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Community-acquired methicillin-resistant *Staphylococcus aureus* bacteremia in Taiwan: risk factors for acquisition, clinical features and outcome

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The prevalence of community-acquired infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in Taiwan has increased markedly in the past decade. This study investigated the risk factors for acquisition, the clinical features, and the outcome of community-acquired MRSA bacteremia. Data were collected from records of 86 patients with community-acquired *S. aureus* bacteremia admitted to a tertiary teaching hospital in Taipei from January 1994 to December 1999. MRSA accounted for 26% (22/86) of isolated pathogens. Over 90% of patients with *S. aureus* bacteremia had one or more underlying diseases. Significantly more patients with MRSA bacteremia [vs methicillin-susceptible *S. aureus* (MSSA) bacteremia] had congenital and valvular heart diseases (18% vs 0%, p=0.004), an initial presentation of acute respiratory failure (32% vs 11%, p=0.022), an implant as a portal of entry (9% vs 0%, p=0.014), and mortality (41% vs 20%, p=0.05). Acute Physiology and Chronic Health Evaluation (APACHE) III score was significantly higher in patients who died than in patients who survived in both the MRSA and MSSA bacteremia groups. Inappropriate treatment was more frequent in patients with MRSA bacteremia than in MSSA bacteremia. When a Gram-positive coccemia is initially noted in a patient with high APACHE III score and/or acute respiratory failure, early and aggressive treatment including glycopeptide should be considered.

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

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection has been clinically important in the United States since the 1960s [1]. Most MRSA infections are hospital-acquired [2]. Between 1990 and 1997, the rate of MRSA infection in nosocomial *S. aureus* bacteremia in Taiwan increased from 32% to 82% [3,4]. In 1980, the first community-acquired MRSA infection was reported in the United States [5]. MRSA is a common isolate and an important pathogen in hospitals worldwide. However, recent reports suggested that community acquisition of MRSA is increasing in frequency. MRSA caused 18.5% of community-acquired *S. aureus* bacteremia in the US in 1996 [2]. The principal risk factors previously identified for acquisition of community MRSA included nursing home residence, intravenous drug use, diabetes mellitus, chronic renal failure, cancer, and acquired immunodeficiency syndrome [2,6,7].

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Community-acquired *S. aureus* bacteremia is a serious condition associated with high complication and mortality rates [8,9]. Lee et al [10] reported that MRSA accounted for 9% (5/55) of community-acquired *S. aureus* infection in Taiwan. This study analyzed the prevalence, risk factors, clinical features, and outcome of patients with community-acquired MRSA bacteremia and compared them to patients with methicillin-susceptible *S. aureus* (MSSA) bacteremia.

Materials and Methods

We reviewed all laboratory records of positive blood cultures for *S. aureus* from January 1994 to December 1999. We then reviewed all medical records of patients with community-acquired *S. aureus* bacteremia. Bacteremia was defined as the presence of at least 1 positive blood culture for *S. aureus*. At least 2 sets of blood cultures were done when patients were admitted before initiation of treatment. *S. aureus* bacteremia was defined as community-acquired if the blood isolate was obtained within 48 h of admission, if it was unrelated to a hospital intervention, and if the patient had not been

hospitalized in any acute-care facility during the previous 1 month [11,12]. Patients with uremia receiving regular hemodialysis, nursing home residents, and patients hospitalized within 1 week of the current admission were excluded [11]. A portal of entry for bacteremia was defined as clinical or bacteriologic evidence of infection at another site. The portal of entry was considered to be respiratory tract only if supported by clinical and radiological evidence, and urinary tract if urgency, frequency of urination, and obvious flank pain occurred. Presence of purulent secretion and inflammatory reaction were the criteria used to define vascular, skin, and wound sources. Patients without bacteriological or clinical evidence of an infection focus other than bacteremia were considered as having an unknown portal [13].

The clinical microbiology laboratory identified isolates from blood culture as *S. aureus*. Confirmation was done by colony morphology, Gram stain with positive cocci, positive catalase, positive glucose fermentation, and positive reaction with the commercial agent Staphaurex plus (Murex, UK). MRSA was identified based on presence of growth of colonies within a 10-mm zone of inhibition after 24 h of incubation at 35°C with a 1-μg oxacillin disk, and MSSA was identified based on the presence of a more than 13-mm zone of inhibition on an oxacillin disk [14,15].

Table 1. Demographic characteristics and underlying diseases of patients with community-acquired *Staphylococcus aureus* bacteremia

Variable	MSSA n = 64 (%)	MRSA n = 22 (%)	*p*
Age (years)	57.1 ± 26.6	55.3 ± 26.9	NS
Male/female	41/23	17/5	NS
Underlying disease			
Diabetes mellitus	24 (38)	7 (32)	NS
HCVD	16 (25)	2 (9)	NS
Malignancy	14 (22)	3 (14)	NS
Chronic renal insufficiency	13 (20)	1 (5)	NS
Implants	8 (13)	5 (23)	NS
CAD	7 (11)	4 (18)	NS
CVA	6 (9)	3 (14)	NS
Cirrhosis of the liver	4 (6)	0	NS
COPD	3 (5)	2 (9)	NS
IVDU	3 (5)	0	NS
Head and spinal cord injury	2 (3)	1 (5)	NS
Gallstone	2 (3)	0	NS
Goodpasture's syndrome	2 (3)	0	NS
Anemia	2 (3)	0	NS
CHD and VHD	0	4 (18)	<0.001
Trauma	1 (2)	0	NS
No underlying disease	5 (8)	3 (14)	NS

Abbreviations: MSSA = methicillin-susceptible *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*; NS = not significant; HCVD = hypertensive cardiovascular disease; CAD = coronary artery disease; CVA = cerebrovascular accident; COPD = chronic obstructive pulmonary disease; IVDU = intravenous drug user; CHD = congenital heart disease; VHD = valvular heart disease

Initial antibiotic therapy was considered appropriate if at least 1 antimicrobial agent to which the bacterium was sensitive *in vitro* had been used after blood culture collection. It was considered inappropriate if the bacterium was not sensitive *in vitro* to the antimicrobial agent used [8].

Outcome was classified into 2 categories: cure and death from *S. aureus* bacteremia. Cure was defined as resolution of clinical signs of infection during therapy and no evidence of recurrent *S. aureus* infection at the time of follow-up 2 weeks later; death from *S. aureus* bacteremia was defined as clinical and microbiologic evidence of infection at the time of death without any other definitive cause within 2 weeks after obtaining the first positive blood culture [16].

Statistical methods

Statistical analysis was performed using Epi Info 5.01 software. Categorical data were compared with chi-squared test or Fisher's exact test. Significance was defined as a p value of <0.05.

Results

Demographic characteristics and underlying diseases

A total of 86 patients with community-acquired *S. aureus* bacteremia were included. There were 64 patients (74%) with MSSA bacteremia and 22 patients (26%) with MRSA bacteremia. The demographic characteristics and underlying diseases of these patients are shown in Table 1. Over 90% of the patients with *S. aureus* bacteremia had one or more underlying diseases. Congenital and valvular heart disease was significantly more common in patients with community-acquired MRSA bacteremia than in MSSA bacteremia (18% vs 0%, $p<0.001$).

Initial clinical presentation and laboratory findings

The initial clinical presentation and laboratory findings for patients with community-acquired *S. aureus* bacteremia are shown in Table 2. The prevalence of acute respiratory failure requiring mechanical ventilator support was significantly higher in patients with

Table 2. Initial clinical and laboratory findings in patients with community-acquired *Staphylococcus aureus* bacteremia

Initial finding	MSSA n = 64 (%)	MRSA n = 22 (%)	*p*
Clinical			
Consciousness change	15 (23)	9 (41)	NS
Fever (>37.7°C)	53 (83)	18 (82)	NS
Hypothermia (<36°C)	4 (6)	2 (9)	NS
Tachycardia (>100/min)	31 (48)	10 (45)	NS
Acute respiratory failure	7 (11)	7 (32)	0.022
Unstable vital signs[a]	6 (9)	3 (14)	NS
Laboratory			
Leukocytosis[b]	42 (66)	15 (68)	NS
Leukopenia[c]	1 (2)	1 (5)	NS
Sets of positive blood cultures (mean)	1.7 1.7	NS	
Monomicrobial	63 (98)	18 (82)	NS
Polymicrobial	1 (2)	4 (18)	NS

Abbreviations: MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus;* NS = not significant

[a]Unstable vital signs was defined as one of the following: intravascular coagulopathy, acute respiratory distress syndrome, septic shock, and multiple organ dysfunction syndrome.

[b]Leukocytosis was defined as a white blood cell count >12 000/mm^3.

[c]Leukopenia was defined as an absolute neutrophil count <500/mm^3.

community-acquired MRSA bacteremia than in patients with MSSA bacteremia (32% vs 11%, p=0.022). In patients with polymicrobial bacteremia, 2 strains of viridans streptococci and 2 strains of *Klebsiella pneumoniae* in MRSA bacteremia, and 1 strain of group A streptococcus in MSSA bacteremia were identified. All of the MRSA isolates were resistant to penicillin, erythromycin, and cefazolin. Sixty eight percent (15/22) of the MRSA isolates were resistant to chloramphenicol, and 86% (19/22) were resistant to clindamycin or gentamicin.

Portal of entry

Table 3 shows the portal of entry for all patients. Implants as a portal of entry were significantly more common in MRSA bacteremia than in MSSA bacteremia (9% vs 0%, p=0.014). The respiratory tract was a more common portal of entry in MRSA bacteremia than in MSSA bacteremia, but this difference was not significant (23% vs 9%, p=0.105).

Metastatic complications

Severe metastatic complications occurring in patients with community-acquired MRSA bacteremia included endocarditis, meningitis, arthritis, and abscess. However, the prevalence of these complications was not significantly different compared to patients with MSSA bacteremia (18% vs 28%, p=0.36) (Table 4).

Table 3. Portal of entry for patients with community-acquired *Staphylococcus aureus* bacteremia

Portal of entry	MSSA n = 64 (%)	MRSA n = 22 (%)	*p*
Skin	21 (33)	8 (36)	NS
Port-A-catheter	3 (5)	0	NS
Urinary tract	7 (11)	1 (5)	NS
Respiratory tract	6 (9)	5 (23)	0.105
Abdomen	6 (9)	1 (5)	NS
Bone	1 (2)	0	NS
Implants[a]	0	2 (9)	0.014
Acute epididymitis	1 (2)	0	NS
Unknown	20 (31)	6 (27)	NS

Abbreviations: MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; NS = not significant.

[a]Implants included ventriculoperitoneal shunt and prosthesis for internal fixation.

Table 4. Metastatic complications in patients with *Staphylococcus aureus* bacteremia

Site of metastatic complication	MSSA n = 64 (%)	MRSA n = 22 (%)	*p*
Abscess of soft tissue	3 (5)	1 (5)	NS
Arthritis	5 (8)	1 (5)	NS
Endocarditis	5 (8)	1 (5)	NS
Meningitis	0	1 (5)	NS
Osteomyelitis	4 (6)	0	NS
Septic thrombophlebitis	1 (2)	0	NS
Total	18 (28)	4 (18)	NS

Abbreviations: MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus;* NS = not significant

Severity of illness, treatment and outcome

Patients with MRSA bacteremia had a higher mortality rate than those with MSSA bacteremia (41% vs 20%, p=0.05). Mortality after bacteremia occurred earlier in MSSA bacteremia than in MRSA bacteremia (Table 5). There was no significant difference in the Acute Physiology and Chronic Health Evaluation (APACHE) III score between patients with MSSA bacteremia and patients with MRSA bacteremia. Inappropriate initial antibiotic treatment was more frequent in patients with MRSA bacteremia than in patients with MSSA bacteremia (68.2% vs 1.6%, p=0.0035). Empiric treatment with cephalosporins, aminoglycosides or clindamycin was initially administered in these patients, but without response, and progression to septic shock ensued. Inappropriate treatment was given in 68% of patients who died from community-acquired MRSA bacteremia.

Table 5. APACHE III score, treatment, and outcome in patients with community-acquired MSSA and MRSA bacteremia

Variable	MSSA n = 64		MRSA n = 22		*p*
	Alive n = 51	Died n = 13	Alive n = 13	Died n = 9	
APACHE III score (mean ± SD)	34.3 ± 16.6	81.7 ± 34.6	34.5 ± 24.9	68.3 ± 16.5	0.29[a]
Treatment					
Appropriate	51	12	4	3	
Inappropriate	0	1 (8%)	9 (69%)	6 (67%)	0.0035[a]
Time from bacteremia to death (days; mean ± SD)	-	4.8 ± 5.7	-	12.0 ± 8.4	0.025

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; MSSA = methicillin-susceptible *S. aureus*, MRSA = methicillin-resistant *S. aureus*

[a]*p* value for comparison between the community-acquired MSSA bacteremia mortality group and the community-acquired MRSA bacteremia mortality group.

Discussion

This study underscores the emergence of MRSA in community-acquired *S. aureus* bacteremia in Taiwan. In patients with underlying congenital and valvular heart disease, an initial presentation of acute respiratory failure and an implant as a portal of entry should lead to the diagnosis of community-acquired MRSA bacteremia when Gram-positive coccemia has been noted initially. The high mortality rate in patients with MRSA bacteremia not receiving appropriate treatment indicates the need for early coverage of MRSA when MRSA bacteremia is suspected.

Diabetes mellitus, human immunodeficiency virus infection, chronic renal failure, malignancy, cirrhosis of the liver, cardiovascular disease, and implantation of a prosthesis have been reported as important underlying conditions associated with development of community-acquired MRSA bacteremia [6,12]. MRSA acquisition has been linked to intravenous drug abuse, cystic fibrosis, and repeated antimicrobial therapy [7,17,18]. However, isolation of MRSA from patients without known risk factors for MRSA acquisition has increased [6,19,20].

The percentage of patients colonized with MRSA has been increasing in recent years. It increased from 3.8% to 9.6% in a rural community in 1994 [21]. A 24% MRSA colonization rate in a child day care center was reported in 1998 [22]. Risk factors for MRSA colonization included tracheostomy, nasogastric intubation, antibiotic therapy, admission to an acute care facility within the previous 6 months, frequent contact with the healthcare environment, the number of surgical procedures that the patient underwent, and nursing home residence [23,24]. Reservoirs of MRSA colonization included the anterior nares, wounds, tracheostomy sites, sputum from intubated patients, and rectal and perineal sites [25]. These findings have led to a concern that MRSA is in the process of becoming endemic in the community.

In this study, there was a 20% mortality rate for community-acquired MSSA bacteremia and a 41% mortality rate for community-acquired MRSA bacteremia (p=0.05). A higher mortality rate in community-acquired MRSA bacteremia than in MSSA bacteremia has been reported previously [13, 26], especially when the lung was the site of entry and shock developed [13]. Rapid detection and identification of methicillin resistance in blood with automated blood culture systems in the clinical microbiology laboratory may diminish the time of culture required and hence avoid inappropriate treatment [27].

In conclusion, MRSA is increasingly important in community-acquired *S. aureus* bacteremia. A high percentage of patients receive inappropriate treatment, and these patients have a high mortality rate. Better alertness to the clinical features and risk factors for developing community-acquired MRSA bacteremia is needed, especially concerning septic patients with acute respiratory failure, patients with underlying implants, and patients with congenital and valvular heart disease. In patients with high APACHE III score and/or with acute respiratory failure, early and aggressive antibiotic treatment including a glycopeptide should be considered when Gram-positive coccemia is noted.

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