



# Comparison of Clinical Outcomes for Glycopeptides and Beta-Lactams in Methicillin-Susceptible *Staphylococcus Aureus* Bloodstream Infections

Yeon Ju La<sup>1</sup>, Hye Rim Kim<sup>2</sup>, Dong Hyun Oh<sup>3</sup>, Jin Young Ahn<sup>4</sup>, and Yong Chan Kim<sup>5</sup>

<sup>1</sup>Department of Internal Medicine, Kangwon National University Hospital, Chuncheon;

<sup>2</sup>Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul;

<sup>3</sup>Department of Internal Medicine, Seoul Medical Center, Seoul;

<sup>4</sup>Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul;

<sup>5</sup>Department of Internal Medicine, Division of Infectious Disease, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Korea.

**Purpose:** This study aimed to provide compelling evidence of anti-staphylococcal beta-lactam use for methicillin-susceptible *Staphylococcus aureus* bloodstream infection (MSSA BSI).

**Materials and Methods:** We retrospectively collected data on patients with MSSA BSI who were admitted to two academic tertiary-care hospitals from 2010 to 2018. Only patients who received nafcillin, cefazolin, vancomycin, or teicoplanin as definitive therapy were included. The primary outcome was 28-day mortality. To perform unbiased comparisons between both treatments, we used inverse probability of treatment weighting (IPTW) analysis.

**Results:** A total of 359 patients were divided into two groups based on the definitive therapy used: beta-lactams (n=203), including nafcillin or cefazolin; and glycopeptides (n=156), including vancomycin or teicoplanin. In the IPTW analysis, glycopeptides were associated with significantly increased odds of 28-day mortality (adjusted odds ratio, 3.37; 95% confidence interval, 1.71–6.61;  $p < 0.001$ ). The rate of primary outcome in prespecified subgroups was largely consistent with the main analysis.

**Conclusion:** Definitive therapy with beta-lactams in patients with MSSA BSI was associated with lower 28-day mortality compared to definitive therapy with glycopeptides.

**Key Words:** Methicillin-susceptible *Staphylococcus aureus*, bloodstream infection, beta-lactams, glycopeptides, inverse probability of treatment weighting

## INTRODUCTION

*Staphylococcus aureus* is an important pathogen causing several infectious diseases. Of those, *S. aureus* bloodstream infection (BSI) has a significant burden of disease.<sup>1</sup> A recent study conducted in Europe using multinational surveillance data

demonstrated that a total of 573951 *S. aureus* BSIs were identified from 2005 to 2018; and during the same period, the annual number of *S. aureus* BSIs increased continuously.<sup>2</sup> Once *S. aureus* is isolated from a BSI, significant morbidity and mortality are observed.<sup>3</sup> Although the mortality associated with *S. aureus* BSI improved in post-antibiotic era, the 30-day mortality rate

**Received:** February 27, 2022 **Revised:** April 5, 2022 **Accepted:** April 20, 2022

**Co-corresponding authors:** Yong Chan Kim, MD, PhD, Department of Internal Medicine, Division of Infectious Disease, Yongin Severance Hospital, Yonsei University College of Medicine, 363 Dongbaekjukjeon-daero, Giheung-gu, Yongin 16995, Korea.

Tel: 82-31-5189-8761, Fax: +82-31-5189-8567, E-mail: amomj@yuhs.ac and

Jin Young Ahn, MD, Division of Infectious Disease, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.

Tel: 82-2-2228-2267, Fax: +82-2-393-6884, E-mail: comebacktosea@yuhs.ac

•The authors have no potential conflicts of interest to disclose.

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remained high; approximately 21% and 31% for methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA), respectively.<sup>4</sup>

Multiple factors have been reported to influence the mortality associated with *S. aureus* BSI.<sup>3</sup> The administration of appropriate antibiotics is critical for the treatment of *S. aureus* BSI. According to the current guidelines, anti-staphylococcal beta-lactam antibiotics are the first-line drugs for MSSA BSI, and switching empirical antibiotics to anti-staphylococcal beta-lactams once the isolate is identified to be MSSA is recommended.<sup>5</sup> However, in the settings with a high prevalence of MRSA, some clinicians tend to continue the initial empiric glycopeptides without changing to anti-staphylococcal beta-lactam antibiotics, even after MSSA BSI is confirmed. Glycopeptides are most likely used as definitive antibiotics in MSSA BSI if patients have severe illness, certain comorbidities, a primary focus that is difficult to treat, and metastatic infection.<sup>6</sup>

Several small studies have demonstrated the inferiority of glycopeptides as definitive antibiotics for MSSA BSI compared to anti-staphylococcal beta-lactam antibiotics.<sup>7-11</sup> However, almost all of them were retrospective observational studies, and no randomized controlled trial has been conducted to compare these drugs. Therefore, there remains the problem of bias in treatment selection and the possibility of residual confounding factors. These limit the ability of explaining the causal relationship between the type of antibiotic used and the treatment outcome.<sup>3</sup> Therefore, the present study aimed to compare the therapeutic effects of glycopeptides and anti-staphylococcal beta-lactams in the treatment of MSSA BSI using inverse probability of treatment weighting (IPTW) analysis, which can reduce selection bias and confounding factors.

## MATERIALS AND METHODS

### Ethics statement

This study was approved by the Institutional Review Board of the Yonsei University Health System Clinical Trials Center (IRB No. 4-2022-0153) and the protocol adhered to the tenets of the Declaration of Helsinki. Since the study was retrospective and the study participants were anonymized, the Institutional Review Board waived the requirement for written consent from the study participants.

### Study design and population

This was a double-center, retrospective, observational, cohort study conducted at Sinchon Severance Hospital and Gangnam Severance Hospital, which are tertiary teaching hospitals at Yonsei University College of Medicine in South Korea. Patients with MSSA BSI from January 2010 to December 2018, who received nafcillin, cefazolin, vancomycin, or teicoplanin as definitive therapy, were included. The following cases were excluded from this study: 1) patients treated without nafcillin, cefazolin,

vancomycin, or teicoplanin; 2) use of empirical antibiotics for more than 6 days; 3) longer duration of empirical antibiotics use compared to that of definitive antibiotics use; 4) age <18 years; and 5) polymicrobial BSI. Patients were divided into the “beta-lactam group” and the “glycopeptide group” according to the definitive antibiotics used after susceptibility results were available. The beta-lactam group received cefazolin or nafcillin as definitive therapy. The glycopeptide group was not exposed to cefazolin and nafcillin until the start of definitive therapy, and received vancomycin or teicoplanin as definitive therapy.

### Data collection and definition

Demographic characteristics of patients were collected using electronic medical records. Laboratory results and clinical data within 24 hours after the identification of BSI were used. All patients were included for analysis only once. Comorbidities were defined according to the International Classification of Diseases, 10th Revision. The primary focus of BSI was classified according to the Centers for Disease Control and Prevention/National Healthcare Safety Network surveillance criteria.<sup>12</sup> Severity of the disease was assessed using the Pitt bacteremia score (PBS), which ranges from 0 to 14. PBS  $\geq 4$  was used to define critical illness.<sup>13,14</sup>

MSSA BSI was defined as the identification of MSSA in one or more blood cultures. BSI occurring within 48 hours after admission was defined as community-acquired BSI. Hospital-acquired BSI was defined as bacteremia that developed more than 48 hours after hospital admission.<sup>15</sup> Empirical antibiotics were defined as antibiotics used after gram-positive cocci were identified in the blood culture. Definitive antibiotics were defined as antibiotics used after susceptibility profiles were determined.

Recurrent BSI was defined as a positive blood culture for MSSA again within 30 days or within 90 days (31 days to 90 days) after the documentation of a negative blood culture. Persistent BSI was defined as a positive blood culture for MSSA after 7 days of effective antibiotic therapy.<sup>16</sup> Hospital stay was measured from the date of the first MSSA BSI to the date of discharge. Adverse drug event was defined as an injury related to the use of definitive antibiotics, including skin rash, cytopenia, hepatitis, acute kidney injury, drug-induced fever, and gastrointestinal symptoms.<sup>17,18</sup>

### Clinical outcomes

The primary endpoint of the current study was a 28-day all-cause mortality. The secondary endpoints included recurrent BSI, persistent BSI, intensive care unit (ICU) admission after BSI, and adverse drug events.

### Statistical analysis

Categorical variables were expressed as number with percentages, and were compared using the  $\chi^2$ -test or the Fisher exact test. Continuous variables, expressed as mean  $\pm$  standard deviation,

tion, were compared using the Student's t-test. To reduce the effect of selection bias in this observational study, baseline characteristics of patients in each group were adjusted using IPTW. Patient's propensity score for receiving glycopeptides was estimated by multivariable logistic regression analysis. Variables selected to generate the propensity score were those shown to be significantly different between two groups or associated with *S. aureus* BSI recurrence or mortality.<sup>19-21</sup> Stabilized weights were applied to avoid extreme weights. Balance between the two groups was assessed using standardized mean differences (SMD), and SMD of <10% after IPTW adjustment was considered optimally balanced.<sup>22</sup>

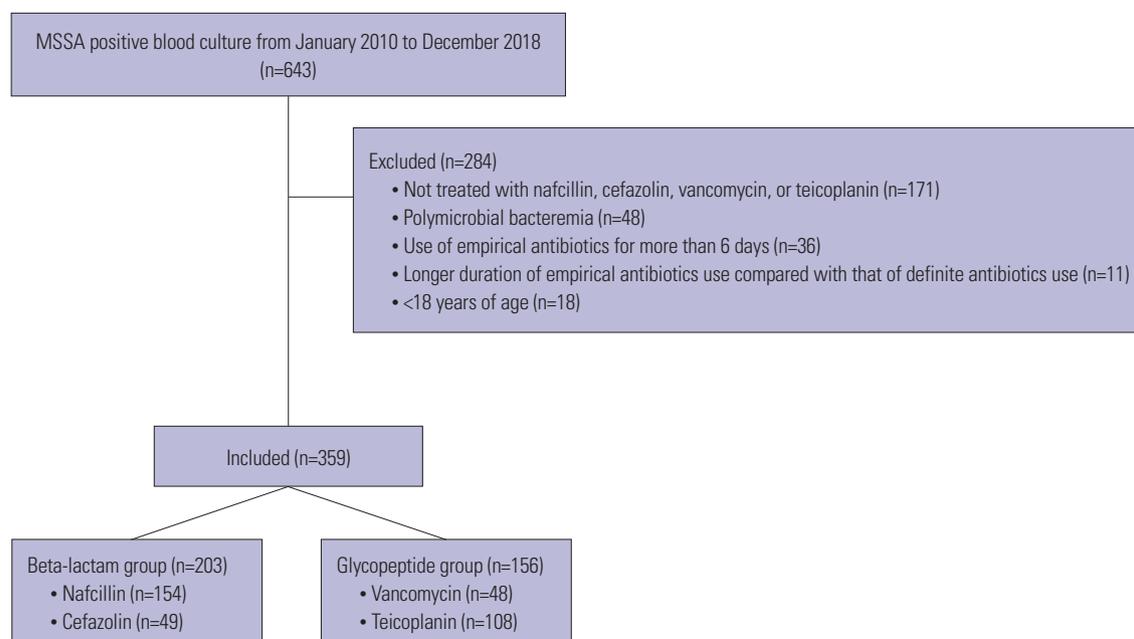
For the comparison of clinical outcomes between the two matched groups, weighted logistic regression analyses using the IPTW were performed to determine the risk of recurrent bacteremia, persistent bacteremia, ICU admission after infection, drug adverse event, and mortality. As potential confounders would remain after adjustment (IPTW), adjustment was further augmented by multivariable logistic regression models (IPTW+multivariable) to estimate the odds ratio (OR) for 28-day mortality using clinically relevant variables, including age, sex, PBS, source control, and primary focus of sepsis. Subgroup analysis was performed to explore the treatment effects of glycopeptides on 28-day mortality in certain groups.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria). *P*-values <0.05 were considered statistically significant.

## RESULTS

### Patient characteristics

A total of 643 patients experienced MSSA BSI from January 2010 to December 2018. Of the 359 patients included in the study, 203 patients were treated with beta-lactams and 156 patients were treated with glycopeptides (Fig. 1). Comparison of clinical characteristics of patients between the beta-lactam and glycopeptide groups are shown in Table 1. Female patients were more common in the glycopeptide group than in the beta-lactam group (41% vs. 34%, *p*=0.171). Patients in the beta-lactam group were older (65.4±14.5 years vs. 62.6±16.9 years, *p*=0.090) and had higher body mass index (22.9±4.4 kg/m<sup>2</sup> vs. 22±4 kg/m<sup>2</sup>, *p*=0.069) than those in the glycopeptide group. However, there were no statistically significant differences in demographics between the two groups. Patients in the glycopeptide group showed a significantly higher rate of having cancer (24.6% vs. 53.2%, *p*<0.001) and healthcare-associated infections (29.6% vs. 62.8%, *p*<0.001) and a higher PBS (1.2±2.6 vs. 2.7±4, *p*<0.001) compared to patients in the beta-lactam group. In contrast, patients in the beta-lactam group showed higher C-reactive protein levels (157.8±105.8 mg/L vs. 120.2±95.8 mg/L, *p*<0.001) and higher proportion of having diabetes mellitus (36.5% vs. 23.7%, *p*=0.010) and performing infection source control (38.9% vs. 16.7%, *p*<0.001) compared to those in the glycopeptide group. The order of primary focus causing MSSA BSI in the beta-lactam group was different from those in the glycopeptide group (*p*<0.001). The most common primary foci in the beta-lactam group were the skin and soft tissues, which accounted for 30.5%. The largest proportion of patients (44.9%) was treated with glycopeptides due to BSI caused by other sources, including central nervous system infections, gastroenteritis, deep neck in-



**Fig. 1.** Flow chart of the study population. MSSA, methicillin-susceptible *S. aureus*.

**Table 1.** Baseline Characteristics of Patients Who Received Anti-Staphylococcal Beta-Lactams or Glycopeptides as Definitive Therapy

Variables	Beta-lactam group (n=203)	Glycopeptide group (n=156)	p value
<b>Demographic</b>			
Female, no. (%)	69 (34)	64 (41)	0.171
Age, yr	65.4±14.5	62.6±16.9	0.090
Body mass index, kg/m <sup>2</sup>	22.9±4.4	22±4	0.069
<b>Laboratory</b>			
White blood cell count per mm <sup>3</sup>	12890.8±7241.2	12442.3±10098.7	0.639
Platelet per mm <sup>3</sup>	209379.3±127822.9	191897.4±131145.5	0.205
Creatinine, mg/dL	1.6±1.8	1.6±2.1	0.768
Total bilirubin, mg/dL	1.2±1.4	1.5±2.9	0.241
Albumin, g/dL	3.1±0.7	3±0.8	0.562
C-reactive protein, mg/L	157.8±105.8	120.2±95.8	<0.001
<b>Comorbidity, no. (%)</b>			
Congestive heart failure	22 (10.8)	24 (15.4)	0.201
Peripheral vascular disease	9 (4.4)	4 (2.6)	0.347
Coronary artery obstructive disease	26 (12.8)	18 (11.5)	0.716
Cerebrovascular accident	24 (11.8)	12 (7.7)	0.197
Dementia	3 (1.5)	4 (2.6)	0.474*
Hemiplegia	6 (3)	4 (2.6)	>0.999*
Pulmonary disease	21 (10.3)	16 (10.3)	0.978
Connective tissue disease	5 (2.5)	5 (3.2)	0.752*
Liver disease	25 (12.3)	25 (16)	0.314
Diabetes mellitus	74 (36.5)	37 (23.7)	0.010
Renal disease	41 (20.2)	26 (16.7)	0.395
Hemodialysis	17 (8.4)	7 (4.5)	0.144
Cancer	50 (24.6)	83 (53.2)	<0.001
Hospital acquired infection, no. (%)	60 (29.6)	98 (62.8)	<0.001
Pitt bacteremia score	1.2±2.6	2.7±4	<0.001
Source control, yes (%)	79 (38.9)	26 (16.7)	<0.001
Metastatic infection, yes (%)	32 (15.8)	15 (9.6)	0.087
<b>Primary focus of bloodstream infection, no. (%)</b>			
Catheter-related	21 (10.3)	12 (7.7)	
Pneumonia	10 (4.9)	17 (10.9)	
Urinary tract	15 (7.4)	5 (3.2)	
Skin and soft tissue	62 (30.5)	22 (14.1)	
Bone and joint	49 (24.1)	10 (6.4)	
Intra-abdominal	6 (3)	20 (12.8)	
Others <sup>†</sup>	40 (19.7)	70 (44.9)	

Variables are displayed as mean±standard deviation, unless otherwise specified.

\*Fisher's exact test; <sup>†</sup>Others include central nervous system infections, gastroenteritis, deep neck infection, and focus unknown.

fections, and unknown primary focus. After IPTW adjustment, baseline characteristics of the two groups were well balanced except for the primary focus of bacteremia, which had an SMD of 13.7% (Supplementary Table 1, only online).

**Outcomes**

After IPTW, the glycopeptide group had higher overall mortality rate (15.9% vs. 39.6%, *p*=0.024), 7-day mortality rate (2.1% vs. 14.1%, *p*<0.001), and 28-day mortality rate (7.7% vs. 30.9%, *p*=0.012) (Table 2) compared to the beta-lactam group. In the weighted logistic regression models using the IPTW method,

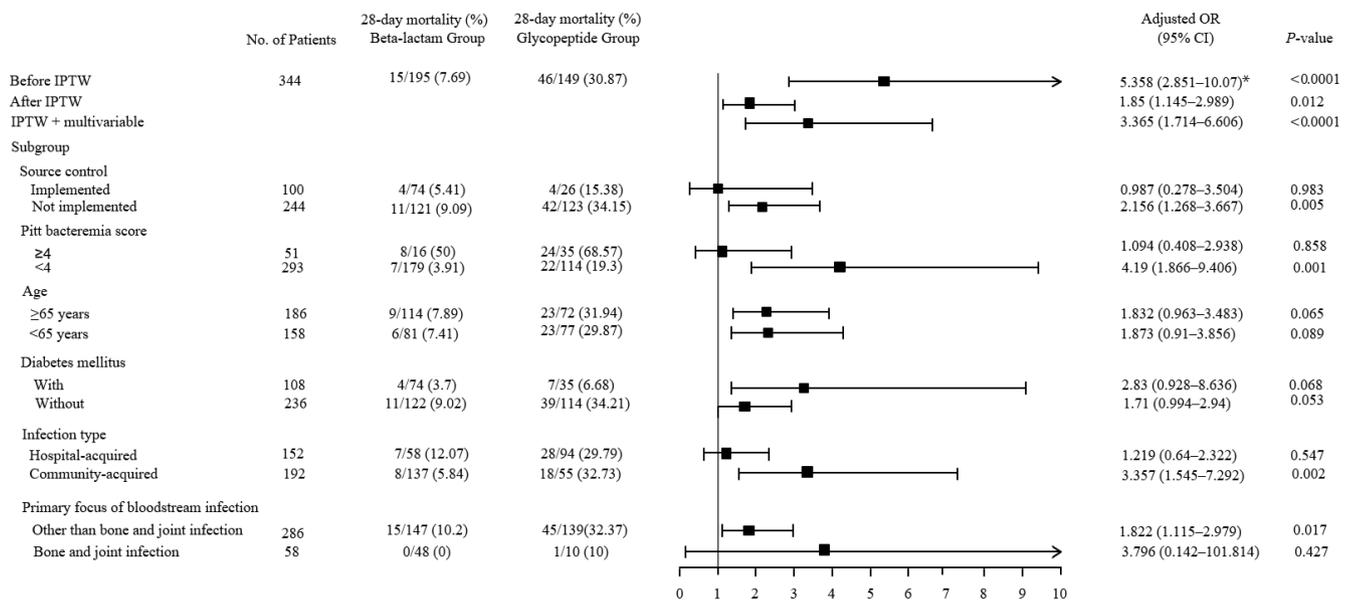
the risk of 28-day mortality was significantly higher in the glycopeptide group than in the beta-lactam group [OR, 1.85; 95% confidence interval (CI), 1.15–2.99]. In contrast, the glycopeptide group had a lower risk for persistent BSI (17.9% vs. 4.0%; OR, 0.28; 95% CI, 0.14–0.60; *p*<0.001) than did the beta-lactam group. The risk of recurrent BSI was low in both groups (2.6% vs. 4.0%; OR, 1.25; 95% CI, 0.33–4.83; *p*=0.743). ICU admission after BSI occurred similarly between the two groups (19.5% vs. 20.8%; OR, 1.35; 95% CI, 0.84–2.17; *p*=0.217). Patients treated with beta-lactams stayed for 29.9±33 days in the hospital after BSI, and a similar duration was observed for those treated with

**Table 2.** Comparison of Clinical Outcomes between Beta-Lactam Group and Glycopeptide Group after Inverse Probability of Treatment Weighting

Variables	Beta-lactam group (n=195*)	Glycopeptide group (n=149*)	Odds ratio <sup>†</sup> (95% CI)	p value
Recurrent bloodstream infection, no. (%)	5 (2.6)	6 (4.0)	1.25 (0.33–4.83)	0.743
Recurrence within 30 days	1 (0.5)	3 (2.0)	2.86 (0.23–35.46)	0.414
Recurrence within 90 days (31 days to 90 days)	4 (2.1)	3 (2.0)	0.84 (0.16–4.48)	0.835
Persistent bloodstream infection, no. (%)	35 (17.9)	6 (4.0)	0.28 (0.14–0.60)	<0.001
ICU admission after infection, no. (%)	38 (19.5)	31 (20.8)	1.35 (0.84–2.17)	0.217
Mortality, no. (%)	31 (15.9)	59 (39.6)	1.64 (1.07–2.52)	0.024
Death within 7 days	4 (2.1)	21 (14.1)	5.17 (2.08–12.85)	<0.001
Death within 28 days (8 days to 28 days)	15 (7.7)	46 (30.9)	1.85 (1.15–2.99)	0.012
Drug adverse event, no. (%)	28 (14.4)	9 (6.0)	0.47 (0.24–0.91)	0.025

CI, confidence interval; ICU, intensive care unit.

\*A total of 15 cases with insufficient data for adjustment (inverse probability of treatment weighting) were excluded; <sup>†</sup>The odds ratio for glycopeptide group compared to beta-lactam group was calculated by weighted logistic regression model using inverse probability of treatment weighting.



**Fig. 2.** Adjusted ORs and 95% CIs for the primary end point in main analysis and various subgroups. \*Unadjusted OR. CI, confidence interval; OR, odds ratio; IPTW, inverse probability of treatment weighting.

glycopeptides (27.5±40 days) (data not shown). As for adverse drug events, patients in the beta-lactam group had a higher risk of adverse events than those in the glycopeptide group (14.4% vs. 6.0%; OR, 0.47; 95% CI, 0.24–0.91; *p*=0.025).

When IPTW was augmented by multivariable logistic regression analyses (IPTW+multivariable) to minimize remnant confounding, glycopeptide use for the treatment of MSSA BSI was associated with significant risk for 28-day mortality (adjusted OR, 3.37; 95% CI, 1.71–6.61; *p*<0.001) (Fig. 2). The results of the subgroup analysis were largely consistent with those of the main analysis. The rate of 28-day mortality in the glycopeptide group showed a higher trend than that in the beta-lactam group across various subgroups, except for the subgroup with source control (Fig. 2). In patients who had eradicable foci and achieved source control, the point estimate for 28-day mortality favored glycopeptides (adjusted OR, 0.99; 95% CI, 0.28–3.50; *p*=0.983).

## DISCUSSION

We demonstrated that glycopeptides as definitive therapy for MSSA BSI were associated with a higher 28-day mortality compared to beta-lactam agents. Although this was found in previous studies,<sup>7–11,23,24</sup> those studies had some limitations. Most of the studies comparing the efficacy of glycopeptides and beta-lactam drugs in MSSA BSI were performed retrospectively,<sup>7–11</sup> which might leave a large number of confounders in comparison. Kim, et al.<sup>10</sup> used propensity scores to adjust for confounders by treatment selection, but only 27 patients were treated with glycopeptides, which made it difficult for their study to be generalized. In addition, there were two prospective observational studies demonstrating the impact of these drugs on MSSA BSI,<sup>23,24</sup> however, one study did not assess the mortality associated with MSSA BSI,<sup>23</sup> and the other study did not balance the patients who were treated with glycopeptides and beta-lactams.<sup>24</sup> To our knowledge, this is the first study using IPTW to

compare mortality in MSSA BSI between patients treated with glycopeptide and beta-lactam in a large cohort. In these clinical studies that compare the mortality as an endpoint, the effects of the patients' selection bias and confounding factors cannot be ignored. Some previous studies attempted to reduce such bias by using propensity score matching, but this could result in the loss of a large number of observations.<sup>10</sup> In contrast to matching the treated and untreated individuals in a select group of confounders, the IPTW approach uses the entire cohort and can address a very large number of confounding variables.<sup>25</sup> In this study, we attempted to compensate bias and the effect of confounding factors by using IPTW while retaining the large cohort. In addition, efforts were made to remove potential constructors by adding multivariable logistic regression models even after IPTW.

We found that many clinicians maintained glycopeptides as definitive therapy, especially for hospital-acquired infections. In fact, the incidence of MRSA BSI decreased since 2005, which was observed in both hospital and community settings.<sup>26</sup> In South Korea, the incidence of MRSA BSI also decreased, but the proportion of MRSA among hospital-acquired *S. aureus* BSI remained high.<sup>27,28</sup> According to the Korean antimicrobial resistance surveillance system, 69.4% of *S. aureus* isolated from hospital-acquired BSI had resistance to ceftazidime, and were considered as MRSA.<sup>29</sup> Clinicians in regions with high prevalence of MRSA appear to have vague anxiety about glycopeptide de-escalation to beta-lactam agents, even though MSSA is confirmed in the blood culture results. Therefore, the first step for improving the survival of MSSA BSI is to relieve this anxiety and reassure clinicians through proper education.

Previous studies have demonstrated that glycopeptide use in MSSA BSI was associated with persistence.<sup>30,31</sup> In contrast, the beta-lactam group had higher incidence of persistent BSI compared to the glycopeptide group in our study. This may be due to empirical antibiotic use in cases of persistent BSI in the beta-lactam group, in which most patients received glycopeptides, as the median duration of empirical therapy was 3 (2–4) days (Supplementary Table 2, only online). Due to the slow bactericidal activity of glycopeptides,<sup>32</sup> empirical therapy with glycopeptides might lead to failure in the early clearance of MSSA, resulting in persistent BSI. Although we did not analyze the impact of empirical antibiotics, it would be important for selecting beta-lactam antibiotics as empirical therapy to reduce persistent BSI if there is no MRSA risk factor. Furthermore, to prove the results shown in our study more clearly, a follow-up study, in which the same empirical antibiotic is administered between groups, is needed in the future.

The most common adverse event found in the beta-lactam group was skin rash (50%), followed by gastrointestinal trouble (21.4%) and drug fever (7.1%). These results were similar to those from a previous study, in which patients who received beta-lactam antibiotics complained about skin rash (10.1%), drug fever (5.1%), as well as nausea and vomiting (1%).<sup>33</sup> Pa-

tients who received glycopeptides were also known to experience several adverse events. Of those, nephrotoxicity was the most frequently reported adverse event, and was especially associated with vancomycin;<sup>34</sup> however, we found that nephrotoxicity was relatively low (11.1%). This may be explained by the type of glycopeptides used in our study. Less than a third of the patients in the glycopeptide group received vancomycin (n=48), whereas most patients received teicoplanin (n=109), which has less nephrotoxic effects than vancomycin.<sup>34</sup> Although more adverse drug reactions occurred in the beta-lactam group compared to the glycopeptide group, no severe case was found and discontinuation of the antibiotics was rare in this study.

As shown in the subgroup analysis of our study, unlike the main analysis results, patients whose infection sources were controlled had 28-day mortality which favored glycopeptides. Possible reasons for this finding may be explained by the pharmacodynamics of glycopeptides, especially vancomycin. Vancomycin had different bactericidal activity according to the inoculum size.<sup>35</sup> The significant bactericidal activity of vancomycin in moderate inoculum disappeared in high inoculum. In addition, tissue penetration of vancomycin is variable and relies on the degree of tissue inflammation.<sup>36</sup> Surgical debridement or eradication of foci may improve the pharmacodynamic properties of glycopeptides, and would be related to clinical outcomes. Therefore, we could consider the use of glycopeptides with source control, if beta-lactams are not available, for the treatment of MSSA BSI.

This study had some limitations. First, due to the retrospective nature of this study, the choice of antibiotics for definitive therapy was not randomly assigned, and there remains selection bias and confounding factors in interpreting the treatment outcomes. However, we applied IPTW to address this issue, and significant differences were not noted between the two groups except for the primary focus of BSI after applying IPTW. In addition, IPTW was further augmented by multivariable logistic regression analysis allowing adjustment for many factors, including the primary focus of sepsis. Second, the effect of empirical therapy on clinical outcomes was not completely controlled in this study. We restricted the inclusion to patients who received empirical therapy for less than 5 days and excluded cases with longer duration of empirical therapy than that of definitive therapy. In addition, the effect of 1 or 2 days of initial antibiotics used until the identification of gram-positive cocci bacteremia was not considered. However, there is a possibility that empiric therapy had an effect on the clinical outcomes. Finally, this study analyzed data from two hospitals in the same city with limited sample size, and the event rates of several clinical outcomes were low. Therefore, the statistical power of the study results might be low, and the generalization of these results requires caution.

In conclusion, this study provides compelling evidence of anti-staphylococcal beta-lactam use for MSSA BSI treatment. Clinicians should discontinue empiric glycopeptides and start

definitive therapy with anti-staphylococcal beta-lactams when MSSA BSI is confirmed. Our findings should be verified through a randomized controlled trial with a larger study population involving multiple centers.

## AUTHOR CONTRIBUTIONS

**Conceptualization:** Yeon Ju La, Dong Hyun Oh, Jin Young Ahn, and Yong Chan Kim. **Data curation:** Yeon Ju La. **Formal analysis:** Hye Rim Kim. **Writing—original draft:** Yeon Ju La. **Writing—review & editing:** Jin Young Ahn and Yong Chan Kim. **Approval of final manuscript:** all authors.

## ORCID iDs

Yeon Ju La <https://orcid.org/0000-0003-2314-3699>  
 Hye Rim Kim <https://orcid.org/0000-0001-9604-7214>  
 Dong Hyun Oh <https://orcid.org/0000-0002-9990-6042>  
 Jin Young Ahn <https://orcid.org/0000-0002-3740-2826>  
 Yong Chan Kim <https://orcid.org/0000-0001-5081-7906>

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