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Brief Original Article

Central line-associated bloodstream infection trend in Brazilian adult intensive care units: an ecological study

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Abstract

Introduction: Central line-associated bloodstream infections are the second most frequent infection in intensive care units. It represents an adverse event of significant magnitude, thus threatening the patient safety. The aim of this study was to analyze the historical trend of central line-associated bloodstream infections in patients in intensive care units, the rate of infection, central venous catheter utilization ratio, type of pathogen and their antimicrobial resistance pattern.

Methodology: This ecological study was performed at 42 intensive care units from a state capital of the Midwest region of Brazil. Central line-associated bloodstream infections notifications were collected from two databases, the Municipal Coordination for Patient Safety and Infection Control at Healthcare Services, from 2012-2016, and the FormSUS (National Health System Data Processing Company), from 2014-2016.

Results: The incidence of central line-associated bloodstream infections was high and stationary in the period (incidence rate of 2.3 to 3.2 per 1,000 catheter days, central venous catheter utilization ratio average 56,9%). The most frequent microorganisms were coagulase-negative *Staphylococcus*, *Klebsiella pneumoniae, Acinetobacter* spp. and *Pseudomonas aeruginosa.* Resistance to 3rd and 4th generation cephalosporins and carbapenems were detected among Gram-negative bacteria, and resistance to oxacillin among Gram-positive bacteria.

Conclusions: Central line-associated bloodstream infections incidence rates were high, however the historical trend remained stationary in adult intensive care units. Infections were mostly caused by coagulase-negative *Staphylococcus, K. pneumoniae*, *Acinetobacter* spp. and *Pseudomonas aeruginosa,* including multi-drug resistant organisms. These findings point to the need of educational strategies addressing the adherence to established preventive measures and to the rational use of antimicrobials.

Key words: Bloodstream infections; catheter-associated infection; intensive care unit; antimicrobial drug resistance.

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Introduction

Intensive care unit (ICU) inpatients are at high-risk for healthcare-associated infections due to factors such as their clinical condition, compromised immune system, and the need of invasive procedures. Central line-associated bloodstream infections (CLBSIs) are the second most frequent infection in these units [1,2], with incidence rate ranging from 1.7 to 44.6 per 1,000 catheter days in developing countries, possibly related to different research methods and the peculiarities of the healthcare institutions [3]. This infection is an adverse event of significant magnitude, since it threatens the patient safety, increases the mortality rates and hospital costs [1,4,5]. The mortality rate reported for bloodstream infection in a Brazilian study was higher (40%) [6] than in the US (27%) [7]. Regarding cost, these infections are very expensive to treat, costing up to US$ 39,000 in the US [5] and, approximately, US$ 90,000 in Brazil [4].

Additionally, the emerging antimicrobial resistance phenomenon among clinically important Gram-positive and Gram-negative bacteria, such as those belonging to the ESKAPE group (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species) is a huge challenge for infection prophylaxis and treatment [8]. Therefore, given the benefit of epidemiological evidence for guiding proper empirical treatment, which may reduce the negative impact of CLBSI for patients and hospital services, this study aimed to analyze the temporal trend of CLBSI in adult ICUs, the incidence of laboratory-confirmed CLBSI, the central venous catheter utilization ratio, the pathogens and their antimicrobial resistance patterns.

Methodology

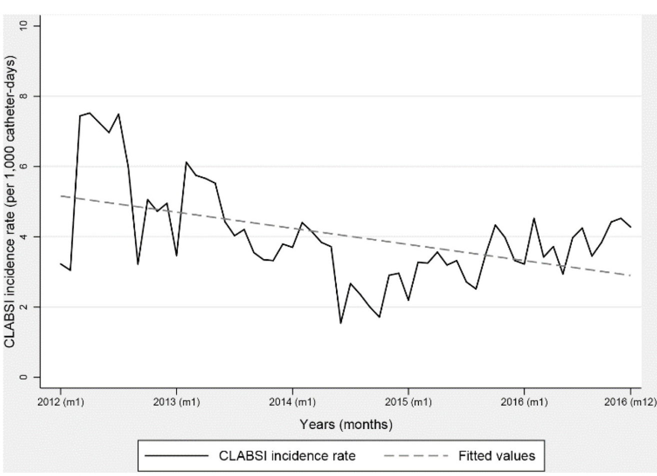
This ecological study was carried out based on CLBSI notifications from 42 adult ICUs located in a state capital of the Midwest region of Brazil.

Data collection

Two databases were used for data collection, the Municipal Coordination for Patient Safety and Infection Control at Healthcare Services (COMCISS), from 2012-2016, and the FormSUS, from 2014-2016, a service provided by the National Health System Data Processing Company (DATASUS) for healthcare-associated infections notification available online. It details the National Information and Informatics Policies, which democratize information and promote transparency in public administration.

All the CLBSI notifications from the adult ICUs were included in this study in order to analyze the temporal trend of infections. Reports identifying microorganisms and their resistance pattern were not available between 2012 and 2013, thus only laboratory-confirmed infections from 2014 onward were included in other analyses performed in this study. Notifications showing repeated, incomplete, or inconsistent data were excluded. The following variables were collected: type of hospital, number of beds, year, number of CLBSI, central venous catheter days, patient days, type of microorganism, and resistance pattern.

Figure 1. Time trend of laboratory-confirmed central line-associated bloodstream infections incidence density at adult intensive care units of a Brazilian state capital, 2012-2016.



CLBSI cases were defined as: bloodstream infection in patients who had used a central venous catheter for more than two days, and were using the central venous catheter on the infection date or had removed it the day before, and the following formula was used to calculate the infection incidence rate [9]:

$$\frac{\text{Absolute number of central line-associated bloodstream infections} \times 1{,}000}{\text{Number of catheter days in the period}}$$

The following formula was used to calculate the central venous catheter utilization ratio [9]:

$$\frac{\text{Number of central venous catheter days } \times 100}{\text{Number of patient days in the period}}$$

Statistical analysis

SPSS 17.0 software was used for descriptive statistical procedures (mean, median, and percentile). CLBSI incidence rate and central venous catheter days were calculated (95% confidence intervals), and associations with a p-value < 0.05 were considered statistically significant. Prais Winsten linear regression model was applied to analyze the temporal trend and CLBSI predictors [10]. Stata 14.0 statistical program was used to perform natural log transformation of CLBSI incidence rate to reduce heterogeneity of residue variance in regression analysis, which was conducted considering the CLBSI incidence rate as dependent variable "Y", and the month as independent variable. Thus, the linear regression equation can be written as follow: $log(Yt) = \beta 0 + \beta 1X$ where: β0 is a constant or intercept, Log (Yt) corresponds to the value, β1 is the linear trend coefficient and X the residual term.

The temporal trend was considered to be increasing, decreasing or stationary. Poisson regression models with robust variance were constructed to determine predictors of CLBSI incidence rate. The model was fit to the variables: year, number of ICU beds, type of hospital, philanthropic institution, and teaching activity.

Ethical aspects

This study was approved by the Ethics Committee of the Clinics Hospital of the Federal University of Goiás (reference number: 1,269,485).

Results

A total of 1,988 healthcare-associated infection notifications were included in this study, and 742 were CLBSI. Most of the ICUs were located at private hospitals (83.3%). From the public services (16.7%), 28.6% of the ICUs were in teaching hospitals. The temporal trend of CLBSI incidence rate was stationary

Table 1. Percentile distribution of the laboratory-confirmed central line-associated bloodstream infections incidence rate and mean number of central venous catheter days (95% CI) at adult intensive care units in a Brazilian state capital, 2014-2016.

Year	No. of hospitals	No of patient days	No. of CLABSI	No of CVC days	CVC utilization ratio*	Rate of CLABSI incidence§	95% CI	Percentile				
								10%	25%	50%	75%	90%
2014	36	160,006	203	88,219	55.13	2.3	2.2-4.5	0	0.68	2.47	5.06	8.24
2015	39	155,317	232	88,118	56.73	2.63	2.2-4.45	0	0.95	2.28	4.3	8.51
2016	41	161,670	307	95,123	58.83	3.22	2.91-5.77	0	1.37	3.02	5.93	11.18
Total	42	476,993	742	271,460	56.91	2.73	2.98-4.4	0	0.95	2.58	5.32	9.48

CLABSI: central line-associated bloodstream infections; CVC: central venous catheter; 95% CI: 95% confidence interval. * Central venous catheter utilization ratio: number of central venous catheter days in the period x 100 / number of patient days in the period; § Laboratory-confirmed central line-associated bloodstream infection incidence rate: absolute no. of CLABSI x 1,000 / no. of patients with catheter days in the period.

(β = -0,006, t-value (significance test) = -1.38, and p = 0,172) (Figure 1).

Although the annual variation in the rate of laboratory-confirmed CLBSI was minor, there was a slight increase in infection incidence from 2.3 (2014) to 3.22 (2016). The percentile distribution of this rate shows an increase in the 90th percentile in 2016, which corresponds to the higher rates. There was no significant variation over time in the central venous catheter utilization ratio (average 56.9%, ranging from 55.13 to 58.83), but there was constant growth (over 50%) during the entire period (Table 1). There was no statistical association between the CLBSI incidence rate and the variables analyzed.

The most frequent pathogens of CLBSI were coagulase-negative *Staphylococcus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter* spp. (Table 2). The highest rates of antimicrobial resistance in 2014 were for *P. aeruginosa* and *Acinetobacter* spp., which were resistant to carbapenems. There was an increase in *Escherichia coli* resistance to 3rd and 4th generation cephalosporins,

Table 2. Distribution of microorganisms notified as etiological agents of laboratory-confirmed central line-associated bloodstream infections in adult intensive care units of a Brazilian state capital, 2014-2016.

Microorganism	N in 2014	%	N in 2015	%	N in 2016	%
Gram-negative						
Acinetobacter spp.[1]	31	14.7	35	13.4	32	10
Enterobacter spp [2]	8	3.8	12	4.6	11	3.4
Escherichia coli	14	6.63	20	7.7	11	3.4
Klebsiella pneumoniae	38	18	43	16.5	54	16.9
Klebsiella oxytoca	-		-		2	0.6
Serratia spp.	8	3.8	9	3.4	14	4.4
Other enterobacteria (*Proteus,Morganella,Citrobacter*)	9	4.3	4	1.5	3	1
Pseudomonas aeruginosa	29	13.8	32	12.2	27	8.4
Burkholderia cepacia complex	-		1	0.4	4	1.2
Stenotrophomonas maltophilia	-		2	0.8	4	1.2
Citrobacter koseri	-		-		1	0.3
Morganella Morganii	-		-		1	0.3
Sphingomonas paucimobilis	-		-		1	0.3
Gram-negative (total)	137	65	158	60.5	165	51.4
Gram-positive						
Staphylococcus aureus	21	9.9	26	10	38	11.9
Coagulase-negative *Staphylococcus*	39	18.5	59	22.6	61	19
S. hominis	-				2	0.7
S. haemolyticus	-		-		4	1.2
S. epidermidis	-		-		4	1.2
S. lugdunensis	-		-		1	0.3
S. caprae	-		-		1	0.3
S. capitis	-		-		1	0.3
Enterococcus spp.[3]	7	3.3	7	2.7	24	7.5
Gram-positive (total)	67	31.7	92	35.3	136	42.4
Fungus						
Candida spp.[4]	7	3.3	11	4.2	20	6.2
Total (all)	211	100	261	100	321	100

[1] *Acinetobacter* spp.: 28 (2016), *Acinetobacter baumannii*: 4 (2016); [2] *Enterobacter cloacae*: 2 (2016), *Enterobacter* spp: 9 (2016); [3] *E. faecalis*: 5 (2014), 6 (2015), 16 (2016), *E. faecium*: 1 (2014), 0 (2015), 4 (2016). *Enterococcus* spp.: 1 (2014), 1 (2015), 4 (2016); [4] *Candida albicans*: 4 (2014), 7 (2015), 10 (2016), *Candida non-albicans*: 3 (2014), 4 (2015), 10 (2016).

while *Enterobacter* spp. exhibited a decline in resistance to 4th generation cephalosporins. Gram-positive bacteria were primarily resistant to oxacillin. Coagulase-negative *Staphylococcus* showed increased resistance to oxacillin, while *S. aureus* demonstrated a declined resistance. The number of antimicrobial-resistant bacteria in 2014, 2015 and 2016 were 138, 150 and 162, respectively. Multiresistant bacteria, those resistant to carbapenems and oxacillin, were also detected (Table 3).

Discussion

A slight decline in CLBSI incidence in ICUs was observed in this study, which also occurred at the national level [11]. Nevertheless, the historical trend was stationary, similar to that observed by the European Center for Disease Prevention and Control [12]. The percentile distribution, the median (50th percentile) and 90th percentile were higher than reported in the US [13].

Laboratory-confirmed CLBSI incidence rate found in this study, 2.73 infections per 1,000 catheter days, was lower than reported in previous studies, which ranged from 2.9 to 19.7 [1,2,14-15]. However, it was higher than the rate in the US, 0.5 per 1,000 catheters days in ICUs [13], and similar to that reported in Europe, 2.4 per 1,000 catheter days [12]. This disparity may be explained by the lack of surveillance legislation; non-compliance with established guidelines; lack of resources; low adherence to hand hygiene; insufficient number of professionals, primarily nurses; and overcrowded hospitals, which are factors that favor the failure of infection preventive measures [14,15].

Central venous catheter utilization ratio in the ICUs was around 56% in this study, similar to the 54% recorded in an investigation conducted in 43 countries, including those from the Latin America [12]. Preventive measures related to insertion, maintenance and removal of catheter has been recommended as measures that substantially contribute to decrease the risk of infection [17,18]. Studies have demonstrated that compliance to CLBSI bundles [18,19] and educational and surveillance measures [20] resulted in reduction in infection rates. Additionally, implementing education, performance feedback, and surveillance of processes and results indicators have improved adherence to infection preventive measures [21].

ESKAPE pathogens were isolated from CLBSI in this study. *K. pneumoniae*, *P. aeruginosa*, *Acinetobacter* spp., and *S. aureus* exhibited a resistance profile to antimicrobials available for infection treatment. Gram-negative bacteria resistant to cephalosporins (3rd and 4th generation) and/or carbapenems, and *S. aureus* resistant to oxacillin were detected in this study, which is similar to findings previously reported [2,15,22]. ESKAPE pathogens have been related to higher mortality rates (2.1%), length of stay (3.3 days), and treatment cost ($5,500) in patients with bloodstream infection compared with patients with non-ESKAPE pathogens in ICU [23].

Coagulase-negative *Staphylococcus*, including those resistant to oxacillin, were the most isolated bacteria from CLBSI in this study. This group of bacteria ise potentially pathogenic to patients with risk factors, such as admission in ICU and use of central venous catheters [24]. Findings of a study performed in

Table 3. Resistance pattern of microorganisms isolated from central line-associated bloodstream infections to antimicrobials in adult intensive care units of a Brazilian capital, 2014-2016.

Pathogen, antimicrobial (ATB)	ATB Resistance in 2014, %	ATB Resistance in 2015, %	ATB Resistance in 2016, %
	N total resistant bacteria = 138	N total resistant bacteria = 150	N total resistant bacteria = 162
Gram-negative			
Enterobacter spp., 4th ceph and carb.	25	16.6	33.3
Enterobacter spp., 4th ceph.	37.5	25	11.1
Escherichia coli, 3rd and/or 4th ceph and carb.	7.1	10	9.1
E. coli, 3rd and/or 4th ceph.	21.4	45	45.4
Klebsiella pneumoniae, 3rd and/or 4th ceph. and carb.	55.3	32.5	48.1
K. pneumoniae, 3rd and/or 4th ceph.	15.8	46.5	33.3
Acinetobacter spp., carb.	80.6	85.7	89.3
Pseudomonas aeruginosa, carb.	82.7	37.5	37
Gram-positive			
Coagulase-negative *Staphylococcus*, oxa.	74.3	78	91.8
S. aureus, oxa.	71.4	38.5	36.8
Enterococcus spp., van.	28.6	0	8.3

4th ceph: 4th generation cephalosporin (cefepime); carb: carbapenems (imipenem and/or meropenem); 3rd and/or 4th ceph: 3rd (ceftriaxone and/or cefotaxime) and/or 4th generation (cefepime) cephalosporins; oxa: oxacillin; van: vancomycin.

a Brazilian hospital, which analyzed oxacillin-resistant coagulase-negative *Staphylococcus* isolated from blood cultures over a period of 20 years, revealed high antimicrobial resistance rates, including reduced susceptibility to vancomycin (2.7%), highlighting the need of rational use of these drugs [25].

The lack of new antimicrobials makes the control and prevention of dissemination of multidrug-resistant microorganisms and the antimicrobial rational use even more urgent, to enable effective treatment of infections [26]. In addition, it is known that acquired resistance to antimicrobials increases hospital costs, overloads health systems, requires more complex treatment, increases hospital stays, and may result in a lack and/or nonexistence of therapies, and death [27]. The lack of adherence to hand hygiene for maintenance and disinfection of catheter hubs may lead to the dissemination of infection-causing microorganisms by healthcare professionals [11]. Thus, infection preventive measures are of the utmost importance, since they promote a reduction of 65% to 70% in infection rates [28]. According to the Centers for Disease Control and Prevention, following government and agency efforts aimed at preventing and controlling healthcare-associated infections, there was a decline of 58% in CLBSI in ICUs in the US [29]. Similarly, a reduction of approximately 54% in this type of infection rate was found after training healthcare professionals for central venous catheter insertion and maintenance [17].

This study has limitations, such as the use of secondary and retrospective data; some of the variables could not be controlled, such as diagnostic criteria, lack of surveillance; and data bank inconsistencies, among others.

In conclusion, the historical trend of CLBSI has remained stable, with high incidence rates in adult ICUs. Coagulase-negative *Staphylococcus*, *K. pneumoniae*, *P. aeruginosa* and *Acinetobacter* spp, including multi-drug resistant bacteria, were the most isolated pathogens. These findings point to the need of educational strategies for the multiprofessional team of ICUs, addressing the adherence to established infection surveillance, preventive measures and the rational use of antimicrobials.

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