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ANALYSIS OF RISK FACTORS FOR MORTALITY IN METHICILLIN-SENSITIVE *STAPHYLOCOCCUS AUREUS* BACTERAEMIA: CEFAZOLIN IS ASSOCIATED WITH BETTER OUTCOME

STAPHYLOCOCCUS AUREUS BAKTERİYEMİLERİNDE MORTALİTE RİSK FAKTÖRLERİNİN ANALİZİ: SEFAZOLİN DAHA İYİ SONUÇLA İLİŞKİLİ

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ABSTRACT

Objective: Methicillin-sensitive *Staphylococcus aureus* (MSSA) is frequent cause of bacteraemias and associated with substantial mortality. We defined risk factors for mortality among patients with either community-acquired (CA) or healthcare-associated (HCA) MSSA bacteraemia with special emphasis on treatment options including cefazolin and other antimicrobials (mainly ampicillin-sulbactam).

Material and Method: All adult patients who were hospitalized and whose blood cultures were positive for MSSA between 2009 and 2014 were included. Patients with CA and HCA MSSA bacteraemia were compared.

Results: 83% of the 127 patients with MSSA bacteraemia had HCA. The mortality rate of patients was 20.5% and this did not differ between patients with either CA or HCA MSSA bacteraemia. In the multivariate analysis, higher comorbidity index (HR 1.557), presence of metastatic foci (HR 2.883), and requirement for ICU support (HR 16.239) were found as independent risk factors for mortality, and cefazolin use was found to be protective against mortality (HR 0.178).

Conclusion: Patients with MSSA bacteraemia should be treated with cefazolin instead of other antimicrobial options, especially in countries where anti-staphylococcal penicillins are not available or in patients who cannot tolerate anti-staphylococcal penicillins, as cefazolin was found to be protective against mortality.

Keywords: Methicillin-sensitive *Staphylococcus aureus*, healthcare associated bacteraemia, cefazolin

ÖZET

Amaç: Metisiline duyarlı *Staphylococcus aureus* (MSSA), önemli bir bakteriyemi etkeni olup, hastalarda ciddi mortaliteye neden olur. Bu çalışmada, toplum kaynaklı (TK) veya sağlık bakımı (SB)'yla ilişkili MSSA bakteriyemilerinde mortaliteye etki eden risk faktörlerinin belirlenmesi amaçlanmıştır. Ayrıca MSSA bakteriyemilerinin tedavi seçeneklerinden sefazolin ve özellikle ampisilin-sulbaktam olmak üzere diğer antimikrobiklerin tedavideki yeterlikleri karşılaştırılmıştır.

Gereç ve Yöntem: 2009-2014 yılları arasında hastanemizde yatarak tedavi edilen ve MSSA bakteriyemisi tanısı konulan erişkin hastalar çalışmaya dahil edildi. TK veya SB ilişkili MSSA bakteriyemisi olan hastalar karşılaştırıldı.

Bulgular: Toplam 127 MSSA bakteriyemili hastanın %83'ü SB ile ilişkiliydi. Mortalite oranı %20,5 olup, TK ve SB MSSA bakteriyemili hastalar arasında fark yoktu. Çok değişkenli analizde yüksek komorbidite indeksi (HR 1,557), metastatik infeksiyon odağı varlığı (HR 2,883) ve yoğun bakım desteğine ihtiyacın olması (HR 16,239) mortalite için bağımsız risk faktörleri, tedavide sefazolin kullanımı ise mortaliteyi azaltan bir faktör olarak saptandı (HR 0,178).

Sonuç: Diğer antimikrobiyallerle karşılaştırıldığında sefazolinle tedavi edilen MSSA bakteriyemilerinde klinik sonuçlar daha iyi belirlendiği için, özellikle antistafilokoksik penisilinlerin bulunmadığı yerlerde veya bu ajanları tolere edemeyen hastalarda diğer antimikrobiklerin yerine sefazolin tercih edilmelidir.

Anahtar Kelimeler: Metisiline duyarlı *Staphylococcus aureus*, sağlık bakımı ile ilişkili bakteriyemi, sefazolin

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INTRODUCTION

Methicillin-sensitive *Staphylococcus aureus* (MSSA) is one of the most frequently isolated causative agents of both healthcare-associated (HCA) and community-acquired (CA) bacteraemia. Mortality related to *S. aureus* bacteraemia is high, ranging from 20% to 30%, and varies as a function of underlying comorbid conditions, presence or absence of metastatic foci, and some features of the microorganism itself, such as a higher vancomycin minimum inhibitory concentration (MIC) level (1-6). Some studies reported an increased risk of mortality among patients with CA MSSA bacteraemia, but there are also reports with conflicting results (7, 8). Although cefazolin is the first choice in most of the current guidelines for the treatment of MSSA bacteraemia in the case of unavailability of anti-staphylococcal penicillins (ASP) like being in our country, other beta-lactams including ampicillin-sulbactam or other cephalosporins, glycopeptides and daptomycin are also used frequently (9). In this study, we analysed the risk factors for mortality among patients with MSSA bacteraemia with special emphasis on CA or HCA infections, and treatment with cefazolin and other antimicrobial treatment options.

MATERIALS AND METHODS

All adult (aged >18 years) patients who were hospitalized in our hospital and whose 2 blood cultures were positive for MSSA in the microbiology laboratory between January 2009 and December 2014 were included in the study. Patients with polymicrobial bacteraemia and those who died without antimicrobial therapy were excluded from the study.

Patients with positive blood cultures for MSSA and clinical and laboratory characteristics of them were retrospectively obtained from the laboratory and hospital databases. The following variables were recorded on previously prepared forms: age, sex, hospital ward (surgical or internal), requirement for intensive care unit (ICU) support, comorbid conditions (cancer, diabetes mellitus, cardiac valve disease, chronic renal failure, haemodialysis, cirrhosis, cerebrovascular accident), Charlson comorbidity index (CCI) (10), presence of echocardiographic examination and metastatic foci, laboratory values such as serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, C-reactive protein (CRP) levels and white blood cell counts at the time of diagnosis of the infection, type of the antibacterial used for the treatment, outcome (mortality), and duration of hospitalization from the blood culture positivity until discharge from hospital or death.

MSSA bacteraemia was defined as the isolation of MSSA from at least two or more bottles of blood cultures with associated symptoms and signs of systemic infection.

Cases of *S. aureus* bacteraemia were classified as HCA or CA. CA bacteraemia was defined as a positive blood culture result obtained at the time of hospital admission or within 48 hours of hospital admission. HCA bacteraemia was defined either nosocomial, (as positive blood culture result obtained from patients who had been hospitalized for ≥48 hours), or non-nosocomial (as a positive blood culture result obtained from a patient within 48 hours of admission if the patient (a) had intravenous medical therapy in the previous 30 days; (b) attended a hospital or haemodialysis clinic or received intravenous chemotherapy in the previous 30 days; (c) was hospitalised in an acute care hospital for 2 days in the previous 90 days; or (d) resided in a nursing home or long-term care facility) (11).

A BacT/ALERT 3D (bioMérieux, Marcy l'Etoile, France) automatic blood culture system was used for blood cultures. Classic methods (Gram-staining, catalase, coagulase, DNAse and cefoxitine susceptibility tests) were used for the identification of MSSA.

Statistical Analysis

Statistical analysis were performed using Statistical Package for the Social Sciences (SPSS) for Windows version 16.0 (SPSS Inc., Chicago, IL, USA). For analysis of risk factors for mortality and comparison of patients with CA and HA MSSA bacteraemia, χ^2 and Student's t-test were used for the univariate analysis of categorical and continuous variables of patients' characteristics, respectively. The univariate effect of the type of antimicrobial treatment on patient survival was investigated using log-rank test. Kaplan-Meier survival estimates were calculated. Cox regression analysis with backward selection was used to determine independent predictors of mortality. Variables found to be significant ($p<0.05$) in the univariate analysis or reported to be risk factors for mortality in the literature were included in the Cox regression analyses. Among correlated factors with similar effects on survival, only those with clinical significance were included. The proportional hazards assumption and model fit were assessed by means of residual (Schoenfeld and Martingale) analysis.

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethic Review Board of Hospital.

RESULTS

A total of 147 adult patients with clinically significant MSSA bacteraemia were identified between January 2009 and December 2014 from the database of the microbiology laboratory. Twenty patients were excluded from the study; 16 were excluded because they received outpatient management, and 4 patients died without receiving antimicrobial treatment. A total of 127 patients were included in the final analysis. Eighty-two (64.6%) patients were men and the median age was 54.4±17.0 years. One hundred five of the 127 (82.7%) patients had HCA MSSA, and 22 (17.3%) had CA MSSA. The comparison of patients with HCA MSSA and CA MSSA is shown in Table 1.

Table 1. Comparison of patients with community acquired methicillin-sensitive *Staphylococcus aureus* bacteraemia and health-care associated methicillin-sensitive *Staphylococcus aureus* bacteraemia.

Characteristics	All patients (n=127)	Community-acquired MSSA bacteraemia (n=22)	Healthcare-associated MSSA bacteraemia (n=105)	p
Sex (male), n (%)	82 (64.6)	17 (77.3)	65 (61.9)	0.171
Age (mean±SD)	54.38±16.98	49.91±16.41	55.31±17.03	0.116
Hospital service (medical), n (%)	87 (68.5)	21 (95.5)	66 (62.9)	**0.002**
Duration of hospital stay, (mean±SD)	20.10±19.82	25.64±19.39	18.94±19.80	0.092
Need for ICU support, n (%)	33 (26.0)	6 (27.3)	27 (25.7)	0.880
Charlson comorbidity index (mean±SD)	4.52±2.41	3.04±1.61	4.83±2.44	**0.001**
Echocardiographic investigation, n (%)	57 (44.9)	15 (68.2)	42 (40.0)	**0.016**
Presence of metastatic foci, n (%)	24 (18.9)	13 (59.1)	11 (10.5)	**<0.001**
WBC, (mean±SD)	12459±8348	15459±7265	11831±8454	**0.019**
Serum CRP level (mean±SD)	209±138	208±108	209±144	0.731
Serum ALT level (mean±SD)	61±120	54±62	62±129	0.443
Serum AST level (mean±SD)	60±123	60±104	60±127	0.426
Serum creatinine level (mean±SD)	1.95±2.01	1.22±0.79	2.10±2.14	0.475
Mortality, n (%)	26 (20.5)	5 (22.7)	21 (20.0)	0.773
Comorbid conditions				
Malignity, n (%)	44 (34.6)	4 (18.2)	40 (38.1)	0.088
Diabetes mellitus, n (%)	27 (21.3)	4 (18.2)	23 (21.9)	1.000
Chronic renal failure, n (%)	33 (26.0)	1 (4.5)	32 (30.5)	**0.014**
Heart valve disease, n (%)	27 (21.3)	9 (40.9)	18 (17.1)	**0.013**
Cerebrovascular accident, n (%)	9 (7.1)	0	9 (8.6)	0.357
Cirrhosis, n (%)	4 (3.1)	0	4 (3.8)	1.000
Immunosuppressive treatment, n (%)	13 (10.2)	1 (4.5)	12 (11.4)	0.464
None, n (%)	18 (14.2)	5 (22.7)	13 (12.4)	0.206
Source of bacteraemia				
Intravenous catheter, n (%)	55 (43.3)	0	55 (52.4)	**<0.001**
Primary, n (%)	16 (12.6)	4 (18.2)	12 (11.4)	0.477
Pneumonia, n (%)	15 (11.8)	3 (13.6)	12 (11.4)	0.724
Surgical site infection, n (%)	13 (10.2)	0	13 (12.4)	0.123
Skin and soft tissue infection, n (%)	11 (8.7)	2 (9.1)	9 (8.6)	1.000
Infective endocarditis, n (%)	11 (8.7)	8 (36.4)	3 (2.9)	**<0.001**
Bone and joint infection, n (%)	6 (4.7)	5 (22.7)	1 (0.9)	**0.001**
Antimicrobial treatment				
Ampicillin-sulbactam, n (%)	47 (37.0)	7 (31.8)	40 (38.1)	0.579
Cefazolin, n (%)	30 (23.6)	9 (40.9)	21 (20.0)	0.036
Other beta-lactams[1], n (%)	24 (18.9)	2 (9.1)	22 (21.0)	0.245
Vancomycin, n (%)	5 (3.9)	2 (9.1)	3 (2.9)	0.207
Vancomycin plus beta-lactam, n (%)	18 (14.2)	2 (9.1)	16 (15.1)	0.737
Daptomycin, n (%)	3 (2.4)	0	3 (2.9)	1.000

MSSA: methicillin-sensitive *Staphylococcus aureus*; ICU: intensive care unit; WBC: white blood cell, CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase

[1]Other beta-lactams (number of patients): Piperacillin-tazobactam (16), ceftriaxone (4), imipenem (2), meropenem (2).

Presence of intravenous catheters (52.4% vs 0%, $p<0.001$), chronic renal failure (30.5% vs 4.5%, $p=0.014$) and higher CCI (Charlson comorbidity index) (4.83 vs 3.04, $p=0.001$) were more frequently seen in patients with HCA MSSA than patients with CA-MSSA. Patients with CA-MSSA underwent more frequent echocardiographic investigations (68% vs 40%, $p=0.016$), were more likely to have heart valve disease (40.9% vs 17.1%, $p=0.013$), infective endocarditis (36% vs 3%,

Table 2. Comparison of methicillin-sensitive *Staphylococcus aureus* bacteraemia patients with and without mortality.

Characteristics	Patients without mortality (n=101)	Patients with mortality (n=26)	p (univariate analysis)	p (multivariate analysis)	HR	%95 CI
Age, year (mean±SD)	53.55±16.76	57.58±17.80	0.286			
Sex (male), n (%)	62 (61.4)	20 (76.9)	0.140			
Hospital service (medical), n (%)	70 (69.3)	17 (65.4)	0.701			
Community acquired infection, n (%)	17 (16.8)	5 (19.2)	0.773			
Duration of hospital stay, (mean±SD)	23.04±20.28	8.69±12.8	**<0.001**			
Need for ICU support, n (%)	12 (11.9)	21 (80.8)	**<0.001**	**<0.001**	16.239	6.021-43.799
Presence of metastatic foci, n (%)	17 (16.8)	7 (26.9)	**0.241**	**0.047**	2.883	1.013-8.210
Echocardiographic investigation, n (%)	49 (48.5)	8 (30.8)	0.105			
WBC, (mean±SD)	12491±8394	12336±8332	0.903			
Serum CRP level (mean±SD)	197.9±127.8	253.7±171.1	0.158			
Serum ALT level (mean±SD)	43.7±58.0	132.1±229.9	0.065			
Serum AST level (mean±SD)	38.0±50.50	149±238.4	**0.003**			
Serum creatinine level (mean±SD)	1.94±2.12	1.97±1.52	0.423			
Charlson comorbidity index (mean±SD)	2.98±1.75	4.15±1.59	**0.001**	**<0.001**	1.557	1.234-1.964
Comorbid conditions						
Malignity, n (%)	34 (33.6)	10 (38.5)	0.647			
Diabetes mellitus, n (%)	22 (21.8)	5 (19.2)	0.772			
Chronic renal failure, n (%)	25 (24.7)	8 (30.8)	0.533			
Heart valve disease, n (%)	19 (18.8)	8 (30.8)	0.184			
Cerebrovascular accident, n (%)	7 (6.9)	2 (7.7)	1.000			
Cirrhosis, n (%)	2 (1.9)	2 (7.7)	0.186			
Immunosuppressive treatment, n (%)	12 (11.9)	1 (3.8)	0.302			
Hemodialysis, n (%)	15 (14.9)	3 (11.5)	1.000			
None, n (%)	17 (16.8)	1 (3.8)	0.119			
Source of bacteraemia						
Intravenous catheter, n (%)	47 (46.5)	8 (30.8)	0.148			
Primary, n (%)	11 (10.9)	5 (19.2)	0.253			
Pneumonia, n (%)	9 (8.9)	6 (23.1)	0.046			
Surgical site infection, n (%)	9 (8.9)	4 (15.4)	0.466			
Skin and soft tissue infection, n (%)	11 (10.9)	0	0.118			
Infective endocarditis, n (%)	8 (7.9)	3 (11.5)	0.695			
Bone and joint infection, n (%)	6 (5.9)	0	0.346			
Antimicrobial treatment						
Ampicillin-sulbactam, n (%)	38 (37.6)	9 (34.6)	0.824			
Cefazolin, n (%)	28 (27.7)	2 (7.7)	**0.038**	**0.037**	**0.178**	**0.035-0.904**
Other beta-lactams[1], n (%)	15 (13.5)	9 (34.6)	**0.022**			
Vancomycin, n (%)	3 (3.0)	2 (7.7)	0.271			
Vancomycin plus beta-lactam, n (%)	15 (14.8)	3 (11.5)	1.000			
Daptomycin, n (%)	2 (2.0)	1 (3.8)	0.500			

ICU: intensive care unit; WBC: white blood cell, CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase
[1]Other beta-lactams (number of patients): Piperacillin-tazobactam (16), ceftriaxone (4), imipenem (2), meropenem (2).

p<0.001), bone and joint infection (22.7% vs 0.9%, p=0.001), metastatic focus (59% vs 10%, p<0.001) and had higher WBC count (15.459 vs 11.831, p=0.019) than patients with HCA-MSSA. The mean mortality rate of patients was 20.5% and did not differ between patients with either CA or HCA MSSA (p=0.77). The comparison of patients' characteristics with and without mortality is shown in Table 2.

Vancomycin alone was used for 5 patients because of empiric choice and allergies against beta-lactam in 3 and 2 patients, respectively. Combined vancomycin and beta-lactam treatment were given empirically to the patients with either health-care (16 patients) or community acquired (2 patients) sepsis. Daptomycin was given to 3 patients with health-care associated infections empirically.

Durations of treatment were not found to be different among patients treated with different types of antimicrobials (p>0.005). Mean durations (±SD) of treatment were found to be 25±24 and 18±18 days for patients treated with cefazolin and other antimicrobials, respectively (p=0.073); 19±18 and 20±20 days for patients treated with ampicilllin-sulbactam and other antimicrobials, respectively (p=0.935); and 22±19 and 19±19 days for patients treated with vancomycin + other beta-lactams and other antimicrobials, respectively (p=0.483).

In the univariate analysis, the requirement for ICU support (p<0.001), higher CCI (p=0.001), AST level (p=0.003) and treatment with antimicrobials other than cefazolin (p=0.038) or other beta-lactams (including piperacillin-tazobactam, ceftriaxone, imipenem, meropenem) (p=0.022) were determined as risk factors for mortality among patients with MSSA.

In the analysis of the univariate effect of types of antimicrobial treatment on survival, it was found that cefazolin was associated with improved survival (log-rank test p=0.023).

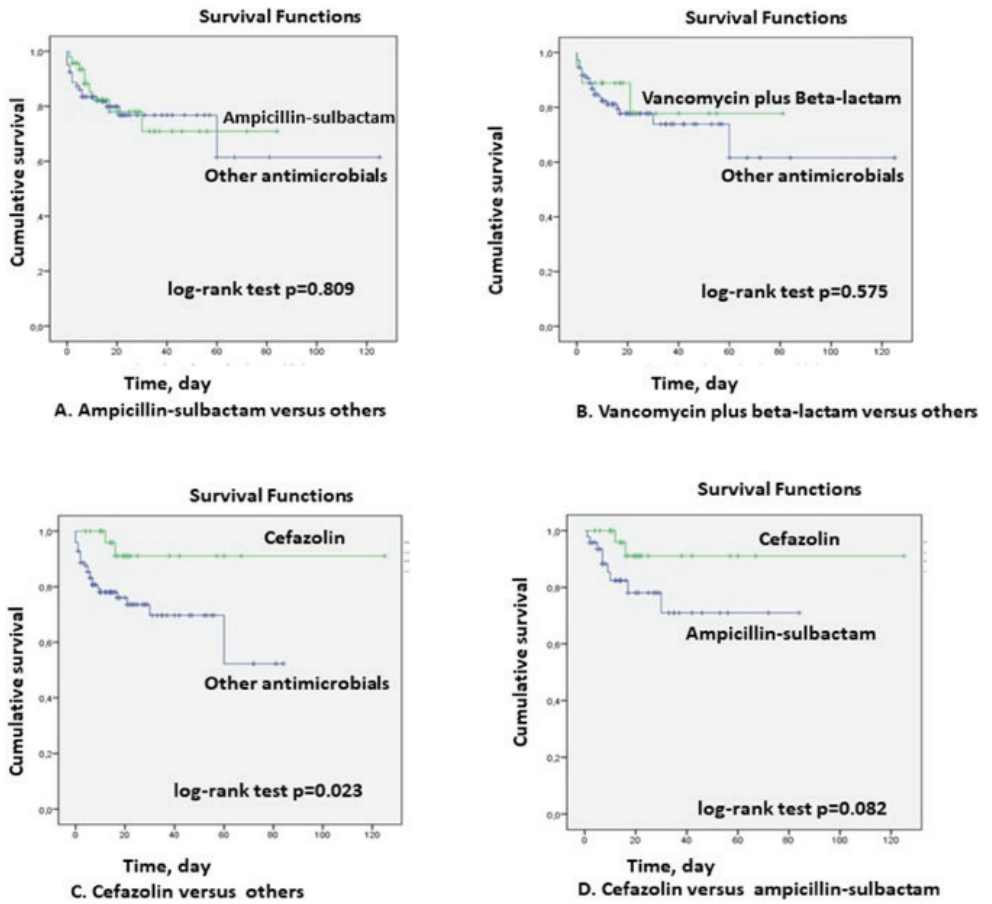

Figure 1: Effects of antimicrobial treatment on survival among patients with methicillin-sensitive *Staphylococcus aureus* bacteraemia. A. Comparison of survival between patients treated with ampicillin-sulbactam and all other antibiotics. B. Comparison of survival between patients treated with vancomycin plus beta-lactam (including piperacillin-tazobactam, imipenem, meropenem) and all other antibiotics. C. Comparison of survival between patients treated with cefazolin and all other antibiotics. D. Comparison of survival between patients treated with cefazolin and ampicillin-sulbactam.

In the subgroup analysis of patients treated with either cefazolin (n=30) or ampicillin-sulbactam (n=47), it was found that the mortality rate of patients treated with cefazolin (2/30, 6.6%) was lower than in patients treated with ampicillin-sulbactam (9/47, 19%); however, it did not reach statistical significance (log-rank p=0.082) (Figure 1).

In the multivariate analysis, higher CCI (HR 1.557), presence of metastatic foci (HR 2.883), and requirement for ICU support (HR 16.239) were found as independent risk factors for mortality among patients with MSSA, and cefazolin use was found to protect against mortality (HR 0.178).

DISCUSSION

In our study, MSSA bacteraemias mainly resulted from HCA infections, 82.7% of the cases had either nosocomial (acquired during hospitalization) or non-nosocomial (acquired in other type of health-care centers like haemodialysis units, nursing home or long-term care facility, etc). The reported rate of HCA infections among MSSA bacteraemia cases is wide ranging, between 27 and 81%, because the increasing numbers of individuals who are treated in outpatient programs make CA and HCA infections progres¬sively overlapped (6, 12-14). Especially after the definition of non-nosocomial HCA infections, it was noticed that like MRSA bacteraemia, MSSA bacteraemia also originated mainly from healthcare-associated infections (15). It is especially important to be aware of preventable risk factors that predispose patients to MSSA bacteraemia because the mortality rate of MSSA bacteraemia is still very high, 20% in our study, which is in accordance with the other reports (16, 17) and healthcare associated infections can be prevented. In a study from Australia, at least one preventable risk factor was defined among 33% of MSSA blood stream infections, and feedback about preventable factors was associated with a reduction in HCA *S. aureus* bacteraemia rates (18). In our study, 43% and 10% of MSSA bacteraemias resulted from IV catheter or surgical site infections, respectively. As a result, nearly 50% of cases had at least one preventable factor of this blood stream infection. Fourteen percent of our patients had undergone haemodialysis and this finding once again highlights the increased risk of this group of patients for MSSA bacteraemia (1). Patients with HCA MSSA had higher CCI and more frequent catheter-related infections and surgical unit hospitalization (p<0.05) than patients with CA MSSA, and patients with CA MSSA were more frequently associated with IE, bone and joint infections, metastatic foci, and underwent more echocardiographic evaluations and cefazolin treatment (p<0.05) than those with HCA MSSA. The mortality rate of HCA and CA MSSA bacteraemia did not differ significantly in our study (p=0.77). The increased risk of mortality reported among patients with HCA *S. aureus* bacteraemia could be attributed to the inclusion of patients with MRSA, confusion of community-onset HCA with community-onset CA infections, or increased risk of comorbidities among HCA infections (1, 7-9). After eliminating all of these confounding factors through the inclusion of only MSSA bacteraemia, using up-to-date definitions for HCA and CA bacteraemia, and analysing independent risk factors, the mortality rate of MSSA bacteraemia was found the same between HCA and CA MSSA bacteraemia in our study. There are also some reports of increased risk of mortality among CA MSSA bacteraemia related to increased complications, especially metastatic foci due to delayed diagnosis and treatment of disease (19). The diagnosis of HCA MSSA bacteraemia could be more rapid than the diagnosis of CA MSSA, which probably contributed to the increased risk of complication and death among patients with CA MSSA reported in some studies (20, 21). In accordance with some published studies (4), the higher CCI of patients with HCA MSSA and higher incidence of metastatic foci among patients with CA MSSA probably contributed to the lack of difference in mortality rates between patients with HCA or CA MSSA in our study.

The presence of metastatic foci was found to be an independent risk factor for mortality in our study and confirms results of other studies (20). It has been clearly described that risk of metastatic foci is significantly increased with prolonged duration of bacteraemia (19). Since the tendency of *S. aureus* for metastatic infection is well known, it is especially important to search with a clinical scoring system, TEE or PET/CT, to find and treat properly metastatic foci in order to decrease the risk of mortality in patients with MSSA bacteraemia (20, 22, 23). Comorbid conditions defined as increased CCI and severity of infection documented as a need to ICU support were found to increase mortality significantly in our study, which have already been demonstrated in several other studies (9, 22).

Cefazolin was found as an independent protective factor against mortality in our study. Although cefazolin has been shown to be effective equally with anti-staphylococcal penicillins (24-28) or have a mortality benefit (29) for treatment of MSSA bacteremia, there have not been studies comparing the effectivenes of cefazolin and other beta-lactams for this indication in situations where ASPs are not availible. In accordance with our study, in a retrospective cohort study of 498 patients with MSSA bacteraemia, treatment with cefazolin was not significantly different from treatment with cloxacillin, whereas treatment with other beta-lactams, including beta-lactam/beta-lactamase inhibitors, second- and third-generation cephalosporins, were associated with higher mortality (12). In a recent study of patients with MSSA bacteraemia and penicillin allergy, cefazolin was found superior to vancomycin for the treatment of MSSA bacteraemia,

with significant difference in mortality rates between patients treated with either cefazolin or vancomycin (19.6% vs 5.9%) (30). It is common practice to use either cefazolin or ampicillin-sulbactam for the treatment of infections caused by MSSA in our country because ASPs are not available. Therefore, we performed a subgroup analysis of patients treated with either cefazolin or ampicillin-sulbactam and found that the mortality rate of patients treated with cefazolin was lower than in patients treated with ampicillin-sulbactam (6.6 % versus 19.1%), although it did not reach statistical significance because of the lower number of patients. Additonal studies are needed to compare the effectiveness of cefazolin and specific beta-lactam agents including ampicillin-sulbactam in the treatment of MSSA bacteraemia.

Our study has some limitations. Although the first choice of *S. aureus* bacteremia is anti-staphylococcal penicillins (ASP) at the moment, we were unable to use them because of the unavailability of this agents in our country. As well as vancomycin and daptomycin are not recommended treatments for MSSA bacteremia, some of our patients were given either vancomycin combined with other beta-lactams or daptomycin because of severe health-care associated sepsis. Some of the variables that could have an effect on the mortality rate such as the duration of blood culture positivity could not be obtained because of retrospective design of the study. Also, metastatic foci could not be investigated properly with TEE or PET/CT in most patients.

Either HAC or CA, MSSA bacteraemia is associated with a high mortality rate, reaching 20%. Like MRSA bacteraemia, the proportion of nosocomial and non-nosocomial HCA infections is quite high, also in MSSA bacteraemia. Consequently, preventive measures are of vital importance. Patients with MSSA bacteraemia should be treated with cefazolin instead of other options including other beta-lactams, glycopeptides and daptomycin because of the associated lower mortality rate with cefazolin, especially in countries where anti-staphylococcal penicillins are not available or in patients who cannot tolerate anti-staphylococcal penicillins.

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