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Original Article

Endocarditis: impact of methicillin-resistant *Staphylococcus aureus* in hemodialysis patients and community-acquired infection

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Background and Purpose: *Staphylococcus aureus* endocarditis showed an increase in the 1990s compared to the 1980s. In order to characterize the clinical and laboratory features of *S. aureus* endocarditis, we retrospectively reviewed the medical charts of patients diagnosed with endocarditis in the 5-year-period between 2000 and 2005.
Methods: From August 2000 to August 2005, 22 patients with a definite diagnosis of infective endocarditis (IE) caused by *S. aureus* were reviewed.
Results: Of the 22 patients reviewed, 16 cases were caused by methicillin-resistant *S. aureus* (MRSA) while the causative agent in the other 6 cases was methicillin-susceptible *S. aureus* (MSSA). Patients with MRSA infections were more likely to show hospital-acquired infections, hemodialysis and ventilator dependence, septic shock, impaired initial renal function, persistent bacteremia, and a higher 3-month mortality rate. MSSA infections in patients were more likely to be community-acquired, and show intravenous drug use and longer days of fever prior to admission. Three patients with MRSA endocarditis, however, presented community-acquired infections. The mortality rate of MRSA endocarditis in hemodialysis patients was 90% (9/10).
Conclusions: MRSA IE is more common than MSSA IE and is associated with a significantly poorer prognosis, especially in patients undergoing hemodialysis. Although most cases of MRSA IE are hospital acquired, we noticed 3 cases of community-acquired MRSA IE. As MRSA IE has been noticed in the community and hemodialysis patients in recent years, and is associated with higher mortalities, strategies for its prevention and management are warranted.

Key words: Community-acquired infections; Endocarditis, bacterial; Methicillin resistance; Renal dialysis; *Staphylococcus aureus*

Introduction

Infective endocarditis (IE) is a life-threatening disease; even following the introduction of antibiotic therapy and valve replacement, the reported early mortality rates after 5-10 years of follow-up range from 25-50% [1-3]. *Staphylococcus aureus* was the most common pathogen (29.5-34.0%) found in large, multicenter, international cohorts of adults with IE [4,5]. Health care-associated infections were the most common form of IE caused by *S. aureus* (39%), and persistent bacteremia was found to be independently associated with IE caused by methicillin-resistant *S. aureus* (MRSA) [4]. IE, caused by both *Staphylococcus* and MRSA, became significantly more common in the 1990s than in the 1980s [6]. However, the emergence of community-acquired MRSA (CA-MRSA) has raised considerable concern, as it may be difficult to treat in outpatients [7-9]. CA-MRSA has been documented in Australia, New Zealand, Europe, the USA, and Canada in patients with no risk factors for nosocomial acquisition of MRSA [10-16]. A recent

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survey by the Centers for Disease Control and Prevention found that the number of centers reporting MRSA from hemodialysis (HD) patients had increased from 40% in 1995 to 71% in 2000 [17]. HD patients have a 30- to 100-fold higher risk of IE [18], and a study found that *S. aureus*, including MRSA, was the causal organism in 63.3% of IE diagnosed in HD patients [19].

We report a 5-year experience in 22 patients with confirmed IE due to *S. aureus*, with particular emphasis on the relative comparison of the disease caused by MRSA, methicillin-susceptible *S. aureus* (MSSA), CA-MRSA, and IE in patients receiving HD, as well as the cause of mortality.

Methods

We performed a retrospective study of cases diagnosed with *S. aureus* IE from August 2000 through August 2005. To meet the Modified Duke criteria [20] for definite IE, patients had to possess either the pathology or bacteriology of infection, or two major, one major and three minor, or five minor clinical criteria.

For each patient, the following parameters were recorded: demographic data, date of admission, laboratory data at admission (white blood cell count, hemoglobin, platelet count, and serum creatinine level), operation (early or late) and date of discharge or in-hospital mortality, duration of fever prior to admission, the portal of entry, community- or hospital-acquired infection, the presence of heart disease (native or prosthetic valve, prior endocarditis, congenital heart disease, rheumatic heart disease, and pacemaker implantation) and comorbidity (cerebrovascular accident, diabetes mellitus, chronic liver disease, chronic renal insufficiency, HD, chronic obstructive lung disease, alcoholism, malignancy, and immunodeficiency), prior antibiotic use within 2 weeks, mechanical ventilation during admission, the involved valves, clinical presentations, outcome, complications, and the causes and rates of mortality.

A CA-MRSA isolate was defined as an MRSA isolate recovered from the clinical culture of a patient who had no established risk factors for MRSA infection. Established risk factors included the isolation of MRSA 2 or more days after hospitalization; a history of hospitalization, surgery, dialysis, or residence in a long-term care facility within 1 year prior to the MRSA culture date; the presence of a permanent indwelling catheter or percutaneous medical device (e.g., tracheostomy tube, gastrostomy tube, or Foley's catheter) at the time of culture; or previous isolation of MRSA [21].

Hospital-acquired MRSA was defined as patients with the above established risk factors and with MRSA isolated after 72 h of hospital admission, or acquired more than 72 h after hospital admission with no clinical manifestation before admission. Persistent bacteremia was defined as the presence of positive blood cultures for *S. aureus* after at least 3 days of anti-staphylococcal antibiotic therapy with in vitro activity against the infecting strain. Early surgery was defined as surgical intervention performed before the completion of the course of antibiotic therapy. Late surgery was defined as surgical intervention performed after the completion of the course of antibiotic therapy. Prior antibiotic use was defined as the use of antibiotics, including in oral form, within 3 months prior to admission.

Differences in frequencies or proportions were analyzed with use of the chi-squared test. Data of continuous variables were reported as mean ± SD, unless otherwise specified. We used the Statistical Package for the Social Sciences for Windows (Version 10.0; SPSS Inc., Chicago, IL, USA) and MS Excel (Microsoft Excel 2001; Microsoft Corporation, Seattle, WA, USA) for all analyses.

Results

During the 5-year period, definite IE accounted for 52 patients. *S. aureus* (42.3%, 22/52) and viridans streptococci (21.1%, 11/52) were the two major pathogens causing IE. Twenty two patients with definite IE due to *S. aureus* were further studied. The mean ages were 61.9 ± 18.5 years for MRSA infections and 46.5 ± 25.9 years for MSSA. Demographic data and clinical characteristics of MRSA IE and MSSA IE are shown in Table 1.

As compared with the MSSA IE patients, those with MRSA IE had an increased presence of hospital acquisition (81.3% vs 0.0%, p=0.0005), comorbidity (68.8% vs 16.7%, p=0.028), and HD patients (62.5% vs 0.0%, p=0.008) on admission. Following admission, MRSA IE patients had an increased rate of septic shock (87.5% vs 33.3%, p=0.001), mechanical ventilation (93.8% vs 33.3%, p=0.002), persistent bacteremia (68.8% vs 0.0%, p=0.004), and mortality (75.0% vs 33.3%, p=0.07). In contrast, MSSA IE patients were more likely to have community acquisition (100.0% vs 18.8%, p=0.0005), intravenous drug abuse history (IVDU; 66.7% vs 6.25%, p=0.0025), and more days of fever before admission (23.2 ± 25.4 vs 4.8 ± 4.4, p=0.002). Otherwise, no statistical difference was noted

Table 1. Demographic data and underlying diseases for patients with infective endocarditis (IE) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) vs methicillin-susceptible *S. aureus* (MSSA)

Variable	Patients with MRSA IE (n = 16) No. (%)	Patients with MSSA IE (n = 6) No. (%)	*p*
Age (years; mean ± SD)	62.7 ± 18.1	46.5 ± 25.9	NS
Male gender	11 (68.7)	5 (83.3)	NS
Acquisition in the community	3 (18.8)	6 (100.0)	0.0005
Comorbidity	11 (68.8)	1 (16.7)	0.0280
Cerebrovascular accident	4 (25.0)	0 (0.0)	NS
Diabetes mellitus	6 (37.5)	0 (0.0)	NS
Chronic liver disease	1 (6.25)	1 (16.7)	NS
Chronic renal insufficiency	2 (12.5)	0 (0.0)	NS
Hemodialysis	10 (62.5)	0 (0.0)	0.0080
Chronic obstructive lung disease	2 (12.5)	0 (0.0)	NS
Alcoholism	2 (12.5)	0 (0.0)	NS
Immunodeficiency	2 (12.5)	0 (0.0)	NS
Prior antibiotic use	10 (62.5)	5 (83.3)	NS
Intravenous drug use	1 (6.25)	4 (66.7)	0.0025
Heart disease			
Native valve	8 (50.0)	5 (83.3)	NS
Prosthetic valve	2 (12.5)	1 (16.7)	NS
Congenital heart disease	1 (6.25)[a]	0 (0.0)	NS
Rheumatic heart disease	1 (6.25)	0 (0.0)	NS
Mitral valve prolapse	1 (6.25)	1 (16.7)	NS
Coronary arterial disease	3 (18.8)	0 (0.0)	NS

Abbreviations: SD = standard deviation; NS = not statistically significant ($p>0.05$)

[a]Tetralogy of Fallot.

regarding age, gender, the presence of heart disease, and cardiac operation (Table 1 and Table 2).

The most common portals of entry for MRSA IE were the sites associated with HD catheters (62.5%, 10/16) and intravenous injections (18.8%, 3/16). The most common portal of entry for MSSA IE was the peripheral intravenous injection site (66.7%, 4/6) due to IVDU (Table 3).

Echocardiographs showed 56.3% (9/16) of vegetation in MRSA IE cases on the mitral valve and 50.0% (3/6) of that in MSSA IE cases on the tricuspid valve.

In MRSA IE patients, factors such as septic shock (66.7%, 8/12), aspiration pneumonia with acute respiratory failure (8.3%, 1/12), heart failure (8.3%, 1/12), multiple brain infarcts (8.3%, 1/12), and multiple organ failures (8.3%, 1/12) were associated with mortality. In MSSA IE patients, septic shock (50.0%, 1/2) and multiple organ failure (50.0%, 1/2) were associated with mortality.

Among the 16 cases of MRSA IE studied, 3 cases were community-acquired (Table 4). Case 1 was a 32-year-old male with underlying congenital heart disease, i.e., tetralogy of Fallot, who sustained high fever for 4 days. He survived after a 2-month antibiotic treatment and cardiac surgery. Case 2 was a 57-year-old male with a past history of heroin IVDU for more than 10 years, who complained of conscious change gradually, erythematous change of bilateral legs and persistent fever for 7 days. Although he received aggressive, adequate antibiotic treatment and emergent surgery (mitral valve replacement), he died after the revisional surgery of mitral valve repair. Case 3 was a 75-year-old female suffering from chills and fever for 4 days and dyspnea for a day. Following admission, MRSA was found on blood culture and cardiac murmur was noted. Transthoracic and transesophageal echocardiographic findings all disclosed vegetation on the aortic valve. She received early valve replacement. Unfortunately, she developed critical illness polyneuropathy with quadriplegia after cardiac surgery. Quadriplegia resolved gradually after aggressive treatment of the underlying infection and rehabilitation. The portal of CA-MRSA infection was most probably a small skin wound on the lower leg (Table 4). In these 3 cases of CA-MRSA IE, the isolates were sensitive in vitro to fusidic acid, trimethoprim-sulfamethoxazole, teicoplanin, vancomycin, and ciprofloxacin; and all were

Table 2. Initial presentation, laboratory data, management, outcome and mortality of methicillin-resistant *Staphylococcus aureus* (MRSA) infective endocarditis (IE) vs methicillin-susceptible *S. aureus* (MSSA) IE

Variable	Patients with MRSA IE (n = 16) No. (%)	Patients with MSSA IE (n = 6) No. (%)	*p*
Fever prior to admission (days; mean ± SD)	4.8 ± 4.4	23.2 ± 25.4	0.002
Laboratory findings (mean ± SD)			
Platelet (k/μL)	155.8 ± 99.4	183.0 ± 124.0	NS
Hemoglobin (g/dL)	9.5 ± 2.3	11.5 ± 3.0	NS
White cell count (/μL)	11,446 ± 5392	18,342 ± 16,829	NS
Serum creatinine (mg/dL)	3.9 ± 2.6	1.5 ± 1.2	0.045
Outcome and complications			
CNS event, including embolization	3 (18.8)	1 (16.7)	NS
Pulmonary embolism	2 (12.5)	2 (33.3)	NS
Acute myocardial infarction	1 (6.25)	0 (0.0)	NS
Extremities embolism	1 (6.25)	0 (0.0)	NS
Spleen embolism	1 (6.25)	0 (0.0)	NS
Renal embolism	1 (6.25)	0 (0.0)	NS
Total embolism	9 (56.3)	3 (50.0)	NS
Heart failure	7 (43.8)	0 (0.0)	NS
Acute renal failure	3 (18.8)	2 (33.3)	NS
Bone/soft tissue infection	2 (12.5)	0 (0.0)	NS
Gastrointestinal bleeding	5 (31.3)	1 (16.7)	NS
Persistent bacteremia	11 (68.8)	0 (0.0)	0.004
Septic shock	14 (87.5)	2 (33.3)	0.001
Mechanical ventilation	15 (93.8)	2 (33.3)	0.002
Cardiac operation			
None	9 (56.3)	3 (50.0)	NS
Early (<1 month)	6 (37.5)	3 (50.0)	NS
Late (>1 month)	1 (6.25)	0 (0.0)	NS
Mortality (at 3 months)	12 (75.0)	2 (33.3)	0.007

Abbreviations: SD = standard deviation; NS = not statistically significant; CNS = central nervous system

resistant to penicillin, erythromycin, oxacillin, and clindamycin.

Ten of the 16 cases of MRSA IE were receiving HD. Their underlying diseases, other than uremia, included diabetes mellitus (n = 6), cerebrovascular accidents (n = 3), alcoholic liver disease (n = 2), and prosthetic valve disease (n = 2). Their mean age was 65.1 years. Fever (n = 8) and/or dyspnea (n = 4) were the major clinical presentations. Vegetations were found on the mitral (70.0%, 7/10) and aortic valves (20.0%, 2/10). Ninety percent (9/10) of the patients died.

Discussion

Although *Streptococcus* is the main causative agent of IE [22,23], *S. aureus* associated with IE is being detected more frequently [5,6]. Cabell et al [24] reported 329 cases of IE, with increased rates of HD dependence, immunosuppression, and *S. aureus* infections, and a decrease in the rate of infection due to viridans group streptococci (p=0.007). They also reported that HD was independently associated with *S. aureus* infections and that patients with *S. aureus* IE had a higher 1-year mortality rate. Our study showed that MRSA IE was more likely to be hospital-acquired (81.3%, 13/16), while MSSA IE was more likely community-acquired (100.0%, 6/6). We found that MRSA IE had more septic shock than MSSA IE [25], and although Hsu and Chu reported that MRSA IE had less systemic embolism than MSSA IE, our findings were not similar [25]. However, like previous studies, this study also found that persistent bacteremia was significantly higher in MRSA IE than MSSA IE (68.8% vs 0.0%) [4,26].

CA-MRSA infection is an emerging disease of worldwide significance [9,16,27]. From 2001 through 2002, 1647 cases of CA-MRSA infection were reported, representing between 8-20% of all MRSA isolates [21]. Miller et al [28] reported that 62% of community-acquired *S. aureus* was due to MRSA. The majority of CA-MRSA infections have been skin and soft tissue infections, and the most common dermatologic

Table 3. Portal of entry for methicillin-resistant *Staphylococcus aureus* (MRSA) infective endocarditis (IE) vs methicillin-susceptible *S. aureus* (MSSA) IE

Portal of entry	Patients with MRSA IE (n = 16) No. (%)	Patients with MSSA IE (n = 6) No. (%)	*p*
Unknown	2 (12.5)	2 (33.3)	NS
Hemodialysis catheter-related site	10 (62.5)	0 (0.0)	0.0080
Intravenous injection site[a]	3 (18.8)	4 (66.7)	0.0310
Central line	2 (12.5)	0 (0.0)	NS
Peripheral line	1 (6.25)	4 (66.7)	0.0025
Skin	1 (6.25)	0 (0.0)	NS

Abbreviation: NS = not statistically significant

[a]Excluding hemodialysis patients.

conditions seen were abscesses, cellulitis, folliculitis, and impetigo. Severe life-threatening infections have also been occasionally described. Crum [29] reviewed 14 cases of severe CA-MRSA infections, where only one case was initially treated with antibiotics effective for MRSA, and found that the mortality rate was 64%; 40% of patients who survived had significant disabilities. Schulz et al [30] reported that CA-MRSA is microbiologically distinct from hospital-acquired MRSA, and has a predilection to cause severe skin and soft tissue infections and a particularly virulent necrotizing pneumonia. Lina et al [31] also reported that CA-MRSA strains typically carry the Panton-Valentine leukocidin genes, which produce cytotoxins that can cause tissue necrosis and leukocyte destruction, and are associated with staphylococcal skin infections and necrotizing pneumonia. Three factors may contribute to the transmission of CA-MRSA — abrasions and lacerations associated with sport and sports equipment, physical contact, and sharing of equipment [32,33]. Many patients have suffered serious morbidity and mortality due to disregard of CA-MRSA as a pathogen in these infections. In the 3 cases of CA-MRSA IE that we studied, case 2 showed cellulitis of bilateral legs due to long-term IVDU, and case 3 had a small skin wound in the leg. All had the prodromal symptoms of fever and general malaise. Cases 1 and 3 survived while case 2 succumbed to severe heart failure and profound septic shock. Although the three CA-MRSA strains were sensitive in vitro to fusidic acid, trimethoprim-sulfamethoxazole, and ciprofloxacin, the choice of antibiotic for endocarditis caused by CA-MRSA needs more study.

IE in HD patients appears to be the most important subgroup [25,34]. Cabell et al [24] collected data from 329 patients with definite or possible IE at the Duke University Medical Center, from 1993 to 1999. They showed that the overall proportion of HD patients in their IE patients was as high as 20.0% and that the proportion of HD patients increased from 6.7% to >20.0% over the 7-year study period. According to the study by Hoen [35], the incidence of IE in HD patients was 1.7-2.0 cases per 1000 patients, which is 50-60 times higher than the overall incidence of IE in France. Chang et al [36] reported that definite IE occurred in 6.2% (18/288) of maintenance HD patients during a

Table 4. Demographic data, underlying diseases, clinical presentations, vegetation location, portal of entry and outcome for community-acquired methicillin-resistant *Staphylococcus aureus* infective endocarditis (n = 3)

Case	Age/gender	Underlying disease	Clinical presentations	Vegetation location	Portal of entry	Outcome
1	32/male	Tetralogy of Fallot	Intermittent fever for 3 months, general malaise, and high fever for 4 days	Aortic valve	Unknown	Survived
2	57/male	Intravenous drug abuse, alcoholism	Erythematous change of bilateral legs, fever, and consciousness change for one week	Mitral valve	Intravenous drug injection site	Died
3	75/female	Nil	Chills and fever for 4 days and dyspnea for one day	Aortic valve	Skin wound of lower leg	Survived

15-year period from 1988 to 2002. In the 52 cases of definite IE patients we studied during 5 years, 11 cases (21.1%, 11/52) were HD patients.

Bacteremia in patients receiving HD is primarily the result of access site infections, followed by access manipulation and procedures, such as dental procedures [37]. Other factors affecting infection rates include the depth of graft, the use of local or systemic prophylactic antibiotics, the presence of remote infection, perigraft lacerations and hematoma after needle puncture, skill at HD procedure, measures for hygiene and aseptic handling of venous catheters [38,39].

Three recent retrospective studies reported that IE in HD patients from 5 dialysis centers had the same findings — *S. aureus* was the predominant causative pathogen, being responsible for 40-80% of the cases, IE in HD patients had a poor prognosis, and in-hospital and 1-year death rates ranged from 25-45% and 46-75%, respectively [19,40,41]. Sexton [42] reported *S. aureus* as the main risk factor for bacteremia and subsequent IE in patients receiving HD. Chang et al [36] reported *S. aureus* (60%, 12/20) as the most common pathogen for IE in patients undergoing HD, and that MRSA was more common than MSSA (40% vs 20%). In our 5-year experience of 52 definite IE cases, 11 cases (21.1%, 11/52) were receiving maintenance HD, with *S. aureus* accounting for 19.2% (10/52) of the cases and all being MRSA. Chang et al [36] reported that the mortality rate for HD patients with IE was 60% (12/20), and that all with MRSA IE on HD died (100%, 8/8). In our study, the mortality rate of *S. aureus* IE (all with MRSA) in HD was 90% (9/10).

Since recent years have seen an obvious increase in the incidence of *S. aureus* and a corresponding increase in the mortality rate of IE caused by MRSA in HD patients, preventive measures need to be taken by following standard infection control measures for general hygiene and the aseptic handling of catheters in HD. Mupirocin nasal ointment led to the eradication of nasal *S. aureus* carriage in 96.3% of surveillance cultures and a significant reduction in the incidence of *S. aureus* bacteremia in HD patients [43], and may be useful in patients with dialysis catheters. Routine echocardiography for the diagnosis of IE in HD patients with MRSA bacteremia should also be highlighted. Due to the high mortality associated with MRSA IE, surgical intervention as well as a more potent regimen to treat MRSA endocarditis, such as combination drug therapy or the use of daptomycin, need to be studied further [26,44,45].

In conclusion, *S. aureus* has become the leading cause of IE in recent years and the mounting number of CA-MRSA infections is increasingly being recognized. A high mortality rate was noted in patients with MRSA endocarditis undergoing maintenance HD. With regard to the prevention of endocarditis, each dialysis should strictly adhere to hygiene rules associated with the HD technique. Since MRSA IE has increased in recent years and is associated with high mortality, strategies for its prevention and treatment are not only warranted but also indispensable.

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