DOI: 10.7860/JCDR/2019/36391.12793

Original Article

Internal Medicine Section

Evaluation of Treatment Responses and Failures of Intensive Care Unit Acquired Blood Stream Infections

ÜMMÜGÜLSÜM GAYGISIZ[1], DILEK ARMAN[2]

ABSTRACT

Introduction: Blood Stream Infections (BSI) are the second or the third most common infections acquired in Intensive Care Units (ICU) following pulmonary infections. Risk factors likely to affect response to treatment in BSI's have been investigated in several studies. However, there have not been any studies in which the predictors of treatment failures have been evaluated to this extent.

Aim: To investigate the treatment response of patients admitted to the ICU with acquired BSI cases and the predictors of treatment failures.

Materials and Methods: The study was based on a cohort study design in which data were collected from all patients with admission to ICU >48 hours during one year. According to the resolution of signs and symptoms of infection, treatment outcomes (n=70) were stratified into two cohorts: 1) successful (n=20); and 2) failure (n=50) treatment. Following risk factors affecting the responses were recorded: source and severity of bacteraemia; Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores; isolated pathogens and resistance profile; appropriate antibiotic initiation; and catheter removal time. Fisher exact tests, contingency coefficients, t-tests, Mann-Whitney-U-test and logistic regression analysis was used to examine risk factors associated with treatment failure predictors.

Results: The high levels of APACHE II detected on the third day of the treatment (OR=1.151) and delayed appropriate treatment with respect to the onset of bacteraemia (OR=1.532) were independent risk factors for treatment failure. The subgroup analyses revealed that other concomitant infections (78%) and superinfection (40%) were the most frequent reasons in the treatment failures.

Conclusion: Delayed appropriate treatment was found to be the most crucial independent reason for treatment failure. Besides, other concomitant infections and superinfection are mostly observed other significant reasons for treatment failure.

Keywords: Cohort study, Critical care, Mortality, Sepsis, Treatment failure

INTRODUCTION

Blood Stream Infections (BSI) are the second or the third most common infections acquired in ICU following pulmonary infections. They have an incidence rate of 4.4%-28.7% [1-4]. Mortality from these infections ranges from 14% to 38% [5-7]. Several studies on ICU patients have revealed that BSI increases mortality 1.6-3.2 folds [2,5,8,9]. The factors which have frequently been studied regarding relationships with mortality in BSIs are old age, the severity of the underlying disease, inappropriate antimicrobial treatment, time of initiation of appropriate treatment, type and resistance of the causative agent and sources of BSIs [2,5,9,10].

When BSIs are lethal and appear in patients with severe diseases, management of their treatment becomes even more critical. Early identification of the BSI characteristics is crucial in order to initiate targeted therapeutic strategies as soon as possible to reduce mortality. In order to predict severity or mortality in critically ill patients, the severity of illness scoring systems has been developed. These scoring systems include widely used APACHE II score [11] and the SOFA score [12]. The APACHE II score is calculated from a patient's age and 12 physiological measurements and is designed to be used for measuring the severity of disease for adult patients admitted to intensive care units. The SOFA score, on the other hand, is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems. The SOFA score can be used for predicting the clinical outcomes of critically ill patients. Together with several other indicators, the APACHE II [11] and SOFA [12] scores were used for predicting treatment failures in the present study. Previous studies about bloodstream infections in ICU have focused mostly on specific causative agents or utilised only SOFA or APACHE II scores [9,13]. There have not been any studies in which the predictors of treatment failures have been evaluated in the same extent as in the present study, in which various factors including both SOFA and APACHE II scores as well as several other predictors of treatment failures were included in multivariate analysis. This study aimed to evaluate responses to treatment and predictors of treatment failures in patients with BSIs acquired in ICUs.

MATERIALS AND METHODS

This is a prospective cohort study performed in four different ICUs with a total of 34 beds; i.e., Anesthesia and Reanimation ICU (12 beds), Internal Diseases ICU (9 beds), Neurology ICU (7 beds), and Neurosurgery ICU (6 beds) in the Medical Faculty of Gazi University between October 2010 and October 2011. Approval was obtained from the Ethical Committee on 14 October 2010 (numbered with B-10-0-IEG-0-15-00-01/67444). The patients aged over 18 years, staying in an ICU for at least ≥48 hours, and diagnosed as BSI acquired from an ICU based on the criteria issued by Center of Disease Control and Prevention (CDC) [14] were included in the study. The patients treated for BSI for less than five days were not included in the study. The concepts, items, and measures used in the study are summarised in [Table/Fig-1] [15].

Monitoring of the Clinical Scores

The patients were followed from admission to the ICUs until the end of treatment for the first BSI attack or until the 14th day of treatment when the duration of treatment was extended for various reasons. APACHE II score [11], SOFA score [12], and diagnoses of sepsis, severe sepsis, and septic shock were recorded on admission to the ICUs, retrospectively 48 hours before development of BSI, retrospectively on the day when BSI developed, and on day 3, day 7, and the last day of treatment. Diagnoses of sepsis, severe sepsis, and septic shock were made according to definitions determined at "2001 International Sepsis Conference" [16].

Item	Definition
Case	The patients (aged over 18 years and staying in an ICU for at least ≥48 hr) diagnosed as primary or secondary BSI acquired in an intensive care unitbetween October 2010 and October 2011.
Time of onset of BSIs	The date when symptoms were present and the causative agent was isolated from the blood culture
Appropriate empirical treatment	The antibiotic treatment: 1) initiated at the time elapsing from obtaining samples for blood culture till getting results of the microbiological tests (a 24-hour period); and 2) found appropriate according to in-vitro sensitivity tests of the causative agent
Treatment targeting the causative agent	Treatment based on initial results of blood cultures and gram staining or results of blood culture and sensitivity tests
Cure	Disappearance of signs and symptoms of the infection
Successful treatment	Cure or presence of clinical improvement
Treatment failure	Lack of improvement in signs and symptoms or death of a patient from BSI
Breakthrough bacteraemia	Situation when clinical signs and symptoms did not improve or worsened despite receiving an appropriate antibiotic for at least 48 hours; isolation of the same causative agent in the blood cultures
Superinfection	Situation when clinical signs and symptoms did not improve or worsened despite receiving an appropriate antibiotic for at least 48 hours; isolation of a different causative agent in the blood cultures
Resistance development	Situation when clinical signs and symptoms did not improve or worsen despite receiving an appropriate antibiotic for at least 48 hours; the same microorganism hadresistanceto the appliedantibiotics
Death due to BSI	The patients whose symptoms did not improve within seven days of BSI and who did not have any other identifiable cause of death but BSI
Predictors of treatment failures	• Presence of a focus of another infection appearing at the onset of or four days after bacteraemia • Appropriateness of empirical treatment • Breakthrough bacteraemia • Superinfection • Resistance development during treatment • Failure to keep the source of infection under control due to conditions other than antibiotic treatment • Presence of non-infectious conditions imitating infection • Deaths due to BSI
Duration of the treatment and the onset day of BSI	Duration of treatment targeting the causative agent and time of initiation of appropriate treatment based on the onset of BSI (day 0)
Microbiological response	Lack of isolation in blood culture specimens collected at least 48 hours after the initiation of treatment for BSI
Comorbidity	The presence of one or more additional diseases or disorders co-occurring with a primary disease or disorder
Charlson comorbidity index	A sum score which predicts the one-year mortality for a patient who may have a range of comorbid conditions (a total of 22 conditions) [15]
Immunosuppression	Partial or complete suppression of the immune response

[Table/Fig-1]: Definitions of the measures and concepts used in the study [15].

STATISTICAL ANALYSIS

Data were analysed with SPSS.15.0. Kolmogorov Smirnov test was used to determine whether collected data were normally distributed. Normally distributed continuous scores were analysed with t-test and data non-normally distributed were analysed with Mann-Whitney U test. Data about categorical variables were analysed with Fisher's-exact test or contingency coefficient. The variables found to be significant in univariate analyses were included into the logistic regression analysis.

RESULTS

Characteristics of the blood stream infection sample: Success and failure groups; The study included 70 patients. Treatment was successful in 20 patients (28.6%) (success group), but it failed in 50 patients (71.4%) (failure group). Of 20 patients treated successfully, 11 (55.0%) had a cure for BSI and 9 (45.0%) had clinical improvement.

The univariate tests results (t-test or Fisher-exact tests) for differences between the "successful" and "failed" treatment groups can be seen in [Table/Fig-2]. In addition to the t-tests for means and Fisher-exact tests for 2×2 tables listed in [Table/Fig-2], the contingency coefficient was calculated for the causative agents or sources and the primary foci of the infection (infection in urinary, respiratory, cardiovascular, gastrointestinal or in intra-abdominal system, or infection related to prosthesis or implant), The characteristics of the BSI observed in the sample are listed in [Table/Fig-3]. There were statistically significant differences in neither in causative agents/sources (p=0.816) nor in the primary foci of the infection (p=0.725) between success and failure groups. Median test (Mann-Whitney-U test) results for APACHE II and SOFA score are presented in [Table/Fig-4,5].

Variables	Successful treatment	Failed treatment	p-value
Sex (n and % of men)	7 (35%)	27 (54%)	0.190[a]
Age	65.35	61.58	0.405[b]
Days elapsed between the appearance of BSI and initiation of an appropriate treatment	0.94	2.35	0.037[b]
Number of comorbidities (mean)	2.60	2.92	0.506[b]
Charlson Comorbidity Index	6.50	6.38	0.739[b]
Immunosuppression (%)	15	30	0.239[a]
Time of catheter removal (mean of days elapsed)	4.11	2.00	0.429[b]

[Table/Fig-2]: Difference between "successful treatment" and "failed treatment" groups in terms of selected criteria.
[a]Fisher-exact test of proportions; [b]t-test of means

Item	N (%)
Type of BSI	
Primary (PBSI)	22 (31.4)
Catheter-related (CR-BSI)	25 (35.7)
Secondary (SBSI)	23 (32.9)
Causative agent	
Gram-positive bacteria	
S.aureus	6 (8.6)
CNS (Coagulase Negative Staphylococci)	9 (12.8)
Enterococcus spp.	10 (14.3)
Gram-negative bacteria	
Pseudomonas spp.	4 (5.7)
Klebsiella spp.	9 (12.9)
E.coli	4 (5.7)
Acinetobacter spp.	18 (25.7)
Stenotrophomonas spp.	1 (1.4)
Candida spp.	
Candida albicans	7 (10.0)
Candida nonalbicans (C.tropicalis)	2 (2.9)

[Table/Fig-3]: Characteristics of the BSIs in the sample (n=70).

Time	Successful treatment	Failed treatment	Total	p-value
On admission to ICUs	18.0 (4-29)	18.0 (8-32)	18.0 (4-32)	0.100
48 hours before BSI developed	17.0 (4-26)	21.0 (8-32)	20.0 (4-32)	0.009
On the day BSI appeared	16.5 (7-29)	23.0 (13-33)	22.0 (7-33)	0.002
The 3rd day of treatment	17.0 (7-33)	23.0 (10-46)	22.0 (7-46)	0.002
The 7th day of treatment	17.0 (4-29)	25.5 (12-38)	23.0 (4-38)	0.001
The last day of treatment	17.5 (4-26)	30.0 (15-45)	25.0 (4-45)	0.001

[Table/Fig-4]: APACHE II median scores (range in parentheses).
p-values refer to Mann-Whitney-U test

As [Table/Fig-2] shows, no statistically significant differences between success and failure groups were found in any of the following

Time	Successful treatment	Failed treatment	Total	p-value
On admission to the ICUs	5.5 (1-12)	6.0 (2-13)	6.0 (1-13)	0.502
48 hours before BSI developed	6.0 (1-11)	6 .0 (2-13)	6.0 (1-13)	0.239
The day BSI appeared	6.0 (2-12)	7.0 (3-13)	7.0 (2-13)	0.064
The 3rd day of treatment	5.5 (1-12)	7.0 (2-16)	7.0 (1-16)	0.003
The 7th day of treatment	5.0 (0-13)	8.0 (2-17)	6.0 (0-17)	0.006
The last day of treatment	5.0 (0-14)	12.0 (5-20)	9.0 (0-20)	0.001

[Table/Fig-5]: SOFA median scores (range in parentheses).
p-values refer to Mann-Whitney-U test

variables: age (range: 19-92), gender (48.6% male), number of comorbidities (range: 0-6), presence of immunosuppression (25.7%), Charlson comorbidity index (range: 0-12), nor the time of catheter removal among catheter-related BSI cases (range: 0-4). Statistically significant differences between failure and success groups were found in days elapsed between the appearance of BSI and initiation of appropriate treatment (range: 0-13).

APACHE II and SOFA scores: In the failure group, APACHE II score was significantly higher 48 hours before the BSI development, on the day of BSI development, on day 3, and day 7, and the last day of treatment [Table/Fig-4]. SOFA score was significantly higher on day 3, on day 7, and the last day of treatment [Table/Fig-5].

Clinical changes in bacteraemia: On the day of BSI initiation, 10 patients (20%) had severe sepsis, and seven patients (14%) had a septic shock in the failure group, and three patients (15%) had severe sepsis, and one patient (5%) had a septic shock in the success group. On the third, the seventh, and the last days of treatment, the number of patients with severe sepsis were 13 (26%), 11 (28%), and 5 (10%), respectively, and the number of patients with septic shock were 9 (18%), 6 (15%), and 32 (64%), respectively, in the failure group. In the success group, only one patient (5%) had a septic shock on the third day of treatment, and the other patients had neither severe sepsis nor septic shock on the third, the seventh, or the last days of treatment.

Microbiological response: After 48-hours of appropriate treatment, the control blood culture was taken from 11 (55%) patients in the successful treatment group, and all of them (100%) had a microbiological response. In the failed treatment group, a microbiological response was present in 17 (40%) of 42 (84%) patients who were taken a control blood culture from. Of the 25 (60%) patients without a microbiological response, 5 (20%) had breakthrough bacteraemia, 14 (56%) had a superinfection, and 6 (24%) had both breakthrough bacteraemia and superinfection. In the remaining 17 patients from whom blood culture could not be taken (24%), the microbiological response was obscure.

Predictors of the treatment failure: Predictors of the treatment failure in the failure group are presented in [Table/Fig-6]. Presence of another infection focus (79%), and superinfection development (40%) were the most frequently observed conditions [Table/Fig-6].

Predictor	N	%
Presence of a coexisting infection focus	38	76.0
Selection of an inappropriate empirical treatment	8	16.0
Breakthrough bacteraemia	11	22.0
Superinfection	20	40.0
Development of resistance during treatment	0	0.0
Failure to keep the infection focus under control due to conditions other than antibiotic treatment	11	22.0
Misdiagnosis (e.g., drug fever, DVT)	0	0.0
Death from BSI	1	2.0

[Table/Fig-6]: Occurrence of predictors of treatment failure among the failure group.

Effects of initial treatment approach on treatment outcome: Of 70 cases of BSI, 40 (57%) were given empirical treatment, and 30 (43%) were given treatment directed towards the causative agent [Table/Fig-7]. All inappropriate treatments initiated in the failure group (16%) were related to the fact that the causative agents were resistant.

Treatment	Success group N=20 (100%)	Failure group N=50 (100%)	Total N=70 (100%)	p-value
Appropriate empirical treatment	13 (65.0%)	18 (36.0%)	31 (44.3%)	0.027
Inappropriate empirical treatment	1 (5.0%)	8 (16.0%)	9 (12.9%)	0.430
Treatment targeting the causative agent	6 (30.0%)	24 (48.0%)	30 (42.9%)	0.169

[Table/Fig-7]: Selection of initial treatment and its effects on treatment outcome.
p-values refer to Fisher's-exact test

Effects of causative agents on the selection of initial treatment: Significantly higher rates of BSI with *S.aureus* were found with empirical treatment (p=0.027), and significantly higher rates of BSI with *Candida spp*. were found with treatment targeting the causative agent (p=0.016).

Multivariate analysis: Data were analysed with logistic regression analysis. Age, gender, and the variables found to be significant [Table/Fig-2] in addition to SOFA and APACHE II scores were included in the analysis. The results of the logistic regression analysis are listed in [Table/Fig-8].

	B	Wald test	p-value	Odds ratio	95% CI
Age	-0.038	2.905	0.088	0.963	0.922-1.006
APACHE II scores on the third day of treatment	0.141	6.855	0.009	1.151	1.036-1.280
Delay in appropriate treatment (days)	0.427	4.554	0.033	1.532	1.035-2.267

[Table/Fig-8]: Results of the logistic regression analysis.

According to the results, the rate of treatment failure was 1.15 times higher in the patients with higher APACHE II scores on the third day of treatment and 1.53 times higher in the patients more prolonged time elapsing from the onset of BSI to initiation of appropriate treatment.

DISCUSSION

In this study, the patients were evaluated in two aspects. First, the success and treatment groups were compared regarding factors likely to influence treatment outcomes. Results showed that higher APACHE II scores on the second day of treatment increased treatment failure by 1.15 times and that the longer time elapsing from the onset of BSI to the initiation of appropriate treatment increased treatment failure by 1.53 times. Second, the analyses showed that the presence of a concurrent infection focus and super infection were the most frequent predictors of treatment failure.

Several studies have investigated when the disease severity should be measured to reveal the real contribution of BSI to mortality in ICUs. Studies have shown that presence of severe disease on admission to the ICU [2,17-20]; on the day when BSI developed [9,13,21,22]; and 24-hours before BSI development [23,24] increase mortality. Based on their meta-analysis of 51 studies, McGregor JC et al., concluded that the optimal time to measure the severity of illness is immediately before the actual onset of BSI while they also recommended that most appropriate time should be 48-hours before the index blood sample is obtained for culture [25]. Another meta-analysis recommended that data should be obtained on admission to the ICU and 24 hours before BSI development [26]. The present authors recorded APACHE II and SOFA scores on the admission to the ICUs, 48-hours before the onset of BSI, and on the 2nd day of BSI development. Also, APACHE II and SOFA scores were calculated on the 3rd, the 7th, and the last days of treatment,

which has not been done in earlier studies. According to the results, APACHE II and SOFA scores on admission to the ICUs did not significantly differ between the success and the failure groups, which is in line with the literature [5,27]. However, the failure group had higher APACHE II scores 48 hours before the onset of BSI and on the day when BSI developed compared to the success group. This suggests that the patients failing to respond to treatment had a more severe disease 48 hours before BSI development. In this group, APACHE II and SOFA scores on the 3rd, the 7th, and the last days of treatment were also higher. The results show that the APACHE II scores can be more indicative than the SOFA scores on the 3rd day of treatment.

The selection of appropriate empirical treatment at the onset of BSI reduces mortality [18,28-30]. Consistent with the literature, the rate of initiation of appropriate empirical treatment was significantly higher in the success group in this study [18,28-30]. Not only the effects of selection of appropriate treatment but also the time of initiation of the treatment on mortality has been studied. Garrouste-Orgeas M et al., found that late initiation of the treatment increased the mortality by 2.6 times [5]. The critical time elapsing from collection of blood culture specimens to initiation of appropriate treatment was reported to be 52 hours by Lodise TP et al., and 72 hours by Anderson DJ et al., [31,32]. In the present study, longer duration increased treatment failure by 1.53 times. The current study showed that the day when BSI developed, and the following day were critical to institute appropriate treatment.

The type of causative agent was found to be important in the early initiation of appropriate treatment. The BSI cases due to *S.aureus* were subjected to empirical treatment more frequently while cases with *Candida* were subjected more frequently to the treatment targeting causative agents. This suggests that infections due to *S.aureus* had a more noticeable clinical onset and, thus, they were more frequently treated with empirical antibiotics whereas those due to *Candida* species had a less overt clinical course and, consequently, were treated with antibiotics targeting causative agents. Moreover, it has been emphasised that the presence of a resistant causative agent causes selection of an inappropriate empirical treatment leading to late initiation of an appropriate treatment [33].

In the current study, the most common three predictors of treatment failure were the presence of a concurrent infection focus, superinfection, and the inability to bring the infection focus under control due to conditions other than antibiotic therapy, and breakthrough bacteraemia. Presence of a concurrent infection focus and superinfection increased the likelihood of treatment failure. Development of infection in more than one focus is not uncommon in ICU patients. In a study by Meduri GU et al., on causes of fever and pulmonary infiltration in ICU patients, 82% of the cases had one or more accompanying infection foci, the most common concurrent infections being pneumonia and catheter infection [34]. Temiz E et al., reported that 41.6% of the cases with a catheter-related urinary tract infection had an accompanying disease [35]. In the present study, 76% of the patients in the failure group had a concurrent infection focus, and BSI was most frequently accompanied by respiratory system infection followed by urinary tract infection. It should always be kept in mind that patients with fever and central venous catheters can have CR-BSI.

LIMITATION

Firstly, the study period was limited to 12 months and four different ICUs in one hospital. Due to these constraints, the sample included 70 patients. With more extended period for data collection and inclusion of more hospitals into the study, the sample size could have been increased. Large sample size would have provided more variation in the cases and allowed more detailed analyses. On the other hand, a longer time period and a larger number of hospitals could have increased the bias caused by hospital-related factors like differences in workload and clinical practices. Similarly, long observation periods lasting several years can lead to unwanted variance in the data, since clinical practices, treatment procedures, and other hospital-related factors tend to change as time passes. Secondly, the findings may not be directly generalisable to different ICUs and hospitals worldwide or even in Turkey. In future studies, a larger sample of hospitals could be included, which would allow us to investigate variation among different hospitals and ICUs.

CONCLUSION

The most important independent variable which had an influence on treatment failure in cases of BSI is the late institution of appropriate treatment. High APACHE II scores detected on the 3rd day of treatment can be a warning about treatment failure. Besides, one of the predictors of treatment failure was the presence of other infections or superinfection. Therefore, careful follow-up of ICU patients and enhanced compliance with precautions of infection control are essential for the detection of multiple infection foci and superinfection.

REFERENCES

[1] Colpan A, Akinci E, Erbay A, Balaban N, Bodur H. Evaluation of risk factors for mortality in intensive care units: a prospective study from a referral hospital in Turkey. American Journal of Infection Control. 2005;33(1):42-47.

[2] Prowle JR, Echeverri JE, Ligabo EV, Sherry N, Taori GC, Crozier TM, et al. Acquired bloodstream infection in the intensive care unit: incidence and attributable mortality. Critical Care (London, England). 2011;15(2):R100.

[3] Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302(21):2323-29.

[4] Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006;34(2):344-53.

[5] Garrouste-Orgeas M, Timsit JF, Tafflet M, Misset B, Zahar JR, Soufir L, et al. Excess risk of death from intensive care unit-acquired nosocomial bloodstream infections: a reappraisal. Clin Infect Dis. 2006;42(8):1118-26.

[6] Rello J, Ricart M, Mirelis B, Quintana E, Gurgui M, Net A, et al. Nosocomial bacteraemia in a medical-surgical intensive care unit: epidemiologic characteristics and factors influencing mortality in 111 episodes. Intensive Care Medicine. 1994;20(2):94-98.

[7] Valles J, Ferrer R. Bloodstream infection in the ICU. Infect Dis Clin North Am. 2009;23(3):557-69.

[8] Bueno-Cavanillas A, Delgado-Rodriguez M, Lopez-Luque A, Schaffino-Cano S, Galvez-Vargas R. Influence of nosocomial infection on mortality rate in an intensive care unit. Crit Care Med. 1994;22(1):55-60.

[9] Pratikaki M, Platsouka E, Sotiropoulou C, Vassilakopoulos T, Paniara O, Roussos C, et al. Risk factors for and influence of bloodstream infections on mortality: a 1-year prospective study in a Greek intensive-care unit. Epidemiology and Infection. 2009;137(5):727-35.

[10] Corona A, Bertolini G, Lipman J, Wilson AP, Singer M. Antibiotic use and impact on outcome from bacteraemic critical illness: the BActeraemia Study in Intensive Care (BASIC). J Antimicrob Chemother. 2010;65(6):1276-85.

[11] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.

[12] Vincent J-L, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996 Jul;22(7):707-10.

[13] Routsi C, Pratikaki M, Sotiropoulou C, Platsouka E, Markaki V, Paniara O, et al. Application of the sequential organ failure assessment (SOFA) score to bacteremic ICU patients. Infection. 2007;35(4):240-44.

[14] Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988 Jun;16(3):128-40.

[15] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases. 1987;40(5):373-83.

[16] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Critical care Medicine. 2003;31(4):1250-56.

[17] Blot S, Cankurtaran M, Petrovic M, Vandijck D, Lizy C, Decruyenaere J, et al. Epidemiology and outcome of nosocomial bloodstream infection in elderly critically ill patients: a comparison between middle-aged, old, and very old patients. Critical Care Medicine. 2009;37(5):1634-41.

[18] Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest. 2000;118(1):146-55.

[19] Laupland KB, Kirkpatrick AW, Church DL, Ross T, Gregson DB. Intensive-care-unit-acquired bloodstream infections in a regional critically ill population. The Journal of Hospital Infection. 2004;58(2):137-45.

[20] Renaud B, Brun-Buisson C. Outcomes of primary and catheter-related bacteraemia. A cohort and case-control study in critically ill patients. Am J Respir Crit Care Med. 2001;163(7):1584-90.

[21] Garnacho-Montero J, Aldabo-Pallas T, Palomar-Martinez M, Valles J, Almirante B, Garces R, et al. Risk factors and prognosis of catheter-related bloodstream infection in critically ill patients: a multicenter study. Intensive Care Medicine. 2008;34(12):2185-93.
[22] Valles J, Leon C, Alvarez-Lerma F. Nosocomial bacteraemia in critically ill patients: a multicenter study evaluating epidemiology and prognosis. Spanish Collaborative Group for Infections in Intensive Care Units of Sociedad Espanola de Medicina Intensiva y Unidades Coronarias (SEMIUC). Clin Infect Dis. 1997;24(3):387-95.
[23] Osih RB, McGregor JC, Rich SE, Moore AC, Furuno JP, Perencevich EN, et al. Impact of empiric antibiotic therapy on outcomes in patients with Pseudomonas aeruginosa bacteraemia. Antimicrob Agents Chemother. 2007;51(3):839-44.
[24] Retamar P, Portillo MM, Lopez-Prieto MD, Rodriguez-Lopez F, de Cueto M, Garcia MV, et al. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. Antimicrob Agents Chemother. 2012;56(1):472-78.
[25] McGregor JC, Rich SE, Harris AD, Perencevich EN, Osih R, Lodise TP, Jr., et al. A systematic review of the methods used to assess the association between appropriate antibiotic therapy and mortality in bacteremic patients. Clin Infect Dis. 2007;45(3):329-37.
[26] Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother. 2010;54(11):4851-63.
[27] Kim PW, Perl TM, Keelaghan EF, Langenberg P, Perencevich EN, Harris AD, et al. Risk of mortality with a bloodstream infection is higher in the less severely ill at admission. Am J Respir Crit Care Med. 2005;171(6):616-20.
[28] Falagas ME, Kasiakou SK, Rafailidis PI, Zouglakis G, Morfou P. Comparison of mortality of patients with Acinetobacter baumannii bacteraemia receiving appropriate and inappropriate empirical therapy. The Journal of Antimicrobial Chemotherapy. 2006;57(6):1251-54.
[29] Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Intern Med. 1998;244(5):379-86.
[30] Zaragoza R, Artero A, Camarena JJ, Sancho S, Gonzalez R, Nogueira JM. The influence of inadequate empirical antimicrobial treatment on patients with bloodstream infections in an intensive care unit. Clinical microbiology and infection. 2003;9(5):412-18.
[31] Lodise TP, Jr., Patel N, Kwa A, Graves J, Furuno JP, Graffunder E, et al. Predictors of 30-day mortality among patients with Pseudomonas aeruginosa bloodstream infections: impact of delayed appropriate antibiotic selection. Antimicrob Agents Chemother. 2007;51(10):3510-15.
[32] Anderson DJ, Engemann JJ, Harrell LJ, Carmeli Y, Reller LB, Kaye KS. Predictors of mortality in patients with bloodstream infection due to ceftazidime-resistant Klebsiella pneumoniae. Antimicrob Agents Chemother. 2006;50(5):1715-20.
[33] Blot S, Vandewoude K, De Bacquer D, Colardyn F. Nosocomial bacteraemia caused by antibiotic-resistant gram-negative bacteria in critically ill patients: clinical outcome and length of hospitalization. Clinical infectious diseases. 2002;34(12):1600-06.
[34] Meduri GU, Mauldin GL, Wunderink RG, Leeper KV, Jr., Jones CB, Tolley E, et al. Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. Chest. 1994;106(1):221-35.
[35] Temiz E, Piskin N, Aydemir H, Oztoprak N, Akduman D, Celebi G, et al. Factors associated with catheter-associated urinary tract infections and the effects of other concomitant nosocomial infections in intensive care units. Scand J Infect Dis. 2012;44(5):344-49.

PARTICULARS OF CONTRIBUTORS:
1. Department of Anesthesiology and Intensive Care, Erzurum Regional Training and Research Hospital, Erzurum, Turkey.
2. Department of Infectious Diseases and Clinical Microbiology, Medical Park Hospitals, Istanbul, Turkey.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Ummügülsüm Gaygsz,
atatürkmah. Çat Yolu cad-25040, Erzurum, Turkey.
E-mail: gulumgay@yahoo.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Mar 15, 2018**
Date of Peer Review: **May 28, 2018**
Date of Acceptance: **Feb 25, 2019**
Date of Publishing: **Apr 01, 2019**