Journal of Nursing and Care

Guimarães et al., J Nurs Care 2017, 6:2
DOI: 10.4172/2167-1168.1000391

Research Article OMICS International

Bloodstream Infection: The Influence of Risk Factors, Etiology and Antimicrobial Therapy on Mortality Rates

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Received date: March 04, 2017; **Accepted date:** April 13, 2017; **Published date:** April 21, 2017

Abstract

Introduction: Inappropriate initial antimicrobial therapy leads to higher mortality in patients with bloodstream infection. This study aimed to evaluate the relationship between risk factors, etiology and antimicrobial therapy on mortality rates of patients with bloodstream infection.

Methods: Between January 2016 to December 2016, 167 patients with bloodstream infection were prospectively evaluated according to the presence or absence of inappropriate antimicrobial therapy of infection. Hospital mortality was the main outcome variable compared between the two study groups.

Results: Infected patients who received inappropriate antimicrobial therapy had statistically more diabetes mellitus, chronic obstructive pulmonary disease, chronic renal disease and death than infected patients who initially received appropriate antimicrobial therapy. Loading dose error and error in starting antimicrobial administration were the most frequently detected error in our study and both were determinant factors related to increased mortality. Initial antimicrobial therapy was maintained, escalation and de-escalation 67.6%, 22.7% and 9.6% of cases, respectively. Coagulase negative staphylococci represented the majority reaching 40.7% and multi-drug resistant microorganisms were detected in 27.3% of infections. There was no observed difference in mortality rates among infections caused by resistant or susceptible microorganisms.

Conclusion: Loading dose error and error in starting antimicrobial administration, were the most frequently detected error in our study and both were determinant factors related to increased mortality. Beside the multiple logistic regression analysis revealed that the delay in starting antimicrobial therapy was the only independent factor that increased mortality.

Keywords: Antimicrobials; Bloodstream infection; Mortality; Intensive care unit; Prescription error

Introduction

Bloodstream infections (BSI) are among the most serious infections acquired by hospitalized patients requiring intensive care [1]. Inappropriate initial antimicrobial therapy leads to higher mortality in patients with BSI [2,3], which are highest in infections due to resistant bacteria [4].

This study intended to evaluate the relationship between risk factors, etiology and antimicrobial therapy on mortality rates of patients with bloodstream infection.

Methods

Study location and patients

The Federal University of Uberlandia Hospital (HC-UFU) is a teaching hospital, with about 520 beds. It is a reference for a public hospital in medium and large standard. The study was prospective, and done in 30 beds Intensive Care Unit (ICU) of the hospital. The ICU serves patients in critical and surgical states. During January 2016 to December 2016, all patients aged ≥ 18 years, who developed bloodstream infection at least 48 h after ICU admission and laboratory-confirmed bloodstream infection were potentially eligible for this investigation and excluded those in which the death occurred within 48 h of ICU admission and patients with incomplete data records. The diagnoses of laboratory-confirmed bloodstream infection were made based on the Centers for Disease Control and Prevention (CDC) guidelines [5].

Bloodstream infection was defined as epidemiologically significant if one or more blood culture was positive with a known pathogen, and at least two blood cultures were positive with the same microorganism taken from blood samples obtained within a 48 h period for the following microorganisms: coagulates-negative staphylococci, *Corynebacterium* sp., *Micrococcus* sp., *Bacillus* sp., *Propionibacterium* sp. or other similar non-pathogenic microorganisms.

This study was approved by the Research Ethics Committee of the Federal University of Uberlandia.

Study design and data collection

We designed a study group, whose intended was to segregate infected patients according to the presence or absence of inappropriate infection antimicrobial therapy. The Hospital mortality was the primary outcome variable compared between the two study groups. Furthermore, throughout the study group was segregated according to the presence or absence of mortality. This was done to identify risk factors for hospital mortality for this group of patients.

With the medical records, it was possible to identify the following characteristics: sex; disease severity based on APACHE II (Acute Physiology and Chronic Clinical Evaluation), a central vein catheter and its duration. The evaluations of patients were made only during their stay in the ICU. The antimicrobial treatment administered in the ICU environment, both prophylactic preoperative antibiotics and antimicrobial empiric treatment of infections suspected evaluated conduit (permanent or exchange) in relation to antimicrobial following microbiological results.

Based on data from the medical records, were possible to obtain details about the prescription and administration of antimicrobial therapy, including de-escalation (discontinuation of antimicrobial treatment or replacement by an antimicrobial with limited spectrum coverage); climbing (adding a new antimicrobial or replacement by a broad spectrum antimicrobial); or maintenance (maintenance initially prescribed antimicrobial or substitution of an antimicrobial with the same profile coverage).

The errors in the prescription were classified as follows: errors in the loading dose (prescribing a higher or lower dose compared to the dose indicated); delayed onset of antimicrobial therapy (more than one hour between prescription and administration of the first antimicrobial dose), dosage (interval between doses higher and lower compared with the doses indicated), incorrect setting of renal function, errors duration of treatment (prescription for more or less days than the indicated period), inappropriate choice (different choice from the literature recommendations), inappropriate adjustment for body weight (in correction dose based on patient weight). To analyze the adequacy of the treatment based on the literature, we used the recommendations of the guidelines for the management and adult health care bloodstream infection [6]. The Sanford Guide to Antimicrobial Therapy used the patterns of decisions on starting time; dose the indicated dose; and adjustments when necessary for the weight and renal function [7]. Error at the start of antibiotic therapy was defined as the Surviving Sepsis Campaign [6] over one hour between the first antimicrobial prescription dose by the attending physician and administration to the patient.

An effective course of antibiotic therapy was judged to be "inappropriate" when it fails in at least one error.

Multidrug-resistant bacteria were defined as bacteria resistant to three or more classes of antimicrobials.

Statistical analysis

All comparisons were unpaired and all significance tests were two tailed. Continuous variables were compared by the test for variables with normal distribution and the sum of Wilcoxon rank test for variables not normally distributed. The χ^2 or Fisher's exact test were used to compare categorical variables. The primary data analysis in comparison infected patients who received inappropriate antibiotic therapy for infected patients receiving appropriate antimicrobial therapy. A second data analysis compared hospital non-survivors to hospital survivors. To determine the relationship between hospital mortality and inappropriate antimicrobial therapy of infection, we used a multiple logistic regression model. Multiple logistic regression analysis was also used to identify independent predictors of mortality in the ICU.

A stepwise approach was used to enter new terms into the logistic regression models where p value less than 0.05 was considered statistically significant. Model over fitting was examined by evaluating the ratio of outcome events to the total number of independent variables in the final models and specific testing for interactions between the independent variables was included in our analyses. All statistical calculations were done using the computer programs Microsoft Excel 2010 and SPSS version 21 for IBM.

Results

A total of 167 consecutive eligible patients were evaluated. The mean age of the patients were 58 years old (ranged from 18 to 92 years), 67.1% were men and 32.9% were women. The hospital stay was on average 28 days. About 50% of patients were admitted to the ICU for a medical diagnosis. One hundred and forty one (84.4%) patients received inappropriate treatment during their stay in the ICU. According to bivariate analysis, infected patients who received inappropriate antimicrobial therapy had statistically more diabetes mellitus (p=0.001), chronic obstructive pulmonary disease (p=0.034), chronic renal disease (p=0.042) and death (p=0.043) than infected patients who initially received appropriate antimicrobial therapy (Table 1). There were no differences in the process of medical care between infected patients receiving inappropriate antimicrobial therapy and infected patients receiving appropriate antimicrobial therapy, according to bivariate analysis. However, it was observed that the infected patients receiving inappropriate antimicrobial therapy about 67% used prophylactic antimicrobials, about 50% used more than three antimicrobials as therapy for infection and length of hospitalization was around 30 days. In general, one hundred percent of patients used central venous catheter (CVC), eighty-two percent of patients have mechanical ventilation (MV) and to have longer duration of central vein catheterization (more than 20 days) (Table 2).

Characteristic	Inappropriate Antimicrobial n=141 N (%)	Appropriate Antimicrobial n=26 N (%)	P value	Survivors n=71 N (%)	Non-survivors n=96 N (%)	P value
Gender, No.						
Male	91 (64.5)	21 (80.8)	0.113	48 (67.6)	64 (66.7)	0.898
Female	50 (35.5)	5 (19.2)		23 (32.4)	32 (33.3)	
Reason for Hospitalization						
Clinic	72 (51.1)	10 (38.5)	0.241	38 (53.5)	44 (45.8)	0.326
Surgical	14 (9.9)	05 (19.9)	0.178	7 (9.9)	12 (12.5)	0.596
Traumatic	24 (17.0)	06 (23.1)	0.462	9 (12.7)	21 (21.9)	0.13
Neurologic	31 (22.0)	05 (19.2)	0.754	17 (23.9)	19 (19.8)	0.519
Comorbidities						
Smoking	31 (22.0)	8 (30.8)	0.152	19 (27.5)	20 (20.4)	0.548
Alcoholism	20 (14.2)	4 (15.4)	0.101	9 (13.0)	15 (15.3)	0.852
Systemic arterial hipertension	62 (44.0)	11 (42.3)	0.89	33 (47.8)	40 (40.8)	0.478
Diabetes mellitus	41 (29.1)	3 (11.5)	0.001*	19 (27.5)	19 (19.4)	0.268
Chronic heart failure	14 (9.9)	4 (15.4)	0.658	9 (13.0)	9 (9.2)	0.332
COPDa	14 (9.9)	1 (3.8)	0.034*	6 (8.7)	8 (8.2)	0.16
Dyslipidemia	6 (4.3)	2 (7.7)	0.874	4 (5.8)	4 (4.1)	0.258
Immunosuppresion	6 (4.2)	1 (3.8)	0.126	2 (2.9)	4 (4.1)	0.269
Chronic renal disease	40 (28.4)	4 (15.4)	0.042*	19 (27.5)	26 (26.5)	0.204
Chronic hepatic disease	15 (10.6)	3 (11.5)	0.785	9 (13.4)	10 (10.2)	0.106
Others[b]	29 (20.6)	5 (19.2)	0.698	17 (24.6)	27 (27.6)	0.635
Mortality	85 (60.3)	11 (42.3)	0.043*	-	-	-

Table 1: Baseline characteristics of the patients, a=COPD: Chronic Obstructive Pulmonary Disease, b=Thyroid disease, arthroses, degenerative diseases, * $P \leq 0.05$ statistically significant.

Variable	Inappropriate Antimicrobial n=141 N (%)	Appropriate Antimicrobial n=26 N (%)	p value	Survivors n=71	Non-survivors n=96	p value
Received corticosteroids, N	6 (4.3)	0 (0.0)	0.999	2 (2.8)	4 (4.2)	0.645
Parenteral Nutrition	13 (9.2)	4 (15.4)	0.69	8 (11.3)	9 (9.4)	0.69
Antibiotic prophylaxis a	95 (67.4)	16 (61.5)	0.563	47 (66.2)	64 (66.7)	0.949
Use of antimicrobial (>3)	69 (48.9)	9 (34.6)	0.183	32 (45.1)	46 (47.9)	0.716
Time of Hospitalization ICU	29.4 (28.9)	23.4 (24.7)	0.323	28.8 (25.0)	28.2 (30.7)	0.896
Central vein catheter (CVC), No	141 (100)	26 (100)	1	71 (100)	96 (100)	1
Duration of	21.4 (23.8)	20.9 (27.4)	0.91	20.7 (23.8)	21.8 (24.8)	0.761
CVC, d						
Urinary tract catheter	116 (82.3)	26 (100)	0.998	61 (85.9)	81 (84.5)	0.783

Nasogastric tube	116 (82.3)	24 (92.3)	0.216	58 (81.7)	82 (85.4)	0.519
Mechanical Ventilation	121 (85.8)	25 (96.2)	0.176	64 (90.1)	82 (85.4)	0.365
Invasive blood pressure	54 (38.3)	9 (34.6)	0.722	23 (32.4)	40 (41.7)	0.223
Drain	29 (20.6)	6 (23.1)	0.773	15 (21.1)	20 (20.8)	0.963

Table 2: Process of care variables*, *Refers to process of care occurring during patients' ICU stay, [a]Administrated in the ICU.

When assessed the antimicrobial prescription errors occurred in patients with bloodstream infection in the use of inappropriate antimicrobials stood out loading dose error (75.8%) and delay in starting antimicrobial therapy (63.1%) (Table 3).

Prescription errors	**N (%)***
Loading dose error	107 (75.8)
Delay in starting antibiotic therapy	89 (63.1)
Dosage	35 (24.8)
Incorrect adjustment for renal function	29 (20.6)
Errors in treatment duration	14 (9.9)
Inappropriate choice	5 (3.5)
Inappropriate adjustment for body weight	2 (1.4)

Table 3: Errors in antimicrobial prescription, * the percentages were calculated based on 141 patients.

The analysis of interference factors in the outcome of patients with bloodstream infection is shown in Table 4. Bivariate analysis of prescription errors revealed significant correlation between prescription errors and death (P=0.042), confirmed by multivariate analysis (P=0.032). Additionally, analysis of the influence of prescription errors on mortality rate revealed significant correlation in loading dose error (P=0.001) and delay in starting antimicrobial therapy (P=0.002). Beside the multiple logistic regression analysis revealed that the delay in starting antimicrobial therapy was the only independent factor that increased mortality (P=0.021). Initial antimicrobial therapy was maintained, escalation and de-escalation 67.6%, 22.7% and 9.6% of cases, respectively.

	Survivors	**Non-survivors**	**Bivariate Analysis P value**	**Multivariate Analysis P value**
	N (%)	**N (%)**		
Prescription errors N=141	55 (39.0)	86 (61.0)	0.042*	0.032*
Loading dose error	27 (49.1)	80 (93.0)	0.001*	0.061
Delay in starting antibiotic therapy	19 (34.5)	70 (81.4)	0.002*	0.021*
Dosage	18 (32.7)	17 (19.8)	0.394	0.159
Incorrect adjustment for renal function	16 (29.1)	13 (15.1)	0.658	0.106
Errors in treatment duration	4 (7.3)	10 (11.6)	0.069	0.142
Inapropriate choice	2 (3.6)	3 (3.5)	0.591	0.152
Inappropriate adjustment for body weight	1 (1.8)	1 (1.2)	0.458	0.155
Initial antimicrobial therapy N=167	69 (41.3)	98 (58.7)	0.078	0.081
De-escalation	3 (4.3)	13 (13.3)	0.061	0.061
Escalation	14 (20.3)	24 (24.5)	0.528	0.196
Maintained	52 (75.4)	61 (62.2)	0.391	0.432

Table 4: Interference factors in the outcome of patients, * $P \leq 0.05$ statistically significant.

And finally, about the microorganisms detected in bloodstream infection, coagulates negative staphylococci represented the majority reaching 40.7% and multi-drug resistant microorganisms were detected in 27.3% of infections. According to the bivariate analysis, there was no observed statistically difference in mortality rates among infections caused by resistant or susceptible microorganisms (Table 5).

Microorganisms	Survivors N (%)	Non-survivors N (%)	P value
N=322	153 (47.5)	169 (52.5)	0.879
Gram-positive			
Staphylococcus coagulase negativa	47 (30.7)	48 (28.4)	0.956
Staphylococcus coagulase negativa MR	13 (8.5)	23 (13.6)	
Staphylococcus aureus	6 (3.9)	13 (7.7)	0.195
Staphylococcus aureus MR	4 (2.6)	5 (3.0)	
Gram-negative			
Acinetobacter baumannii	14 (9.2)	17 (10.1)	0.171
Acinetobacter baumannii MR	9 (5.9)	10 (5.9)	
Pseudomonas aeruginosa	7 (4.6)	11 (6.5)	0.259
Pseudomonas aeruginosa MR	6 (3.9)	6 (3.5)	
Klebsiella pneumoniae	4 (2.6)	4 (2.4)	0.465
Klebsiella pneumoniae MR	3 (2.0)	2 (1.2)	
Escherichia coli	3 (2.0)	4 (2.4)	0.435
Escherichia coli ESBL	2 (1.3)	2 (1.2)	
Fungi			
Candida spp.	16 (10.5)	6 (3.5)	0.092
Others Microorganisms a	3 (2.0)	7 (4.0)	0.261

Table 5: Interference of microorganisms in the outcome of patients, a=*Stenotrophomonas maltophilia* (2) *Enterococcus faecalis* (n=2) *Serratia marcescens* (n=3), *Enterococcus faecalis* (n=1), *Streptococcus beta hemolítico* (2), ESBL=beta-lactamase producing extended spectrum, MR=Multiresistant, * $P \leq 0.05$ statistically significant.

Discussion

Despite the widespread use of antimicrobial therapy in ICUs, few clinical studies have examined the influence of the appropriateness of antimicrobial therapy on patient outcomes. In this study, only the infected patients were examined and showed a statistically significant association between the initial administration of inappropriate infections and hospital mortality antimicrobial therapy for adult patients who require ICU admission. Multiple logistic regression analysis, controlling for potential confounding variables, demonstrated risk of hospital mortality it was bigger among infected patients receiving inappropriate antimicrobial therapy compared with patients who did not possess this risk factor. We also identified that diabetes mellitus; chronic obstructive pulmonary disease and chronic renal disease were statistically associated with the administration of inappropriate antimicrobial therapy. Several studies [1,8] suggest that infected patients with chronic diseases who received inappropriate antimicrobial treatment were significantly more likely to die during their Hospitalization. As also described by Wong et al. [8], the significance of these findings are that they may help to explain, at least in part, the differences in hospital mortality observed between various groups of ICU patients. More importantly, these data could help to improve existing strategies for the treatment of suspected infection among critically ill patients.

Patients with nosocomial bloodstream infections, often have received prior antimicrobial therapy and have prolonged lengths of stay in the hospital, both factors predisposing to colonization and subsequent infection with antimicrobial-resistant [9,10]. Additionally, several studies [11-13] suggest that nosocomial bacteremia due to antimicrobial-resistant pathogens usually occur following previous antimicrobial therapy and are associated with worse patient outcomes. In this series, although antimicrobial prophylaxis, use of more than three antimicrobials and prolonged lengths of stay in the hospital occur more frequently in patients with inappropriate antimicrobial therapy, there was no significant correlation with mortality by multiple logistic regression analysis.

Acquired infections, especially infections initially treated with inappropriate antimicrobial therapy, are associated with an excess mortality above that attributable to patients' severity of illness at the time of ICU admission [14,15]. Loading dose error and error in starting antimicrobial administration were the most frequently detected error in our study and both were determinant factors related to increased mortality. The inappropriate loading dose was probably due to an inability to reach proper antimicrobial concentrations at the target site. The lack of knowledge and attention in the initial administration of higher doses or at shorter intervals were determinants for the development of unfavorable outcomes among these patients. Additionally, the delay in starting antimicrobial therapy probably occurred due to a lack of communication between multidisciplinary teams to immediately administer the antimicrobial as soon as bloodstream infection was diagnosed. The complex system of drug prescription also included other circumstances that contribute to errors, such as lack of attention, excessive workload, lack of communication between teams, and lack of knowledge and training of prescriber physicians. Errors in prescribing antimicrobial agents cause short- and long-term consequences that are not just restricted to individuals: they can lead to not only inappropriate clinical response and increased morbidity and mortality, but also involve the community by contributing to increased bacterial resistance [16]. The increased mortality in patients with delayed start of antimicrobial treatment in this study agreed with other reports emphasizing the relationship between the early administration of antimicrobials and reduced mortality [17,18].

Surviving Sepsis Campaign emphasizes the importance of daily revaluation of antimicrobial therapy. According to the results, culture proliferation assays in order to interrupt the treatment, where possible, to reduce antimicrobial resistance, cost and toxicity [6]. In our study, there was a greater percentage of initial antimicrobial therapy maintained (67.7%), followed by escalation (22.8%) and de-escalation (9.5%). The high maintenance rate of the antimicrobial scheme has been described in the literature [19]. Although the intention of reducing possible antimicrobial resistance, toxicity and costs, the treatment of climbing is even less likely for infections caused by drug-resistant infections, as well as described by Koupetori et al. [20]. Some studies [20,21] have found that mortality rates were significantly reduced after de-escalation of antimicrobial treatment with reduction of super infections, but this was not observed in our study.

Staphylococcus aureus and antimicrobial-resistant Gram-negative bacteria are among the pathogens responsible for bloodstream

infections, which are usually associated with the poorest outcomes [22]. Interestingly, these are the same pathogens most commonly associated with the initial administration of inappropriate antimicrobial therapy in our study. However, no significant correlation with the occurrence of death. The lack of association between bacterial resistance and mortality has also been described in the literature [23] and can be explained by differences between study populations, pre-existing co morbidities, infection severity, and rate of inappropriate empirical treatment.

The limitation of this study is that only the really infected patients were included and not to the whole ICU population where patients often exhibit signs and symptoms of infection that are the consequence of non-infectious causes may be negatively impacted by the overuse of antibiotics. This is demonstrated by Hranjec et al., that showed that patients managed under an aggressive treatment protocol (start of antimicrobial treatment within 12 h of blood culture, without the culture result) had a more rapid start of treatment, a lower chance of receiving initially appropriate treatment, a prolonged duration of antimicrobial treatment and significantly lower survival [24].

Conclusion

In conclusion, this study observed that loading dose error and error in starting antimicrobial administration were the most frequently detected error in our study and both were determinant factors related to increased mortality. Multiple logistic regression analysis revealed the delay in starting antimicrobial therapy was the only independent factor that increased mortality. Our findings suggest that efforts aimed at reducing the administration of inappropriate antimicrobial therapy could improve patient outcomes.

Conflict of Interest

The authors declare that there is no conflict of interest.

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