J Microbiol Immunol Infect
2004;37:16-23

Epidemiology of community-acquired *Staphylococcus aureus* bacteremia

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Received: February 21, 2003 Revised: June 26, 2003 Accepted: July 8, 2003

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important nosocomial pathogen which has been isolated with increasing frequency in recent decades. Community-acquired MRSA (CA-MRSA) infections have also become increasingly important in recent years. This study retrospectively analyzed the risk factors, duration of hospitalization, yearly trend and seasonal variation in prevalence, and antibiotic susceptibility of isolates of community-acquired *S. aureus* (CASA) bacteremia and CA-MRSA bacteremia from patients treated in a teaching hospital in northern Taiwan. A total of 104 clinical isolates of CASA bacteremia were collected between January 1999 and December 2001. Among these, 35 (33.7%) were identified as MRSA. After multivariate analysis, the independent risk factors for developing CA-MRSA bacteremia were diabetes mellitus (p=0.028), chronic obstructive lung disease (p=0.037), and renal insufficiency (p=0.041). Only 6 (17.1%) patients in the MRSA group had no identified risk factors. Most of the isolates of CA-MRSA had a high degree of resistance to most antibiotics, including clindamycin (71.4%), trimethoprim-sulfamethoxazole (65.7%), and chloramphenicol (41.2%). No major trend or seasonal variation in the prevalence was found during the study period. No difference in mortality related to resistance pattern was found. Although CA-MRSA is not the major pathogen in community-acquired bacteremia, it should be included in the differential diagnosis of Gram-positive bacterial bloodstream infection, especially in those patients with risk factors. Early empiric therapy with glycopeptides in these patients may reduce morbidity and mortality.

Key words: Bacteremia, community-acquired infections, methicillin resistance, *Staphylococcus aureus*

Since the introduction of antibiotics in the 1940s and their subsequent widespread use, bacteria have acquired their own ways to survive under the pressure of antimicrobial agents. Resistant strains of bacteria have become a major health problem in the world. Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most important nosocomial pathogens in many hospitals worldwide. It was first documented in Taiwan in the early 1980s [1]. The prevalence of nosocomial MRSA infections has increased remarkably in recent decades [2,3]. In most hospitals in Taiwan, MRSA accounts for more than 60% of *S. aureus* isolates [2]. A number of recent reports have indicated the emergence of community-acquired strains of MRSA (CA-MRSA) [4-18]. Due to the lack of systematic, population-based surveillance of community-acquired strains of *S. aureus*, the true prevalence of CA-MRSA infections in Taiwan remains unclear. The incidence of MRSA among patients in outpatient settings has been estimated to be 40% [19]. Few studies have investigated the characteristics of community-acquired *S. aureus* (CASA) bacteremia in Taiwan. This retrospective study analyzed the differences in underlying diseases, laboratory data, recent antibiotic use, and duration of hospitalization between patients with community-acquired methicillin-susceptible *S. aureus* (CA-MSSA) bacteremia and CA-MRSA bacteremia. The trends and seasonal variation in the prevalence of isolates, their antimicrobial susceptibility, and mortality rate were also analyzed.

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Materials and Methods

Definition

All patients included in this study were adults (≥18 years of age) who were admitted to Taipei Veterans General Hospital (a 2900-bed acute-care teaching hospital in northern Taiwan) between January 1, 1999 and December 31, 2001 and had *S. aureus* bloodstream infection (one or more sets of positive blood cultures).

The classification of CASA bacteremia required all of the following criteria to be met: blood culture performed within the initial 48 hours after hospital admission; the patient had not been hospitalized in an acute-care setting within one year before the isolation of MRSA; transfer from other hospitals occurred within 48 hours after admission; no history of renal dialysis (hemodialysis or peritoneal dialysis), residence in a nursing home or surgery in the recent one year; no permanent indwelling catheter or percutaneous medical device (e.g., Foley catheter, tracheostomy) present at the time of admission. Duplicate isolates from the same patient were excluded and data for the first isolate of *S. aureus* was recorded for further analysis. Patients were regarded as having significant bacteremia if multiple sets of blood cultures were positive for *S. aureus* or at least 1 set was positive and the patient had clinical symptoms and signs of infection. The medical records of all patients with CASA bacteremia were reviewed and the following data were analyzed: demographic data (age, gender); underling diseases [such as diabetes mellitus, chronic obstructive lung disease (under medical control with or without exacerbation), chronic renal insufficiency (serum creatinine ≥1.5 mg/dL), malignancy, congestive heart failure, cirrhosis of liver, chronic skin disease, and immune status]; duration of hospitalization; antibiotic use in the prior month; intravenous drug addiction; and susceptibility testing of *S. aureus* isolates. A total of 104 patients with CASA were identified and included in this study.

Microbiologic methods

During the study period, 20 mL or more of blood was obtained for each culture and inoculated in media for processing on the BACTEC NR-660 (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA). Identification of *S. aureus* was based on colony morphology on trypticase soy agar supplemented with 5% sheep blood (BBL, Microbiology Systems, Cockeysville, MD, USA), Gram stain, and a positive BACTi^{Tm} Staph (Remel Ltd, Lenexa, KS, USA) latex test. The *S. aureus* isolates were screened for methicillin resistance by the disk-diffusion method, using Mueller-Hinton agar (BBL, Microbiology System), a 1 μg oxacillin disk and incubation for 24 h at 35°C [20]. The susceptibilities of isolates were tested by the disk-diffusion method according to the guidelines recommended by the National Committee for Clinical Laboratory Standards [20]. The antimicrobial disks (BBL, Microbiology Systems) used for susceptibility test included ampicillin (10 μg), cefazolin (30 μg), oxacillin (1 μg), chloramphenicol (30 μg), gentamicin (10 μg), clindamycin (2 μg), erythromycin (15 μg), trimethoprim-sulfamethoxazole (1.25 μg/23.75 μg), tetracycline (30 μg), vancomycin (30 μg), and teicoplanin (30 μg).

Statistical methods

The results were analyzed using a commercially available software package (SPSS, version 11.0, SPSS Inc., Chicago, IL, USA). For categorical data, proportions were compared with chi-squared test. The means and medians of continuous variables were compared by the Student's *t* test or Mann-Whitney *U* test, depending on the distribution of data. Multivariate analysis was performed by logistic regression. All tests of significance were 2-tailed; a *p* value of 0.05 or less was considered statistically significant.

Results

From January 1999 to December 2001, a total of 9174 positive blood cultures were obtained in the clinical laboratory, 1672 (18.2%) of which were *S. aureus*. No significant yearly difference (p=0.771) in the number of *S. aureus* isolates was found. 1102 patients with *S. aureus* bacteremia were identified. A total of 104 patients (104/1102, 9.44%) met the study criteria for CASA bacteremia. Among these 104 patients, 35 (33.7%) had methicillin-resistant strains and 69 (66.3%) had methicillin-susceptible stains isolated (Table 1). These 104 patients were included in the study and their medical records were analyzed. The results of comparison of demographic data, underling diseases, previous history of antimicrobial therapy, duration of hospitalization, and intravenous drug use between MSSA and MRSA groups are summarized in Table 2. There were 69 patients in the MSSA group and 35 in the MRSA group. Infections occurred year-round, and there were no significant differences between patients with MRSA bacteremia and those with MSSA bacteremia with regard to gender or age (mean age for MRSA patients, 66.74 ± 17.09 years and for MSSA patients, 64.02 ± 20.21 years). The age of most patients was greater than 50 years (>70%), and age was not found to be related to drug susceptibility of the isolate. This phenomenon may have been due to the setting of this hospital, where most of the patients are elderly veterans.

After multivariate analysis, chronic obstructive pulmonary disease (p=0.037), chronic renal

Table 1. Comparative yearly data for CASA bacteremia and CA-MRSA bacteremia between 1999 and 2001

Variable	1999	2000	2001	*p*
No. of all episodes	3123	3179	2872	
No. of SA episodes (%)	558 (17.9)	620 (19.5)	494 (17.2)	0.771
No. of CASA	37	35	32	
No. of CA-MRSA (%)	17 (45.9)	10 (28.6)	8 (25)	0.063

Abbreviations: CASA = community-acquired *Staphylococcus aureus*; CA = community-acquired; MRSA = methicillin-resistant *Staphylococcus aureus*; SA = *Staphylococcus aureus*

insufficiency (p=0.041) and diabetes mellitus (p=0.028) were the remaining independent risk factors for acquiring CA-MRSA bacteremia. Patient characteristics including presence of malignancy, previous antibiotic usage, congestive heart failure, liver cirrhosis, chronic skin lesions, immune status or intravenous drug addiction were not significantly different between the 2 groups. Patients in the MRSA group were more likely to have 2 or more risk factors for *S. aureus* bacteremia than those in the MSSA group (37.7% vs 74.3%, p<0.001). Most patients in the MRSA group had more than 1 risk factor; only 6 patients (17.1%) did not have any identified risk factors. These 6 cases occurred in an even time distribution during the 3-year study period. Among these 6 patients (male/female, 4/2; mean age, 56 years), soft tissue infection (2 patients) and respiratory tract infection (2 patients) were the most common presentations. The remaining 2 patients had urinary tract infection and primary bacteremia, respectively. All received glycopeptide therapy empirically or after isolation of the pathogen and none of them died. The length of stay in hospital was not significantly different between the 2 groups (median, 21 days for MRSA group and 17 days for MSSA group, p=0.587). No major differences in the laboratory data were found on univariate analysis, including peripheral blood white cell count, blood pressure, body temperature, C-reactive protein level, and platelet count. The proportion of cases which met the criteria for systemic inflammatory response syndrome was not significantly different between the MSSA and MRSA groups (75% vs 78%). Although more cases of CASA and CA-MRSA bacteremia occurred in the late autumn and early winter (Fig. 1), this variation was not significant.

Table 2. Comparison of clinical characteristics between patients with MSSA and MRSA bacteremia

	MSSA (n = 69)	MRSA (n = 35)	*p*
Gender (M/F)	51/18	27/8	NS
Age (years) [mean ± SD][a]	64.02 ± 20.21	66.74 ± 17.09	NS
Risk factor [n (%)][b]			
Diabetes mellitus	16 (23.5)	15 (42.9)	0.028
COPD	3 (4.4)	8 (14.3)	0.037
CHF	3 (4.4)	5 (14.3)	NS
Solid tumor	4 (5.9)	2 (5.7)	NS
Hematologic tumor	3 (4.4)	0	NS
Renal insufficiency	8 (11.8)	11 (31.4)	0.041
Cirrhosis of liver	5 (7.4)	4 (11.4)	NS
Chronic skin lesions	6 (8.8)	4 (111.4)	NS
Immunosuppression	1 (1.5)	1 (2.9)	NS
Prior antibiotic use	0	2 (5.7)	NS
IVDU	2 (2.9)	1 (2.9)	NS
No of risk factors ≥2	26 (37.7)	26 (74.3)	<0.001
Length of stay (days)[c]	49 (17)	25 (21)	NS

Abbreviations: CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; IVDU = intravenous drug user; NS = not significant; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*

[a]Data are mean ± SD.

[b]Total of 103 patients included in calculation (1 male was excluded).

[c]Hospitalized more than 3 days: data are total number (median).

The pattern of drug susceptibility in the 2 groups is shown in Table 3. Isolates of CA-MRSA showed a high degree of resistance to most antibiotics; 8.6% of MRSA isolates (3/35) were susceptible to erythromycin, 28.6% (10/35) to clindamycin, 58.8% (21/35) to chloramphenicol, 34.3% (12/35) to trimethoprim-sulfamethoxazole, and 31.4% (11/35) to gentamicin. Although there was a decreasing proportion of CA-MRSA in the 3 successive years, no significant trend (p=0.063) in the prevalence of CA-MRSA bacteremia was found. There was no significant difference in the mortality rate between patients with MRSA and MSSA who received appropriate treatment, either empirically or within 24 h after isolation of pathogen (7.7% vs 28.6%, p=0.056).

Discussion

Methicillin-resistant *S. aureus* has emerged as an important nosocomial pathogen worldwide in recent

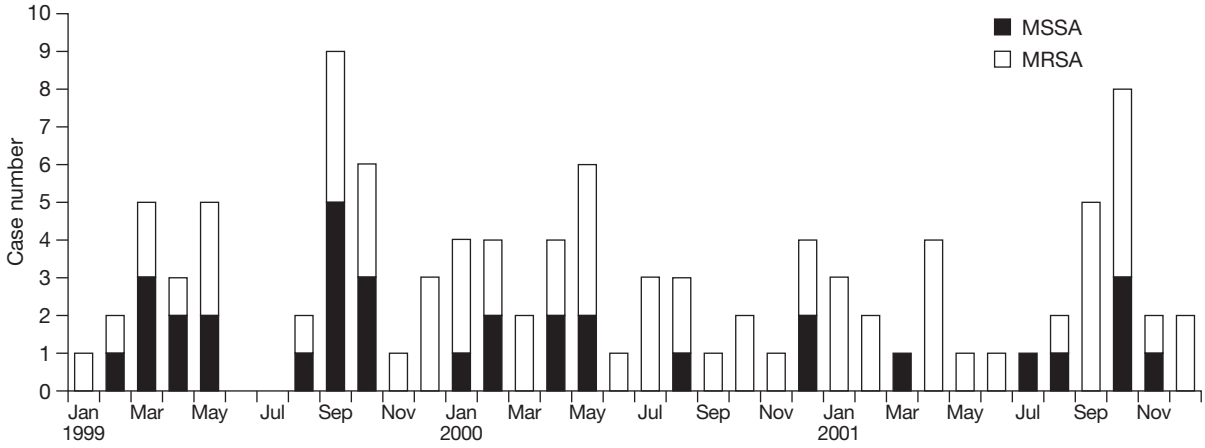

Fig. 1. Seasonal distribution of all community-acquired MSSA and MRSA isolates by month from January 1, 1999 through December 31, 2001.

decades. Methicillin-resistant *S. aureus* was first reported in the United States in 1961 and has continued to evolve since its first appearance [6,14]. In Taiwan, MRSA was first documented in the early 1980s [1]. Until recently, infections caused by MRSA were restricted primarily to hospitals and healthcare institutions [5,14]. The prevalence of CASA and CA-MRSA infections and risk factors for these infections have increased in recent years, and MRSA is no longer considered solely as a nosocomial organism.

In previous reports, 13 to 48% of cases of *S. aureus* bacteremia were CASA bacteremia [21-23]. The MRSA proportion of CASA bacteremia ranged from 4% to 18.5% [4,22,24]. In this study, 9.44% of cases were CASA bacteremia and the MRSA proportion was 33.7%. This MRSA proportion is higher than in previous reports. These differences in the percentage of CASA bacteremia and MRSA proportion might be due to the use of different definitions of CASA bacteremia in different studies and patterns of antibiotic usage in different studies. If MRSA was isolated not only from the bloodstream, 21 to 74% of cases were attributed to community-acquired infections [12-15,17]. Prior studies also described that most CA-MRSA cases had skin or soft tissue infections and the most common sources of MRSA bateremia were skin and soft tissue, followed by urinary tract, lower respiratory tract, and intravascular catheters [5,11,14,17].

Table 3. Antimicrobial susceptibility pattern in MSSA and MRSA isolates

Antimicrobial agent	MSSA (n = 69) n (%)	MRSA (n = 35) n (%)
Ampicillin	63 (91.3)	35 (100)
Cefazolin	0 (0)	34 (97.1)
Chloramphenicol	5 (7.2)	14 (41.2)
Clindamycin	6 (8.7)	25 (71.4)
Erythromycin	11 (15.9)	32 (91.4)
Gentamicin	2 (2.9)	24 (68.6)
Penicillin G	63 (91.3)	35 (100)
TMP/SMX	1 (1.4)	23 (65.7)
Vancomycin	0 (0)	0 (0)
Teicoplanin	0 (0)	0 (0)

Abbreviations: MSSA = methicillin-sensitive *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*; TMP/SMX = trimethoprim-sulfamethoxazole

The risk factors associated with nosocomial MRSA are well recognized, including prolonged hospitalization, receiving care in an intensive care unit, preceding antimicrobial therapy, surgical procedures, and contact with patients known to be colonized or infected with MRSA [25,26]. In an early study, CA-MRSA was primarily associated with intravenous drug use [27]. In more recent reports, the principal risk factors for CA-MRSA infections have included recent hospitalization, prior antimicrobial therapy, presence of indwelling urinary catheter, intravenous drug use, admission from another hospital, nursing home residence, and underlying diseases such as cardiovascular and pulmonary diseases, diabetes mellitus, malignancy, and chronic skin diseases [12,14,28]. For *S. aureus* bacteremia, analogous risk factors for acquiring resistant strains at the time of admission or in non-hospital situations have also been described [5,24]. Most of these risk factors are healthcare-associated, such as recent hospitalization, presence of indwelling urinary catheter, and nursing home residence. We used a stricter definition

to compare those patients in MSSA and MRSA groups in this study. More patients in the MRSA group than the MSSA group had 2 or more risk factors ($p<0.001$), and chronic obstructive pulmonary disease, chronic renal insufficiency, and diabetes mellitus were the independent risk factors for acquiring CA-MRSA bloodstream infection. In contrast to previous studies, MRSA bacteremia was related to intravenous drug use in only 1 patient (2 in the MSSA group) and no association between drug addiction and infection with a resistant strain was found. As in previous studies [21, 24], the risk factors identified were usually healthcare-associated and most patients in the MRSA group had at least 1 risk factor. In contrast with other studies [11,14,15,18,29], only 6 (17.1%) patients with MRSA bacteremia had no discernible risk factors. Similar to previous reports, soft tissue and respiratory tract infections were the most common sources in these 6 patients. In a recent meta-analysis, the prevalence of MRSA was low among patients without risk factors [26]. Difference in the proportion of patients without risk factors in different studies might be attributable to diverse sites of specimen collection, or differences in case definition and the population studied. In this study, patients in the MRSA group had more prolonged hospital stay than those in the MSSA group (21 days vs 17 days). This finding is similar to the results of Morin and Hadler [21].

Although more cases of CASA and CA-MRSA bacteremia occurred in the late autumn and early winter in this study, no significant seasonal variation was found, similar to a previous study [21]. A possible explanation for this observation may be related to airborne dispersal of *S. aureus* in association with an upper respiratory tract infection [30]. Although *S. aureus* is transmitted primarily by direct contact with colonized or infected patients, or via inanimate environment, airborne transmission plays a role in colonization of the anterior nares and the development of infection [12,30-34]. The anterior nares are the main reservoir site for *S. aureus* and most colonized persons are asymptomatic [26,31, 35]. The estimated nasal carriage rates in adults are 25 to 40%, and higher rates have been found in injection drug users, and in patients with insulin-dependent diabetes mellitus or dermatologic conditions, patients undergoing dialysis, patients undergoing specific immunotherapy, HIV-infected patients, and healthcare workers [32,33,36]. Colonization of *S. aureus* can be transient, intermittent, or persistent (from months to years) [33,35,37], and nasal *S. aureus* carriage plays an important role in the pathogenesis of infection [36]. Recently, von Eiff et al found that a substantial proportion of *S. aureus* bacteremia appeared to originate endogenously from the nasal reservoir [35]. No more than 10% of healthy nasal carriers disperse *S. aureus* into the air [30]. Whether this rate is the same for patients with healthcare-associated risk factors is unknown.

Differences in antimicrobial susceptibility patterns between nosocomial-acquired and CA-MRSA have been well documented in numerous studies. CA-MRSA is considered to be more susceptible to antibiotics other than β-lactams, especially clindamycin [7,11,13,15-17, 38,39]. The susceptibility rate of MRSA to clindamycin varied widely in previous studies, ranging from 42 to 100% [11,16,17,21,28,39]. In contrast to these studies, only 28.6% of isolates in this study were susceptible to clindamycin. Pediatric studies have found a different pattern of CA-MRSA resistance between children with and without risk factors. CA-MRSA in children with risk factors was more likely to be a multiresistant strain in several previous studies [7,18,29]. The findings in this study were similar, with CA-MRSA in patients without risk factors being more susceptible to trimethoprim-sulfamethoxazole (50% vs 31%), gentamicin (50% vs 27.6%) and clindamycin (33.3% vs 24.1%).

Have MRSA been introduced into the community? Chambers found that dissemination of penicillin-resistant *S. aureus* into the community followed when the rate of penicillin resistance among hospital-acquired *S. aureus* exceeded 40-50% [31]. With the increasing percentage of MRSA in nosocomial infections (more than 60% of nosocomial *S. aureus* isolates are resistant strains), such dissemination of MRSA into the community is anticipated.

Bacteremia due to *S. aureus* is associated with mortality rates of 15 to 60% [40]. In this series, patients who received appropriate antimicrobial treatment, either empirically or started within 24 hours after isolation of the pathogen, had mortality rates of 7.7% for MSSA and 28.6% for MRSA. No significant difference in mortality was found between these 2 groups ($p=0.056$). Similar results were reported by previous studies [5,41]. On the contrary, in a recent meta-analysis, MRSA bacteremia was associated with a significantly higher mortality rate than MSSA bacteremia [40]. Lack of adjustment for confounding factors may explain this heterogeneity in findings for mortality. Further studies are needed to clarify the difference in mortality between patients with increased susceptibility and those infected with resistant strains.

Generally speaking, the major risk factors for CA-MRSA infection appear to be those already identified as risk factors for nosocomial MRSA [26]. In this study, we excluded many healthcare-associated risk factors (e.g., nursing home care, permanent indwelling catheter, chronic dialysis), but those patients with underlying diseases (such as renal disease, pulmonary disease and diabetes mellitus) were still more likely to have MRSA infection. One possible explanation is that these patients visit outpatient settings more frequently than the general population, and methicillin-resistant *S. aureus* can be acquired very quickly from any clinical contact [6,9]. Subsequent nasal carriage and long-term persistence in the anterior nares may explain the presence of MRSA in the community [10] and later infection. Increasing numbers of patients carrying MRSA are discharged into the community, and intrafamily transmission has also been documented [6,10,13,14,21,31,42-44]. As the extent of persistence of nasal carriage of *S. aureus* and the precise site of acquisition of MRSA are uncertain, further study of these aspects of community spread are needed [12,26,40].

There were several limitations in this study: the findings of this retrospective study require confirmation using a prospective design; only bloodstream infection was included; information about prior visits to outpatient clinics other than our hospital and risk factors in family members were not considered; some cases of nosocomial MRSA may have been misclassified as CA-MRSA; and the data were collected from only one hospital and thus may not be representative of the larger Taiwanese population. In order to accurately estimate the prevalence and risk factors for acquiring CASA and CA-MRSA infections, a greater number of sites of specimen collection, a prospective, population-based study design, and a detailed history review by interview are needed.

Despite these limitations, the results of this study still indicate that *S. aureus* should be included in the differential diagnosis of pathogens in patients with bacteremia who are intravenous drug users, those with skin or soft tissue infections, and those who have intravascular devices in place. In treating bloodstream infection or other invasive infections caused by *S. aureus*, resistant strains should be suspected in patients with risk factors (chronic obstructive pulmonary disease, renal diseases, and diabetes mellitus) and glycopeptides should be used empirically. For patients without these risk factors with suspected mild MRSA infection, such as soft tissue infection, antibiotics other than β-lactams (e.g., clindamycin, gentamicin, chloramphenicol, or trimethoprim-sulfamethoxazole) may be used empirically while awaiting the culture report. Inappropriate use of glycopeptides can result in emergence of resistant strains, such as vancomycin-resistant enterococci, which makes further management increasingly problematic. Isolation and standard precautions such as hand-washing should be rigorously applied in cases with suspected CA-MRSA infection. Surveillance of MRSA carriage state in hospitalized and discharged patients may reduce the rate of nosocomial and community-associated MRSA bacteremia.

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