



Hemodialysis catheter-related bloodstream infections: a single-center experience

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ABSTRACT

Introduction: In hemodialysis (HD) patients, catheter-related bloodstream infections (CRBSI) cause significant morbidity and mortality.

Objectives: We analyzed dialysis CRBSI incidence, associated factors, and the spectrum of the causative organisms.

Patients and Methods: Patients aged ≥ 18 years either on maintenance HD or with acute kidney injury having CRBSI (NKF-KDOQI criteria) were included in this prospective observational study and patients with other infections were excluded. Blood, catheter tip culture, and antibiogram were analyzed. All patients were initially treated with antibiotics covering both gram-positive and gram-negative pathogens.

Results: Of 921 catheters (882 patients) included, 212 (23%) had CRBSI, of which 69(32.5%) and 143 (67.5%) had culture-positive probable CRBSI and culture-negative possible CRBSI respectively. 131 (61.8%) were < 60 years, 133 (62.7%) were males, 177 (83.5%) had diabetes, 141 (66.5%) had leukocytosis and 172(81.1%) had positive procalcitonin. In addition, 193 (91%) had uncuffed catheters and 162 (76.4%) had jugular catheters. Our study showed a CRBSI incidence of 13.39/1000 catheter days, median catheter days, and median time to CRBSI was 40 and 17.2 days respectively. 41 (19.3%) catheters were salvaged (with antibiotic administration or guidewire exchange) and 42 (19.8%) had exit site infection. Gram-positive coagulase-negative *Staphylococcus aureus* (CoNS) (n=31; 44.9%) followed by extended-spectrum beta-lactamase (ESBL) enteric gram-negative organisms (n=30; 43.4%) were common isolates and remaining had fungal etiology (n=8; 11.7%). In our study, the mortality rate was 6.6% (n=14).

Conclusion: The incidence of CRBSI was high in our population. In culture-positive cases, gram-positive organisms contributed marginally higher than gram-negative organisms. CoNS and ESBL enteric gram-negative organisms are the commonest isolates. More than two-thirds of patients with CRBSI had diabetes mellitus and leukocytosis at presentation.

Implication for health policy/practice/research/medical education:

This study highlights the importance of varying incidence rates and etiology of catheter-related bloodstream infections (CRBSIs) across centers, use of empirical antibiotics covering both gram-positive and gram-negative organisms, and emphasizes the fact that each center has to audit its CRBSIs microbiological spectrum and modify empirical antibiotics accordingly.

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Introduction

About 81-90 % of end-stage renal disease (ESRD) patients are initiated on hemodialysis (HD) through central venous catheters in the developing world. We cannot argue the role of dialysis catheters as they can be easily inserted and immediately used, however, these HD catheters are

not without problems (1). Besides thrombosis, catheter-related bloodstream infection (CRBSI) is one of the most feared complications. Morbidity, mortality, and healthcare expenses have increased as a result of CRBSI secondary to increasing in sepsis, costs of hospitalizations, changes in catheters, and antibiotic administration (2).

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The mean incidence of CRBSI (per 1000 catheter days) for untunneled and tunneled HD catheters have been reported to be 5.0 episodes (3.8-6.5) and 3.5 episodes (1.6–5.5) respectively. Among untunneled catheters, the infection rate for femoral catheters is the highest (7.6 episodes), followed by internal jugular catheters (5.6 episodes) and least with subclavian catheters (2.7 episodes) (3-6).

Contributory host-related factors are immune deficiency, malnutrition, previous CRBSI, *Staphylococcus aureus* nasal carriage, diabetes, extremes of age, and catheter-related factors are the site of insertion, duration in situ for more than 14 days, barrier precautions, type of catheter, antibiotic lock, multiple lumens, thrombosis, repeated catheterization and increased manipulation (4,7). The spectrum varies by region and center, with gram-positive microorganisms accounting for the majority of cases in India and studies from the United States of America and gram-negative in Europe (8-10).

Objectives

We studied the incidence of CRBSI, associated factors, causative pathogens, and their antibiogram in patients on HD.

Patients and Methods

Study design

This was a prospective observational study conducted from March 2017 to September 2018 at a tertiary care hospital.

Inclusion criteria: All patients aged ≥ 18 years with CRBSI due to venous access inserted for HD as per National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) definition.

Exclusion criteria: Age < 18 years and another documented source for the bloodstream infection.

CRBSI definition

In patients with fever with chills and rigors, unexplained hypotension, and altered sensorium with a normal catheter exit site or tunnel, CRBSI was classified into (11); **Definite:** the same organism should be found from catheter tip culture (> 15 colony forming units per catheter segment) as well as blood culture with no other obvious source of infection.

Probable: symptoms should subside with antibiotic therapy with or without catheter removal and organisms grow only in blood culture with no growth from the catheter tip.

Possible: symptoms subside after antibiotic treatment or after removal of the catheter with no laboratory evidence of bloodstream infection.

Catheter days were counted from the time the catheter was inserted to the time the blood cultures were sent.

CRBSI incidence: defined as the number of episodes/ total catheter days of all catheters (days between insertion and

removal) $\times 1000$. Patients who had their first episode of CRBSI were included; however, repeated catheter insertions in the same patient were not considered.

Diagnosis of CRBSI

Blood cultures and catheter tips for culture were obtained as per the following protocol:

A. Blood cultures: Blood was collected from the dialysis circuit (if symptoms were during dialysis) or a peripheral vein (if symptoms occurred off dialysis) and the dialysis catheter (10 ml each under sterile conditions). They were promptly injected into culture media (BACT/ALERT SA, BioMérieux, Durham, NC, USA).

B. Catheter tip: Skin was cleansed with 70% alcohol followed by catheter removal and the final three inches was cut in a sterile tube and sent to the microbiological laboratory.

Serum procalcitonin was measured by the time-resolved amplified cryptate emission (TRACE) technique (B-R-A-H-M-S PCT™ sensitive KRYPTOR™, Thermo Fisher Scientific, Waltham, MA, USA).

Microbiological methods

Identification of organisms

Gram-negative organisms were identified by growth on triple sugar iron agar, urease testing, citrate consumption, methyl red/Voges Proskauer test, Indole/ hydrogen sulfide detection, and mannitol motility test. Gram-positive cocci were identified using catalase and coagulase assays.

Catheter tip

Endoluminal catheter flush culture and extraluminal Maki's rollover plate method were used.

Antibiogram

Clinical and Laboratory Standards Institute (CLSI) endorsed the Kirby-Bauer disk diffusion method was used.

Management of CRBSI

Empirical antibiotics: The empirical antibiotic policy at our center for the management of CRBSI is intravenous (IV) vancomycin (20mg/kgbw loading dose post-dialysis) and IV ceftazidime (1g post-dialysis). This antibiotic regimen was continued or modified based on the type of organisms and antibiotic sensitivity pattern.

Salvaged catheters: included those which were either retained or exchanged over a guidewire under strict aseptic precautions within 21 days.

Statistical analysis

Analysis was conducted on IBM SPSS statistical software version 20.0 for Windows (SPSS Incorporation, Chicago, Illinois, USA). Data was conveyed as mean for continuous variables and percentage frequency for categorical variables. The chi-square test was applied to analyze any

significant difference between the groups and the *P* value was checked at a 5% level of significance.

Results

Of 921 catheters (882 patients) included, 212 (23%) had CRBSI contributing to 7164 catheter days and the majority were ESRD patients (*n* = 794; 90%) and the remaining had acute kidney injury, rapidly progressive renal failure, or acute on chronic kidney disease.

Of CRBSIs, 69(32.5%) and 143(67.5%) had culture-positive probable CRBSI and culture-negative possible CRBSI respectively (as per NKF-KDOQI criteria

CRBSI incidence rate

The CRBSI incidence rate was 13.39 episodes/1000 catheter days. There were no definite CRBSIs as the dialysis catheter tip cultures were negative for any growth. The incidence rate for culture-positive probable (*n* = 69) and culture-negative possible (*n* = 143) CRBSIs were 4.35 and 9.04 per 1000 catheter days respectively. Median catheter days as a whole was 40 days and the median time to CRBSI was 17.2 days. A total of 41 HD catheters were salvaged and there were 42 cases of dialysis catheter-related exit-site infection during the study (Table 1) (*n* = 212).

CRBSI associated risk factors

Host related

Of 212 CRBSI cases, 133 (62.7%) were males and 81 (38.3%) elderly patients (>60 years). Diabetes mellitus, hypertension, and ischemic heart disease were seen in 177 (83.5%), 152 (71.6%), and 40 (18.9%) respectively (Table 2).

Lab parameters

One hundred forty-one (66.5%), 35 (16.5%) and 25 (11.8%) patients had leukocytosis (>11 000 per mm³) with left shift, leukopenia (<4000 per mm³) and thrombocytopenia (<100 000 per mm³) respectively. Procalcitonin was positive (>0.5 µg/L) in the majority (*n* = 172; 81.1%) of the patients with CRBSI (Table 2).

Catheter-related

Of 212 CRBSI cases, 162 (76.4%) had internal jugular

vein catheters and the remaining femoral vein catheters. 193 (91%) were uncuffed catheters and 171 (80.7%) were double-lumen catheters (Table 2).

Microbiological spectrum and antibiogram of organisms causing CRBSI

Organisms identified were gram-positive in 31 (44.9%), 30 (43.4%) had gram-negative and 8 (11.7%) had fungal (*Candida* species) etiology (Figure 1). Among gram-positive coagulase-negative *Staphylococcus aureus* (CoNS) was the commonest pathogen isolated (*n* = 15; 48.4%) and others were methicillin sensitive and resistant *S. aureus*, and *Enterococcus* (Figure 2). *Klebsiella pneumoniae* was the commonest among gram-negative CRBSIs (*n* = 7; 23.3%), followed by *Escherichia coli*, *Pseudomonas*, *Acinetobacter* and others (Figure 3). The majority of gram-positive organisms isolated were susceptible to the empirical antibiotic administration (Table 3), while the majority of gram-negative organisms were extended-spectrum beta-lactamase (ESBL) generating strains with only a few multidrug-resistant isolates (Table 4).

Mortality

14 cases (6.6%) succumbed to septic shock with multiorgan dysfunction during the study period.

Discussion

Despite high rates of infection and mortality in developing

Table 2. Factors associated with CRBSI

Factors	CRBSI (<i>n</i> = 212)
Host related	
Age	
<60 years	131 (61.7%)
>60 years	81 (38.3%)
Gender	
Males	133 (62.7%)
Females	79 (37.3%)
Comorbidities	
Diabetes mellitus	177 (83.4%)
Hypertension	152 (71.6%)
Ischemic heart disease	40 (18.8%)
Lab parameters	
Leukocytosis (>11 000 per mm ³) with left shift	141 (66.5%)
Leukopenia (<4000 per mm ³)	35 (16.6%)
Thrombocytopenia (<100 000 per mm ³)	25 (11.8%)
Procalcitonin (>0.5 µg/L)	172 (81.1%)
Catheter-related	
Jugular catheters	162 (76.4%)
Femoral catheters	50 (23.6%)
Uncuffed catheters	193 (91%)
Double lumen catheters	171 (80.7%)

Table 1. CRBSI incidence rate

Variables	Catheters	Catheter days	Incidence rate (per 1000 catheter days)
Total	921	15832	
Non-CRBSI	709 (77%)	8668	
CRBSI			
Total	212 (23%)	7164	13.39
Probable	69 (32.5%)	2887	4.35
Possible	143 (67.5%)	4277	9.04

Abbreviation: CRBSI, Catheter-related bloodstream infection.

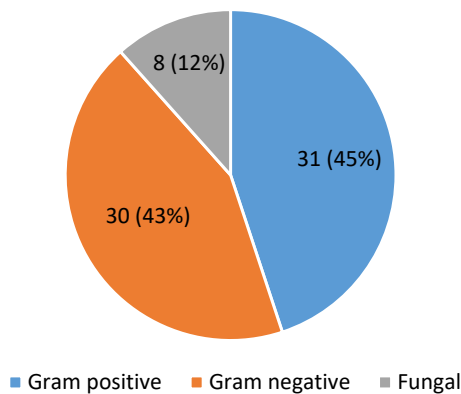


Figure 1. Spectrum of organisms causing CRBSI.

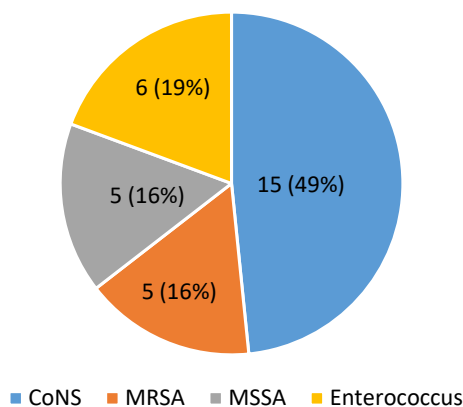


Figure 2. Causative organisms of gram positive CRBSIs.

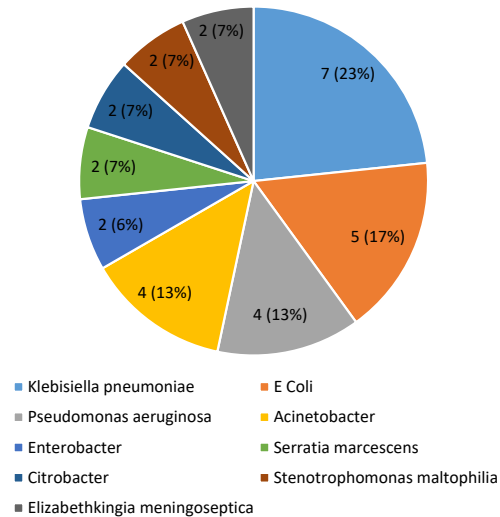


Figure 3. Causative organisms of gram negative CRBSIs.

countries, temporary HD catheters are an essential tool in the majority of ESRD patients while initiating HD due to their low-cost and ease of insertion. For financial and logistic reasons, many patients delay the creation of permanent vascular access with <50% having a working arteriovenous fistula at the time of initiating HD (2, 12). This is similar to our study wherein the majority of cases of CRBSI were ESRD patients who were initiated on HD.

In our study, 212 (23%) had CRBSI, of which 69 (32.5%) were culture-positive probable CRBSIs and 143 (67.5%) had culture-negative possible CRBSIs which is higher when compared to prior studies (15-25%) (2, 5, 11-13). However, this study is similar to a recent Indian study by Sethi et al (12) wherein during the study period of 2 months 74 (61.67%) cases of CRBSI were documented. Among these cases, 46 (62.2%) were definitive/probable CRBSIs and 28 (37.8%) were culture-negative possible CRBS. The possible explanation for such high blood culture positivity is increased recognition and reporting of organisms as legitimate bloodstream infections (as opposed to contaminants) and the frequent use of wide-spectrum antibiotics, which exerts selection pressure on the growth of these causal pathogens.

Our study had no definite case of CRBSI as per NKF-

KDOQI criteria which is similar to the study by Sethi et al (12). This is probably due to changes in temperature during transport to the microbiology laboratory and a varied period before cultures are collected from the catheter tip. The median time to CRBSI was 17.2 days in our study which is lower compared to 24.5 days in the research by Agrawal et al (2). In our study, 41 (19.3%) catheters were salvaged by either antibiotic administration or guidewire exchange.

Our CRBSI incidence rate was 13.39 episodes/1000 catheter days which is higher than other studies which range from 1.6 to 8.5 per 1000 catheter days (14-17). However, this study is identical to the study by Weijmer et al (18) from the Netherlands where an analysis of 272 catheters (11 612 catheter-days and 235 untunneled catheters) reported an incidence rate of 15.6 and 20.2 for untunneled jugular and femoral catheters respectively. The use of NKF-KDOQI criteria for diagnosis rather than the Centers for Disease Control and Prevention (CDC) or the Infectious Diseases Society of America (IDSA) criteria resulted in a greater incidence rate of CRBSI in our study (15). The reference studies for CRBSI use CDC/IDSA criteria which are regarded as stringent, arduous, expensive, and inadequate because quick catheter removal for tip culture is not feasible in developing countries, and most laboratories in our setting do not record differential time to positivity.

Gender did not affect incidence in our study, however unlike this study elderly (>60 years) had a higher chance as also reported in studies by Tao et al (19) and Murea et al (20) wherein patients aged 60 years and older on dialysis had approximately 50% to 60% higher incidence of CRBSI. The reasons mentioned above are possibly due to immunosenescence, atypical symptoms/presentation in the elderly and delayed diagnosis.

A higher occurrence of CRBSI in diabetics was seen in this study which is similar to studies by Nassar and

Table 3. Antibiogram of gram-positive organisms causing CRBSI

Antibiotics	CoNS (n=15)	MSSA (n=5)	MRSA (n=5)	Enterococcus (n=6)
Gentamicin	S	S	R	R
Ceftriaxone	S	R	R	R
Ciprofloxacin/Ofloxacin	S	S	R	R
Oxacillin	S	S	R	R
Doxycycline/Tetracycline	S	S	S	S
Penicillin-G	R	S	R	R
Rifampicin	S	S	R	R
Vancomycin	S	S	R	S
Linezolid	S	S	S	S
Clindamycin	S	S	S	R
Teicoplanin	S	S	S	R

CoNS; Coagulase-negative *Staphylococcus aureus*, MSSA; Methicillin sensitive *Staphylococcus aureus*, MRSA; Methicillin-resistant *Staphylococcus aureus*; S; Sensitive, R; Resistant.

Table 4. Antibiogram of gram-negative organisms causing CRBSI

Antibiotics	<i>Klebsiella</i> (n=7)	<i>E. coli</i> (n=5)	<i>Pseudomonas</i> (n=4)	<i>Acinetobacter</i> (n=4)	<i>Enterobacter</i> (n=2)	<i>Citrobacter</i> (n=2)
Amikacin	S	S	S	S	S	R
Gentamicin	S	S	S	S	S	R
Ampicillin	S	R	R	S	S	R
Ceftriaxone	R	S	R	R	R	S
Cefepime	S	S	S	S	S	S
Ceftazidime	S	R	S	S	R	R
Trimethoprim-sulfamethoxazole	R	R	R	R	S	R
Ciprofloxacin/Ofloxacin	S	S	S	S	S	S
Doxycycline/Tetracycline	S	S	S	S	S	S
Piperacillin-Tazobactam	S	S	S	S	S	S
Cefaperazone-Sulbactam	S	S	S	S	S	S
Imipenem/Meropenem	S	S	R	S	S	S

S; Sensitive, R; Resistant.

Ayus (21) and Allon (22) which have confirmed that hyperglycemia causes impaired functioning of neutrophils such as phagocytosis, chemotaxis, and decreased cytokine production as well as reduced Th1 dependent immunity, thus leading to a state of immunosuppression.

In this study leukocytosis with left shift was seen in 144 (66.5%) CRBSIs which was similar to the recent Indian study by Agrawal et al (2). Leucopenia was seen in 35 (16.5%) cases and thrombocytopenia in 25 (11.8%) patients, most of whom had gram-negative etiology for CRBSI, the possible explanation for which was reported by François et al (23) as that due to endotoxin-induced inhibition of neutrophil, platelet production and differentiation in the marrow. *Pseudomonas*, *Acinetobacter*, and *Klebsiella* are more likely to cause thrombocytopenia. This study showed positive procalcitonin in 172 (81.1%) CRBSIs which is similar to a study by Agrawal et al (n=52) (2) in which both gram-positive and gram-negative organisms had higher procalcitonin levels and Hamada et al (24) wherein 16/36 CRBSI patients had positive procalcitonin. In our study analysis of catheters, the site did not influence CRBSI similar to studies by Sethi et al (12) and Agrawal et al (2).

In contradiction to other studies from South Asia (2,3,7),

our study showed predominantly gram-positive CRBSIs. The most common organism isolated was CoNS followed by *Klebsiella pneumoniae* and *Candida* species in our study. This is similar to Western literature wherein it has been reported that CoNS, *S. aureus*, *Enterobacteriaceae*, and *Candida* species as the causative organisms associated with CRBSIs in percutaneously inserted non-cuffed catheters (14). Our study result is also similar to Indian studies by Shah et al (n=40) (25) and Sethi et al (n=74) (12) wherein the majority were caused by *S. aureus* and *Enterobacteriaceae* (*Klebsiella*) for gram-negative CRBSIs. The use of antibiotics (selection pressure), colonization of catheters by patient's skin flora, and increased recognition of these organisms may all contribute to the increased prevalence of gram-positive CRBSIs (7,9,12,14,25). CRBSI causal organisms found in our research population may differ from those found in other centers, thus highlighting the importance of each center studying its microbiological spectrum and modifying empirical antibiotics accordingly.

Conclusion

Our patients had a significant incidence of CRBSI. Gram-positive organisms contributed marginally more than gram-negative organisms to the culture-positive instances.

CoNS and ESBL producing gram-negative bacilli were the most common isolates. The presence of diabetes mellitus and leukocytosis were important associations seen in more than two-thirds of CRBSI patients.

Limitations of the study

- A key limitation in the study is that it was located in a single-center.
- As our study had a limited sample size, it's difficult to extrapolate the results.
- CDC/IDSA criteria were not used for identifying CRBSI.

Authors' contribution

MVB, RAP, and SPN were the principal investigators of the study. MVB, RAP, SPN, and IRR were included in preparing the concept and design. SPN, IRR, SVS, and DR revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript, and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The study protocol was approved by the institutional ethics committee of Kasturba Medical College, Manipal Academy of Higher Education (IEC 214/2017). Accordingly, informed consent was obtained from each patient enrolled in the study. Besides, ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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