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Bloodstream infection in patients with end-stage renal disease in a teaching hospital in central-western Brazil

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ABSTRACT

Introduction: Vascular access in patients undergoing hemodialysis is considered a critical determinant of bloodstream infection (BSI) and is associated with high morbidity and mortality. The purpose of this study was to investigate the occurrence of BSI in patients with end-stage renal disease using central venous catheters for hemodialysis. **Methods**: A cohort study was conducted in a public teaching hospital in central-western Brazil from April 2010 to December 2011. For every patient, we noted the presence of hyperemia/exudation upon catheter insertion, as well as fever, shivering, and chills during hemodialysis. **Results:** Fifty-nine patients were evaluated. Thirty-five (59.3%) patients started dialysis due to urgency, 37 (62.7%) had BSI, and 12 (20%) died. Hyperemia at the catheter insertion site (64.9%) was a significant clinical manifestation in patients with BSI. Statistical analysis revealed 1.7 times more cases of BSI in patients with hypoalbuminemia compared with patients with normal albumin levels. The principal infective agents identified in blood cultures and catheter-tip cultures were *Staphylococcus* species (24 cases), non-fermentative Gram-negative bacilli (7 cases of *Stenotrophomonas maltophilia* and 5 cases of *Chryseobacterium indologenes*), and *Candida* species (6). Among the *Staphylococci* identified, 77.7% were methicillin-resistant, coagulase-negative *Staphylococci*. Of the bacteria isolated, the most resistant were *Chryseobacterium indologenes* and *Acinetobacter baumannii*. **Conclusions:** Blood culture was demonstrated to be an important diagnostic test and identified over 50% of positive BSI cases. The high frequency of BSI and the isolation of multiresistant bacteria were disturbing findings. *Staphylococcus aureus* was the most frequently isolated microorganism, although Gram-negative bacteria predominated overall. These results highlight the importance of infection prevention and control measures in dialysis units.

Keywords: Catheter. Bloodstream infection. Chronic renal patients. Bacteremia. Hemodialysis.

INTRODUCTION

End-stage renal disease (ESRD) is considered a global public health problem[1]. In Brazil, the number of patients with ESRD undergoing renal replacement therapy increased from 42,695 in 2000 to 92,091 in 2010. As many as 90.6% of patients with ESRD receive hemodialysis, and 13.6% of these patients receive non-tunneled catheters[2]. The survival and quality of life of these patients depend on the continued good functioning of dialysis access sites[3]. Bloodstream infection (BSI) is the leading cause of hospitalization and the second most common cause of death among patients receiving regular hemodialysis[4,5].

Controlling infection in these patients is a challenge for healthcare staff because hemodialysis is an invasive procedure with an inherent infection risk. Furthermore, catheters are often manipulated during hemodialysis sessions, and patients receiving hemodialysis are immunodeficient[6].

Primary BSIs are among the most common nosocomial infections. Data suggest that 60% of hospital-acquired bacteremia cases are associated with the use of central venous catheters (CVCs)[7]. Metastatic sites of infection occur frequently and can include endocarditis, vertebral osteomyelitis, spinal epidural abscess, and septic arthritis[8]. Despite the importance of BSIs, few studies have investigated this issue in patients with ESRD in Brazil. Instead, they have mostly focused on microbiological laboratory surveillance, without association of the results with clinical data[9,10].

The isolation of the etiologic agent and determination of antimicrobial susceptibility profile are important for achieving better prognoses. The emergence of multiresistant bacteria is a well-recognized problem. Therefore, surveillance studies are important for the monitoring of the emergence of these microorganisms, especially in immunocompromised patients, such as those undergoing hemodialysis.

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The purpose of this study was to describe BSI in patients with ESRD using CVCs, describe the patients' characteristics, identify the etiologic agents, and analyze the catheter-related variables considered as risk factors for BSI.

METHODS

Study design

This paper reports on a prospective cohort study of 59 patients with ESRD receiving hemodialysis by means of a CVC at a Brazilian tertiary care teaching hospital in the State of Mato Grosso do Sul from April 2010 to December 2011. The principal outcome investigated was BSI.

Data collection and BSI surveillance

Included in the study were patients with ESRD using catheters and recently admitted to the hospital's hemodialysis ward, patients undergoing hemodialysis who lost an arteriovenous fistula (AVF) or a catheter, and patients with implanted tunneled or non-tunneled catheters. The sample included both ESRD inpatients and outpatients. All subjects included in the study were adults and agreed to participate. Individuals in intensive-care units and children were excluded.

Patients were followed up until four months post-catheterization. All CVCs were inserted using aseptic techniques according to the protocol recommended by the Hospital Infection Control Committee.

Data were collected during the hemodialysis sessions. We collected at least two peripheral blood samples from all patients who had signs and symptoms of BSI. Blood was collected in compliance with the criteria of the National Agency of Sanitary Surveillance[11]. The catheter insertion sites were inspected, and blood and/or catheter-tip cultures were monitored. Nursing staff trained in hemodialysis changed the dressings and manipulated the catheters using rigorous aseptic techniques. At the end of each hemodialysis session, the catheter lumens were aseptically locked with heparin. The catheters were not filled with any other thrombolytic agent or antimicrobial solution, and the connectors were not part of a closed access system.

For every patient, we checked for the presence of hyperemia at the catheter site, exudation upon catheter insertion, and symptoms such as fever, shivering, and chills during each hemodialysis session. Demographic, clinical, and laboratory data were collected from medical records and from the hospital's laboratory database.

Empirical systemic antibiotic therapy was initiated whenever the patients developed fever or shivering. Vancomycin and ceftazidime were the first choices for the initiated antibiotic regimen. The regimen was adjusted, if necessary, once the results of blood culture tests became available. The catheter was removed if fever or shivering symptoms persisted for more than 48h. In cases suggestive of BSI, according to medical criteria, the catheter tip was removed and subjected to culture. One week after antibiotic therapy initiation, new blood cultures were collected.

Microbiological tests

Blood cultures were performed in the hospital's microbiology laboratory. The laboratory used a Bactec automated system (Becton Dickinson, Sparks, USA) for blood culture tests and a Vitek2 Compact automated system (BioMérieux, Durham, NC, USA) for the identification of pathogens and antimicrobial susceptibility profiling of blood samples. In cases of blood cultures with the same microorganism for one month or consecutive months, only one agent was considered.

Definitions

Bacteremia and candidemia were defined as clinical signs or symptoms of infection along with at least two blood cultures that tested positive for bacteria or yeasts of the genus *Candida*[12].

Diagnosis of CVC-related BSI was defined as at least one blood culture and catheter tip culture with the same agent, with clinical manifestations of infection and no other apparent source of infection[13].

Bacteria were considered multidrug-resistant when exhibiting resistance to different classes of antimicrobial medications[7].

Hypoalbuminemia was defined as serum albumin levels of less than 3.5g/dL[4].

Statistical analysis

To investigate the possible associations between the study variables, chi-square tests, chi-square tests for trends, and Fisher's exact test were applied, and the relative risks were calculated with 95% confidence intervals. Cox regression analysis was used to estimate the adjusted relative risks using variables with significance levels lower than 20% and those of clinical and epidemiological relevance. BioEstat 5.0 (Sociedade Mamirauá, Belém, Brazil) and Epi Info (version 3.5.3) were used for the statistical analyses[14,15]. Statistical significance was defined as $p \leq 0.05$.

Ethical considerations

Our study was approved by the Research Ethics Committee of the Federal University of Mato Grosso do Sul (permit 1687/2010). All individuals who agreed to participate in the study signed informed consent forms stating that they were freely participating.

RESULTS

Of the 59 patients with ESRD using CVCs for hemodialysis, 30 (50.8%) developed bacteremia, 7 (11.6%) had mixed bacteremia and fungemia, and 22 (37.3%) had no evidence of BSI. The overall infection rate was 62.8% (95% CI, 50.4-75.1%).

The only patient who used a tunneled catheter developed BSI. Among the other 58 patients who used non-tunneled catheters, bloodstream infection developed in 62%.

Of the patient group, 54.2% were female and 44% were older than 60 years. All patients were adults, and their ages ranged

from 23-85 years (median, 58 years). The inpatients comprised 96.7% of the study population. Twelve (20%) patients died during the study period.

The demographic and clinical characteristics of the patients are shown in **Table 1**. Bivariate analysis indicated that the BSI frequency was 1.7 times higher in patients with hypoalbuminemia (76.5%) compared with patients with normal albumin levels. The main signs and symptoms observed in patients with BSI were chills, 35 (94.6%); shivering, 34 (91.9%); and hyperemia at the time of CVC insertion, 24 (64.9%).

In total, 114 CVCs were inserted during the study period, and 111 (97.4%) of these were non-tunneled devices. The catheters were inserted into the right jugular vein in 45% of the catheterizations. None of the variables related to CVC use were associated with the development of BSI (**Table 2**).

With regard to changes in or evolution of vascular access, 31 patients were switched from non-tunneled to arteriovenous catheters, and 16 patients progressed to tunneled catheters.

Thirty-seven patients developed BSI, and 19 (50%) of these patients were catheterized because they lacked an AVF that could be used. In the other patients (50%), the need for urgent hemodialysis required catheterization.

Multivariate analysis revealed no association between BSI in hemodialysis patients and the following variables: hypoalbuminemia ($p = 0.220$; 95% CI $0.75 < RR < 3.44$), gender ($p = 0.368$; 95% CI $0.69 < RR < 2.69$), indication for catheterization (loss, maturation, or awaiting AVF) ($p = 0.670$; 95% CI $0.58 < RR < 2.35$), number of catheter sites ($p = 0.690$; 95% CI $0.54 < RR < 2.54$), length of catheterization (days) ($p = 0.701$; 95% CI $0.99 < RR < 1.01$), and number of hemodialysis sessions ($p = 0.924$; 95% CI $0.96 < RR < 1.04$).

TABLE 1 - Number and percentage of hemodialysis patients according to study variables and occurrence of bloodstream infection.

	Bloodstream infection					
	yes (n = 37)		no (n = 22)		RR	
Variables	n	%	n	%	(95% CI)	p
Gender						
male	20	74.1	7	25.9	1	[b]0,097
female	17	53.1	15	46.9	1.39 (0.94-2.07)	
Age (years)						
23-40	7	63.6	4	36.4	1	[c]0,831
41-60	13	59.1	9	40.9	1.08 (0.61-1.90)	
61-85	17	65.4	9	34.6	0.97 (0.57-1.65)	
Diabetes						
yes	15	57.7	11	42.3	1	[b]0,479
no	22	66.7	11	33.3	0.87 (0.58-1.30)	
Hypoalbuminemia						
yes	26	76.5	8	23.5	1	[b]0,011
no	11	44.0	14	56.0	1.74 (1.08-2.81)	
Recent surgery						
yes	18	62.1	11	37.9	1	[b]0,920
no	19	63.3	11	36.7	0.98 (0.66-1.45)	
Use of corticosteroids						
yes	3	75.0	1	25.0	1	[d]1,000
no	34	61.8	21	38.2	1.21 (0.66-2.22)	
Number of hemodialysis sessions						
< 25	11	55.0	9	45.0	1.14 (0.69-1.88)	
from 25 to 35	11	73.3	4	26.7	0.85 (0.55-1.32)	
> 35	15	62.5	9	37.5	1	[c]0,641

Note: If $p \leq 0.05$, differences are statistically significant. RR: relative risk; [b]Chi-square test; [c]Chi-square test for trend; [d]Fisher's exact test.

TABLE 2 - Number and percentage of patients undergoing hemodialysis according to catheter use and occurrence of bloodstream infection.

	Bloodstream infection					
	yes (n = 37)		no (n = 22)		RR	
Catheter	n	%	n	%	(95% CI)	p
Indication						
arteriovenous fistula[b]	18	75.0	6	25.0	1	[c]0,106
urgency	19	57.6	16	42.4	1.38 (0.94-2.02)	
Difficulties in catheter insertion						
yes	24	66.7	12	33.3	1	[c]0,432
no	13	56.5	10	43.5	1.18 (0.77-1.81)	
Number of sites						
three or more	12	80.0	3	20.0	1	[d]0.078
two	12	63.2	7	36.8	1.27 (0.83-1.94)	
one	13	52.0	12	48.0	1.54 (0.98-2.42)	
Length of catheterization (days)						
≤ 50	14	60.9	9	39.1	1.19 (0.73-1.95)	
51 to 100	15	60.0	10	40.0	1.21 (0.75-1.97)	
> 100	8	72.7	3	27.3	1	[d]0,574

Note: If p≤0.05, differences are statistically significant. When present, the category *no information* was not included in the test calculations. RR: relative risk; [b]Loss, maturation, or awaiting arteriovenous fistula; [c]Chi-square test; [d]Chi-square test for trend.

Table 3 lists the microorganisms isolated from blood and catheter-tip cultures. Of the 124 blood cultures, 65 (52.4%) tested positive. Gram-positive cocci (n = 18; 27.7%) were the most common microorganism observed, and *Staphylococcus aureus* accounted for most of the gram-positive infections. Among the Gram-negative bacteria isolated (n = 28; 43.1%), *Stenotrophomonas maltophilia* was the most prevalent. Six *Candida* species were isolated, the most prevalent of which were *Candida parapsilosis* complex species.

In 10 patients, the same type of microorganism was isolated from the blood and catheter-tip cultures. Among these cultures, the most frequently isolated pathogens were *S. aureus* (6) and the *Burkholderia cepacia* complex (4). There was no significant difference between the prior use of antibiotics and multidrug resistance of microorganisms (p = 0.751; RR = 0.80; 95% CI, 0.26 to 2.48).

Of the 15 *S. aureus* isolates observed in the blood and catheter-tip cultures, only one was resistant to methicillin. Seven out of nine coagulase-negative *Staphylococcus* (CNS) isolates were resistant to this antibiotic. All *S. epidermidis* (n = 7) isolates were resistant to methicillin. Of the 14 enterobacteria isolated, none produced beta-lactamase, and one isolate of *Enterobacter cloacae* was resistant to ertapenem. One of the two *Pseudomonas aeruginosa* isolates was resistant to ceftazidime, cefepime, imipenem, meropenem, ciprofloxacin, and piperacillin-tazobactam. *Acinetobacter baumannii* (3) and *Chryseobacterium indologenes* (5) were among the most resistant Gram-negative bacteria.

DISCUSSION

The prevention and control of bacterial and fungal infections in patients with ESRD receiving hemodialysis via CVCs is a constant concern for health professionals. Although CVCs are an important component in the management of patients with ESRD, these catheters also significantly contribute to BSIs[10].

In the present study, most patients were older than 58 years, a finding that corroborates those of Sesso et al.[2] A previous study[16] conducted in a teaching hospital in Campo Grande indicated that most patients admitted to medical wards with CVC-related complications were older than 60 years. Patients with advanced age tend to be immunologically impaired, and they often have co-existing chronic diseases, such as systemic hypertension and diabetes. We also observed co-existing chronic disease in our patients, and our findings corroborate those of other researchers[17].

To our knowledge, this is the first study in central-western Brazil to describe BSIs in patients with ESRD receiving hemodialysis. The prevalence of BSIs in our group of patients was much higher (62.8%) than that among patients attending a hemodialysis center in Pakistan (25%)[18].

A study by Brito et al.[19] on nosocomial infection in the neonatal intensive care unit of the Uberlândia University Hospital, in Brazil, demonstrated that BSI was the main cause of nosocomial infection (69.3%) and indicated that CVC use was an independent risk factor (p < 0.05) for nosocomial infection.

TABLE 3 - Microorganisms responsible for bloodstream infection in hemodialysis patients.

	Number of blood cultures (n = 65)		Number of catheter-tip cultures (n = 21)	
Microorganism	n	%	n	%
Gram-positive cocci	18	27.7	12	57.1
Staphylococcus aureus	10	15.4	5	23.8
Staphylococcus epidermidis	2	3.1	5	23.8
Enterococcus faecalis	4	6.2	1	4.8
Staphylococcus capitis	1	1.5	-	-
Staphylococcus hominis	1	1.5	-	-
Kocuria kristinae	-	-	1	4.8
Gram-negative bacilli and cocci	28	43.1	10	47.6
Stenotrophomonas maltophilia	7	10.8	-	-
Chryseobacterium indologenes	5	7.7	-	-
Pseudomonas aeruginosa	2	3.1	-	-
Burlkholderia cepacia	3	4.6	2	9.5
Acinetobacter baumanii	-	-	3	14.3
Enterobacter cloacae	4	6.2	3	14.3
Escherichia coli	3	4.6	1	4.8
Aeromomas hydrophila	2	3.1	-	-
Klebsiela pneumonia	1	1.5	-	-
Ralstonia mannitolilytica	1	1.5	-	-
Fungi	6	9.2	-	-
Candida parapsilosis complex	3	4.6	-	-
Candida guilliermondii	2	3.1	-	-
Candida albicans	1	1.5	-	-

Even though previous studies[9,18] reported that prolonged use of CVCs increases the risk of BSI, we observed no evidence to support this claim. In the present study, no association was observed between the long-term use of CVCs and the increased occurrence of BSI. This finding is possibly related to the small number of patients evaluated, methodological difficulties inherent in prospective studies, and specific features of the cohort (type of patients and restricted sample group).

Bivariate analysis revealed that hypoalbuminemia was a significant risk factor for BSI in our patient group. It is well known that hypoalbuminemia is associated with disease severity. Lukowsky et al.[4] observed that during the first 90 days of hemodialysis, one-third of all patient deaths were associated with albumin levels of less than 3.5g/dL. Thus, the identification and treatment of hypoalbuminemia may decrease the risk of infection.

Our results indicated a higher incidence of chills and shivering in patients who developed BSI, which was expected because these symptoms were criteria for blood culture collection. Hyperemia at the site of catheter insertion was suggestive of BSI ($p < 0.05$), corroborating the results of a previous study[20].

In the present investigation, non-tunneled catheters were the most frequently used catheters. Our results suggest that these catheters should be avoided in patients with ESRD due to the associated high risk of infection. We recommend that temporary catheters be replaced as soon as possible with AVFs or arteriovenous grafts. A tunneled CVC should be implanted if this is not possible[18,21].

In our study, the right jugular vein was the most common access route for CVC. This finding is similar to the findings of Jones et al.[22] The jugular vein is the preferred access point for CVCs, as subclavian vein stenosis can be avoided and because the site allows for future preparation of AVFs[21]. Nevertheless, Grothe et al.[23] reported that patients receiving hemodialysis who had CVCs inserted in the jugular vein were 56% more likely to develop BSI than those who had catheters implanted in the subclavian vein.

We also observed that a large percentage of our patients (n = 35; 59.3%) began hemodialysis due to an emergency situation and therefore required CVCs. This finding is similar to the results of other studies[24,25]. We believe that these emergency cases were related to delayed diagnosis of ESRD.

Although blood culture tests are considered the gold standard in the diagnosis of bacteremia and fungemia, previous studies reported variable sensitivity of these tests in detecting these infections and low sensitivity in identifying patients treated with antimicrobials[11,26]. The high (52.4%) percentage of positive blood cultures in our study may be a result of the nature of the population investigated. Patients receiving hemodialysis are most often individuals who present with concomitant chronic illnesses, and they are prone to immunodeficiency.

Similar to the findings of Bevilacqua et al.[27], we observed that Gram-negative bacteria were predominant among the isolates. The infections caused by non-fermenting Gram-negative bacilli, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Chryseobacterium indologenes*, and *Stenotrophomonas maltophilia*, are difficult to treat because they are highly resistant, can cause outbreaks of nosocomial infection, and are often associated with high mortality rates[28,29].

In this study, *Staphylococcus aureus* was the most frequent pathogen observed in blood cultures. Classically, these pathogens are often associated with BSIs because they are part of the skin microbiota. To date, numerous reports have indicated that BSIs associated with *Staphylococcus aureus* are serious and can result in severe metastatic infections such as sepsis, endocarditis, and endophthalmitis[30,31].

BSIs caused by *S. aureus* require aggressive treatment, including catheter removal. In addition, if the infection does not resolve within 72h[30], transesophageal echocardiography should be performed to rule out other potential sources of infection.

The emergence of multidrug-resistant gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative *Staphylococcus* (MRSCN), and vancomycin-resistant *Enterococcus* spp. (VRE), complicates the management of infections caused by these agents[32].

The isolation of *Kocuria kristinae* in the catheter-tip cultures is a rare finding. Dunn et al.[33], previously described a case of severe intravascular infection complicated by septic pulmonary embolus and thrombosis in a patient with hyperemesis gravidarum as a result of this pathogen and the use of parenteral nutrition by a CVC.

Candida yeasts, which are recognized as opportunistic pathogens, gain access to the bloodstream due to skin breakdown and are predominantly found in immunodeficient patients[34]. Non-*albicans Candida* species, such as *Candida parapsilosis*, have emerged as important infectious agents[35]. This pathogen can secrete glycosylated proteins that form biofilms in solution and adhere to plastic materials such as intravascular catheters[36]. Brito et al.[37] reported that *Candida parapsilosis* candidemia is associated with neutropenia, the use of CVCs, and chemotherapy.

Two patients had positive blood cultures for *Candida guilliermondii* for long periods, namely 6 and 12 months. Because of the clinical condition of these patients and the difficulty of establishing new venous access, nephrologists chose not to remove the catheters. Based on a previous study[35], *C. guilliermondii* can be considered an emerging candidemia pathogen in central-western Brazil.

We propose that in a hemodialysis unit a multidisciplinary team should conduct surveillance studies to detect BSIs. To this end, the necessary measures to prevent bacteremia and other complications associated with infection in patients with ESRD can be instituted in a timely manner. Since our study was conducted, one of the measures instituted to reduce the rate of BSI in patients with ESRD is the use of connectors in closed access systems and the exchange of these connectors every seven days. Other measures should also be implemented, such as the training of multidisciplinary teams to specifically take care of CVCs in patients with ESRD. The use of antibiotic seals and thrombolytic agents is also recommended.

In conclusion, it is important to identify which pathogens cause BSIs among patients in hemodialysis units because this information will guide initial therapy[27]. Surveillance studies by multidisciplinary teams are necessary so that appropriate measures can be implemented to prevent bacteremia and other complications associated with infection in patients with ESRD. We observed a high prevalence of Gram-negative, bacteria-related BSIs among our patients with ESRD who received hemodialysis via a CVC.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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