Role of echocardiography in uncomplicated *Staphylococcus aureus* catheter-related bloodstream infections

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### Abstract

Uncomplicated bacteremia and catheter-related bloodstream infection (CRBSI) are frequently suggested as factors associated with low risk of infective endocarditis in *Staphylococcus aureus* bacteremia (SAB). Nevertheless, guidelines recommend that echocardiography in all patients with SAB. We evaluated the effects of echocardiography on patient outcomes. Patients with uncomplicated *S. aureus* CRBSI were retrospectively identified between January 2013 and June 2018 at a 1950-bed, tertiary-care university hospital. Treatment failure was defined as any case of relapse or all-cause death within 90 days. Of 890 SAB patients, 95 with uncomplicated *S. aureus* CRBSI were included. Thirty-two patients underwent echocardiography within 30 days of their first positive blood culture. Two patients who underwent echocardiography revealed right-sided infective endocarditis. One patient who did not undergo echocardiography experienced recurrent SAB (peripheral CRBSI) 85 days after his first positive blood culture. There were no SAB-related deaths. The Kaplan–Meier curves of treatment failure showed no significant differences between patients who did and did not undergo echocardiography (P = .77). In multivariable analysis, risk factors for treatment failure were liver cirrhosis (hazard ratio: 9.60; 95% confidence interval: 2.13–43.33; P < .003) and other prostheses (hazard ratio: 63.79; 95% confidence interval: 5.05–805.40; P = .001). This study did not verify the putative association between treatment failure and implementation of echocardiography in patients with uncomplicated *S. aureus* CRBSI. Given the low observed rates of adverse outcomes, routine echocardiography might not be obligatory and could be performed on an individual basis.

**Abbreviations:** CRBSI = catheter-related bloodstream infection, IE = infective endocarditis, IQR = interquartile range, SAB = *Staphylococcus aureus* bacteremia, TEE = transeosophageal echocardiography, TTE = transthoracic echocardiography.

**Keywords:** catheter-related bloodstream infection, echocardiography, *Staphylococcus aureus*, uncomplicated bacteremia

### 1. Introduction

*Staphylococcus aureus* bacteremia (SAB) is a serious infection associated with high morbidity and mortality because it often causes metastatic infections and complications including infective endocarditis (IE).<sup>1</sup> *S. aureus* is one of the most common pathogens of IE, and the frequency of IE among SAB ranges between 2.7% and 23.4%.<sup>2–4</sup> Because of the risk of IE, current guidelines recommend echocardiography in all patients with SAB.<sup>2,3</sup> However, despite these recommendations, the frequency and strategy of echocardiography in patients with SAB vary among hospitals, and management decisions are often made without echocardiography.<sup>6,7</sup> Furthermore, many studies have attempted to identify groups at low risk of IE among patients with SAB and evaluated the necessity of echocardiography, especially transeosophageal echocardiography (TEE).<sup>8–20</sup> These studies have identified factors associated with IE and suggested that patients at low risk of IE may need not TEE or even transthoracic echocardiography (TTE).

Among the factors associated with low risk of IE in patients with SAB, uncomplicated bacteremia and catheter-related bloodstream infection (CRBSI) have been frequently suggested, although the definitions of those were different among studies.<sup>11–14</sup> Furthermore, uncomplicated CRBSI can be treated with a minimum of 14 days of antibiotic, even if TEE shows silent vegetation.<sup>15,21,22</sup> Therefore, implementation of echocardiography may offer minimal or no benefit to these patients. We...
performed the present study to evaluate the role of echocardiography in patients with uncomplicated *S. aureus* CRBSI by comparing clinical outcomes depending on the implementation of echocardiography.

2. **Methods**

2.1. **Study population**

We retrospectively identified patients (age ≥ 18 years) with *S. aureus* isolated from ≥1 blood culture and symptoms or signs of infection (fever ≥ 38°C, chills, or hypotension) who were treated from January 2013 to June 2018 at Samsung Medical Center, a 1950-bed tertiary-care university hospital in Seoul, South Korea. Only the first blood culture was included in the study. We excluded patients with complicated bacteremia, polymicrobial bacteremia (isolation of more than 1 microbial species from an episode), and cases that were not treated for SAB considered to represent contamination. The patients who had only 1 positive blood culture collected from the central catheter were excluded, because their positive blood culture may represent colonization of the catheter rather than true bacteremia. Patients who were discharged or died within 7 days from initial positive culture also were excluded. Follow-up data were collected for 90 days, if not until death or loss of follow-up.

2.2. **Definition and data acquisition**

Complicated bacteremia was identified if patients satisfied at least one of the following criteria:[5]

1) persistent bacteremia;
2) no defervescence within 3 days of initiating effective therapy;
3) evidence of metastatic sites of infection;
4) presence of implanted intracardiac prostheses.

Endocarditis was excluded from the criteria because occurrence of IE was one of the outcomes in this study. Only patients who met the modified Duke criteria for definite IE were considered to represent IE.[23] Persistent bacteremia was defined as persistently positive blood cultures for ≥4 days (documented) or no negative follow-up blood culture within 4 days (possible).[9] Initial effective therapy was defined as intravenous antibiotics with in vitro activity against isolated *S. aureus* excluding single aminoglycoside or rifampicin.[24] Defervescence was defined as an afebrile state in which tympanic body temperature remained lower than 38.0°C for at least 48 hours. Metastatic infection was defined as deep-seated infection caused by hematogenous seeding, including osteomyelitis, psoas muscle abscess, septic pulmonary embolism, mycotic aneurysm, septic cerebral emboli, and supplicative thrombophlebitis. If metastatic infection was not clearly distinguished from primary infection, the decision depended on the clinician’s judgement. The onset of bacteremia was classified as nosocomial, healthcare associated, or community acquired.[25] Nosocomial bacteremia was defined as positive blood culture obtained from patients who had been hospitalized for 48 hours or longer. Healthcare-associated bacteremia was defined as positive blood culture obtained within 48 hours of admission from a patient who fulfilled any of the following criteria:

1) received intravenous therapy at home, received wound care or specialized nursing care through a healthcare agency, or received intravenous medical therapy in the previous 30 days;
2) attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the previous 30 days;
3) was hospitalized in an acute care hospital for at least 2 days in the previous 90 days;
4) or resided in a nursing home or long-term care facility.

Otherwise, we classified the infection as community acquired. Definite CRBSI was defined by any of following[12,22]:

1) growth of >10² colony-forming units from a catheter tip by quantitative culture;
2) differential time to positivity meeting CRBSI criteria;
3) evidence of inflammation at the catheter insertion site and absence of another identified source of bacteremia.

Primary bacteremia in patients with intravascular catheter without other definitive source of bacteremia was considered to represent probable CRBSI.[12]

Additional collected data were the following: age, sex, microbiologic and echocardiographic data, underlying diseases, laboratory data, immunosuppression, and duration of antibiotic treatment. Echocardiographic data were included within 30 days of the first positive blood culture and classified as negative, equivocal, or positive findings.[26] The equivocal findings included no visible vegetation but native valves with more than mild thickening, calcification, or valvular regurgitation and extremely poor or non-diagnostic views. Positive findings were defined by visible vegetations.

2.3. **Blood culture and antibiotic susceptibility testing**

All blood cultures were obtained from peripheral veins or central venous catheters (CVCs). A Bactec-9240 system (Becton Dickinson, Sparks, MD) or a BacT/Alert 3D system (bioMérieux Inc., Marcy l’Étoile, France) was used for blood cultures. A Vitek II automated system (bioMérieux Inc.) was used for antibiotic susceptibility testing.

2.4. **Study outcomes**

To evaluate the usefulness of echocardiography in uncomplicated cases of *S. aureus* CRBSI, the outcome measures were occurrence of IE, relapse, SAB-related death, all-cause death, and treatment failure within 90 days after initial positive blood culture. Relapse was defined as reappearance of SAB with an organism showing an identical antimicrobial susceptibility profile.[27] SAB-related death was considered if death occurred within 10 days of SAB, with sepsis continuing up to death and no other infectious cause.[7] Treatment failure included any cases of relapse or all-cause death.

2.5. **Statistical analysis**

Continuous variables are presented as median (interquartile range [IQR]) or mean ± standard deviation, and categorical variables as frequency count (percentage). Comparisons of continuous variables between patients who did and did not undergo echocardiography were performed using Student’s t test or the Mann–Whitney U test according to the results of normality tests. Fisher’s exact test or chi-square test was used to compare categorical variables. The relationship between treatment failure and the implementation of echocardiography was evaluated by the Kaplan–Meier method using the log-rank test. Univariate Cox proportional hazard models were used to identify risk
factors associated with treatment failure. Variables with $P$ value $< .05$ in the univariate analysis and implementation of echocardiography were included in multivariable analysis using the forward conditional method. If the variable did not satisfy the proportional hazard assumption verified by log minus log plot, time-dependent covariate was included in the model. $P$ values were two-tailed, and those lower than 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (2017, IBM Corp., Armonk, NY).

3. Results

3.1. Study population

A total of 890 patients with SAB were identified during the study period. Four hundred eighty-nine patients who satisfied at least 1 criterion defining complicated bacteremia were excluded (Fig. 1). Overall, 95 patients with uncomplicated $S. aureus$ CRBSI were included (Table 1). Nine cases were censored before relapse or death within 90 days, including 4 patients who underwent echocardiography (follow-up duration of censored cases: median 28 days).

3.2. Demographic characteristics and echocardiographic data

None of the patients had history of previous IE or intravenous drug use. Fifty-five patients had metastatic tumor or hematologic malignancy, and 58 were immunocompromised or neutropenic. The group that did not undergo echocardiography included more neutropenic patients and lower Charlson comorbidity index scores, shorter duration of total treatment, and greater tendency toward retention of central venous catheter.

Echocardiography was performed in 32 patients (time to echocardiography: median 4.5 days [IQR 2.25–8 days]; TTE: 28 patients, TEE: 1 patient, both: 3 patients). Echocardiographic findings were 19 negative, 11 equivocal, and 2 positive (6.3%) results. Eleven equivocal findings included 6 valve abnormalities and 9 poor echo views. One patient with a positive finding showed a catheter tip with vegetation in the right atrium (Table 2, patient 1). The other patient with a positive finding showed a negative finding on TTE, but TEE showed vegetation on the tricuspid valve (Table 2, patient 2). Both patients had leukemia and history of immunosuppression and did not have murmur or any peripheral signs of IE.

3.3. Outcomes

Two patients were diagnosed with right-sided IE although the sources of bacteremia were classified as probable CRBSI (Table 2). Relapse of SAB occurred in 1 patient who did not undergo echocardiography after 85 days from initial positive blood culture. Relapse event was identified as peripheral CRBSI. The first SAB of this patient was treated with vancomycin for 12 days. He was retreated with vancomycin for 14 days without performance of echocardiography and showed resolution without complications or further relapse.

Seven patients died within 90 days of onset of SAB, including 3 patients who underwent echocardiography (Supplementary Table 1, http://links.lww.com/MD/G57). Median time to death from onset of SAB was 24 days (IQR: 20–66 days). There were no SAB-related deaths. Overall 30-day and 90-day mortality rates were 4.4% and 8.1%, respectively. Kaplan–Meier curves of treatment failure showed no significant differences between groups (Fig. 2, $P = .77$).

3.4. Risk factors for treatment failure

In a univariate Cox proportional hazard model, possible risk factors were liver cirrhosis, other prostheses, and Charlson
comorbidity index (Table 3). Because implementation of echocardiography did not satisfy the proportional hazard assumption, time-dependent Cox regression analysis was conducted for multivariable analysis. Independent risk factors were liver cirrhosis (hazard ratio: 9.60; 95% confidence interval: 2.13–43.33; P = .003) and other prostheses (hazard ratio: 63.79; 95% confidence interval: 5.05–805.40; P = .001). Implementation of echocardiography was not associated with treatment failure.

4. Discussion

This study did not show a significant association between the implementation of echocardiography and treatment failure in patients with uncomplicated S. aureus CRBSI. Furthermore, overall rates of relapse and IE were low in our study population. These results are similar to those of a previous study. Of 62 patients with uncomplicated S. aureus CRBSI and primary nosocomial bacteremia, only 20 underwent echocardiography, and none developed IE during 3 months of follow-up. However, the criteria used to identify complicated bacteremia were different from those used in the present study in that persistent bacteremia and defervescence were evaluated from the day of catheter removal. We evaluated the actual duration of bacteremia and defervescence from initiation of effective therapy, stricter criteria than in the previous study. Furthermore, because our criteria were according to the guideline, the results of this study could reflect actual clinical situations.

Multiple factors influence mortality of SAB, including host factors, pathogen-host interactions and pathogen-specific factors. Liver cirrhosis and the presence of other prostheses were independent risk factors for treatment failure in this study. These results are consistent with previous studies that patients with liver cirrhosis showed higher mortality than those with other diseases and the presence of one or more comorbidities has been associated with mortality of SAB. However, because SAB-related death was not identified in this study, it may be that underlying diseases rather than SAB contributed to the outcomes (Supplementary Table 1, http://links.lww.com/MD/G57).

Most previous studies evaluating the benefits of echocardiography in SAB included substantial groups of patients who did not undergo echocardiography (range: 13–79%). These results are similar to those of recent studies included heterogeneous sources of bacteremia, and the duration of treatment was either prolonged or was not considered, factors that could conceal undetected IE and obscure the benefits of echocardiography in patients with SAB.

We evaluated patients with uncomplicated CRBSI to enable shorter treatment duration and verified 2 weeks of duration, steps that would highlight the effects of echocardiography. Nonetheless, this study did not verify a beneficial role of echocardiography on treatment outcome. The prevalence of IE in patients with low risk is very low, between 0% and 5%. These results are similar to those of the present study that identified 2 IE patients among the study population. Interestingly, both patients were diagnosed with right-sided IE. Intravenous drug user and intravascular catheter are major risk factors for right-sided IE, the manifestations of which are considerably different from those of left-sided IE. Furthermore, right-sided IE has more favorable outcomes probably because right-sided valve dysfunction and pulmonary emboli cause minimal hemodynamic derangement. Because of these differences from left-sided IE, criteria for identifying complicated bacteremia may be insufficient for excluding right-sided IE. Nonetheless, 2-week therapy, the current recommended treatment for uncomplicated SAB, could be used...
to treat undiagnosed right-sided IE in CRBSI. One previous study showed that a 2-week monotherapy regimen of intravenous cloxacillin was equivalent to cloxacillin plus gentamicin administered for 2 weeks to treat right-sided IE.\[31\]

Relapse of SAB occurred in only 1 patient, who had a hematologic malignancy and immunocompromised state. Calculating from first negative blood culture, the treatment duration of the first episode was 10 days, less than the 14 days recommended.\[5\] Furthermore, if the patient had silent vegetation, treatment with vancomycin might have been insufficient due to its limited bactericidal activity and poor penetration into vegetation.\[32\] Such factors might contribute to relapse of SAB. However, given the long interval between the 2 SAB events, and the second episode was related with peripheral catheter, there

### Table 2
Clinical characteristics of 2 patients with infective endocarditis and 1 patient with relapse.

| Patient | Age, yrs | Sex | Source (methicillin-resistance) | Underlying diseases | Onset | Immunosuppression/neutropenia | Prostheses/hemodialysis | Time to CVC removal, d | Time to TTE/TEE, d | Comments | Duration of treatment, (IV), d |
|---------|----------|-----|--------------------------------|---------------------|-------|-----------------------------|------------------------|----------------------|-------------------|-----------|-----------------------------|
| 1       | 31       | F   | Probable CRBSI (MSSA)          | Healthcare-associated | ALL   | Chemotherapy/N              | Long-term CVC/N        | 11                   | 5/11              | Both TTE and TEE showed vegetation-like lesions (1.59 × 0.91 cm) in the right atrium. | 29 (19)   |
| 2       | 54       | F   | Probable CRBSI (MSSA)          | Nosocomial           | AML, allogenic HSCT | Steroid/N | N/N                       | NA                     | 5/7               | TEE showed oscillating linear material (2.4 cm) on tricuspid valve. | 34 (34)   |
| 3       | 54       | M   | Definite CRBSI (MRSA)          | Nosocomial           | Lymphoma | Chemotherapy/N              | Long-term CVC/N        | 1                    | NA                | Peripheral CRBSI occurred after 85 d. | 12 (12)   |

ALL = acute lymphocytic leukemia, AML = acute myeloid leukemia, CRBSI = catheter-related bloodstream infection, CVC = central venous catheter, IV = intravenous, MRSA = methicillin-resistant Staphylococcus aureus, MSSA = methicillin-susceptible Staphylococcus aureus, NA = not available, TEE = tranesophageal echocardiography, TTE = transthoracic echocardiography.

### Table 3
Factors associated with treatment failure of uncomplicated S. aureus CRBSI.

| Factor | Univariate analysis | Multivariable analysis |
|--------|---------------------|------------------------|
|        | HR (95% CI)         | P                      | HR (95% CI)         | P                      |
| Liver cirrhosis | 7.46 (1.77–31.47) | .006                   | 9.60 (2.13–43.33)  | .003                   |
| Other prostheses | 35.70 (3.15–404.84) | .004                   | 63.79 (5.05–805.40)  | .001                   |
| Charlson comorbidity index (per 1 point) | 1.28 (1.02–1.60) | .03                   |                         |                        |
| No echocardiography | 1.00 (0.97–1.03) | .98                   |                         |                        |

CI = confidence interval, CRBSI = catheter-related bloodstream infection, CVC = central venous catheter, HR = hazard ratio, IV = intravenous, MRSA = methicillin-resistant Staphylococcus aureus.
is the possibility of reinfection. Although echocardiography was not performed for second SAB, endocarditis was less likely considering there was no another relapse after treatment of the second bacteremia.

Despite many previous studies, it remains uncertain whether echocardiography is beneficial in SAB patients at low risk of IE. Herriot et al. stated that the testing threshold for TEE was a 1.1% probability of IE, and that none of the available criteria could be reduced below this probability. On the contrary, they showed that the survival benefit of any echocardiography strategy compared with 2 weeks of empirical therapy was marginal in patients at low risk of IE, using decision analysis and Monte Carlo simulation. It may be difficult to statistically demonstrate the non-inferiority of outcomes depending on testing strategy in a population with a low prevalence of the disease.

Our study has several limitations. First, the influence of selection bias could not be excluded because of inherent limitations of our study design. Second, we used broad criteria to define CRBSI, and a certain portion of the study population may represent cases of primary nosocomial or healthcare-associated bacteremia. However, intravascular catheters, including peripheral catheters, are significant contributors to S. aureus primary nosocomial bacteremia. Third, it is difficult to draw clear conclusions because the sample size was small and the outcome events were rare. However, it would be difficult to include enough patients at low risk of IE in the study to ensure sufficient statistical power.

In conclusion, we did not verify an association between treatment failure and the implementation of echocardiography in patients with uncomplicated S. aureus CRBSI. Given the observed low rates of adverse outcomes, empirical treatment without echocardiography may be an alternative treatment option for such patients in resource-limited settings.

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