

Bloodstream infections in intensive care unit: retrospective study in a teaching hospital

Infecções da corrente sanguínea em unidade de terapia intensiva: estudo retrospectivo em um hospital de ensino

Betina Brixner¹ • Nayanna Dias Bierhals² • Caio Fernando de Oliveira³ • Jane Dagmar Pollo Renner⁴

RESUMO

O objetivo deste estudo foi verificar os fatores de risco e perfil epidemiológico dos pacientes diagnosticados com infecção de corrente sanguínea, bem como os microrganismos responsáveis pela infecção. Estudo transversal, em que foi realizado um levantamento das hemoculturas e dados dos pacientes internados em unidade de terapia intensiva adulto com diagnóstico de infecção de corrente sanguínea, durante o ano de 2016. Foram coletadas informações referente ao paciente e sua internação, bem como ao agente responsável pela infecção e seu perfil de resistência. Foram incluídas 24 hemoculturas positivas para crescimento bacteriano. A média de idade dos pacientes foi de $53,9 \pm 21,1$ anos e 54,5% dos pacientes acometidos pela infecção eram homens. Dos pacientes, 59,1% apresentavam histórico de doença cardíaca, sendo que destes, 63,6% foram a óbito. As bactérias Gram positivas foram mais relacionadas com a infecção, em que 54,2% eram *Staphylococcus coagulase negativa* e destes, 76,9% foram resistentes meticilina. Identificou-se que o sexo masculino, indivíduos idosos e com histórico de alguma comorbidades prévia, com destaque para as doenças cardíacas, foram os mais acometidos com bacteremia. Quanto ao agente bacteriano responsável pela infecção, o *Staphylococcus coagulase negativa* foi o mais relacionado aos casos diagnosticados, bem como o seu alto perfil de resistência deste microrganismo frente a meticilina.

Palavras-chave: Bacteremia; Fatores de Risco; Diagnóstico; Unidade de Terapia Intensiva.

ABSTRACT

The objective of this study was to verify the risk factors and epidemiological profile of the patients diagnosed with bloodstream infection, as well as the microorganisms responsible for the infection. A cross-sectional study was carried out in which blood cultures were collected and data were collected from patients admitted to an adult intensive care unit with a diagnosis of bloodstream infection during the year 2016. Information about the patient and hospitalization was collected, as well as the agent responsible for the infection and its resistance profile. 24 blood cultures positive for bacterial growth were included. The mean age of the patients was 53.9 ± 21.1 years and 54.5% of the patients affected by the infection were men. Of the patients, 59.1% had a history of heart disease, of which 63.6% died. Gram positive bacteria were more related to infection, in which 54.2% were coagulase negative *Staphylococcus* and of these, 76.9% were resistant to methicillin. It was identified that the male sex, elderly individuals and with history of some previous comorbidities, especially heart diseases, were the most affected with bacteremia. As for the bacterial agent responsible for the infection, Coagulase negative *Staphylococcus* was the most related to the diagnosed cases, as well as its high resistance profile of this microorganism against methicillin.

Keywords: Bacteremia; Risk factors; Diagnosis; Intensive Care Unit.

NOTA

¹Farmacêutica. Mestra em Promoção da Saúde pela Universidade de Santa Cruz do Sul (UNISC). RS, Brasil. E-mail: betinabrixner@yahoo.com.br

²Acadêmica do Curso de Farmácia e bolsista de iniciação científica na Universidade de Santa Cruz do Sul (UNISC). RS, Brasil. E-mail: nayanna.db@outlook.com

³Farmacêutico bioquímico. Pós-doutorando do programa de pós graduação em Promoção da Saúde da Universidade de Santa Cruz do Sul (UNISC). RS, Brasil. E-mail: caiofarm@yahoo.com.br

⁴Farmacêutica Bioquímica. Doutora em Biologia Celular e Molecular pela Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS). Docente do departamento de Biologia e Farmácia e do programa de pós graduação em Promoção da Saúde na Universidade de Santa Cruz do Sul (UNISC). RS, Brasil. E-mail: janerrenner@unisc.br



INTRODUCTION

Among the Health Care Related Infections (IRAS) that can affect a critically ill patient, bloodstream infection (CHI) is one of the most frequent⁽¹⁻³⁾. This site is classified as the third most affected by infections in the Intensive Care Units (ICU), both in the world and Brazil, being responsible for causing, respectively, 15.1% and 10.1% of IRAS in this hospitalization unit^(1,2).

Considered a serious infectious disease, due to the invasion of microorganisms in the circulating blood and at risk of carrying microorganisms to other organs, ICS is responsible for causing unfavorable clinical outcomes^(4,5). In addition to morbidity and mortality, this infection is also associated with an increase in hospitalization time and high expenses for diagnostic and medication procedures⁽⁶⁾.

The diagnosis of CHI is challenging, in which the detection, microbial identification and susceptibility test results are extremely important for the initiation of adequate antibiotic therapy, since the earlier its initiation, the better the prognosis and the chances of survival of the patient⁽⁴⁾.

Due to this public health problem, the present study aimed to trace an epidemiological profile of the patients affected by ICS, as well as the microorganisms responsible for causing this infection.

METHOD

This is a cross-sectional retrospective study, carried out through the ICS survey of patients hospitalized in an adult ICU during the period from January to December 2016, in a teaching hospital in the interior of Rio Grande do Sul - RS, Brazil. This is a large philanthropic hospital with 232 beds available, of which 10 are for the adult ICU. It is important to emphasize that this ICU serves clinical and surgical patients, but it attends more hospitalizations of clinical origin. It is also considered a reference for high complexity care in the areas of orthopedics and traumatology, as well as in care for high-risk pregnant women.

To select the samples used in this study, a clinical analysis laboratory, located near the hospital, was used to generate and make available a report of all the blood cultures performed during the study period. Subsequently, the blood cultures that came from patients admitted to the adult ICU were identified, selecting only those with a positive result for bacterial growth. After that, an active search was carried out in the computerized system (MV 2000®) of the hospital, using a questionnaire to fill in information about the patient and his hospitalization, as well as the pathogen responsible for ICS and its antimicrobial resistance profile.

It should be noted that blood cultures were performed by the clinical analysis laboratory, which uses au-

tomated techniques (*Bactec*® and *AutoScan 4 System*®) in order to streamline and qualify the results for patients in critical health.

As inclusion criteria for this study, we have the patients with a diagnosis of SBI, of both sexes and over the age of 13 years. As exclusion criteria, those patients whose charts were not complete, making it impossible to collect the variables and the CSI caused by fungi.

Data were analyzed in SPSS version 23.0 (SPSS Inc., Armonk, NY, USA), where the descriptive statistics of the variables were evaluated by frequency, mean and standard deviation. The associations between the categorical variables were evaluated using the Chi-square test, considering a statistically significant result a value of $p \leq 0.05$.

This study is part of a mother project titled "Development of molecular methods in the diagnosis of microorganisms and genes involved in bacterial resistance", which was approved by the Research Ethics Committee of the University of Santa Cruz do Sul, under Report No. 1,540 .110 / 2016 and CAEE No. 55494716.3.0000.5343.

RESULTS

During the study period, 85 automated blood cultures were requested in the adult ICU, and for each patient two samples were collected at different locations. After the selection of the samples, 31 blood cultures showed positive results and, after the exclusion criteria, the study remained with a total of 24 samples.

Analyzing the data, it was verified that in two cases there was a recurrent infection of the blood stream, thus, the population variables were calculated according to the number of patients with the diagnosis of the infection (Table 1). The age of the patients affected by SBI ranged from 14 to 80 years, with a mean age of 53.9 ± 21.1 .

The length of stay of these patients in the ICU ranged from 2 to 38 days, with an average of 12.0 ± 9.4 days. Table 2 shows that among the patients with a diagnosis of HF, 20 (90.9%) presented previous history of diseases, and the heart was found more frequently in this study. In addition, it is also possible to visualize that 14 (63.6%) of these patients died, presenting statistically significant results when comparing the number of patients with SBI who died and who had a history of heart disease, indicating that this pathology may relation to the deaths of patients with a diagnosis of CHI.

Of the 24 ICS found in this study, it was observed that in 23 (95.8%) cases the patients presented signs indicative of infection, such as fever and / or hypotension and, as a result of these clinical conditions, there was a need to confirm ICS and pathogenic microorganism through automated blood culture. It was also verified

that in 13 (54.2%) samples of blood cultures collected, the patients were using previous antibiotic therapy for treatment or prophylaxis.

Table 3 indicates the causative agents of ICS in this study, and it is possible to observe the predominance of these Gram positive bacterial infections. *Staphylococcus coagulase negative (SCoN)* was the microorganism most related to ICS in this ICU, with 13 (54.2%) cases and of these, 10 (76.9%) were considered methicillin resistant coagulase negative staphylococci (MRSCoN).

Table 4 shows that most of these infections are nosocomial and there was no relationship between the use of an invasive medical device and the origin of SCI.

DISCUSSION

It is extremely important to evaluate the bacteria involved in cases of nosocomial infections; in this way it is possible to avoid situations of outbreaks of multiresistant microorganisms and to control this worrisome public health problem, due to the increase in morbidity and mortality and other factors that directly reflect the safety of the hospitalized patient⁽⁷⁾.

The ICS were more prevalent in male patients, corroborating with other studies^(2,4,6,8). Although IRAS is not associated with the use of invasive medical devices, there are data in the literature showing that men are predisposed to develop infection in this site; since they have a higher risk of bacterial colonization in their skin, and there should be intensified care in the placement of the central venous catheter and during its stay^(8,9). Thus, the high ICS rates in males are related to the higher risk of the skin microbiota and also in relation to the still unknown anatomical distinctions between the sexes⁽⁸⁾.

Of the 24 bacteremias included in this study, 17 were of nosocomial origin, and only two were associated with the use of an invasive medical device. The use of catheters is considered a potential risk factor for CHF, especially for ICU patients, but it is possible to reduce indices when correctly applying all steps of the catheter-related infection prevention bundle^(9,10). There was also a notification of ICS associated with the invasive device, of community origin; the patient used a urinary catheter because he underwent hemodialysis in a medical clinic. The trend of infection prevalence in hemodialysis patients is increased due to the use of central venous catheters^(1,2,11). In view of this, it is indispensable to educate the multiprofessional team and the patients, to adopt preventive measures that must be properly applied in hemodialysis treatment units^(11,12).

In the present study, 59.1% of patients who were diagnosed with CHF were 60 years of age or older. The vulnerability of the geriatric population leaves them more prone to develop bacteremia, since they have some chronic disease, physiological changes (immunodepression, for example) and malnutrition^(13,14). A cohort study conducted in 8 hospitals located in the states of North Carolina and Virginia, USA, showed that when the elderly patient is diagnosed with CHF, there is an increase in mortality, an increase in length of hospital stay (10 days), reaching a value of 43.000,00 dollars in additional hospital expenses⁽¹⁵⁾.

Regarding the presence of previous comorbidities, 59.1% of the patients had some heart disease. In addition, statistically significant results were obtained for patients diagnosed with CHF with underlying heart disease and unfavorable clinical outcome, in which 50% died. These

TABLE 1 – Data of patients with a diagnosis of SBI and type of hospitalization in the adult ICU of a teaching hospital. Santa Cruz do Sul, RS, Brazil, 2016.

VARIABLES		n (%)
Gender		
	Female	10 (45,5)
	Male	12 (54,5)
Age group		
	≤ 18 years old	2 (9,1)
	19-30 years old	3 (13,6)
	40-59 years old	4 (18,2)
	≥ 60 years old	13 (59,1)
Type of hospitalization		
	Clinic	18 (81,8)
	Elective surgery	2 (9,1)
	Emergency surgery	2 (9,1)
TOTAL		22 (100,0)

Source: research data.



TABLE 2 – Relationship of previous pathologies of patients with a diagnosis of HFI hospitalized in the adult ICU of a teaching hospital. Santa Cruz do Sul, RS, Brazil, 2016.

HISTORY OF DISEASE	COMORBITIES				DISCHARGE				
	Yes	No	Total	p*	High	Transference	Death	Total	p*
	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	n (%)	
Cardiac									
Yes	13 (59,1)	0 (0)	13 (59,1)	0,075	1 (4,5)	1 (4,5)	11 (50,0)	13 (59,1)	0,035
No	7 (31,8)	2 (9,1)	9 (40,9)		5 (22,7)	1 (4,5)	3 (13,6)	9 (40,9)	
Pulmonar									
Yes	1 (4,5)	0 (0)	1 (4,5)	0,746	0 (0)	0 (0)	1 (4,5)	1 (4,5)	0,741
No	19 (86,4)	2 (9,1)	21 (95,5)		6 (27,3)	2 (9,1)	13 (59,1)	21 (95,5)	
Neurologic									
Yes	2 (9,1)	0 (0)	2 (9,1)	0,639	1 (4,5)	0 (0)	1 (4,5)	2 (9,1)	0,711
No	18 (81,8)	2 (9,1)	20 (90,9)		5 (22,7)	2 (9,1)	13 (59,1)	20 (90,9)	
Malignancy									
Yes	1 (4,5)	0 (0)	1 (4,5)	0,746	0 (0)	0 (0)	1 (4,5)	1 (4,5)	0,741
No	19 (86,4)	2 (9,1)	21 (95,5)		6 (27,3)	2 (9,1)	13 (59,1)	21 (95,5)	
Endocrinological									
Yes	4 (18,2)	0 (0)	4 (18,2)	0,484	0 (0)	1 (4,5)	3 (13,6)	4 (18,2)	0,247
No	16 (72,7)	2 (9,1)	18 (81,8)		6 (27,3)	1 (4,5)	11 (50)	18 (81,8)	
Acute renal									
Yes	1 (4,5)	0 (0)	1 (4,5)	0,746	0 (0)	0 (0)	1 (4,5)	1 (4,5)	0,741
No	19 (86,4)	2 (9,1)	21 (95,5)		6 (27,3)	2 (9,1)	13 (59,1)	21 (95,5)	
Renal Chronic									
Yes	1 (4,5)	0 (0)	1 (4,5)	0,746	0 (0)	0 (0)	1 (4,5)	1 (4,5)	0,741
No	19 (86,4)	2 (9,1)	21 (95,5)		6 (27,3)	2 (9,1)	13 (59,1)	21 (95,5)	
Hepatic									
Yes	1 (4,5)	0 (0)	1 (4,5)	0,746	0 (0)	0 (0)	1 (4,5)	1 (4,5)	0,741
No	19 (86,4)	2 (9,1)	21 (95,5)		6 (27,3)	2 (9,1)	13 (59,1)	21 (95,5)	
Immunodeficiency									
Yes	3 (13,6)	0 (0)	3 (13,6)	0,556	2 (9,1)	1 (4,5)	0 (0)	3 (13,6)	0,040
No	17 (77,3)	2 (9,1)	19 (86,4)		4 (18,2)	1 (4,5)	14 (63,6)	19 (86,4)	
TOTAL	20 (90,9)	2 (9,1)	22 (100,0)		6 (27,3)	2 (9,1)	14 (63,6)	22 (100,0)	

Note: *Pearson's Chi-square test.

Source: research data.

TABLE 3 – Microorganisms causing ICS and mechanisms of phenotypic resistance found in the adult ICU of a teaching hospital. Santa Cruz do Sul, RS, Brazil, 2016.

VARIABLES		n (%)
ICS-causing micro-organism		
Gram positive		
	SCoN	13 (54,2)
	<i>Enterococcus</i> spp.	3 (12,5)
	<i>Staphylococcus aureus</i>	2 (8,3)
Gram negative		
	<i>Klebsiella pneumoniae</i>	2 (8,3)
	<i>Escherichia coli</i>	2 (8,3)
	<i>Acinetobacter</i> spp.	1 (4,2)
	<i>Serratia</i> spp.	1 (4,2)
Mechanism of phenotypic resistance		
	MRSCoN/MRSA	10 (41,7)
	ESBL	2 (8,3)
	Absent/Not tested	12 (50,0)
TOTAL		24 (100,0)

Note: SCoN (*Staphylococcus* negative coagulase); MRSCoN (*Staphylococcus* coagulase negative resistant to methicillin); ESBL (β -Lactamase Extended Spectrum).

Source: research data.

TABLE 4 – Relationship between invasive device use and ICS origin in patients hospitalized in the adult ICU of a teaching hospital. Santa Cruz do Sul, RS, Brazil, 2016.

Origin of Infection	Infection linked to invasive device use			p*
	Yes	No	Total	
	n (%)	n (%)	n (%)	
Community	1 (4,2)	6 (25,0)	7 (29,2)	0,875
Nosocomial	2 (8,3)	15 (62,5)	17 (70,8)	
TOTAL	3 (12,5)	21 (87,5)	24 (100)	

Note: *Pearson's Chi-square test.

Source: research data.

data corroborate with a study carried out in Belgium (13), in which among the 109 patients with CHF, 80 (73.4%) had some cardiovascular disease. In addition, a multicenter study (1) conducted in different ICUs worldwide found that in patients with a clinical diagnosis of infection, heart failure was one of the risk factors independently associated with an increased risk of death during hospitalization.

Clinical hospitalization was highlighted in this study when compared to other types of hospitalization, which may be a possible reflection of the age group and/or the presence of one or more previous comorbidities of the individuals participating in this study. In view of the above, this result is in line with another study⁽¹⁶⁾, which shows a greater number of hospitalizations in clinical ICU, corresponding to 4,407 long-term admissions. Relating these data to the length of stay in the ICU, the mean of this study was 12 days, differently from another⁽¹⁵⁾, which

obtained a mean hospitalization of 23 days for patients diagnosed with ICS. This time may be even higher when the SCI is caused by a multiresistant microorganism, which can reach 37.2 days of hospitalization⁽⁶⁾. The length of hospital stay is partially related to episodes of HFI, in which the longer the exposure period of the critical patient, the greater the risk of nosocomial infection⁽¹⁵⁻¹⁷⁾.

Among the reported SCIs, the majority of the cases in this study were due to infection by *Staphylococcus coagulase negative* (SCoN), a microorganism found in the human skin microbiota, but have been an important pathogen related to nosocomial infections⁽¹⁸⁾. This result corroborates with another study⁽¹⁹⁾, which found that the SCoN were the bacteria that caused the most frequent SCI in the patients studied. Another study⁽⁴⁾, which also used an automated blood culture method, isolated the following Gram positive bacteria: *Staphylococcus aureus* (52%), SCoN (32%), *Enterococcus* spp. (8%) and *Strepto-*

coccus pneumoniae (8%); and Gram negative: *Escherichia coli* (40.9%), *Klebsiella* spp. (27.3%), *Pseudomonas aeruginosa* (22.7%), *Citrobacter* spp. (9.1%).

In addition to being one of the main causative agents of SCI, SCoN has been presenting strains resistant to antimicrobials, especially those that are resistant to methicillin⁽¹⁸⁾. The resistance rate phenotypically detected in this study for MRSCoN is in line with another study⁽²⁰⁾, which demonstrated a high rate of methicillin-resistant *Staphylococcus*, in which 70% of the isolates of *Staphylococcus epidermidis* were resistant to the antibiotic tested. The emergence of these resistant strains of SCoN further complicates the clinical picture of the patient and the treatment of infections, and it is necessary to adopt new antimicrobial therapies that act effectively in the different species of bacteria belonging to the SCoN group⁽¹⁸⁾.

Although the study is carried out in the adult ICU of a single hospital, it is important to investigate the ICS in order to know the profile of the pathogens responsible for the infectious process, as well as to determine if the bac-

terial spread can be related to the contamination crises of the hospital environment and hands of health professionals. The limitations were the difficulty of finding data referring to the variables searched in the electronic charts, generating sample exclusion and the short period analyzed. It is worth mentioning that further studies are needed, covering more adult ICUs, which will allow the identification of the ICS profile in hospitals in the region, as well as the possible risk factors for the development of the infection, either in relation to the patient's previous comorbidities or associated with the use of invasive medical devices.

CONCLUSION

In this study we can identify that the male sex and elderly individuals were the most affected with ICS in the ICU. In addition, it was found that the vast majority of patients with CHF had previous comorbidities, especially cardiac diseases. It can also be identified that the SCoN was the bacterial agent most involved with the cases of ICS in the studied ICU, in which the majority had resistance to oxacillin.

REFERENCES

1. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; 302(21):2323-2329. <http://dx.doi.org/10.1001/jama.2009.1754>
2. Silva E, Dalfior Junior L, Fernandes HS, et al. Prevalence and outcomes of infections in Brazilian ICUs: a subanalysis of EPIC II study. *Rev Bras Ter Intensiva*. 2012; 24(2):143-150. <http://dx.doi.org/10.1590/S0103-507X2012000200008>.
3. Rutkowska K, Przybyła M, Misiólek H. Healthcare-associated infections in a newly opened intensive care unit. *Anaesthesiol Intensive Ther*. 2013, 45(2):62-66. <http://dx.doi.org/10.5603/AIT.2013.0014>
4. Vasudeva N, Nirwan PS, Shrivastava P. Bloodstream infections and antimicrobial sensitivity patterns in a tertiary care hospital of India. *Ther Adv Infect Dis*. 2016; 3(5):119-127. <http://dx.doi.org/10.1177/2049936116666983>
5. Scerbo MH, Kaplan HB, Dua A, et al. Beyond Blood Culture and Gram Stain Analysis: A Review of Molecular Techniques for the Early Detection of Bacteremia in Surgical Patients. *Surg Infect (Larchmt)*. 2016; 17(3):294-302. <http://dx.doi.org/10.1089/sur.2015.099>
6. Riu M, Chiarello P, Terradas R, et al. Incremental cost of nosocomial bacteremia according to the focus of infection and antibiotic sensitivity of the causative microorganism in a university hospital. *Medicine* 2017; 96(17):e6645. <http://dx.doi.org/10.1097/MD.0000000000006645>.
7. Agência Nacional de Vigilância Sanitária (ANVISA). National Program for Prevention and Control of Infections Related to Health Care (2016-2020). Brasília, DF: ANVISA; 2016. Disponível em: <<http://portal.anvisa.gov.br/documents/33852/3074175/PNPCIRAS+2016-2020/f3eb5d51-616c-49fa-8003-0dcb8604e7d9>>. Acesso em: 01 mai. 2018
8. Cohen B, Choi YJ, Hyman S, et al. Gender differences in risk of bloodstream and surgical site infections. *J Gen Intern Med*. 2013; 28(10):1318-25. <http://dx.doi.org/10.1007/s11606-013-2421-5>
9. Luft D, Schmoor C, Wilson C, et al. Central venous catheter-associated bloodstream infection and colonisation of insertion site and catheter tip. What are the rates and risk factors in haematology patients? *Ann Hematol*. 2010; 89(12):1265-75. <http://dx.doi.org/10.1007/s00277-010-1005-2>
10. Silva ACSS, Santos EI, Penha RS, et al. Brazilian scientific evidence about primary infection of the bloodstream in pediatric patients. *Rev Enf Atual*. 2018; 82(20):62-70.
11. Suzuki M, Satoh N, Nakamura M, et al. Bacteremia in hemodialysis patients. *World J Nephrol*. 2016; 5(6):489-496. <http://dx.doi.org/10.5527/wjn.v5.i6.489>
12. Fram D, Okuno MF, Taminato M, et al. Risk factors for bloodstream infection in patients at a Brazilian hemodialysis center: a case-control study. *BMC Infect Dis*. 2015; 15:158. <http://dx.doi.org/10.1186/s12879-015-0907-y>
13. Reunes S, Rombaut V, Vogelaers D, et al. Risk factors and mortality for nosocomial bloodstream infections in elderly patients. *Eur J Intern Med*. 2011; 22(5):e39-44. <http://dx.doi.org/10.1016/j.ejim.2011.02.004>
14. Ma HY, Hung IC, Huang YH, et al. Prognostic factors of health care-associated bloodstream infection in adult patients ≥40 years of age. *Am J Infect Control*. 2018; 46(1):111-114. <http://dx.doi.org/10.1016/j.ajic.2017.07.003>
15. Kaye KS, Marchaim D, Chen TY, et al. Effect of nosocomial bloodstream infections on mortality, length of stay, and hospital costs in older adults. *J Am Geriatr Soc*. 2014; 62(2):306-11. <http://dx.doi.org/10.1111/jgs.12634>
16. Alberti C, Brun-Buisson C, Burchardi H, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med*. 2002; 28(2):108-21. <http://dx.doi.org/10.1007/s00134-001-1143-z>
17. Nelson RE, Samore MH, Jones M, et al. Reducing time-dependent bias in estimates of the attributable cost of health care-associated methicillin-resistant *Staphylococcus aureus* infections: a comparison of three estimation strategies. *Med Care*. 2015; 53(9):827-34. <http://dx.doi.org/10.1097/MLR.0000000000000403>
18. Becker K, Heilmann C, Peters G. Coagulase-negative staphylococci. *Clin Microbiol Rev*. 2014; 27(4):870-926. <http://dx.doi.org/10.1128/CMR.00109-13>
19. Kolonen A, Sinisalo M, Huttunen R, et al. Bloodstream infections in acute myeloid leukemia patients treated according to the Finnish Leukemia Group AML-2003 protocol - a prospective nationwide study. *Infect Dis (Lond)*. 2017; 49:799-808. <http://dx.doi.org/10.1080/23744235.2017.1347814>
20. Hashem AA, Abd El Fadeal NM, Shehata AS. In vitro activities of vancomycin and linezolid against biofilm-producing methicillin-resistant staphylococci species isolated from catheter-related bloodstream infections from an Egyptian tertiary hospital. *J Med Microbiol*. 2017; 66(6):744-52. <http://dx.doi.org/10.1099/jmm.0.000490>