MAJOR ARTICLE

Methicillin-Resistant *Staphylococcus aureus* (MRSA) Nares Colonization at Hospital Admission and Its Effect on Subsequent MRSA Infection

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Background. Asymptomatic colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) has been described as a risk factor for subsequent MRSA infection. MRSA is an important nosocomial pathogen but has currently been reported in patients without typical risk factors for nosocomial acquisition. This study was designed to evaluate the impact of asymptomatic nares MRSA colonization on the development of subsequent MRSA infection. The incidence of MRSA infection was examined in patients with and patients without MRSA or methicillin-susceptible *S. aureus* (MSSA) colonization at admission to the hospital and in those who developed colonization during hospitalization.

Methods. Patients admitted to 5 representative hospital units were prospectively evaluated. Nares samples were obtained for culture at admission and during hospitalization. Laboratory culture results were monitored to identify all MRSA infections that occurred during the study period and 1 year thereafter.

Results. Of the 758 patients who had cultures of nares samples performed at admission, 3.4% were colonized with MRSA, and 21% were colonized with MSSA. A total of 19% of patients with MRSA colonization at admission and 25% who acquired MRSA colonization during hospitalization developed infection with MRSA, compared with 1.5% and 2.0% of patients colonized with MSSA ($P < .01$) and uncolonized ($P < .01$), respectively, at admission. MRSA colonization at admission increased the risk of subsequent MRSA infection, compared with MSSA colonization (relative risk [RR], 13; 95% confidence interval [CI], 2.7–64) or no staphylococcal colonization (RR, 9.5; 95% CI, 3.6–25) at admission. Acquisition of MRSA colonization also increased the risk for subsequent MRSA infection, compared with no acquisition (RR, 12; 95% CI, 4.0–38).

Conclusion. MRSA colonization of nares, either present at admission to the hospital or acquired during hospitalization, increases the risk for MRSA infection. Identifying MRSA colonization at admission could target a high-risk population that may benefit from interventions to decrease the risk for subsequent MRSA infection.

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a progressively more important human pathogen since its initial description in 1961 [1] and the first documented outbreak of infection in 1968 [2]. The most recent data from the National Nosocomial Infections Surveillance System of the Centers for Disease Control and Prevention showed in August 2003 that MRSA on average accounts for 57% of *S. aureus* isolates causing nosocomial infection in intensive care units (ICUs) [3]. This is higher than the reported prevalence of 35%–50% for 1995–1999 [4]. Risk factors for MRSA colonization have been well described [5]. Rates of colonization or infection with MRSA vary by geographic location, type of health care facility, and the specific population being studied. In acute-care settings, the prevalence of MRSA colonization varies depending on patient location within the facility. The reported prevalence of MRSA infection or colonization in the ICU has been 4%–8% [6, 7]. The prevalence of MRSA colonization in the general inpatient setting has been reported to be 0.18%–7.2% [8–10], with a prevalence of nosocomial acquisition of up to 1.7% [11, 12]. Community-acquired colonization has recently been de-

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scribed as an important reservoir of MRSA, with a reported prevalence of 1.3%–2% [13, 14].

Whether MRSA is more virulent than methicillin-susceptible *S. aureus* (MSSA) is a controversial issue. There have been those whose findings support increased virulence of MRSA, compared with MSSA [15–17], those who demonstrate no difference in virulence [18–20], and still others whose conclusions are equivocal [21]. Those who argue that MRSA is more virulent than MSSA have demonstrated higher mortality associated with MRSA bacteremia in analyses that controlled for other factors [15–17]. Other investigators have demonstrated that inappropriate antimicrobial therapy, comorbid conditions, and advanced patient age—rather than methicillin resistance—account for increased mortality associated with MRSA bacteremia [18–20]. However, there are studies in which MRSA infection or colonization were demonstrated as leading to increased risk of subsequent MRSA infection during the same hospitalization [22, 23] and up to 18 months after hospital discharge [24]. The reported rate of subsequent MRSA infection after identification of MRSA colonization is ~30% [24–26]. This increased risk of infection with MRSA has led some to recommend screening all patients [12, 24] or those at highest risk [27, 28] for colonization at admission to the hospital. This study was designed to measure the prevalence of MRSA colonization at admission to our institution (Brooke Army Medical Center; Ft. Sam Houston, TX) and to determine its impact on subsequent MRSA infection.

METHODS

Data were obtained from a prospective observational study of subjects who were admitted to 5 systematically chosen representative inpatient hospital units. The study was approved by the Brooke Army Medical Center institutional review board. All patients admitted between 1 June 2002 and 31 August 2002 were eligible for inclusion. The observed hospital units included a general medical/surgical ward, a medical ICU, a surgical ICU, a trauma ICU, and a monitored step-down unit, the patients of which, taken together, represent our typical inpatient population. The study hospital is a tertiary care military medical training center located in San Antonio, Texas, that had 203 available inpatient beds during the study period. This facility serves a patient population of active-duty and retired military personnel and their dependents. Individuals in this population receive the majority of their medical care from the military health care system in San Antonio. Additionally, the facility is a level 1 trauma center that treats a limited number of civilian trauma patients who would otherwise not be eligible for care within the system.

Nares cultures were performed within 48 h after admission to an observed hospital unit. Cultures were also performed when patients were transferred to other study units, weekly during prolonged hospital stays, and at hospital discharge. One sterile culture swab (BBL Culture Swab; Becton Dickinson) was used to sample both nares. The swab sample was streaked onto 5% sheep blood agar (BBL Stacker plates; Becton Dickinson) and colistin-nalidixic acid (CNA) agar (Columbia CNA agar with 5% sheep blood Stacker plates; Becton Dickinson) and incubated for 18–24 h at 37°C in 5% CO_2. If no growth was detected, plates were incubated for another 24 h. Colonies with β-hemolytic activity and properties consistent with those of staphylococci were screened for catalase activity (3% H_2O_2), and if they tested positive, they were then screened with a rapid slide agglutination test for coagulase and protein A (Staphaurex; Remel). Coagulase-positive organisms were confirmed with a tube coagulase test (BBL coagulase plasmas; Becton Dickinson) and were inoculated onto oxacillin screen agar (BBL stacker plates). Susceptibility testing of MRSA isolates was conducted by Vitek system GPS-105 cards (bioMerieux).

Information recorded for study patients included age, sex, length of hospital stay, and number of nares cultures completed. If *S. aureus* was detected in the admission culture, the patient was identified as having been initially colonized with either MRSA or MSSA. If the admission culture was negative for *S. aureus* but results of a subsequent nares culture during the course of hospitalization were positive, the patient was identified as having acquired MRSA or MSSA colonization. Patients without *S. aureus* identified in any nares culture during hospitalization were identified as having not been colonized with *S. aureus.*

All patients included in the study were followed to determine whether they developed clinical infection with MRSA. Patients were followed during the 3-month study period and for 1 year thereafter, through 31 August 2003. MRSA infection was defined as recovery of the organism from either normally sterile sites (blood samples or urine specimens without a Foley catheter in place) or nonsterile sites concomitant with a diagnosis of infection by the primary physician caring for the patient. Nonsterile sites included indwelling vascular catheters, skin and soft tissue, and sputum. All patients included in the study also had their names compared with those from the list of patients previously known to have infection or colonization with MRSA in our hospital.

The precision of relative risks for MRSA infection was determined by the method for calculating 95% CIs described by Altman [29]. Statistical significance (i.e., the *P* value) was calculated for the difference in rates of MRSA infection by Fisher's exact test [30]. The hypothesis that MRSA infection was dependent on age was evaluated with the independent-sample Student's *t* test. The hypothesis that MRSA infection was dependent on length of stay was evaluated with the Mann-Whitney rank sum test. Difference in descriptive statistics among evaluated patients and excluded patients was completed with the Mann-Whitney rank sum test.

Table 1. Demographic and clinical characteristics of 758 admitted patients for whom cultures of nares were performed to assess methicillin-resistant *Staphylococcus aureus* (MRSA) colonization status.

Study unit	Sex, no. of patients with MRSA/total no. in unit (%)		Age, mean years (range)	Length of stay, days	
	Male	Female		Mean	Median (range)
Medical/surgical	157/347 (45)	190/347 (55)	49 (17–87)	3.9	2 (1–40)
Intensive care					
Medical	53/96 (55)	43/96 (45)	65 (18–101)	6.6	3 (1–96)
Surgical	50/67 (75)	17/67 (25)	46 (8–84)	14	8 (1–85)
Trauma	54/74 (73)	20/74 (27)	59 (18–101)	10	7 (1–63)
Step-down	88/174 (51)	86/174 (49)	67 (20–93)	5.2	3 (1–67)
Total	402/758 (53)	356/758 (47)	56 (8–101)	6.1	3 (1–96)

RESULTS

During the study period, 758 of 990 patients admitted to the observed units had nares cultures performed within 48 h after admission to the hospital. The mean age was higher for patients admitted to the medical ICU, the trauma ICU, and the monitored step-down unit (table 1; $P < .01$). Among patients admitted to the surgical and trauma ICUs, the mean and median length of stay was longer ($P < .01$) and there were proportionally more men ($P < .03$). Cultures were performed an average of 1.7 times (range, 1–6 times) for each patient during hospitalization. There were no significant differences with respect to sex ($P = .223$) or length of stay ($P = .163$) for patients who did not have a culture completed within 48 h of admission, and thus these are not included in the evaluation. Patients who were not included in the evaluation were less frequently admitted to a medical-surgical ward (22% vs. 45%; $P < .01$) and were more frequently admitted to the telemetry unit (47% vs. 23%) than were patients who were included. They were older (mean age, 60 years; $P < .01$) than those who were included in the study.

Of the 758 study patients, 163 were initially colonized with *S. aureus.* Twenty-six patients (3.4%; 95% CI, 2.1–4.7) were colonized with MRSA, and 137 (21%; 95% CI, 18–24) were colonized with MSSA (table 2). The incidence of subsequent MRSA infection for those initially colonized with MRSA was close to 10 times the incidence for patients colonized with MSSA or not colonized with *S. aureus* at admission ($P < .01$ for both) (table 3). The relative risk (RR) for developing MRSA infection was much higher for those colonized with MRSA at admission, compared with those colonized with MSSA (RR, 13; 95% CI, 2.7–64) or those not colonized with *S. aureus* (RR, 9.5; 95% CI, 3.6–25) at admission. Patients who subsequently developed MRSA infection were older (mean age, 69 years; range, 29–91 years; $P = .015$) and were admitted for a longer period (mean length of stay, 16 days; range, 1–67 days; $P < .01$). They also tended to be admitted to a monitored unit ($P = .10$). Table 4 describes the infections that occurred in these patients, including the time of onset and whether they occurred during the same or a future hospitalization.

In addition to presenting with colonization at admission, there were patients who acquired colonization during the study period. There were 394 patients who had ⩾1 nares culture completed during hospitalization, of whom 25 had a change in their nares colonization status. Twelve (3.0%) of these patients acquired MRSA, 3 of whom were initially colonized with MSSA. Five patients (2.0%) were in the medical-surgical ward, none were in the medical ICU, 1 (2.4%) was in the surgical ICU, 4 (8.9%) were in the trauma ICU, and 2 (4.3%) were in the monitored step-down unit. Of these patients, 25% later developed MRSA infection. The relative risk for developing MRSA infection for patients who acquired MRSA colonization was also higher, compared with those who were not colonized with *S. aureus* (RR, 12; 95% CI, 4.0–38; $P < .01$).

There was 1 patient who developed infection with MRSA who was known to have previous infection with MRSA. This patient

Table 2. *Staphylococcus aureus* colonization in patients for whom nares were cultured at admission.

Study unit	*S. aureus* colonization status, no. of patients/total no. screened in unit (%)	
	MRSA	MSSA
Medical/surgical	7/347 (2.0)	57/300 (19)
Intensive care		
Medical	7/96 (7.3)	18/90 (20)
Surgical	2/67 (3.0)	16/57 (28)
Trauma	3/74 (4.1)	13/68 (19)
Step-down	7/174 (4.0)	33/152 (22)
Overall	26/758 (3.4)[a]	137/667 (21)[b]

NOTE. MSSA, methicillin-susceptible *S. aureus.*
[a] 95% CI, 2.1–4.7.
[b] 95% CI, 18–24.

Table 3. Subsequent methicillin-resistant *Staphylococcus aureus* (MRSA) infection, by *S. aureus* colonization status at admission.

	MRSA colonization at admission, no. (%) of patients		MSSA colonization at admission, no. (%) of patients		No colonization at admission, no. (%) of patients	
Study unit	Total	MRSA infection	Total	MRSA infection	Total	MRSA infection
Medical/surgical	7	1 (14)	57	0 (0)	283	2 (0.7)
Intensive care						
Medical	7	2 (29)	18	1 (5.6)	71	1 (1.4)
Surgical	2	0 (0)	16	0 (0)	50	3 (6.0)
Trauma	3	0 (0)	13	0 (0)	57	2 (3.5)
Step-down	7	2 (29)	33	1 (3.0)	134	4 (3.0)
Overall	26	5 (19)[a]	137	2 (1.5)[b]	595	12 (2.0)[c]

NOTE. MSSA, methicillin-susceptible *S. aureus*.

[a] 95% CI, 3.9–34.

[b] $P < .01$ (incidence not large enough to calculate 95% CI).

[c] 95% CI, 0.9–3.1; $P < .01$.

was not colonized with MRSA at admission to the medical-surgical ward, but repeated screening later identified colonization before infection. There were 6 other patients in the study group who had previously been identified with MRSA infection. Four of these 6 patients were colonized with MRSA at admission, 1 acquired colonization during hospitalization, and 1 was never identified with MRSA colonization during the study period. This patient had 2 cultures with negative results during the hospital stay that followed the admission culture for which negative results were obtained.

Table 4. Methicillin-resistant *Staphylococcus aureus* (MRSA) infection, according to *S. aureus* colonization characteristics at admission.

Colonizing isolate, by patient no.	Infection type	Time from *S. aureus* colonization to MRSA infection, days	Hospitalization in which MRSA infection occurred[a]
MRSA			
1	Toe amputation site abscess	6	Concurrent
2	Bacteremia	7	Concurrent
3	Central catheter infection	9	Concurrent
4	Right axillary abscess	24	Future
5	Right BKA site abscess	60	Future
MSSA			
6	Bacteremia	82	Future
7	LLE soft tissue abscess	268	Future
None			
8	Bacteremia	9	Concurrent
9	Osteomyelitis	22	Concurrent
10	Bacteremia	23	Concurrent
11	Abdominal wound abscess	8	Future
12	Pneumonia	31	Future
13	Pneumonia	42	Future
14	RLE BKA site abscess	77	Future
15	LLE BKA site abscess	87	Future
16	Osteomyelitis	336	Future

NOTE. BKA, below the knee amputation; LLE, left lower extremity; MSSA, methicillin-susceptible *Staphylococcus aureus;* RLE, right lower extremity.

[a] Data limited to 1 year after the hospital stay during which MRSA colonization was initially identified.

Table 5. Antibiotic susceptibility patterns of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates.

Antibiotic to which MRSA was susceptible	MRSA type, % susceptible	
	Colonizing isolates (n = 56)	Infecting isolates (n = 30)
Ampicillin	0	0
Cefazolin	4	0
Ciprofloxacin	9	13
Clindamycin	27	7
Erythromycin	4	3
Rifampin	100	90
Tetracycline	96	93
TMP-SMZ	96	97
Vancomycin	100	100

NOTE. All isolates tested positive for β-lactamase production. TMP-SMZ, trimethoprim-sulfamethoxazole.

The susceptibility patterns for MRSA isolates obtained from nares cultures and for those causing clinical infection were similar (table 5). Nares isolates from patients initially colonized with MRSA were more susceptible to tested antibiotics than were isolates from those who acquired colonization. The isolates that caused infection in patients who were initially colonized with MRSA had the exact same susceptibility patterns as the colonizing isolates from these patients. Isolates that caused infection in patients who were not colonized with *S. aureus* or in those who acquired MRSA colonization before infection tended to be more resistant to the tested antibiotics, which is consistent with patterns of hospital-acquired MRSA. The isolates of 1 of the 3 patients who acquired colonization and were later infection with MRSA also had the same susceptibility patterns. The other 2 patients had isolates that varied by either clindamycin or ciprofloxacin susceptibility only.

DISCUSSION

The prevalence of initial MRSA colonization in this study was 3.4%, with 3.0% of patients subsequently acquiring MRSA colonization. In this study, patients colonized with MRSA were at much higher risk of subsequent MRSA infection than were those colonized with MSSA or those not colonized with *S. aureus.* There was a 10-fold increase in the rate of infection between these groups, with a significant difference in relative risk. Antibiogram data for these isolates suggest that the colonizing isolates were the same isolates that subsequently caused infection in these patients.

Recent reports have demonstrated a similar increased risk of subsequent MRSA infection for MRSA-colonized patients. Huang and Platt [24] reported on subsequent MRSA infection in 209 adult patients newly identified with MRSA infection or colonization. They retrospectively identified these patients from infection-control records and found that 29% developed MRSA infections over the next 18 months. One-half of the infections occurred after discharge from the hospital. Mest et al. [31] reported on a smaller group of patients, compared with our study, who were in the surgical ICU. They screened all patients preoperatively for MRSA colonization of nares and found that 4% were colonized with MRSA. Twenty-six percent of these patients developed MRSA infection, compared with 1.3% of those who were not colonized. They hypothesized that preoperative MRSA colonization of nares significantly increased the risk for subsequent postoperative MRSA infection. Roghmann et al. [23] retrospectively studied the risk associated with MRSA colonization of ulcers and the subsequent development of MRSA infection in a cohort of patients with chronic sacral decubitus and diabetic foot ulcers. They found that 30% of ulcers were colonized with MRSA. Seventeen percent of patients with MRSA-colonized ulcers developed subsequent MRSA bacteremia, compared with only 1% of the patients without colonization. Roghmann et al. [23] reasoned that MRSA colonization of chronic ulcers increases the risk for MRSA bacteremia.

Other studies evaluated cohorts of MRSA-colonized patients. Coello et al. [22] observed a group of 479 patients colonized with MRSA. Of these patients, 11% developed MRSA infection during the course of hospitalization, but Coello et al. [22] did not compare this risk with that for noncolonized patients. They demonstrated that ICU patients had an increased risk of subsequent MRSA infection, compared with medical patients, which was similar to our results that showed that MRSA infections tended to occur in patients admitted to monitored units (table 3). Garrouste-Orgeas et al. [25] also reported on a cohort of MRSA-colonized patients who were treated in the ICU. In their study, Garrouste-Orgeas et al. [25] observed patients during hospitalization but not after discharge, and they identified MRSA colonization in 10% of medical-surgical ICU patients, with 27% developing MRSA infection, compared with <1% of noncolonized patients who developed MRSA infection during hospitalization.

The limitations of our study include the relatively small number of MRSA infections that were identified. The conclusions based on this data are statistically significant; however, a larger data set would strengthen these conclusions. A small data set may introduce sampling bias, because of the small numbers of infections found. There were also a number of patients who were not included in the study because they were not screened within 48 h after admission or not screened at all. The demographic data of this population did not differ significantly from those of patients in the study group, but the former were more frequently admitted to the medical surgical or telemetry units. It is possible that the failure to include this population could have introduced sampling error, which could affect the overall conclusions. Additional review, however, demonstrated

that this group did not have a significant number of MRSA infections that would have changed the study outcomes.

This study supports the results of previously published reports and further demonstrates the natural course of MRSA colonization of nares. Most of the previous studies identified MRSA colonization for inpatients and the associated risk for subsequent infection during the same hospitalization. As demonstrated by Huang and Platt [24], one-half of these infections occurred after hospital discharge. These studies typically retrospectively identified patients who had MRSA colonization at some point during the hospitalization—not necessarily at admission, as our study did—or observed a cohort of MRSA-colonized or -infected patients without comparing them with noncolonized patients. By sampling a group of consecutively admitted patients and observing them for >1 year, we were able to define the incidence of subsequent infection in a prospective manner.

We have demonstrated that MRSA colonization of nares, both at admission and hospital-acquired, increases the risk for subsequent MRSA infection. Our data suggest that further investigation of patients at risk for MRSA infection is warranted on the basis of the presence of MRSA colonization. It may be possible to focus infection-control measures on a high-risk group of MRSA-colonized patients to decrease the incidence of subsequent MRSA infection. This study has demonstrated that an ICU patient population would be best suited for this because it had the highest risk for MRSA colonization of nares and the highest incidence of subsequent MRSA infection.

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