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RATES OF CARRIAGE OF METHICILLIN-RESISTANT AND METHICILLIN-SUSCEPTIBLE *STAPHYLOCOCCUS AUREUS* IN AN OUTPATIENT POPULATION

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ABSTRACT

OBJECTIVES: To assess the prevalence of and the clinical features associated with asymptomatic *Staphylococcus aureus* colonization in a healthy outpatient population, and to compare the characteristics of colonizing methicillin-resistant *S. aureus* (MRSA) strains with those of strains causing infection in our community and hospital.

SETTING: Outpatient military clinics.

METHODS: Specimens were obtained from the nares, pharynx, and axillae of 404 outpatients, and a questionnaire was administered to obtain demographic and risk factor information. MRSA strains were typed by pulsed-field gel electrophoresis (PFGE) and evaluated for antibiotic susceptibility. Antibiograms of study MRSA strains were compared with those of MRSA strains causing clinical illness during the same time period.

RESULTS: Methicillin-susceptible *S. aureus* (MSSA) colonization was present in 153 (38%) of the 404 asymptomatic out-

patients, and MRSA colonization was present in 8 (2%). Detection of colonization was highest from the nares. No clinical risk factor was significantly associated with MRSA colonization; however, a tendency was noted for MRSA to be more common in men and in those who were older or who had been recently hospitalized. All colonizing MRSA strains had unique patterns on PFGE. In contrast to strains responsible for hospital infections, most colonizing isolates of MRSA were susceptible to oral antibiotics.

CONCLUSIONS: MRSA and MSSA colonization is common in our outpatient population. Colonization is best detected by nares cultures and most carriers of MRSA are without apparent predisposing risk factors for acquisition. Colonizing isolates of MRSA are heterogeneous and, unlike nosocomial isolates, often retain susceptibility to other non-beta-lactam antibiotics (*Infect Control Hosp Epidemiol* 2003;24:439-444).

Staphylococcus aureus infections are responsible for substantial morbidity and mortality in hospitals around the world.¹⁻⁴ Serious infections resulting from autoinoculation by known nasal carriers of *S. aureus* have been confirmed in numerous institutional settings, including cardiac care units, general medicine wards, dialysis units, and intensive care units.⁵⁻⁷ Reducing colonization has been correlated with decreased infection rates.⁸ In the healthy outpatient population, however, the significance of *S. aureus* colonization is unknown. It is likely this colonization represents a reservoir for staphylococcal disease outbreaks.⁹ Fundamental epidemiologic information regarding the demographic, regional, and clinical characteristics associated with *S. aureus* colonization, as well as information regarding the genetic and antibiotic resistance patterns typical of the colonizing organisms, is critical to our efforts to contain the spread of disease.

We undertook this study to determine the prevalence of *S. aureus* colonization in a community population and to compare recovered strains of methicillin-resistant *S. aureus* (MRSA) with isolates from infections both in and outside of the hospital.

METHODS

Subjects

The subjects for this prospective study were drawn from a military beneficiary outpatient population served by our facility. This population includes approximately 146,000 active duty and retired military personnel and their families. Subjects recruited were outpatients visiting the U.S. Army Health Clinic at Schofield Barracks or hospital-based clinics including pediatrics, infectious diseases, dermatology, and family practice. Although they used the same medical facilities, these subjects had different occupations and educational backgrounds, engaged in different recreational activities, and lived in different areas. Every patient entering a designated clinic during the study period was offered the chance to participate in the study, regardless of the reason for coming to the clinic. Informed consent was obtained prior to collecting data or obtaining bacterial specimens. The study protocol was approved by the Human Use Committee at Tripler Army Medical Center. Investigators adhered to the policies for protection of human subjects as prescribed in the federal law pertaining to this.¹⁰

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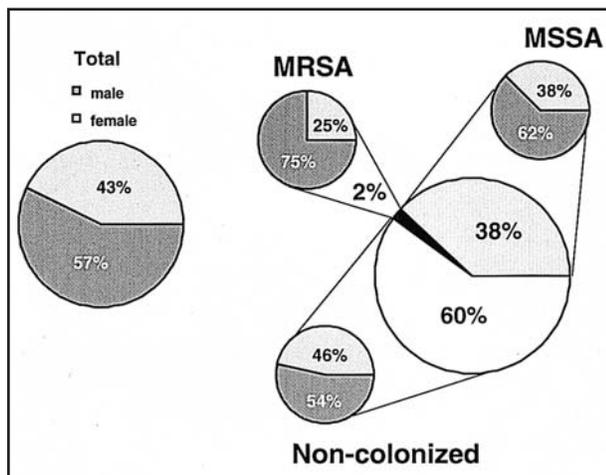


FIGURE 1. Rates of *Staphylococcus aureus* colonization and distribution of gender among 404 outpatients who were non-colonized, colonized with methicillin-resistant *Staphylococcus aureus* (MRSA), or colonized with methicillin-susceptible *S. aureus* (MSSA).

A questionnaire was administered to solicit information regarding patient age, time on the island of Hawaii, time associated with the military, health status, frequency and last date of hospitalization, antibiotic use, household contacts with illness, and reason for the clinic visit. Swabs were used to obtain samples from each participant's nares, axillae, and pharynx. The study was conducted from December 2000 to January 2001.

Laboratory Procedures

Clinical specimens obtained using swabs (Baxter Culturette System; Baxter Healthcare Corp., Deerfield, IL) were inoculated onto 5% sheep blood agar (Remel, Lenexa, KS). Bacterial cultures were incubated at 35°C for 24 hours in ambient air. Morphologically distinct colonies were tested for coagulase and protein A using Staphaurex (Remel). *S. aureus* isolates were tested for growth on MRSA Screen Agar (Hardy Diagnostic, Santa Maria, CA). Antimicrobial susceptibility testing was performed on all *S. aureus* isolates (VITEK; bioMérieux, Hazelwood, MO). Antibiotics used in this testing included cefazolin, clindamycin, erythromycin, oxacillin, penicillin, trimethoprim/sulfamethoxazole (TMP/SMX), and vancomycin.

Pulsed-field gel electrophoresis (Bio-Rad, Hercules, CA) was performed on all recovered MRSA isolates. The specific technique used has been previously described.¹¹ Strain 8325 was the control MRSA (control plugs, group 1; Bio-Rad).

For comparison, MRSA isolates were grouped into strain types based on antibiotic susceptibility testing patterns (antibiograms). By definition, all MRSA isolates were susceptible to vancomycin and resistant to oxacillin, penicillin, and cefazolin in vitro. Susceptibility of MRSA isolates to clindamycin and TMP/SMX was used to define antibiograms. Strain groupings were arbitrarily designated R, resistant to clindamycin and TMP/SMX; I, resistant

to either clindamycin or TMP/SMX; and S, sensitive to both clindamycin and TMP/SMX. Study strains were compared with infection-associated clinical MRSA isolates identified by our hospital laboratory during a 3-month period overlapping the study period. Infection-associated clinical isolates were grouped by the setting in which they were obtained: outpatient ward, inpatient ward, or inpatient intensive care unit.

Statistics

Data are expressed as mean \pm standard error of the mean or percentages for each group. Average ages among non-colonized, MRSA-colonized, and methicillin-susceptible *S. aureus* (MSSA)-colonized patients were compared using a one-way analysis of variance followed by a Tukey-Kramer test for multiple comparisons. Comparisons of percentages between patients (non-colonized vs MRSA, non-colonized vs MSSA, and MRSA vs MSSA) or between culture sites (nares vs pharynx vs axillae) were performed using chi-square tests. For all tests, a *P* value of less than .05 was considered significant.

RESULTS

In the 2-month period of evaluation, 404 (22%) of 1,846 eligible clinic patients volunteered and were enrolled in the study. Two percent (8 of 404) of these enrolled outpatients were colonized with MRSA and 38% with MSSA (Fig. 1). Ages ranged from 2 months to 91 years, with the average being 32.6 ± 1.0 years. Seventeen percent of the subjects were younger than 18 years and 7.6% were older than 65 years. MSSA carriers were significantly younger (29.1 ± 1.3 years) than non-colonized patients (34.6 ± 1.3 years; $P < .05$) (Table 1). By contrast, those colonized with MRSA tended to be older than both MSSA-colonized and non-colonized patients, but this was not statistically significant due to the small number of MRSA-colonized patients who were identified. The gender distribution among the non-colonized patients (54% male and 46% female) was similar to that among all patients studied (57% male and 43% female), whereas males made up 62% of the patients colonized with MSSA and 75% of the patients colonized with MRSA (Fig. 1).

There was no statistically significant association between colonization rates and the number of clinic visits per year, the frequency of antibiotic use, the recent use of antibiotics, a history of personal chronic illness or chronic illness in a family member, or military status (active duty, dependent, or retiree) (Table 1). There was a tendency, however, for MRSA colonization to be more common in those patients who had been hospitalized within the year prior to the time of the study: 38% MRSA versus 12% MSSA or 12% non-colonized. Table 2 provides the raw clinical data for the eight MRSA-colonized individuals.

The nares provided the best yield for determining MRSA colonization status, with 88% of the positive cultures derived from this site (Table 3). Thirty-eight percent of the MRSA-positive cultures could be detected from

the pharynx. None of the eight cases of MRSA colonization were detected by swabbing the axillae. The nares and the pharynx were also better than the axillae in determining MSSA colonization. Ninety-seven percent of all MSSA-positive cultures were from the nares and the pharynx together, whereas only 9% were from the axillae.

Pulsed-field gel electrophoresis was used to characterize seven of the eight MRSA specimens (one specimen was not viable at the time of testing). All tested isolates had distinct banding patterns (Fig. 2).

Antibiotic susceptibility patterns (antibiograms) for colonizing MRSA isolates were compared with those for infection-derived MRSA isolates (Fig. 3). Seven (87.5%) of 8 colonizing strains of MRSA were sensitive to both oral clindamycin and TMP/SMX, whereas a single strain was resistant to clindamycin but not to TMP/SMX. Intermediary and multidrug-resistant strains of MRSA were more common in the isolates responsible for clinical infection, with the highest percentage of resistant strains seen in the intensive care unit (60.0%; $P < .01$) followed by the inpatient wards (14.3%) and the outpatient clinics (5.6%).

DISCUSSION

S. aureus is a common community and nosocomial pathogen of growing concern due to multidrug-resistant clones of MRSA.¹² Although hospitals have generally been perceived to be the source of these highly resistant strains, more recent studies document the emergence of MRSA infections within the general community and among individuals lacking frequent hospital or antibiotic exposure.¹³⁻¹⁹ This evolving epidemiology of MRSA may be parallel to the patterns of penicillinase-producing strains of *S. aureus* of several decades ago, and warrants close monitoring.²⁰ Unrecognized colonization of staphylococcus on the skin or mucous membranes may be a significant reservoir accounting for the spread of MRSA infections.⁵⁻⁷

We found *S. aureus* carriage to be common in an asymptomatic outpatient military population in Hawaii, with 40% of the population colonized at a single point in

TABLE 1
COMPARISON OF DEMOGRAPHIC DATA OF NON-COLONIZED PATIENTS, PATIENTS COLONIZED WITH METHICILLIN-SUSCEPTIBLE *STAPHYLOCOCCUS AUREUS*, AND PATIENTS COLONIZED WITH METHICILLIN-RESISTANT *S. AUREUS*

	Non-Colonized (n = 243)	MSSA (n = 153)	MRSA (n = 8)
Mean age, y (\pm SEM)	34.6 (\pm 1.3)	29.1 (\pm 1.3)*	39.3 (\pm 10.7)
Male	54%	62%	75%
> 6 mo in Hawaii	84%	82%	75%
> 6 clinic visits per year	28%	23%	38%
> 3 antibiotics per year	8%	7%	0%
Antibiotics within the past 6 mo	32%	31%	25%
Hospitalizations within the past year	12%	12%	38%
History of chronic illness	16%	14%	12%
History of contact with chronic illness	9%	11%	0%

MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*; SEM = standard error of the mean.

*Significantly different from non-colonized ($P < .05$); there were no significant differences between the MRSA and the MSSA groups.

time. Two percent of this population harbored strains of MRSA. These figures match or exceed those found in the literature and support evidence that the prevalence of MRSA in the general population is increasing, both in and out of hospitals.^{14,21-24}

Due to the significant healthcare implications of emerging bacterial resistance, further studies are clearly needed to confirm the prevalence and monitor the trends of MRSA colonization within community populations. Disparate study designs make it difficult to render direct comparisons between our study and other studies. Many previous studies have been limited to retrospective chart reviews from hospital admissions records or prospective

TABLE 2
CHARACTERISTICS AND RISK FACTORS OF THE PATIENTS COLONIZED WITH METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Patient No.	Gender	Age (y)	Time	Seen in Clinic	Inpatient	Antibiotics	Antibiotics	History of	Family
			in Hawaii > 6 Mo	or Hospital > 6 Times per Year	Within 1 Year	> 3 Times per Year			
1	Female	23	Yes	No	Yes	No	No	No	No
2	Male	26	Yes	No	No	No	Yes	No	No
3	Male	30	Yes	No	No	No	No	No	No
4	Male	78	Yes	Yes	Yes	No	No	Yes	No
5	Male	24	No	No	No	No	Yes	No	No
6	Female	42	Yes	Yes	No	No	No	No	No
7	Male	0.5	No	Yes	Yes	No	No	No	No
8	Male	90	Yes	No	No	No	No	No	No

TABLE 3
DETECTION OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*
AND METHICILLIN-SUSCEPTIBLE *S. AUREUS* IN THE NARES,
PHARYNX, AND AXILLAE

Site	MRSA Detected (n = 8)	MSSA Detected (n = 152)
Nares	7 (88%)	110 (72%)
Nares only	5 (63%)	60 (39%)
Nares and pharynx	2 (25%)	41 (27%)
Nares and axillae	0 (0%)	6 (4%)
Nares, pharynx, and axillae	0 (0%)	3 (2%)
Pharynx	3 (38%)	81 (53%)
Pharynx only	1 (13%)	37 (24%)
Pharynx and nares	2 (25%)	41 (27%)
Pharynx and axillae	0 (0%)	0 (0%)
Pharynx, axillae, and nares	0 (0%)	3 (2%)
Axillae	0 (0%)	14 (9%)
Axillae only	0 (0%)	5 (3%)
Axillae and nares	0 (0%)	6 (4%)
Axillae and pharynx	0 (0%)	0 (0%)
Axillae, nares, and pharynx	0 (0%)	3 (2%)

MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*.

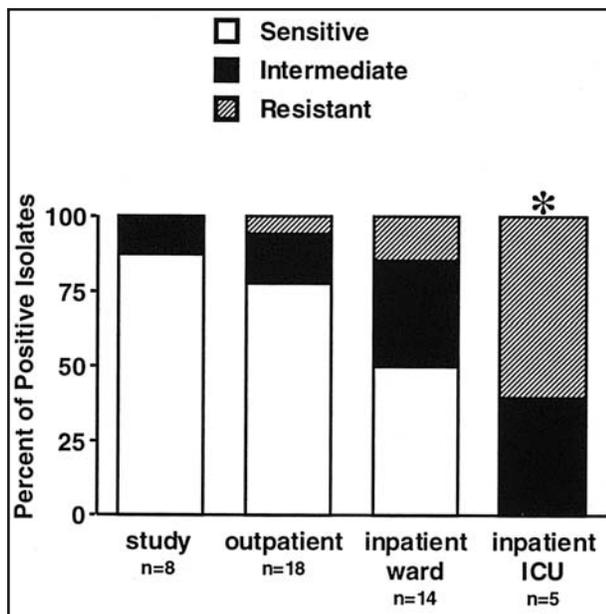


FIGURE 3. Antibiograms of colonizing strains of methicillin-resistant *Staphylococcus aureus* compared with those of strains causing infection during the same period from outpatients, ward inpatients, and intensive care unit (ICU) inpatients. "Sensitive" indicates strains with antibiotic sensitivity to clindamycin and trimethoprim/sulfamethoxazole (TMP/SMX); "intermediate" indicates strains with antibiotic sensitivity to either clindamycin or TMP/SMX; and "resistant" indicates strains with antibiotic resistance to clindamycin and TMP/SMX. * = Inpatient ICU strains were significantly more resistant than strains in outpatient or study groups ($P < .01$).

evaluations of newly hospitalized patients.^{13,19,24-26} Others have focused on populations with a particular clinical feature, such as age or disease category, or on groups attending isolated clinics, nursing homes, or day care cen-

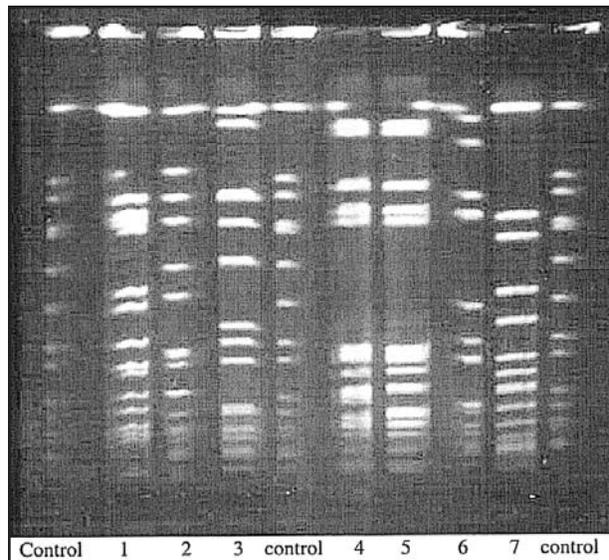


FIGURE 2. Results of pulsed-field gel electrophoresis for seven study colonizing strains of methicillin-resistant *Staphylococcus aureus* (one specimen was not available for analysis).

ters.^{18,21,23} Our study was prospective and attempted to sample a broad representative of the local community during clinic visits, but needs to be repeated with larger populations and longer follow-up.

Community-acquired MRSA has most commonly been attributed to high-risk populations, such as those with chronic illnesses or frequent hospital contact.⁴ Of concern are reports of MRSA infection and colonization among individuals with no apparent risk factors, suggesting the insidious expansion of this organism within our communities.²⁷ Although the small number of carriers in our diverse outpatient study population limited our analysis of risk factors, none of six clinical features was found to be significantly associated with MRSA colonization.

Future studies with larger population samples may reveal stronger healthcare-related risk factors, such as recent hospitalization, which tended to be more common among MRSA-colonized subjects than among non-colonized subjects identified in our study (38% vs 12%, respectively; $P = .09$; power = .37). The association between community MRSA and recent hospitalization has been frequently reported, and is not unexpected given the high rates of MRSA within hospitals.^{7,20,28} *S. aureus* isolates from infections identified in our hospital laboratory during the 2-year period before the study revealed prevalence rates of MRSA of 50%, 41%, and 15% in the hospital intensive care unit, the inpatient ward, and the outpatient community clinics, respectively. Identification of *S. aureus* carriage may need to be considered when discharging patients from the hospital to the community. Persistent carriage states are not uncommon, and these individuals could become reservoirs for future infections.^{14,16,22,24,25}

We also noted a tendency for MRSA colonization to occur more frequently in older men. Interestingly, a simi-

lar tendency was observed in another evaluation of *S. aureus* colonization done at our institution close to the time of this study among more than 500 newly hospitalized patients.²⁹ Although the importance of gender is currently unclear, higher prevalence rates among older populations probably reflect the greater likelihood that these individuals have had chronic illnesses and hospital contact. These implications take on added weight given the burgeoning aging population in developed countries.

S. aureus colonization is known to occur in the skin, anterior nares, and pharynx.¹² Although no gold standard for determining colonization exists, most studies report MRSA colonization rates from data obtained by nasal cultures.^{21,22,24,30,31} Because some investigators have found that sites other than the nares have higher sensitivity in children, a secondary objective of this study was to determine which of three body sites was the most sensitive for detecting *S. aureus* colonization in the asymptomatic outpatient population.²³ Our findings confirm the conclusions of others that for single swab assessment, the anterior nares is the site with the highest yield for detecting *S. aureus* colonization.^{18,30}

Pulsed-field gel electrophoresis revealed great heterogeneity in the community strains of colonizing MRSA. A similar analysis of eight MRSA isolates obtained from infections identified in the intensive care unit and inpatient wards of our hospital during the same period as this study showed six different isolates, none of which had banding patterns similar to those of our outpatients. These findings argue against a single point source (such as our hospital) for acquisition of colonization, and suggest a more complicated epidemiology, likely influenced by multiple factors.

In comparing the antibiotic resistance patterns of our outpatient colonizing isolates of MRSA with those of MRSA isolates recovered from infections during the study period, we found that intensive care unit infection strains were multidrug resistant, ward infection strains had intermediate antibiotic susceptibilities, and outpatient infection strains and study colonizing strains of MRSA had broad antibiotic susceptibility. Notably, the single colonizing MRSA isolate found in this study with an intermediate antibiotic resistance profile corresponded to the only subject with MRSA colonization who had a history of chronic illness and recent hospitalization (1 and 2 months prior to the study for the treatment of cancer). During his inpatient stays, this patient had been treated with levofloxacin. This may be significant in light of recent reports that fluoroquinolones may increase the presence and persistence of highly resistant strains of MRSA.³¹

The practical issue of how to control the emerging threat of MRSA within communities and hospitals is complicated by the remarkable ability of this organism to develop antibiotic resistance.²⁰ This feature has recently been underscored by reports of *S. aureus* resistance to vancomycin, mupirocin, and linezolid.³²⁻³⁴ The current study revealed that MRSA was harbored asymp-

tomatically within the nares of a community population. These strains show great heterogeneity and suggest acquisition from multiple sources. Colonizing MRSA isolates most commonly show broad antibiotic susceptibility. However, increasingly resistant strains of MRSA may be observed in individuals with recent hospitalizations. Future infection control strategies may need to take into account both nosocomial and community acquisition of MRSA.

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