

Comparative Outcomes of Ampicillin-Sulbactam versus Cefazolin for Methicillin- Susceptible Staphylococcus aureus Infective Endocarditis: A Multicentre Cohort Study

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Abstract

Purpose

Antistaphylococcal penicillins and cefazolin are recommended as first-line therapies for methicillin-susceptible *Staphylococcus aureus* (MSSA) infective endocarditis (IE). However, in countries where antistaphylococcal penicillins are unavailable, alternative β -lactams are frequently used. Clinical data on ampicillin-sulbactam for MSSA IE are lacking. We compared outcomes of cefazolin and ampicillin-sulbactam in patients with MSSA IE.

Methods

In this multicentre retrospective cohort study using the Türkiye Endocarditis Group registry, adult patients with definite MSSA IE diagnosed between 2014 and 2023 who received cefazolin or ampicillin-sulbactam as definitive therapy for at least 75% of the treatment course were included. The primary outcome was in-hospital mortality; secondary outcomes were recurrence and 1-year all-cause mortality.

Results

Eighty-nine patients were included (cefazolin, $n = 67$; ampicillin-sulbactam, $n = 22$). Baseline characteristics were similar between groups, although right-sided IE was more frequent in the ampicillin-sulbactam group. In-hospital mortality was 22.4% and 4.5%, respectively ($p = 0.105$). One-year mortality was lower with ampicillin-sulbactam (20.0% vs. 47.5%, $p = 0.037$), but this association was not significant after multivariable adjustment (OR 0.27, 95% CI 0.07–1.02, $p = 0.053$). Comorbidity was independently associated with increased mortality (OR 4.38, 95% CI 1.08–17.78, $p = 0.039$), whereas cardiac surgery was associated with improved survival (OR 0.25, 95% CI 0.08–0.81, $p = 0.020$).

Conclusion

Ampicillin-sulbactam and cefazolin were associated with similar major clinical outcomes in MSSA IE. Ampicillin-sulbactam may represent an alternative treatment option when standard antistaphylococcal agents are unavailable. Larger prospective studies are warranted.

Introduction

Staphylococcus aureus is currently the leading causative pathogen of infective endocarditis (IE), accounting for approximately 30% of all cases, of which nearly 70% are caused by methicillin-susceptible *S. aureus* (MSSA) strains (1, 2). Current international and national guidelines recommend antistaphylococcal penicillins (ASPs) or cefazolin as first-line agents for the treatment of MSSA IE (3, 4).

Unlike ASPs, cefazolin is susceptible to the inoculum effect, a phenomenon characterized by reduced antimicrobial activity in the presence of high bacterial burdens (5, 6). Because IE is typically associated with a large bacterial inoculum, concerns have been raised regarding the effectiveness of cefazolin in this setting. Nevertheless, several clinical studies have demonstrated that cefazolin is not associated with higher mortality rates than ASPs in MSSA bacteremia or IE, leading to its widespread acceptance as an alternative first-line therapy (7–11).

Although numerous β -lactam antibiotics demonstrate in vitro activity against MSSA, clinical evidence suggests that not all β -lactams are equally effective in severe MSSA infections (12). Similar to cefazolin, ampicillin-sulbactam has also been shown to exhibit an inoculum effect against MSSA isolates in experimental and microbiological studies (13). In Türkiye, where antistaphylococcal penicillins are not available, cefazolin is commonly used for the treatment of MSSA IE. However, ampicillin-sulbactam is also frequently prescribed for MSSA bacteremia in routine clinical practice (14). Preliminary evaluation of the nationwide Türkiye Endocarditis Group (TEG) cohort revealed that, although less commonly than cefazolin, ampicillin-sulbactam is also used in patients with MSSA IE. Despite its clinical use, ampicillin-sulbactam is not currently recommended by major guidelines as an alternative treatment option for staphylococcal IE, and its role in the management of severe MSSA infections remains uncertain. Furthermore, clinical data evaluating its effectiveness specifically in MSSA IE are lacking.

Therefore, we aimed to compare the clinical outcomes of patients with MSSA IE treated with cefazolin or ampicillin-sulbactam and to determine whether ampicillin-sulbactam is associated with poorer prognosis or could be considered a potential alternative therapeutic option in this setting.

Methods

Study Design and Study Population

This multicentre retrospective cohort study was based on a prospectively established TEG registry. Among the 40 participating TEG centres, 19 with eligible patients with culture-confirmed MSSA IE were included.

Patients were included if they had received either cefazolin or ampicillin-sulbactam as definitive therapy for at least 75% of the total duration of targeted antimicrobial treatment. Patients were categorized into two groups according to the predominant definitive treatment received: (1) the cefazolin group and (2) the ampicillin-sulbactam group. Patients who received alternative definitive antimicrobial regimens, combination definitive therapy with another anti-staphylococcal agent, died within the first 72 hours of hospitalization, or were transferred to another institution before completion of treatment were excluded.

Demographic characteristics, comorbidities, predisposing conditions, mode of acquisition, echocardiographic findings, presenting symptoms, clinical manifestations, complications, laboratory parameters, imaging findings, antimicrobial treatment data, and clinical outcomes were extracted from the cohort database and medical records. Complications included cerebral, pulmonary, splenic, and

peripheral embolic events, intracranial hemorrhage, splenic abscess, heart failure, acute kidney injury, and spondylodiscitis, as documented by clinical and radiological evaluation.

Study Endpoints

The primary endpoint was all-cause in-hospital mortality. Secondary endpoints included recurrence of IE and one-year all-cause mortality.

Definitions

IE was defined according to the 2015 European Society of Cardiology (ESC) modified Duke criteria (15). Microbiological diagnosis was established by positive blood culture and/or valve culture yielding MSSA. According to the presumed source of infection, IE was classified as community-acquired or non-community-acquired. Recurrence was defined as either relapse or reinfection occurring after completion of antimicrobial therapy. Duration of bacteraemia was defined as the interval between the first and last positive blood cultures for MSSA. Cardiac surgery was defined as valve repair or valve replacement performed during the index hospitalization for the treatment of IE. Acute kidney injury was defined as an increase of ≥ 0.3 mg/dL in serum creatinine from baseline. Chronic kidney disease was defined as a documented baseline serum creatinine concentration > 1.4 mg/dL before the onset of IE. Patients presenting with heart failure, sepsis, and/or acute kidney injury attributable to IE were classified as having severe disease.

Statistical Analysis

Continuous variables were assessed for normality using visual methods (histograms and probability plots) and analytical tests (Kolmogorov–Smirnov and Shapiro–Wilk tests). Normally distributed continuous variables are presented as mean $\pm$ standard deviation (SD) and were compared using Student's t-test. Non-normally distributed continuous variables are presented as median (interquartile range [IQR]) and were compared using the Mann–Whitney U test. Categorical variables are presented as frequencies and percentages and were compared using the chi-square test or Fisher's exact test, as appropriate. Factors associated with one-year mortality were initially evaluated by univariate analysis. Variables associated with one-year mortality at a significance level of $p < 0.05$ in univariate analyses were considered candidates for multivariable analysis. A backward stepwise multivariable logistic regression model was constructed to identify independent predictors of one-year mortality. Variables were sequentially removed according to their statistical contribution to the model. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 31.0 (IBM Corp., Armonk, NY, USA). A two-sided p value < 0.05 was considered statistically significant.

Results

Patient Characteristics

Among 156 patients with definite MSSA IE identified from the Türkiye Endocarditis Group cohort between 2014 and 2023, 89 met the eligibility criteria and were included in the analysis. Of these, 67 patients received cefazolin and 22 received ampicillin-sulbactam as definitive therapy. The mean age of the study population was 53.5 ± 18.5 years, and 55 patients (61.8%) were male. The most common comorbidities were hypertension, diabetes mellitus, and chronic kidney disease, while 23.6% of patients had multiple comorbid conditions. Predisposing factors included degenerative valvular heart disease (23.6%), hemodialysis (16.8%), prosthetic heart valves (15.7%), and intravenous drug use (15.7%), whereas no identifiable predisposing condition was present in 18.0% of patients.

At the time of diagnosis, transthoracic echocardiography (TTE) was performed in 84 patients (94.4%), while five patients underwent transesophageal echocardiography (TEE) alone. IE was diagnosed by TTE in 66 patients (74.2%), by TEE alone in 21 patients (23.6%), and by positron emission tomography/computed tomography (PET/CT) alone in two patients (2.2%). Overall, TEE was performed in 77.5% of patients and PET/CT in 7.9%. The most frequently involved valves were the mitral valve (39.3%), aortic valve (30.3%), and tricuspid valve (19.0%). Community-acquired IE accounted for 64.0% of cases.

Emboic complications were observed in 46 patients (51.7%), including cerebral, pulmonary, and peripheral embolic events. Acute kidney injury occurred in 13 patients (14.8%). Cardiac surgery was performed in 34 patients (38.2%), and 82.0% of patients presented with severe disease. Overall in-hospital mortality and one-year all-cause mortality were 18.0% and 40.7%, respectively.

Baseline demographic characteristics, comorbidities, predisposing factors, clinical manifestations, laboratory findings, complications, and disease severity were comparable between the cefazolin and ampicillin-sulbactam groups. However, right-sided IE was more common among patients treated with ampicillin-sulbactam (Table 1).

Antimicrobial Treatment Characteristics

Empirical antimicrobial therapy was initiated in 59 (66.3%) patients. Vancomycin was the most frequently prescribed empirical agent (50.8%), and 80% of vancomycin-treated patients received combination therapy. Gentamicin was the most common companion antibiotic, whereas ceftriaxone, meropenem, and ampicillin-sulbactam were the most frequently used β -lactam agents. There was no significant difference between treatment groups regarding the time to initiation of empirical therapy. However, the interval between empirical therapy and transition to definitive therapy was longer in the ampicillin-sulbactam group than in the cefazolin group (4 [2] vs. 3 [2] days, $p = 0.029$).

Patterns of empirical antimicrobial selection were generally similar between groups. All patients who initially received empirical ampicillin-sulbactam were switched to cefazolin after the diagnosis of IE.

was established. Notably, none of the patients in the definitive ampicillin-sulbactam group had received ampicillin-sulbactam as empirical therapy.

Sequential oral therapy was administered to 14 patients (15.7%), most commonly with cephalexin (n = 6) or amoxicillin-clavulanate (n = 5). Among patients with available follow-up data no significant differences were observed between treatment groups regarding time to defervescence or time to blood culture sterilization.

Clinical outcomes

No significant differences were observed between the cefazolin and ampicillin-sulbactam groups with respect to the primary endpoint of in-hospital mortality or the secondary endpoint of recurrence. One-year all-cause mortality was significantly lower among patients treated with ampicillin-sulbactam than among those treated with cefazolin (20.0% vs. 47.5%, $p = 0.037$) (Table 2).

Risk Factors for One-Year Mortality

In univariate analyses, the presence of comorbidities and heart failure at presentation were associated with increased one-year mortality. In contrast, tricuspid valve involvement and cardiac surgery performed for the treatment of IE were associated with improved survival. Because pulmonary embolism is closely linked to right-sided IE and tricuspid valve involvement, it was excluded from the multivariable model to avoid collinearity and overadjustment. Variables significantly associated with one-year mortality in univariate analyses were entered into a backward stepwise multivariable logistic regression model (Table 3). In the final model, comorbidity (OR, 4.38; 95% CI, 1.08–17.78; $p = 0.039$) remained independently associated with increased mortality, whereas cardiac surgery (OR, 0.25; 95% CI, 0.081–0.808; $p = 0.020$) remained independently associated with improved survival. Although ampicillin-sulbactam treatment was associated with lower one-year mortality in univariate analyses, this association did not remain statistically significant after adjustment for potential confounders (OR, 0.27; 95% CI, 0.071–1.017; $p = 0.053$).

Discussion

To our knowledge, this is the first study specifically comparing ampicillin-sulbactam and cefazolin as definitive treatment options for MSSA IE. In this multicentre cohort, no significant differences were observed between the two treatment strategies with respect to in-hospital mortality, recurrence, or one-year mortality after adjustment for potential confounders. Although one-year mortality appeared lower among patients receiving ampicillin-sulbactam, this association did not remain statistically significant in multivariable analysis. These findings suggest that ampicillin-sulbactam may represent a reasonable alternative therapeutic option for MSSA IE, particularly in settings where standard antistaphylococcal agents are unavailable.

Clinical data regarding the use of ampicillin-sulbactam in MSSA IE are currently lacking. Most available evidence originates from studies of MSSA bacteraemia. During a cefazolin shortage in Japan, Uda et al. reported that ampicillin-sulbactam could serve as an effective alternative β -lactam therapy for MSSA bacteraemia (16). Similarly, Hirai et al. observed no significant differences in 30-day or 90-day mortality between ampicillin-sulbactam and cefazolin, although ampicillin-sulbactam was associated with a higher incidence of liver enzyme elevations (17). Furthermore, empirical treatment with β -lactam/ β -lactamase inhibitor combinations has not been associated with increased mortality in MSSA bacteraemia (18). Collectively, these findings support the possibility that ampicillin-sulbactam may provide acceptable clinical outcomes in severe MSSA infections.

In contrast, previous work from our centre demonstrated that cefazolin was associated with more favourable outcomes than ampicillin-sulbactam and other β -lactam agents in MSSA bacteraemia (14). In addition, microbiological studies performed in our institution showed that ampicillin-sulbactam may be more susceptible than cefazolin to the inoculum effect, particularly among strains producing type A β -lactamase (19). These observations appear inconsistent with the findings of the present study and warrant further consideration.

Several explanations may account for this discrepancy. First, treatment practices in Türkiye may differ from those reported in previous bacteraemia studies. Because national IE treatment recommendations advocate high-dose ampicillin-sulbactam (up to 12 g/day), clinicians frequently administer substantially higher doses in endocarditis than in uncomplicated bacteraemia. It is therefore conceivable that higher drug exposure may partially overcome the inoculum effect and improve treatment efficacy in high-burden infections such as IE.

Second, experimental evidence supports the biological plausibility of ampicillin-sulbactam activity in severe staphylococcal infections. Animal models have demonstrated improved efficacy of ampicillin-sulbactam when higher sulbactam concentrations are used against β -lactamase-hyperproducing *S. aureus* strains (20). Moreover, ampicillin-sulbactam has shown substantial bactericidal activity in experimental models of staphylococcal endocarditis (21). These observations suggest that under appropriate pharmacokinetic and pharmacodynamic conditions, ampicillin-sulbactam may retain clinically meaningful activity even in infections characterized by a high bacterial burden.

Third, another explanation relates to the impact of empirical antimicrobial therapy. Patients with IE frequently receive broad-spectrum antimicrobial treatment before microbiological confirmation and initiation of definitive therapy. Such early treatment may substantially reduce bacterial burden before targeted therapy is commenced, potentially diminishing the clinical relevance of the inoculum effect. Because empirical treatment regimens in our cohort were highly heterogeneous and frequently included combination therapy, the independent contribution of empirical antimicrobial exposure could not be adequately assessed.

Although ampicillin-sulbactam treatment was associated with lower one-year mortality in univariate analysis, this effect was no longer significant after adjustment for confounding factors. One possible

explanation is the higher proportion of right-sided IE in the ampicillin-sulbactam group. Right-sided IE is generally associated with more favourable outcomes than left-sided disease (22). However, in our cohort, endocarditis location itself was not independently associated with one-year mortality, suggesting that any confounding effect related to disease location was likely limited.

The presence of comorbidities emerged as an independent predictor of one-year mortality. This finding is consistent with previous studies demonstrating that chronic underlying illnesses substantially influence outcomes in both MSSA bacteraemia and IE. Large meta-analyses have shown that mortality associated with *S. aureus* bacteraemia remains considerable, particularly among elderly patients and those with significant comorbidity burdens (23). Similarly, recent nationwide epidemiological data from Türkiye identified chronic kidney disease, advanced age, and staphylococcal aetiology as important determinants of mortality in IE (2). Our findings further emphasize the importance of host-related factors in determining long-term outcomes.

In contrast, cardiac surgery was independently associated with improved survival. This observation supports the established role of timely surgical intervention in selected patients with MSSA IE. Recent evidence suggests that clinical management strategies, source control, and surgical treatment may exert a greater influence on patient outcomes than microbiological characteristics such as inoculum effect or bacterial genotype (24). Our results are consistent with these observations and underscore the critical importance of appropriate source control and multidisciplinary endocarditis team management.

This study has several limitations. First, its retrospective observational design precludes causal inference and leaves the possibility of residual confounding. Second, the relatively small number of patients in the ampicillin-sulbactam group limited statistical power and may have increased the risk of type II error. Third, microbiological factors such as inoculum effect, β -lactamase type, and pharmacodynamic parameters were not systematically evaluated. In addition, detailed safety data were unavailable, preventing comparisons of treatment-related adverse events. Nevertheless, this study provides valuable real-world evidence from multiple centres across Türkiye and represents one of the few clinical investigations evaluating ampicillin-sulbactam in MSSA IE.

In conclusion, no significant differences in mortality or other major clinical outcomes were observed between ampicillin-sulbactam and cefazolin in patients with MSSA IE. While comorbidities were independently associated with increased mortality, cardiac surgery was associated with improved survival. These findings suggest that clinical outcomes in MSSA IE are influenced not only by the choice of β -lactam agent but also by patient characteristics and the adequacy of source control. Ampicillin-sulbactam may therefore be considered an alternative treatment option when standard antistaphylococcal agents are unavailable. Prospective studies incorporating microbiological and pharmacodynamic assessments are needed to further clarify its role in the management of MSSA IE.

Declarations

Conflicts of interest/Competing interests

The authors declare no competing interests.

Ethical Approval:

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Başkent University Faculty of Medicine Ethics Committee (Decision No. KA22/298; July 5, 2022).

Consent to participate:

As this was a retrospective study and all procedures were performed as part of routine clinical care, the Ethics Committee did not require informed consent from the participants.

Clinical trial number

Not applicable.

Consent for publication

All authors consented to publication of the manuscript.

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Author Contribution

All authors contributed to the study and commented on previous versions of the manuscript.

Conceptualisation: S.B., N.S., S.S.Y., O.K.A., E.M.S., S.O.O.; Data curation: S.B., E.M.S., N.S., A.A., S.S.Y., D.S., S.O.O., E.T.T.; Methodology: S.B., N.S., D.S., S.O.O., S.S.Y., O.K.A.; Formal analysis: S.B., S.S.Y., N.S.; Supervision: A.A., S.S.Y., O.K.A.; Writing original draft: S.B., S.S.Y., N.S., E.M.S., O.K.A., D.S., M.A., S.O.O., E.T.T.; Writing review editing: S.B., N.S., S.S.Y., O.K.A., A.A.; All authors read and approved the final manuscript.

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Data Availability

The datasets generated during and/or analysed during the current study are available in the Seniha Başaran repository. Data are available in the hospital's electronic medical records.

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Tables

Table 1. Baseline demographic, clinical, laboratory, and echocardiographic characteristics of patients with methicillin-susceptible *Staphylococcus aureus* infective endocarditis according to definitive antibiotic therapy

Characteristics	Cefazolin (N=67)	Ampicillin- sulbactam (N=22)	p value
Age, mean $\pm$ SD	53.9 $\pm$ 17.4	52.2 $\pm$ 21.9	0.101
Male sex, n (%)	41 (61.2)	14/22 (63.6)	0.838
Predisposing conditions	54 (80.6)	19 (86.4)	0.751
Rheumatic fever sequelae, n (%)	5 (7.5)	0	0.327
Prosthetic valve, n (%)	13 (19.4)	1 (4.5)	0.174
Intracardiac device, n (%)	4 (6.0)	3 (13.6)	0.358
Bicuspid aortic valve, n (%)	4 (6.0)	1 (4.5)	1.000
Congenital heart disease, n (%)	6 (9.0)	1 (4.5)	0.676
Intravenous drug use, n (%)	9 (13.4)	5 (22.7)	0.299
Degenerative heart disease, n (%)	13 (19.4)	8 (36.4)	0.104
Previous IE episode, n (%)	3 (4.5)	1 (4.5)	1.000
Comorbidities	49 (73.1)	13 (59.1)	0.214
Hypertension, n (%)	24 (35.8)	4 (18.2)	0.185
Diabetes mellitus, n (%)	20 (29.9)	4 (18.2)	0.408
Chronic kidney disease, n (%)	10 (14.9)	6 (27.3)	0.191
Hemodialysis, n (%)	10 (14.9)	5 (22.7)	0.396
Coronary artery disease, n (%)	10 (14.9)	1 (4.5)	0.280
Chronic obstructive pulmonary disease, n (%)	4 (6.0)	1 (4.5)	1.000
Malignancy, n (%)	3 (4.5)	1 (4.5)	1.000
Autoimmune disease, n (%)	7 (10.4)	0	0.186
Multiple comorbidities, n (%)	17 (25.4)	4 (18.2)	0.575
Type of acquisition: Community-acquired, n (%)	41 (61.2)	16 (72.7)	0.328
Endocarditis side			
Left side	47 (70.1)	12 (54.5)	0.179
Mitral, n (%)	29 (43.3)	6 (27.3)	0.182
Aortic, n (%)	21 (31.3)	6 (27.3)	0.719
Right side	14 (20.9)	10 (45.5)	0.024

Tricuspid, n (%)	11 (16.4)	6 (27.3)	0.261
Pulmonary, n (%)	1 (1.5)	0	1.000
Lead, n (%)	2 (3.0)	4 (18.2)	0.031
Endocard, n (%)	3 (4.5)	0	0.572
Clinical findings			
Systolic blood pressure, mean $\pm$ SD, (N=82)	115 $\pm$ 19	114 $\pm$ 24	0.401
Murmur, n (%), (N=84)	30 / 62 (48.4)	8 / 22 (36.4)	0.330
Splenomegaly, n (%), (N=75)	13 / 55 (23.6)	6 / 20 (30.0)	0.575
Heart failure, n (%), (N=84)	23 / 63 (36.5)	5 / 21 (23.8)	0.285
Sepsis, n (%), (N=83)	14 / 62 (22.6)	7 / 21 (33.3)	0.327
Severe illness, n (%)	55 (82.1)	18 (81.8)	1.000
Laboratory data			
White blood cell (/ μ L), median [IQR], (N=87)	12400 [7785]	15705 [8550]	0.155
Hemoglobin (g/dL), mean $\pm$ SD, (N=86)	10.2 $\pm$ 2.2	11.1 $\pm$ 1.7	0.067
Platelet count (/ μ l), median [IQR], (N=87)	206000 [143000]	173000 [124275]	0.420
CRP (mg/L), mean $\pm$ SD, (N=83)	177.3 $\pm$ 114.1	228.0 $\pm$ 122.2	0.862
ALT (U/L), [IQR], (N=86)	26 [29]	28 [36]	0.392
Creatinine (mg/dL), [IQR], (N=87)	1.15 [1.55]	1.25 [2.30]	0.554
Albumin (g/dL), mean $\pm$ SD, (N=85)	2.94 $\pm$ 0.68	2.84 $\pm$ 0.60	0.622
Complications			
Cranial embolism, n (%)	13 (19.4)	4 (18.2)	1.000
Pulmonary embolism, n (%)	10 (14.9)	6 (27.3)	0.191
Peripheral embolism, n (%)	11 (16.4)	2 (9.1)	0.506
Acute renal failure, n (%)	7 (10.4)	5 (22.7)	0.143
Spondylodiscitis, n (%)	3 (2.9)	1 (4.5)	1.000
Splenic infarct/abscess, n (%)	3 (4.5)	1 (4.5)	1.000

ALT, alanine aminotransferase; CRP, C-reactive protein; IQR, interquartile range; SD, standard deviation

Table 2. Comparison of treatment characteristics and clinical outcomes between cefazolin and ampicillin-sulbactam therapy in patients with methicillin-susceptible *Staphylococcus aureus* infective

endocarditis

Characteristics	Cefazolin (N=67)	Ampicillin- sulbactam (N=22)	p value
Cardiac surgery for treatment, n (%)	27 (40.3)	7 (31.8)	0.478
Empirical treatment, n (%)	47 (70.1)	12 (54.5)	0.179
Antibiotics in empirical treatment ^a			
Vancomycin, n (%)	24 / 47 (51.1)	6 / 12 (50.0)	0.948
Ceftriaxone, n (%)	8 / 47 (17.0)	3 / 12 (25.0)	0.679
Ampicillin-sulbactam, n (%)	10 / 47 (21.3)	0	0.105
Meropenem, n (%)	9 / 47 (19.1)	2 / 12 (16.7)	1.000
Gentamicin, n (%)	8 / 47 (17.0)	3 / 12 (25.0)	0.141
Piperacillin/tazobactam, n (%)	4 / 47 (8.0)	7 / 12 (58.3)	0.653
Combined empirical treatment, n (%)	24 / 47 (51.1)	4 (18.2)	1.000
Sequential oral treatment, n (%)	10 (14.9)		
Time to antibiotic initiation (hours), median [IQR], (N=84)	17 [45]	4 [71]	0.077
Time to blood culture clearance (days), median [IQR], (N=69)	5 [4]	4 [2]	0.158
Duration of fever (days), median [IQR], (N=41)	3 [2]	2.5 [2]	0.322
Empirical treatment duration (days), median [IQR], (N=58)	3 [2]	4 [2]	0.029
Definitive treatment duration (days), median [IQR]	38 [18]	40 [14]	0.048
Treatment duration (days), median [IQR]	42 [17]	43 [16.7]	0.275
Total length of stay (days), median [IQR]	42 [23]	45 [17]	0.447
In-hospital mortality, n (%)	15 (22.4)	1 (4.5)	0.105
One-year all-cause mortality, n (%), (N=81)	29 / 61 (47.5)	4 / 20 (20.0)	0.037
Recurrence, n (%), (N=68)	4 / 51 (7.8)	1 / 17 (5.9)	1.000

IQR, interquartile range; SD, standard deviation

^aThe most frequently chosen antibiotics in empirical treatment

Table 3. Univariate and multivariate logistic regression analyses of risk factors associated with one-year mortality in patients with methicillin-susceptible *Staphylococcus aureus* infective endocarditis

	Univariate analysis			Multivariate analysis	
Characteristics	Survivors (N=48)	Died (N=33)	<i>p</i> value	OR (95% Confidence interval)	<i>p</i> value
Age, mean ± SD	49.8 ± 18.0	59.1 ± 18.0	0.026		
Male sex, n (%)	31 (64.6)	19 (57.6)	0.524		
Comorbidity, n (%)	29 (60.4)	29 (87.9)	0.011	4.38 (1.081- 17.785)	0.039
Community acquired, n (%)	33 (68.8)	18 (54.5)	0.193		
Endocarditis side					
Left side	29 (61.7)	25 (78.1)	0.123		
Mitral, n (%)	16 (33.3)	16 (48.5)	0.171		
Aortic, n (%)	15 (31.3)	10 (30.3)	0.928		
Right side	16 (34.0)	6 (18.8)	0.137		
Tricuspid, n (%)	14 (29.2)	2 (6.1)	0.011		
Pulmonary, n (%)	1 (2.1)	0	1.000		
Lead, n (%)	1 (2.1)	4 (12.1)	0.153		
Endocard, n (%)	2 (4.2)	1 (3.0)	1.000		
Clinical findings					
Heart failure, n (%), (N=76)	10/45 (22.2)	15/32 (46.9)	0.023		
Sepsis, n (%), (N=76)	11/44 (25.0)	9/32 (28.1)	0.760		
Complications					
Cranial embolism	10/48 (20.8)	7/33 (21.2)	0.967		
Pulmonary embolism			0.011		
Peripheral embolism	14/48 (29.2)	2/33 (6.1)	0.096		
Spondylodiscitis	5/48 (10.4)	8/33 (24.2)	1.000		
	2/48 (4.2)	2/33 (6.1)			

Admission laboratory findings					
	12400 [7348]	12650 [6488]	0.328		
White blood cell (/ μ L), median [IQR], (N=79)	10.8 $\pm$ 1.9 206000 [14200]	9.8 $\pm$ 2.4 195000 [134750]	0.058 0.980		
Hemoglobin (g/dL), mean $\pm$ SD, (N=78)	215 $\pm$ 124	158 $\pm$ 108	0.050		
Platelet count ($\times 10^3/\mu$ l), median [IQR], (N=79)	27 [34] 1.00 [1.42]	26.5 [30] 1.58 [2.01]	0.566 0.130 0.630		
CRP (mg/L), mean $\pm$ SD, (N=75)	2.8 $\pm$ 0.6	2.9 $\pm$ 0.7			
ALT (U/L), median [IQR], (N=78)					
Creatinine (mg/dL), median [IQR], (N=79)					
Albumin (g/dL), mean $\pm$ SD, (N=77)					
Cardiac surgery for treatment, n (%)	24 (50.0)	7 (21.2)	0.009	0.25 (0.081-0.808)	0.020
Ampicillin-sulbactam treatment, n (%)	16 (33.3)	4 (12.1)	0.037	0.27 (0.071-1.017)	0.053
Empirical treatment, n (%)	31 (64.6)	23 (69.7)	0.631		
Combined empirical treatment, n (%)	15/31 (48.4)	13/23 (56.5)	0.554		
Time to receipt of empiric therapy (hours), median [IQR], (N=78)	20 [22]	6 [34]	0.449		
Empirical treatment duration, (days), median [IQR], (N=53)			0.139		
Time for blood culture to become negative (days), median [IQR], (N=64)	3 [3]	3 [2]			
Recurrence, n (%), (N=68)	4 [2]	5 [4]	0.264		
	4/38 (10.5)	1/27 (3.7)	0.393		

ALT, alanine aminotransferase; CRP, C-reactive protein; OR, odds ratio; SD, standard deviation