Le Infezioni in Medicina, n. 1, 45-51, 2024
doi: 10.53854/liim-3201-6

Risk factors for therapeutic failure in adults with methicillin-resistant *Staphylococcus aureus* (MRSA) infection treated with vancomycin in a high-complexity hospital in Cali, Colombia

Carlos Mauricio Muriel[1,2], Jose Fernando García-Goez[1], Delia Ortega[2], Diana Martínez[3], Diego Rosselli[2,4]

[1]Fundación Valle de Lili, Cali, Colombia;
[2]Pontificia Universidad Javeriana, Cali, Colombia;
[3]Institute of Statistics, Universidad del Valparaiso, Chile;
[4]Clinical Epidemiology and Biostatistics Department, Pontificia Universidad Javeriana, Bogotá, Colombia

Received 5 October 2023, accepted 24 January 2024

SUMMARY

Objective: To determine the risk factors associated with therapeutic failure of vancomycin in hospitalized adult patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections.
Design: Case-control study.
Setting: Conducted in a high complexity hospital in Cali, Colombia.
Participants: Adult hospitalized from January 1, 2015, to December 31, 2021, with MRSA infections with confirmed microbiological isolation.
Methods: Cases were patients with therapeutic failure of vancomycin (mortality, poor clinical improvement, change of antibiotic used, early relapse, or persistence of positive blood cultures) and control patients were those who did not present failure. Significant variables from the bivariate analysis were included in a multiple analysis with an asymmetric logistic regression model.
Results: A total of 105 patients were included in the study, 28 in the treatment group and 77 in the control group. The median age was 49 years and 59 (56%) of participants were men. The following variables: age (OR 1.034; 95% CI 1.007-1.061, p=0.011), osteomyelitis/septic arthritis (OR 6.035; 95% CI 2.282-15.956, p=0.000) and minimum inhibitory concentration (MIC) (OR 5.971; 95% CI 1.321-26.979, p=0.020) were found to be independent risk factors associated with therapeutic failure of vancomycin. Vancomycin trough levels were not different between cases and controls (OR 0.976; 95% CI 0.911- 1.044, p=0.478).
Conclusions: When a multiple analysis was performed to control for confounding factors, only 3 variables were found to be significant and were considered risk factors for therapeutic failure of vancomycin in adult patients with MRSA infection: age, MIC, and osteomyelitis/septic arthritis.

Keywords: Methicillin-resistant *Staphylococcus aureus*, risk factors, vancomycin therapeutic failure, vancomycin treatment failure, diminished susceptibility to vancomycin.

INTRODUCTION

Infections caused by *Staphylococcus aureus* have always been of special interest in everyday clinical practice. This pathogen is responsible for multiple community-acquired and nosocomial

Corresponding author
Carlos Mauricio Muriel
E-mail: maurocarlos10@hotmail.com

infections, which are considered of public health concerns [1, 2]. Over time, these infections have undergone various changes due to the marked resistance to commonly used antibiotics. A significant percentage of current community-acquired staphylococcal infections are caused by Methicillin-Resistant *Staphylococcus aureus* (MRSA), a bacterium that exhibits resistance to all beta-lactam antibiotics. Simultaneously, an even higher percentage of nosocomial staphylococcal infections are attributed to the same bacteria [3, 4].

Historically, glycopeptides have been the first-line antibiotics in the treatment of MRSA infections, especially in hospitalized patients. Vancomycin, a glycopeptide, celebrates its 65th anniversary in 2023 and continues to be frequently used [5]. Unfortunately, in recent decades, it has experienced a loss of its effectiveness. Considering that vancomycin is one of the most widely used antibiotics in Colombia and worldwide for this type of infection and that therapeutic failure has become a common problem, research is needed to identify the risk factors that may trigger this phenomenon.

Some risk factors that can determine therapeutic failure to vancomycin have been studied; however, there are still knowledge gaps, especially in our context.

The main objective of this study is to characterize a population of patients with MRSA infection at a high-complexity hospital in Cali, Colombia, who experience therapeutic failure to vancomycin, and to identify associated risk factors. Some previously studied risk factors include: Minimum Inhibitory Concentration (MIC) >1.5 µg/mL, vancomycin trough levels <15 µg/mL, previous exposure to vancomycin, chronic kidney disease in haemodialysis patients, and septic foci such as osteomyelitis and bacterial endocarditis, among others [3, 6-10].

PATIENTS AND METHODS

A case-control study was conducted at a single high-complexity center in the city of Cali, Colombia. Data were collected from all adult patients diagnosed with MRSA infection, who had confirmed microbiological isolation in culture from blood, urine, central nervous system, central catheters, other body secretions such as pleural fluid, ascitic fluid, pericardial fluid, bronchoalveolar lavage, skin ulcers or wounds, and tissue biopsies. The information was obtained from the infection control committee's records and medical histories. For data collection, the secure and anonymous database BD Clinic was used. Patients with terminal illness, asymptomatic colonization, and those infected with multiple microorganisms where it was not possible to differentiate the responsible pathogen for therapeutic failure were excluded.

Definition of a case (Vancomycin Therapeutic Failure):

One or more of the following five criteria:

1. In-hospital death in patients with MRSA infection who received vancomycin treatment, after 48 hours of initiating the antibiotic.
2. Persistence of positive blood cultures after 5 days of starting vancomycin treatment.
3. Change of antibiotic due to little improvement.
4. Persistence of unresolved signs and symptoms of infection for at least 4 days of vancomycin treatment.
5. Early relapse within the first 30 days after discontinuing vancomycin treatment.

Definition of control: Patients with MRSA infection who did not experience therapeutic failure.

Sample size: The sample size estimation was done considering a power of 0.8 and an alpha error of 0.05, resulting in a total of 185 patients, with 62 cases and 123 controls.

Ethical aspects: This study was approved by the local ethics committee. The project adhered to international standards governing human research (2013 Helsinki Declaration and 2016 CIOMS guidelines), and was deemed a risk-free study.

Statistical analysis: Initially, an exploratory analysis of the data was performed to observe variable distribution and outliers. Subsequently, a bivariate analysis was conducted to look for associations using odds ratios (OR). Categorical variables were measured using Fisher's exact test, and for quantitative variables, the OR estimation was done through simple logistic models. Shapiro-Wilk revealed all continuous variables to be abnormally distributed.

Finally, a multiple logistic regression model was adjusted for therapeutic failure, selecting variables based on their level of significance in the bivariate analysis; those with p-values less than 0.2 entered the final model. Each adjusted OR was reported with its respective 95% confidence interval. The stepwise backward method was used to

select and discard different variables. The model was diagnosed by estimating Pearson and Deviance residuals. The possibility of multicollinearity of explanatory variables was evaluated using the Variance Inflation Factor (VIF), and the potential for specification error in the model was checked through link tests. All analyses were carried out using STATA version 15 software.

RESULTS

A total of 105 patients were included in the study. The median age was 49 years (interquartile range (IQR) 30-65), and 59 (56%) were male. The most common co-morbidity was diabetes mellitus (18%), followed by advanced chronic kidney disease (5%). The most frequent primary source of infection was skin and soft tissue (51%), followed by bacteraemia (38%), pneumonia (16%), and osteomyelitis or septic arthritis (12%). The median vancomycin trough levels were 17.21 (IQR 11.62 - 23.83); this parameter is generally measured multiple times in hospitalized patients with MRSA infection, so our study reported the average for each patient. The median MIC of the isolates was 1 µg/mL, and only 3 patients had isolates with MIC levels greater than 1.5 µg/mL. Sociodemographic and clinical data between cases and controls are shown in Table 1.

Out of the 105 patients included in the study, 28 (27%) experienced therapeutic failure to vancomycin, while 77 (73%) had a successful treatment outcome. Vancomycin trough levels could only be determined in 47 participants. There were no sta-

Table 1 - Demographic characteristics and risk factors of patients with MRSA.

Variables	*Therapeutic failure*		
	Controls (n=77)	*Cases (n=28)*	*General (n=105)*
	n (%)	*n (%)*	*n (%)*
Age, median [IQR] (years)	43 [28-58]	61 [50-73]	49 [30-65]
Gender			
Female	31 (40.3)	15 (53.6)	46 (43.8)
Male	46 (59.7)	13 (46.4)	59 (56.2)
Diabetes	10 (13.0)	9 (32.1)	19 (18.1)
Cirrhosis	0 (0)	0 (0)	0 (0)
Chronic kidney disease (CKD)	4 (5.2)	1 (3.6)	5 (4.8)
Endocarditis	1 (1.3)	1 (3.6)	2 (1.9)
HIV	1 (1.3)	1 (3.6)	2 (1.9)
Immunosuppressive treatment or chemotherapy	25 (32.5)	8 (28.6)	33 (31.4)
Osteomyelitis or septic arthritis	6 (7.8)	7 (25.0)	13 (12.4)
Skin or soft tissue infection	41 (53.3)	13 (46.4)	54 (51.4)
Catheter-related infection	8 (10.4)	2 (7.1)	10 (9.5)
Pneumonia	10 (13.0)	7 (25.0)	17 (16.2)
Central nervous system infection	7 (9.1)	1 (3.6)	8 (7.6)
Bacteremia	25 (32.5)	15 (53.6)	40 (38.1)
Vancomycin trough levels (µg/mL), median (IQR), n=47	17.6 (12.5-23.6)	15.7 (10.7-23.8)	17.21 (11.6-23.8)
Minimum inhibitory concentration (MIC) (µg/mL), median (IQR), n=104	1 (1-1)	1 (1-1)	1 (1-1)
Charlson index, median (IQR)	2 (0-3)	3,5 (2-5)	2 (0-4)
Previous use of vancomycin, n=73	19 (24.7)	6 (21.4)	25 (23.8)

Notes: IQR = interquartile range.

Table 2 - Bivariate analysis of the factors associated with therapeutic failure to vancomycin.

	OR (95% CI)			
Variables	*OR*	*Inf*	*Sup*	*p-value*
Age	1.04	1.017	1.069	0.001*
Gender				
Female	0.58	0.223	1.527	0.224
Male				
Diabetes	3.12	0.960	9.915	0.026*
Cirrhosis				
CKD	0.67	0.013	7.262	0.730
Endocarditis	2.81	0.035	223.786	0.451
HIV	2.81	0.035	223.786	0.451
Immunosuppressive treatment or chemotherapy	0.83	0.278	2.322	0.704
Osteomyelitis or septic arthritis	3.94	0.997	15.689	0.018*
Skin or soft tissue infection	0.76	0.291	1.978	0.536
Catheter-related infection	0.66	0.065	3.652	0.616
Pneumonia	2.23	0.632	7.430	0.139*
Central nervous system infection	0.37	0.008	3.133	0.346
Bacteremia	2.40	0.903	6.375	0.049*
Vancomycin trough levels (µg/mL)	0.97	0.911	1.044	0.478
MIC (µg/mL)	4.91	0.599	40.398	0.138*
Charlson index	1.23	1.046	1.463	0.013*
Previous use of vancomycin	0.94	0.251	3.277	0.925

*Model candidate variables.

tistically significant differences in the outcome of therapeutic failure compared to the control group (OR 0.976; 95% CI 0.911-1.044, p=0.478). In the bivariate analysis, age was identified as a risk factor for therapeutic failure, with a median age of 43 years (IQR 28-58) among controls and 61 years (IQR 50-73) among cases (OR 1.043; 95% CI 1.017-1.069, p=0.001). Some infectious foci were associated with therapeutic failure to vancomycin. Patients who did not achieve cure had a higher chance of having osteomyelitis or septic arthritis (OR 3.94; 95% CI 0.99-15.68, p=0.018) or bacteraemia (OR 2.40; 95% CI 0.903-6.375, p=0.049) compared to those who achieved cure. The bivariate analysis data can be observed in Table 2.

An asymmetrical multiple logistic regression analysis was conducted to determine associations while controlling for confounding factors. This model was chosen considering that the assumption of symmetrical cases and controls was not met. A robust method was selected to improve the estimation of parameter standard error. Variables with p-value <0.20 were included in the model. The results of the multiple analysis with adjusted odds ratios (aOR) can be observed in Table 3. It was found that age (aOR 1.034; 95% CI 1.007-1.061, p=0.011), osteomyelitis/septic arthritis (aOR 6.035; 95% CI 2.282-15.956, p=0.000), and MIC (aOR 5.971; 95% CI 1.321-26.979, p=0.020) were risk factors associated with the primary outcome of therapeutic failure with vancomycin.

DISCUSSION

Our study analyzed a group of patients with confirmed MRSA infection, determining some possible associations with variables that could explain the primary outcome of therapeutic failure to vancomycin. The median age among patients

Table 3 - Multiple analysis of factors associated with therapeutic failure to vancomycin.

	OR not adjusted 95% CI				*OR adjusted 95% CI*			
Variables	*OR*	*Inf*	*Sup*	*p-value*	*OR*	*Inf*	*Sup*	*p-value*
Age	1.04	1.017	1.069	0.001	1.03	1.007	1.061	0.011
Osteomyelitis or septic arthritis	3.94	0.997	15.68	0.018	6.03	2.282	15.95	0.000
Pneumonia	2.23	0.632	7.430	0.139	1.97	0.827	4.712	0.125
MIC	4.91	0.599	40.39	0.138	5.97	1.321	26.97	0.020
Charlson index	1.23	1.046	1.463	0.013	1.14	0.967	1.360	0.114

who experienced therapeutic failure was higher compared to those who achieved cure. Age was a conclusive risk factor both in the bivariate analysis (OR 1.043; 95% CI 1.017-1.069, p=0.001) and in the multivariate analysis (OR 1.034; 95% CI 1.007-1.061, p=0.011).

We found a large effect size for the variable osteomyelitis or septic arthritis, with an adjusted OR of 6.035; 95% CI 2.282-15.956, and a p-value of 0.000. This is consistent with studies like the one by El Nekidy et al., which reported an OR of 11.07; 95% CI 3.2-38.48 [8]. The therapeutic failure observed in this cohort of patients could be due to poor penetration of vancomycin into the bone. Although this study was designed as an association model, the results could be inferred as predictors of a poor prognosis. This could lead to changes in current management protocols for patients with osteomyelitis or septic arthritis with confirmed microbiological isolation.

Bacteraemia was a risk factor in the bivariate analysis, but it lost its significance when entering the multiple model, possibly due to the small sample size, which limits the study's power.

The variable pneumonia was not statistically significant in the bivariate analysis; however, it met criteria to enter the multiple model due to its p-value (<0.2). When exploring this variable, we found that its distribution was higher among cases compared to controls (25% vs. 10%), raising the question of whether a larger sample size could have revealed a significant difference. At this time, we can only describe it as an interesting observation that should be considered in future research.

One of the main objectives of the study was to demonstrate a possible lack of association between elevated vancomycin trough levels and better treatment effectiveness. This hypothesis is generally accepted, and an ideal range of trough levels ≥15 mg/L has been determined. However, the literature is controversial, with studies that have not found a real benefit, and some research even reports a higher incidence of adverse effects such as nephrotoxicity at trough levels ≥15 mg/L [6, 11-13].

There are studies suggesting a lack of association between the trough levels of vancomycin considered optimal (>15 mg/L) and the effectiveness of treatment. In a cohort study conducted between January 2013 and December 2015 in two university hospitals in Israel, involving 285 patients with vancomycin-susceptible MRSA infection (MIC ≤2 mg/L), a group of patients with trough levels ≥15 mg/L was compared against one with lower levels. There were no differences in terms of mortality, 46/131 (35.1%) vs. 41/154 (26.6%), with an adjusted odds ratio of 0.63 (95% CI 0.28-1.43); nor in secondary outcomes of adverse events, clinical success, and microbiological success [11].

In a meta-analysis that included 17 observational studies of patients with Gram-positive cocci infection, mainly MRSA, patients with trough levels greater than or equal to 15 mg/L were compared against a control with lower levels. It was found that there were no differences in therapeutic failure outcomes (RR 0.91, 95% CI 0.67-1.24) and all-cause mortality (RR 1.14, 95% CI 0.81-1.59). On the contrary, high serum concentrations of vancomycin were associated with an increased risk of nephrotoxicity (RR 2.06, 95% CI 1.52-2.79) [6].

In a cohort study involving 124 patients with MRSA bacteraemia, it was observed that mortality was more frequent in older patients (aHR 1.03, 95% CI 1.01-1.06, p 0.006) and those with pneumonia (aHR 3.86, 95% CI 1.83-8.12, p<0.001). Of the 63 patients treated with vancomycin, only 14 (22.6%) achieved the desired minimum levels of 15 to 20 mg/L, indicating the difficulty in reaching that goal. This study also assessed the outcome of persistent bacteraemia, which was observed in patients diagnosed with endocarditis (p <0.001) and those with low minimum levels of vancomycin (p <0.014); however, no relationship was found with the minimum inhibitory concentration (MIC) of vancomycin [14].

In our study, we did not find significant differences in vancomycin trough levels between patients who experienced therapeutic failure and the control group. It is important to note that only 47 patients had measurement of vancomycin trough levels in the study, which may have lacked power to determine a real association, and the results could be subject to random error.

In the literature review, we did not find the average vancomycin MIC in patients with MRSA infection in our setting. Therefore, one of the study's objectives was to document this parameter in the analyzed cohort. Currently, a MIC >2 µg/mL is considered to confirm resistance to vancomycin, but the susceptibility of the bacteria in isolates with MIC of 1.5 to 2 µg/mL is not entirely clear.

In our study, an association was found between the MIC variable and therapeutic failure to vancomycin (aOR 5.971; 95% CI 1.321-26.979, p=0.020). However, no patient had an MIC >2 µg/mL, so *in vitro* resistance was not documented.

In a meta-analysis, the association of high MIC, defined as ≥1.5 mg/L, was studied with some therapeutic failure outcomes in adult patients with MRSA bacteremia. A total of 13 studies with 2089 patients were included. The overall mortality of 27% in high MIC vs. 23% in low MIC was not statistically significant (RR 1.2; 95% CI 0.86-1.68; p=0.28). Among the secondary outcomes measured, no differences were found in persistent bacteraemia, severe sepsis, acute renal failure, or complications from haematogenous dissemination such as bacterial endocarditis or septic arthritis [15].

In a cohort study conducted at a tertiary-level hospital in Seoul, Korea, involving 385 patients, a paradoxical relationship was found between low vancomycin MIC (<1.5 µg/mL) and severe sepsis or septic shock (aOR, 0.53; 95% CI, 0.34 to 0.84) [16]. This is an interesting and contradictory finding compared to the results of our research. However, it should be noted that vancomycin susceptibility was not associated with increased mortality, which is an important criterion for therapeutic failure in our study.

Therapeutic failure with vancomycin was more frequent in patients with a MIC of 2 µg/mL in the studied cohort. We also observed that among the 26 patients with MIC < 2 µg/mL, therapeutic failure mainly occurred in patients with bacteremia (58%), soft tissue infection (46%), and a Charlson index greater than 2 (65%), and was only seen in 35% of patients with diabetes mellitus and 27% of those diagnosed with osteomyelitis or septic arthritis. The Charlson index is a 10-year survival scale that increases in score for elderly patients and those with multiple comorbidities. This could explain why patients with low and sensitive MIC had poor outcomes.

Thus, a significant association was found between therapeutic failure to vancomycin in patients with MRSA infection and the variables age, MIC, and osteomyelitis/septic arthritis. This relationship persisted after controlling for confounding factors with an asymmetric logistic regression model.

As a limitation of the study, the desired sample size was not achieved, which significantly affected the statistical power, and therefore, the results should be interpreted with caution. However, it is important to note that all available cases during the study period at the institution were included. The participation of a single center may limit the generalization of the findings. It is recommended to conduct further research with a larger and more diverse sample size, possibly in a multicenter setting, to validate and extend these findings.

A potential limitation of the study is that the vancomycin dosage was not considered due to difficulty in measuring this variable, as in some cases, this dosage may be adjusted multiple times based on vancomycin trough levels. However, we do not believe it to be a significant variable since our hospital adheres to the international recommendation of the suggested initial dose of 15-20 mg/kg. Special consideration might be given to patients with advanced chronic kidney disease where the dosage can be variable; however, due to the limited number of participants (5 or 4.8%), we consider it possibly not to be a determining variable in our study.

The duration of treatment was also not measured as we believe this variable could be influenced by the severity and co-morbidities of the patient. Possibly, the duration of vancomycin treatment in patients who experienced therapeutic failure may have been shorter than in the control group, given the awareness in our hospital to act promptly in the face of a deteriorating condition and modify the antibiotic regimen. However, it needs to be acknowledged as a potential weakness of the study.

Despite the limitations in the sample size, conclusive differences were found, which suggests that the documented risk factors in the study are significant and could encourage larger multicenter investigations. It is noteworthy that, to the best of our knowledge, there are no other studies evaluating risk factors for therapeutic failure to vancomycin in hospitalized patients with MRSA infection in Colombia, making our results potentially valuable.

Recognizing these limitations in the study, it is essential to consider the need for future research with a more appropriate sample size to confirm and expand our findings. Furthermore, the results of our study can serve as a starting point for future investigations and contribute to a better understanding of therapeutic failure to vancomycin in patients with MRSA infection in our country.

Conflicts of interest
All authors report no conflicts of interest relevant to this article.

Funding
This study was supported and funded by the Fundación Valle del Lili.

REFERENCES

[1] Cuevas Ó, Cercenado E, Goyanes MJ, et al. *Staphylococcus spp*. en España: Situación actual y evolución de la resistencia a antimicrobianos (1986-2006). *Enferm Infecc Microbiol Clin*. 2008; 26(5): 269-277.
[2] Cortes JA, Gomez CA, Cuervo SI, Leal AL. Implicaciones en salud pública de *Staphylococcus aureus* meticilino resistente adquirido en la comunidad en Bogotá, Colombia. *Rev Salud Publica (Bogota)*. 2007; 9(3): 448-454.
[3] Mensa J, Barberán J, Llinares P, et al. Guia infecciones por SAMR. *Rev Esp Quimioter*. 2008; 21(4): 234-258.
[4] Guzmán-Blanco M, Mejía C, Isturiz R, Alvarez C, et al. Epidemiology of meticillin-resistant *Staphylococcus aureus* (MRSA) in Latin America. *Int J Antimicrob Agents*. 2009; 34(4): 304-308.
[5] Rose W, Volk C, Dilworth TJ, Sakoulas G. Approaching 65 years: Is it time to consider retirement of vancomycin for treating methicillin-resistant *Staphylococcus aureus* endovascular infections? *Open Forum Infect Dis*. 2022; 9(5): ofac137.
[6] Meng L, Fang Y, Chen Y, Zhu H, Long R. High versus low vancomycin serum trough regimen for Gram-positive infections: A meta-analysis. *J Chemother*. 2015; 27(4): 213-220.
[7] Aston JL, Dortch MJ, Dossett LA, Creech CB, May AK. Risk factors for treatment failure in patients receiving vancomycin for hospital-acquired methicillin-resistant *Staphylococcus aureus* pneumonia. *Surg Infect (Larchmt)*. 2010; 11(1): 21-28.
[8] El Nekidy WS, El-Masri MM, Ghazi IM, Soong D. Factors predicting vancomycin therapy outcomes in hemodialysis outpatients and the role of the nephrology stewardship pharmacist. *Hemodial Int*. 2019; 23(4): 449-457.
[9] Dombrowski JC, Winston LG. Clinical failures of appropriately-treated methicillin-resistant *Staphylococcus aureus* infections. *J Infect*. 2008; 57(2): 110-115.
[10] Walraven CJ, North MS, Marr-Lyon L, Deming P, Sakoulas G, Mercier RC. Site of infection rather than vancomycin MIC predicts vancomycin treatment failure in methicillin-resistant *Staphylococcus aureus* bacteraemia. *J Antimicrob Chemother*. 2011; 66(10): 2386-2392.
[11] Yahav D, Abbas M, Nassar L, et al. The association of vancomycin trough levels with outcomes among patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections: Retrospective cohort study. *PLoS One*. 2019; 14(4): e0214309.
[12] Barriere SL, Stryjewski ME, Corey GR, Genter FC, Rubinstein E. Effect of vancomycin serum trough levels on outcomes in patients with nosocomial pneumonia due to *Staphylococcus aureus*: A retrospective, post hoc, subgroup analysis of the phase 3 ATTAIN studies. *BMC Infect Dis*. 2014; 14(1): 1-5.
[13] Tongsai S, Koomanachai P. The safety and efficacy of high versus low vancomycin trough levels in the treatment of patients with infections caused by methicillin-resistant *Staphylococcus aureus*: a meta-analysis. *BMC Res Notes*. 2016; 9(1): 1-16.
[14] Forstner C, Dungl C, Tobudic S, Mitteregger D, Lagler H, Burgmann H. Predictors of clinical and microbiological treatment failure in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia: a retrospective cohort study in a region with low MRSA prevalence. *Clin Microbiol Infect*. 2013; 19(7): E291-E297.
[15] Ishaq H, Tariq W, Talha KM, et al. Association between high vancomycin minimum inhibitory concentration and clinical outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: a meta-analysis. *Infection*. 2021; 49(5): 803-811.
[16] Kim T, Chong YP, Park KH, et al. Clinical and microbiological factors associated with early patient mortality from methicillin-resistant *Staphylococcus aureus* bacteremia. *Korean J Intern Med*. 2019; 34(1): 184.