that the selective pressure exerted by some antibiotic therapies may facilitate recolonization by resistant strains.[14]

Host conditions favoring MRSA colonization observed in our study did not differ from those reported in other significant outbreaks,[5,27–31] such as older age, length of ICU stay, multiple antibiotic therapy, intravascular devices, mechanical ventilation, tracheostomy, and pressure ulcers. Beside these factors, MRSA carriers had significantly higher SAPS than did MSSA carriers, revealing poorer clinical condition on admission. However, the ICU mortality was similar between MRSA and MSSA carriers, suggesting that these differences had little clinical significance.

In patients on hemodialysis, several studies have emphasized the risk of bacteremia among nasal staphylococcal carriers and, more importantly, some have showed the eradication of such carriage to be highly effective in the reduction of staphylococcal infection rates.[11–13] Recently, a French multicenter study performed in five polyvalent ICUs with a high endemic rate of MRSA colonization detected the

TABLE II
Risk Factors for Nosocomial S aureus Bacteremia among Nasal Carriers Admitted to ICU

	Bacteremia (n = 32)	No Bacteremia (n = 115)	*P* Value
Mean age (yrs) (±SD)	45.7 (±21.6)	44.2 (±18.7)	0.724
Sex: male/female (%)	20 (62.5)/12 (37.5)	87 (76)/28 (24)	0.139
Severity of the underlying diseases			
McCabe Group 1 (%)	24 (75)	79 (68.7)	0.491
SAPS at ICU admission (±SD)	11.3 (±2.9)	10.6 (±3.5)	0.341
SAPS at day of colonization (±SD)	11.1 (±3.1)	9.9 (±3.5)	0.064
Surgery (%)	16 (50)	53 (46.1)	0.847
Primary diagnosis:			
COPD (%)	4 (12.5)	8 (6.9)	0.294
Polytrauma (%)	14 (43.8)	54 (47)	0.747
Malignancy (%)	6 (18.8)	10 (8.7)	0.195
Liver disease	2 (6.3)	12 (10.4)	0.735
Heart Disease (%)	1	14 (12.1)	0.192
Type of carriage			
MRSA colonization (%)	24 (75)	39 (33.9)	<0.01
ICU stay* d (±SD)	9.7 (±12.1)	15.1 (±14)	0.036
Antibiotic Therapy†			
Antibiotic therapy (%)	21 (65.6)	106 (92.2)	<0.01
Beta-lactams (%)	16 (50)	97 (84.3)	<0.01
Aminoglycosides (%)	8 (25)	18 (15.7)	0.220
Glycopeptide (%)	4 (12.5)	57 (12.5)	<0.01
Quinolones (%)	10 (31.3)	23 (20)	0.177
Other antibiotics (%)	8 (25)	27 (23.5)	0.858
Devices in place*			
Mechanical ventilation (%)	28 (87.5)	100 (87)	0.935
Urinary catheter (%)	31 (96.9)	111 (96.5)	0.922
Intravascular catheterization:			
≥3 I.V. catheters (%)	20 (62.5)	50 (43.5)	0.056

* From day of detection of nasal staphylococcal carriage to discharge (or bacteremia for bacteremic patients).
† Patients with one or more antibiotics from day of detection of nasal staphylococcal carriage to discharge (or bacteremia for bacteremic patients).
A Cox proportional hazard regression analysis (see methods) showed: MRSA colonization (RR, 3.9; 95%; CI, 1.6–9.8) and antibiotic therapy (RR, 0.04; 95% CI, 0.01–0.1) as the independent risk factors for *S aureus* bacteremia.

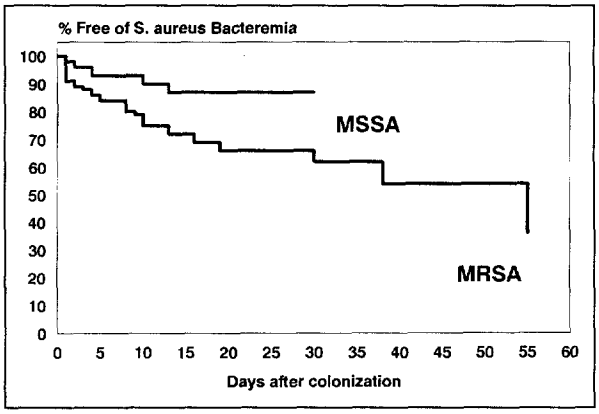

Figure 2. Kaplan-Meier estimated probability of developing *S aureus* bacteremia after nasal colonization among both groups of carriers.

presence of prior nasal colonization among patients with subsequent MRSA infections.[25]

In our series, episodes of *S aureus* bacteremia occurred almost exclusively in patients with previous nasal colonization, and most were due to definite or probable infections of intravascular catheters. Overall, these observations suggest that the majority of episodes of *S aureus* bacteremia are due to the patient's own flora, either community acquired or nosocomial acquired throughout cross transmission during hospitalization.

A recent study by Muder et al[32] reported a higher rate of staphylococcal infections among MRSA carriers than among MSSA carriers, suggesting that methicillin-resistant strains could be more virulent; however, differences in infection rates could be ascribed to underlying diseases. Similarly, we observed a significantly higher number of *S aureus* bacteremia among MRSA carriers. Therefore, we performed a proportional-hazards regression analysis, which identified MRSA carriage as an independent risk factor for bacteremia. It should be taken into account that, while the majority of variables regarding significant contributing factors for bacteremia are easily defined, others such as intravascular catheterization (which comprises days, number, and types of intravascular catheters) are not; in fact, the days of intravascular catheterization variable is similar to the

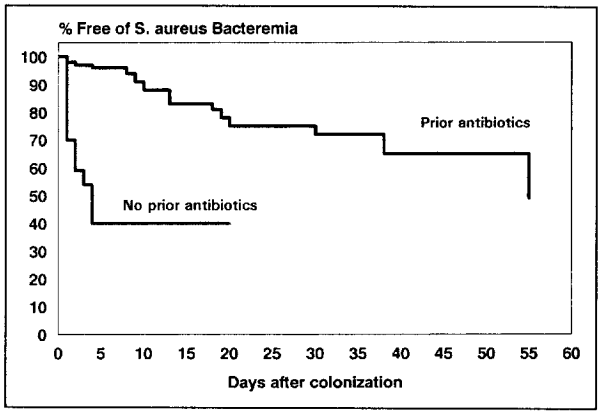

Figure 3. Kaplan-Meier estimated probability of developing *S aureus* bacteremia in patients receiving antibiotic therapy and in patients not given antibiotic therapy.

TABLE III
Antibiotic Therapy during Staphylococcal Carriage

MRSA Carriers	Bacteremia (n = 24)	No Bacteremia (n = 39)	*P* Value
Antibiotic therapy (%)	17 (70.8)	38 (97.4)	<0.01
Beta-lactams* (%)	13 (54.2)	32 (82.1)	0.017
Beta-lactams† (%)	10/20 (50)	9/14 (64.3)	0.409
Aminoglycosides (%)	7 (29.2)	7 (17.9)	0.298
Glycopeptide (%)	4 (16.7)	25 (64.1)	<0.01
Quinolones (%)	10 (41.7)	13 (33.3)	0.504
Other antibiotics (%)	8 (33.3)	21 (53.8)	0.112
MSSA Carriers	**Bacteremia (n = 8)**	**No Bacteremia (n = 76)**	***P* Value**
Antibiotic therapy (%)	4 (50)	68 (89.5)	<0.01
Beta-lactams (%)	3 (37.5)	65 (85.5)	<0.01
Aminoglycosides (%)	1 (12.5)	11 (14.5)	0.870
Glycopeptide (%)	0 (0)	32 (42.1)	0.051
Quinolones (%)	0 (0)	10 (13.2)	0.603
Other antibiotics (%)	0 (0)	6 (7.9)	0.917

* All patients with betalactam therapy; 26 of them were on simultaneous vancomycin therapy.
† Patients with betalactam therapy but without simultaneous vancomycin therapy.

days of ICU admission variable. Another limitation of our study is that it is not known whether measurement of SAPS is an adequate score for evaluating clinical condition defined as a risk factor for bloodstream infection in ICU patients.

Whether different infection rates were due to differences in intrinsic virulent properties among staphylococcal strains or to differences in clinical conditions of carriers, or to both, is difficult to assess.[33–37] In addition, some in vitro studies have failed to demonstrate different virulence factors, such as adherence, survival, enterotoxin, hemolysins, and coagulase production between MSSA and MRSA strains.[38–40]

Another finding of the study was that the administration of antibiotic therapy during staphylococcal colonization may diminish the probability of developing bacteremia. This was especially evident for patients receiving glycopeptide antibiotics. However, it should be emphasized that the administration of prophylactic antibiotics for preventing nosocomial bacteremia is not currently an accepted clinical practice.

Several conclusions can be drawn from our experience: among ICU patients, nasal carriers of *S aureus* are at higher risk for *S aureus* bacteremia than are noncarriers; therefore, attempts to eradicate carrier state may be clinically useful. During outbreaks, patients with MRSA carriage are at very high risk of developing bacteremia. Besides the reinforcement of other control measures, improving care of intravascular catheters could reduce the incidence of bacteremic episodes. Further studies are needed to evaluate results derived from eradication of nasal carriage in ICU patients.

REFERENCES

1. Boyce JM. Increasing prevalence of methicillin-resistant *Staphylococcus aureus* in the United States. *Infect Control Hosp Epidemiol.* 1990;11:639–642.
2. Panlilio AL, Culver DH, Gaynes RP, et al. Methicillin-resistant *Staphylococcus aureus* in U.S., 1975–1991. *Infect Control Hosp Epidemiol.* 1992;13:582–586.
3. Voss A, Milatovic D, Wallrauch-Schwarz C, et al. Methicillin-resistant *Staphylococcus aureus* in Europe. *Eur J Clin Micro Infect Dis.* 1994,13:50–55.
4. Faoagali JL, Thong ML, Grant D. Ten years' experience with methicillin-resistant *Staphylococcus aureus* in a large Australian hospital. *J Hosp Infect.* 1992;20:113–119.
5. Thompson RL, Cabezudo I, Wenzel RP. Epidemiology of nosocomial infections caused by methicillin-resistant *Staphylococcus aureus*. *Ann Intern Med.* 1982;97:309–317.
6. Boyce JM, White RL, Spruill EY. Impact of methicillin-resistant *Staphylococcus aureus* on the incidence of nosocomial staphylococcal infections. *J Infect Dis.* 1983;148:763.
7. Pujol M, Peña C, Pallares R, et al. Risk factors for nosocomial bacteremia due to methicillin-resistant *Staphylococcus aureus*. *Eur J Clin Micro Infect Dis.* 1994;13:96–102.
8. Weinstein HJ. The relation between the nasal staphylococcal carriage state and the incidence of post-operative complications. *NEJM.* 1959;260:1303–1308.
9. Henderson RJ, Williams REO. Nasal disinfection in prevention of postoperative staphylococcal infection of wounds. *BMJ.* 1961;2:330–333.
10. Kluytmans JAJW, Mouton JW, Ijzerman EPF, et al. Nasal carriage of *Staphylococcus aureus* as a major risk factor for wound infections after cardiac surgery. *J Infect Dis.* 1995;171:216–219.
11. Yu VL, Goetz A, Wagener M, et al. *Staphylococcus aureus* nasal carriage and infection in patients on hemodialysis. Efficacy of antibiotic prophylaxis. *NEJM.* 1986;315:91–96.
12. Chow JW, Yu VL. *Staphylococcus aureus* nasal carriage in hemodialysis patients: its role in infection and approaches to prophylaxis. *Arch Intern Med.* 1989;149:1258–1262.
13. Boelaert JR, De Baere YA, Geernaert MA, et al. The use of nasal mupirocin ointment to prevent *Staphylococcus aureus* bacteraemias in haemodialysis patients: an analysis of cost-effectiveness. *J Hosp Infect.* 1991;19(suppl B):41–46.
14. Working Party Report. Revised guidelines for the control of epidemic methicillin-resistant *Staphylococcus aureus*. *J Hosp Infect.* 1990;16:351–377.
15. Casewell MW, Hill RLR. The carrier state: methicillin-resistant *Staphylococcus aureus*. *J Antimicrob Chemother.* 1986;18,suppl A:1–12.

16. McCabe WR, Jackson GG. Gram negative bacteremia. *Am J Med.* 1962;110:847–855.
17. Le Gall JR, Loirat P, Alpérovich A, et al. A simplified acute physiology score for ICU patients. *Crit Care Med.* 1984;12:975–977.
18. Garner JS, Jarvis WR, Emori TG, et al. CDC definitions for nosocomial infections, 1988. *Am J Infect Control.* 1988;16:128–140.
19. NCCLS. *Performance Standards for Antimicrobial Disk Susceptibility Test. 4th ed.* Approved standard M2-A4.NCCLS, Villanova, Penn; 1990.
20. Dominguez MA, de Lencastre H, Liñares J, Tomasz A. Spread and maintenance of a dominant methicillin-resistant *Staphylococcus aureus* (MRSA) clone during an outbreak of MRSA disease in a Spanish hospital. *J Clin Microbiol.* 1994;32:2081–2087.
21. Willems FTC. Epidemiology of nasal carriage of *Staphylococcus aureus.* In: van der Meer JWM, ed. *Nasal Carriage of Staphylococcus aureus. A Round-Table Discussion.* Amsterdam: Excerpta Medica; 1990:3–6.
22. Tuazon CU, Perez A, Kishaba T, Sheagren JN. *Staphylococcus aureus* among insulin-injecting diabetic patients: an increased carriage rate. *JAMA.* 1975;231:1272.
23. Weinke T, Schiller R, Fehrenbach FJ, Pohle H.D. Association between *Staphylococcus aureus* nasopharyngeal colonization and septicemia in patients infected with the human immunodeficiency virus. *Eur J Clin Micro Infect Dis.* 1992;11:985–989.
24. Regnier B, Decré D. Eradication of nasal carriage of *Staphylococcus aureus* by mupirocin in an intensive care unit. In: van der Meer JWM, ed. *Nasal Carriage of Staphylococcus aureus. A Round-Table Discussion.* Amsterdam: Exerpta Medica; 1990:7–14.
25. Brun-Buisson C, Rauss A, Legrand P, et al. Traitement du portage nasal de *Staphylococcus aureus* par la mupirocie nasal et prévention des infections acquises en préanimation. Etude multicentrique contrôlée. *Med Mal Infect.* 1994;24:1229–1239.
26. Ward TT. Comarison of in vitro adherence of methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* to human nasal epithelial cells. *J Infect Dis.* 1992;166:400–404.
27. Crossley K, Loesch D, Landesman B, et al. An outbreak of infections caused by *Staphylococcus aureus* resistant to methicillin and aminoglycosides. I. Clinical studies. *J Infect Dis.* 1979;139:273–287.
28. Peacock JE, Marsik FJ, Wenzel RP. Methicillin-resistant *Staphylococcus aureus*: introduction and spread within a hospital. *Ann Intern Med.* 1980;93:526–532.
29. Linnemann CC, Mason M, Moore P, et al. Methicillin-resistant *Staphylococcus aureus*: experience in a general hospital over four years. *Am J Epidemiol.* 1982;115:941–950.
30. Cohen SH, Morita MM, Bradford M. A seven-year experience with methicillin-resistant *Staphylococcus aureus. Am J Med.* 1991;91(suppl 3B):233S–237S.
31. Coello R, Jimenez J, Garc[ilac]a M, et al. Prospective study of infection, colonization and carriage of methicillin-resistant *Staphylococcus aureus* in an outbreak affecting 990 patients. *Eur J Clin Micro Infect Dis.* 1994;13:74–81.
32. Muder RR, Brennen C, Wagener MM, et al. Methicillin-resistant staphylococcal colonization and infection in a long-term care facility. *Ann Intern Med.* 1991;114:107–112.
33. Myers JP, Linnemann CC. Bacteremia due to methicillin-resistant *Staphylococcus aureus. J Infect Dis.* 1982;145:532–536.
34. Craven DE, Kollisch NR, Hsieh CR, et al. Vancomycin treatment of bacteremia caused by oxacillin-resistant *Staphylococcus aureus*: comparison with B-lactam antibiotic treatment of bacteremia caused by oxacillin-sensitive *Staphylococcus aureus. J Infect Dis.* 1983;147:137–143.
35. Lewis E, Saravolatz LD. Comparison of methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* bacteremia. *Am J Infect Control.* 1985;13:109–114.
36. French GL, Cheng AFB, Ling JM, et al. Hong Kong strains of methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* have similar virulence. *J Hosp Infect.* 1990:15;117–125.
37. Hershow RC, Khayr WF, Smth N. A comparison of clinical virulence of nosocomially acquired methicillin-resistant *Staphylococcus aureus* infections in a university hospital. *Infect Control Hosp Epidemiol.* 1992;13:587–593.
38. Coleman DC. Methicillin-resistant *Staphylococcus aureus*: molecular epidemiology and expression of virulence determinants. In: Cafferkey MT, ed. *Methicillin-Resistant Staphylococcus aureus. Clinical Management and Laboratory Aspects. Infectious Disease and Therapy.* New York: Marcel Dekker; 1992:37–56.
39. Duckworth GJ, Jordens JZ. Adherence and survival properties of an epidemic methicillin-resistant strain of *Staphylococcus aureus* compared with those of methicillin-sensitive strains. *J Med Microbiol.* 1990:32;195–200.
40. Joerdens JZ, Duckworth GJ, Williams RJ. Production cf virulence factors by epidemic methicillin-resistant *Staphylococcus aureus* in vitro. *J Med Microbiol.* 1989:30;245–252.