

COLONIZATION WITH METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN ICU PATIENTS: MORBIDITY, MORTALITY, AND GLYCOPEPTIDE USE

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ABSTRACT

OBJECTIVE: To determine the impact of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization on the occurrence of *S aureus* infections (methicillin-resistant and methicillin-susceptible), the use of glycopeptides, and outcome among intensive care unit (ICU) patients.

DESIGN: Prospective observational cohort survey.

SETTING: A medical-surgical ICU with 10 single-bed rooms in a 460-bed, tertiary-care, university-affiliated hospital.

PATIENTS: A total of 1,044 ICU patients were followed for the detection of MRSA colonization from July 1, 1995, to July, 1 1998.

METHODS: MRSA colonization was detected using nasal samples in all patients plus wound samples in surgical patients within 48 hours of admission or within the first 48 hours of ICU stay and weekly thereafter. MRSA infections were defined using Centers for Disease Control and Prevention standard definitions, except for ventilator-associated pneumonia and catheter-related infections, which were defined by quantitative distal culture samples.

RESULTS: One thousand forty-four patients (70% medical patients) were included in the analysis. Mean age was 61 ± 18 years; mean Simplified Acute Physiologic Score (SAPS) II was 36.4 ± 20 ; and median ICU stay was 4 (range, 1-193) days. Two hundred thirty-one patients (22%) died in the ICU. Fifty-four patients

(5.1%) were colonized with MRSA on admission, and 52 (4.9%) of 1,044 acquired MRSA colonization in the ICU. Thirty-five patients developed a total of 42 *S aureus* infections (32 MRSA, 10 methicillin-susceptible). After factors associated with the development of an *S aureus* infection were adjusted for in a multivariate Cox model (SAPS II >36: hazard ratio [HR], 1.64; $P=.09$; male gender: HR, 2.2; $P=.05$), MRSA colonization increased the risk of *S aureus* infection (HR, 3.84; $P=.0003$). MRSA colonization did not influence ICU mortality (HR, 1.01; $P=.94$). Glycopeptides were used in 11.4% of the patients (119/1,044) for a median duration of 5 days. For patients with no colonization, MRSA colonization on admission, and ICU-acquired MRSA colonization, respectively, glycopeptide use per 1,000 hospital days was 37.7, 235.2, and 118.3 days. MRSA colonization per se increased by 3.3-fold the use of glycopeptides in MRSA-colonized patients, even when an MRSA infection was not demonstrated, compared to non-colonized patients.

CONCLUSIONS: In our unit, MRSA colonization greatly increased the risk of *S aureus* infection and of glycopeptide use in colonized and non-colonized patients, without influencing ICU mortality. MRSA colonization influenced glycopeptide use even if an MRSA infection was not demonstrated; thus, an MRSA control program is warranted to decrease vancomycin use and to limit glycopeptide resistance in gram-positive cocci (*Infect Control Hosp Epidemiol* 2001;22:687-692).

Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a cause of endemic nosocomial infections throughout the world. Among the consequences of extensive glycopeptide use, vancomycin-resistant enterococci species¹ and, more recently, glycopeptide-intermediate *S aureus*²⁻⁵ are harbingers of a major therapeutic problem for the third millennium, rendering interventions to eliminate MRSA, or at least to limit the spread of MRSA, more important than ever. The results of the European Prevalence of Infection in Intensive Care (EPIC)⁶ study reported that the highest prevalence of MRSA strains was found in Italy (81%) and France (78.6%). Moreover, MRSA strains were endemic in several health centers: burn units, dialysis centers, long-term-care facilities, and intensive

care units (ICUs). The epidemiology of staphylococcal colonization in ICU patients and its clinical consequences are still poorly understood, because few detailed epidemiological studies have been carried out in this setting. In particular, the effect of MRSA colonization on patient mortality is largely unknown.

In our hospital, where MRSA has been endemic for many years, we evaluated the consequences of MRSA colonization in a large cohort of critically ill patients to assess the relation between MRSA colonization and the occurrence of *S aureus* nosocomial infections, to examine the influence of MRSA colonization on mortality, and to evaluate the impact of MRSA colonization on glycopeptide use.

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METHODS

Study Population

This prospective study was conducted in a medical-surgical ICU having 10 single-bed rooms at the Fondation Hôpital Saint Joseph (Paris, France), a 460-bed, adult, tertiary-care, university-affiliated hospital. From July 1, 1995 to July 1, 1998, all consecutive patients who were admitted in the ICU were enrolled in the study and evaluated for MRSA colonization. Only the first ICU admission during the same hospital stay was included in the analysis.

For each patient, we extracted from the ICU database the following parameters: age, gender, severity of illness on admission using the Simplified Acute Physiologic Score (SAPS) II,⁷ need for mechanical ventilation during the first 24 hours, reason for ICU admission, transfer from wards, duration of ICU stay, and ICU mortality.

A computerized pharmacy database was used to determine the patient's daily use of glycopeptides during ICU stay. The reason for glycopeptide use was reviewed retrospectively by one of the investigators (HK).

As this study was only epidemiological and no invasive measures were required to study patients, the Institutional Review Board of Fondation Hôpital Saint Joseph waived the need for informed consent.

Microbiological Surveillance

The detection of MRSA colonization was assessed on nasal samples collected on the admission day or within the first 48 hours of ICU stay, and every Tuesday until MRSA was detected. Samples of wounds in surgical patients also were assessed. Samples were obtained using premoistened cotton-tipped swabs.

MRSA were detected by their ability to grow on Chapman agar containing 4 mg/L of oxacillin after incubation for 24 hours at 37°C. As a presumptive test, Pastorex Staph-plus (Sanofi Diagnostics Pasteur SA, Marnes-La Coquette, France) was used. Isolates were confirmed for identification as *S aureus* by their ability to ferment mannitol and a positive reaction to coagulase.

Definitions of Colonization and Infection

Colonization was considered if one nasal sample was positive for MRSA. Colonization was reported as ICU-acquired only if there was no history of prior MRSA colonization or infection and no positive sample had been detected on admission, plus at least one surveillance sample yielding MRSA after 48 hours of hospitalization. Colonization on admission included patients known to have been colonized outside of the ICU.

S aureus nosocomial infections were infections occurring at least 48 hours after ICU admission, without incubation on admission. Ventilator-associated pneumonia was defined by a new and persistent infiltrate on chest radiograph and a positive quantitative culture of a distal sampling from either a broncho-alveolar lavage (10^4 colony-forming units [CFUs]/mL)⁸ or a plugged telescopic-brush catheter (10^3 CFUs/mL).⁹ A diagnosis of catheter-related infection was established if there were general signs of

infection together with culture of the catheter tip yielding at least 10^3 CFUs/mL.¹⁰ The other types of MRSA infections were defined according to Centers for Disease Control and Prevention (CDC) standard definitions.¹¹

Infection Control Program

From the time of the study until the present, the following infection control program to limit the spread of MRSA has been used in the unit: screening of all admitted patients for MRSA; isolation of all patients until they are proven not to be colonized; identification of MRSA patients by adding a flag in their chart; and reinforced barrier precautions with gloves and gowns for all contacts. Hand washing with a 10% povidone-iodine antiseptic preparation is performed before and after each patient contact. Nasal decontamination with mupirocin was not used.

The antibiotic choice for infections depended on clinical conditions, microbiological results, and the physician's discretion. However, to regulate the use of glycopeptides, we instituted a policy that required completion of a glycopeptide continuation form to continue the drug after 72 hours. Subsequent therapy was based on culture-documented resistant organism or, in case of negative cultures, reevaluation and approval by the senior physicians of the unit.

Statistical Analysis

Bivariate analyses used the Mann-Whitney or Fisher's Exact Test for uncensored data and the log-rank test for censored data. Comparison between the consumption of glycopeptides per 1,000 days during non-colonized, colonized, and infected periods was performed assuming a Poisson distribution within each of the groups. All of the variables tested were introduced under their native coding into the multivariate models except age and SAPS II, which were categorized according to the median value observed in the entire sample.

Risk factors for MRSA carriage at admission.

An unconditional logistic regression analysis was performed with variables recorded on ICU admission with a P value of $\leq .2$, as assessed by univariate analysis, to control for all confounding factors. Variables were introduced into the logistic regression in a backward manner to construct the final model; the significance level for staying in the model was 0.1.

Risk factors for ICU death.

The main endpoint was overall survival from the ICU. Patients who were discharged alive from the ICU were censored at the time of their discharge. The Kaplan-Meier estimate of survival was computed. We first studied the prognostic value for death of several baseline characteristics (age, SAPS II, gender, transfer from ward, tracheal intubation, reason for ICU admission). The search for prognostic factors was based on the log-rank test, which compares the distribution of survival times in several subsets. Variables found to be associated with the outcome (ie, influencing the survival time) by the log-rank test at the 5% level were then entered into a Cox model. Thus, variables that did not add any information to the remainders were not kept in the model. A backward procedure allowed us to select sequentially the variables that

were significantly related to outcome, as tested by the likelihood ratio test at the 10% level. Hazard ratios (HRs) were computed (with 95% confidence intervals [CI₉₅]) and were used to measure relative risk. As a second step, MRSA acquisition was introduced in the final model. The risk of death (ie, the probability that an individual [i] died at a time [t], conditional on his having survived to that time) on p explanatory covariates, Zi(t), was expressed through the Cox model as follows:

$$\alpha_i(t, Z_i) = \alpha_0(t) \exp(\beta_1 t Z_{i1}[t] + \beta_2 t Z_{i2}[t] + \dots + \beta_n t Z_{in}[t]),$$

where the p covariates appearing in the model with a corresponding β coefficient either were assessed at baseline ($Z_i(t) = Z_i$), such as SAPS II or intubation, or were time-dependent (eg, the acquisition of MRSA). The time-dependent variables took the "0" value before MRSA acquisition and took the "1" value between the time of MRSA acquisition and the time of ICU discharge.

Risk factors for *S aureus* infection. The time to acquisition of the first MRSA infection was computed. The statistical procedure used was similar to that used for computing ICU death.

Statistical analyses were performed using BMDP (BMDP, Los Angeles, CA). Levels of significance were represented by *P* values derived from two-sided tests. Unless indicated, a *P* value of $\leq .05$ was considered to indicate statistical significance.

RESULTS

Colonization

From July 1, 1995 to July 1, 1998, 1,044 patients were admitted to the ICU and constituted the study group. The 1,044 patients had a mean age of 61 ± 18 years and 741 (71%) of them were medical patients. The mean SAPS II score was 36.4 ± 20 . We obtained a total of 2,104 surveillance samples (mean, 2.01 per patient; median, 1; range, 1-28). One hundred forty-eight samples (7%) were positive from the nasal site. The median ICU stay was 4 (range, 1-193) days. Of the 1,044 patients, 106 (10.1%) had MRSA colonization. Of the 106 MRSA cases, 54 (5.1%) were imported and 52 (4.9%) were ICU-acquired, with a ratio of acquired to imported of 0.96. The Figure displays the proportion of ICU patients remaining free from MRSA colonization, by duration of ICU stay. The Table shows the demographics and clinical characteristics of the colonized and non-colonized patients. In a stepwise logistic regression that included age, severity on admission (using the SAPS II score), need of endotracheal tube before admission, the medical status of the patient, and having been transferred from a ward, only two factors remained independently associated with MRSA colonization on admission: transfer from wards (odds ratio [OR], 2.79; CI₉₅, 1.4-5.58; *P* = .002) and intubation at admission (OR, 2.89; CI₉₅, 1.51-5.53; *P* = .004).

Risk Factors for *S aureus* Infection

A total of 42 *S aureus* infections occurred in 35 patients: 32 were MRSA and 10 were methicillin-sensitive *S*

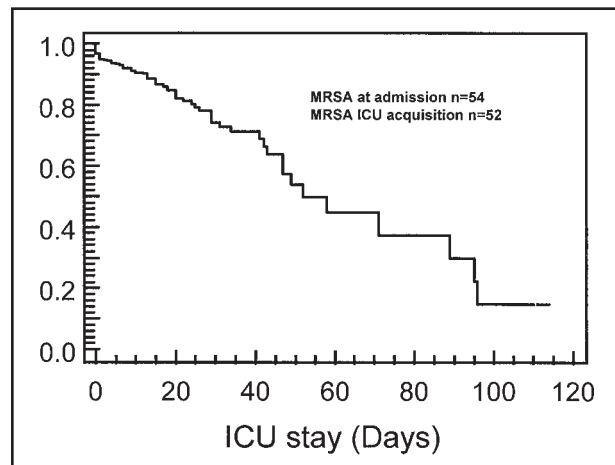


FIGURE. Kaplan-Meier estimates of patients free from methicillin-resistant *Staphylococcus aureus* (MRSA) colonization during their intensive care unit (ICU) stay.

aureus ([MSSA] ventilator-associated pneumonias, 6; catheter-related infections, 4). MRSA infections included 14 ventilator-associated pneumonias, 10 catheter-related infections or primary bacteremias, 4 urinary infections, 3 wound infections, and 1 sinusitis. Among these 35 patients, 29 (83%) were colonized with MRSA. Seven patients were colonized and infected on the same day. For the remaining, the median time between the detection of colonization and the diagnosis of *S aureus* infection was 12.5 (range, 1-66) days.

In univariate analysis, patients with *S aureus* infections were more often male (28/35 vs 605/1,009; *P* = .02) and transferred from a hospital ward (24/35 vs 504/1,009; *P* = .036). They were more severely ill on ICU admission (SAPS II score, 43.5 vs 36.2; *P* = .04) and more frequently intubated (35/35 vs 544/1,009; *P* < .001). *S aureus* infections occurred more frequently in patients colonized with MRSA on admission (7/35 vs 46/1,009; *P* < .001).

When the first episode of infection was taken into account, only three variables were independently associated with the occurrence of *S aureus* infections: SAPS II score >36 (HR, 1.64; CI₉₅, 0.8-3.39; *P* = .09), male gender (HR, 2.23; CI₉₅, 1.4-9.5; *P* = .05), and colonization with MRSA (HR, 3.84; CI₉₅, 1.80-8.08; *P* = .0003).

Risk Factors for ICU Mortality

The crude ICU mortality was 231 (22%) of 1,044. Crude ICU death was higher in colonized compared to non-colonized patients (37.7% vs 20.4%; *P* = .0001; Table) and in infected compared to non-infected patients (15/35 vs 221/1,009; *P* = .003). Eight variables were significantly associated with ICU mortality in univariate analysis (age, male gender, transfer from wards, SAPS II score, OMEGA score, intubation before ICU admission and during the first 24 hours of ICU stay, reason for admission, and MRSA colonization on admission) and were considered for inclusion in the multivariate model. Only two factors were retained in the multivariate analysis as independently associated with

TABLE
DEMOGRAPHIC AND CLINICAL DATA FOR METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* COLONIZED AND NON-COLONIZED PATIENTS

Variable	Colonized	Non-Colonized	P
Number	106	938	
Age, y	65.3±12.8	60.6±18.7	.01
Gender (male:female)	72:34	563:374	.14
SAPS II (±SD)	41.10±15.4	35.9±20.5	.01
Mechanical ventilation, no. (%)	96 (90.5%)	482 (51.4%)	.0001
Reason for ICU admission, no. (%)*			
Medical	58 (54.7%)	689 (73.3%)	.0001
Scheduled surgery	11 (11.3%)	91 (9.7%)	
Unscheduled surgery	37 (35.6%)	158 (16.8%)	
OMEGA†	533.4±539	98.3±162	.0001
Transfer from wards, no. (%)	75 (70.7%)	448 (47.7%)	.0001
Length of stay, d (±SD)	33.8±34.8	7.3±10.2	.0001
ICU mortality, no. (%)	40 (37.7%)	192 (20.4%)	.0001

Abbreviations: ICU, intensive care unit; SAPS II, Simplified Acute Physiologic Score; SD, standard deviation.

* Patients were classified as having a surgical admission when they were operated on within 1 week before or after ICU admission and as having a medical admission otherwise.

† The intensity of care was determined by the French OMEGA score.¹² This score describes 47 diagnostic and therapeutic items, weighted from 1 to 10 points, according to the required work load, and divided into three categories. The OMEGA 1 reported 28 items, recorded only once during a stay even though they had been performed several times (such as use of a central line or vasoactives drugs). The OMEGA 2 reported 11 items recorded every time they were performed (such as dialysis or endoscopic or radiographic procedure). The OMEGA 3 reported 8 items recorded every day (such as mechanical ventilation or continuous monitoring). The total OMEGA score is obtained by adding all OMEGA points.

ICU mortality: SAPS II >36 (HR, 4.26; CI₉₅, 2.85-6.36; *P*<.0001) and intubation during the first 24 hours of ICU stay (HR, 3.67; CI₉₅, 2.01-6.68; *P*<.0001). MRSA colonization did not influence mortality (HR, 1.01; CI₉₅, 0.71-1.44; *P*=.94) when it was forced into the Cox model at the last step.

Use of Glycopeptides

Of the 1,044 patients, 119 (11.4%) received a glycopeptide, mainly vancomycin, for a median duration of 5 (range, 1-47) days, with a median daily dose of 1 g. Of the 32 MRSA infections, 30 (94%) were treated with a glycopeptide. The non-colonized patients received glycopeptides for 37.7 days per 1,000 hospital-days, mainly for empirical use (46), prophylaxis (5), and infections (coagulase-negative staphylococci, 8; enterococci, 2). Among the 46 uses of empirical treatment, glycopeptide was stopped in 48 hours in 27 patients after negative cultures and continued in the 19 remaining cases for more than 48 hours, with no documented infection.

The 54 patients colonized with MRSA on admission received 235.2 days of glycopeptide per 1,000 hospital-days. Glycopeptides were used for MRSA infections in 11 patients and empirically in 16 others; 13 patients received empirical glycopeptides for more than 48 hours.

The 52 patients with ICU-acquired colonization received 118.3 days of glycopeptide per 1,000 hospital-days. The reasons for glycopeptide use were as follows: MRSA infections, 19; empirical treatment, 18; prophylaxis, 1; and selective digestive decontamination, 1. Fourteen (78%) of 18 instances of empirical glycopeptide use were for less than 48 hours.

The number of days of glycopeptide use per 1,000 hospitalization days was influenced by MRSA infections

(139.2 before vs 522.4 after MRSA infections in patients colonized with MRSA on admission, and 29.3 before vs 246.5 after MRSA infections in patients with ICU-acquired MRSA colonization). Interestingly, MRSA status alone increased by more than threefold the use of glycopeptides in colonized, non-infected MRSA patients compared to non-colonized patients (117.1 vs 35.6 days/1,000 hospital-days; *P*<.0001).

DISCUSSION

Our study was undertaken to examine, in a large cohort of ICU patients, the effects of MRSA colonization on the occurrence of *S aureus* infections, the use of glycopeptides, and outcome. We found that MRSA colonization was a risk factor for the development of *S aureus* infection, suggesting (as have others¹³) that cases of MRSA do not replace, but rather add, to the cases due to MSSA. MRSA colonization increased greatly the use of glycopeptides in colonized and non-colonized patients. The crude ICU mortality of MRSA-colonized patients was higher than that of non-colonized patients. However, MRSA acquisition during ICU stay was not an independent risk factor for ICU death.

Our study showed that 10% of ICU patients had MRSA colonization, with a ratio of acquired to imported cases of 0.96. Our incidence of MRSA colonization was in line with a recent report in ICU patients in the same area in France.¹⁴ To define the high-risk population having MRSA colonization on admission better, we analyzed the characteristics of these patients in a multivariable model. We found that MRSA colonization was recovered more often in patients referred from wards (OR, 2.79) and in patients intubated before ICU admission (OR, 2.89). Further study is needed to develop and vali-

date a score allowing us to discriminate patients at risk for MRSA colonization on admission.

Previous studies have reported that higher severity of illness on admission was a predisposing factor for the acquisition of nosocomial infections.^{14,15} Higher severity of illness on admission and MRSA colonization were found to be independent risk factors for the occurrence of *S aureus* (either MSSA or MRSA) infections. Eighty-three percent of the infected patients were previously or simultaneously colonized with MRSA. Several studies found nasal *S aureus* carriage to be a risk factor for acquiring *S aureus* infections in medical¹⁶⁻¹⁸ and surgical¹⁹⁻²² patients. High-level nasal carriage of *S aureus* was found to be an independent risk factor for developing surgical-site infections with *S aureus*.²¹ It is unlikely that the propensity of MRSA to favor *S aureus* infections is higher than that of MSSA. The specific role of MRSA in favoring *S aureus* infections in the ICU probably is due to the high number of patients who received antimicrobials in the ICU. Most of the antibacterials used are active against MSSA strains and might prevent MSSA infections.¹⁵ In 1998, for 52% of the patient-ICU-days, the patients received at least one antimicrobial active against MSSA (co-amoxiclav, tazobactam, third-generation cephalosporins, imipenem, fluoroquinolones, or oxacillin). Our database did not provide individual information about the use of these antimicrobials, and further study is needed to confirm this hypothesis.

The crude mortality in our ICU cohort was 22%; mortality rates among the patients with colonization and infection were 38% and 43%, respectively. Factors independently associated with ICU mortality were those previously reported in ICU patients: severity of illness on admission and need for mechanical ventilation.²³ The relation between MRSA colonization and mortality deserves further comment. Although the crude ICU mortality of MRSA-colonized patients was significantly higher than for non-colonized patients (38% vs 20%), we found that acquisition of MRSA did not influence mortality in ICU patients, even in the presence of an infection. This result might be because patients free of MRSA infections could have another nosocomial infection or other dynamic events occurring during ICU stay that could influence outcome.²⁴ Our study assessed only the consequences of MRSA colonization and infection.

Few studies have analyzed separately the colonized (non-infected) and infected patients with MRSA as a factor for ICU mortality. In a study by Girou et al¹⁴ that differentiated carriage (one MRSA-positive nasal or cutaneous sample), colonization (one MRSA-positive clinical sample without signs of infection), and MRSA infection, the mortality (33% vs 38% in our study) among carrier patients was significantly less than the mortality in MRSA-colonized or MRSA-infected patients (45% vs 57%, respectively). In a small population of burn patients, a case-control study did not demonstrate a difference in mortality between colonized and infected patients with MRSA.²⁵

Vancomycin use was largely dependent on whether or not MRSA was endemic in the unit.²⁶ The concern that

glycopeptide use should be a public health priority has intensified since the first report of glycopeptide-intermediate *S aureus* being isolated in 1996.²⁷ Moreover, vancomycin use was demonstrated as a risk factor for acquiring vancomycin-resistant enterococci.²⁸ In 1995, the Hospital Infection Control Practices Advisory Committee recommendations for the control of vancomycin-resistant enterococci emphasized vancomycin restriction as crucial to prevent the spread of vancomycin resistance.²⁹ Several methods have been proposed to restrict vancomycin use, such as a vancomycin continuation form,³⁰ stop orders, and educational interventions,³¹⁻³³ but the effects of these appeared to be transient.³³ Our study showed that MRSA carriage influenced glycopeptide use in both non-colonized and colonized patients, even when an infection was not demonstrated. This suggests that the best approach to limit the spread of glycopeptide resistance will be concomitant measures to decrease MRSA colonization pressure, inappropriate vancomycin use, and perhaps control of broad-spectrum antimicrobial use as suggested by Monnet et al.³⁴ MRSA control programs in hospitals have been more often discussed than implemented, despite recent studies showing the benefits of reducing MRSA carriage.³⁵ A recent cost-benefit analysis demonstrated that a MRSA control program was beneficial compared to no isolation when MRSA colonization on admission ranged from 1% to 7%.³⁶ An antibiotic-control program could be another important measure to limit MRSA spread. A recent study³⁷ failed to demonstrate that prior total antimicrobial use was a risk factor for MRSA colonization, but prior fluoroquinolone use was identified as a risk factor for the acquisition of MRSA colonization.³⁸

In conclusion, our study demonstrated that MRSA colonization increased the risk of methicillin-resistant and methicillin-susceptible *S aureus* infections without influencing ICU mortality. MRSA colonization influenced glycopeptide use, in both non-colonized and colonized non-infected MRSA patients. Accordingly, strict measures to limit MRSA colonization should be the cornerstone of infection control programs to regulate glycopeptide use.

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