ORIGINAL ARTICLE

Title

Haemodialysis Central Line-Associated Blood Stream Infections: Incidence, Risk factor, and Antibigram

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Abstract

Background Central-line associated bloodstream infection (CLABSI) is one of the complications of using a temporary HD catheter and also increases patient's morbidity and mortality. Identifying CLABSI risk factors and causative micro-organisms are important for setting prevention policies. There were no data regarding CLABSI in hemodialysis in Indonesia

Objective: This study identified the epidemiology and risk factor of HD CLABSI and to aid in the choice of empiric antibiotics therapy given to patients with HD CLABSI

Method: This study was an analytical observational study with a cross-sectional design conducted at the Inpatient Installation of Dr. Soetomo General Hospital in August 2018 - January 2019. The study population was patients with installed non-tunneled double lumen hemodialysis catheters for more than two calendar days. The inclusion criteria in this study were the patient 18-60 years old and any clinical presentation of fever, chills, and or hypotension. HD patients who presented with other sources of infection were excluded from the study. Data analysis was performed using SPSS v.23.

Results: In this study, 42 subjects were included in the composition of male: female 24: 18, with an average age of 49.62 years. The incidence of CLABSI is 11,3 /1000 catheter days. The results of blood cultures by gram-negative bacteria were 51.86%, and gram-positive bacteria were 48.14%. The most frequent causal organism found was *Staphylococcus aureus* by 25.9%. Based on gram-staining, *Staphylococcus aureus* was 53.84% of the gram-positive bacteria found, whereas the most frequent gram-negative bacteria was *Enterobacter clo-*

acae (53.84%). Antibiotics that have the highest sensitivity to gram-positive bacteria are Fosfomycin, Teicoplanin, and Chloramphenicol. Antibiotics that have the highest sensitivity to gram-negative bacteria are Cefoperazone Sulbactam, Imipenem, and Meropenem. There was a statistically significant relationship between DM and CLABSI events (OR = 3.896; p 0.037). There was a statistically significant relationship between hypoalbuminemia and the incidence of CLABSI (OR = 4,524; p 0,023).

Conclusion: This study found *S. aureus* was the most common cause of CLABSI. Our study was unusual as a high prevalence of gram-negative bacteremia was found in HD patients. Diabetes mellitus and hypoalbuminemia increase the risk of CLABSI in hemodialysis patients.

Keywords: chronic kidney disease, CLABSI, antibiogram, diabetes mellitus, hypoalbuminemia

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INTRODUCTION

Temporary vascular access by central venous catheter (CVC) is widely used in hemodialysis. The incidence of central line-associated bloodstream infection (CLABSI) is one of the complications of using a temporary HD catheter, and is one of the causes of

HD patient morbidity and mortality. The relative risk of bacteremia is nearly seven times in dialysis catheter use compared to native arteriovenous fistulas.^{1,2} Some studies mention factors that influence the risk of CLABSI events, including advanced age, diabetes mellitus, anemia, hypoalbuminemia, hyperferritinemia, catheter insertion, and duration of in situ catheter placement.^{2,3} Identifying bacterial profile and CLABSI risk factors is important for setting prevention policies.⁴

There was no data regarding CLABSI in hemodialysis in Indonesia. This research aimed to evaluate the incidence of CLABSI, the bacterial profile of CLABSI, and risk factor diabetes mellitus and hypoalbuminemia in Soetomo General Hospital, as a national referral hospital.

METHODS

The study was an analytical observational study with a cross-sectional design. The study was conducted in the hemodialysis unit of Soetomo General Hospital on September 2018 – February 2019. The subjects were consecutively recruited based on inclusion criteria. Our hospital ethics and research committee approved all subjects.

The population in this study were the patients of routine dialysis who have inserted a non-tunneled catheter for >2 calendar days. The inclusion criteria in this study were the patient 18-60 years old and any clinical presentation of fever, chills, and or hypotension. The exclusion criteria in this study were other sources of infection besides the confirmed hemodialysis catheter with clinical examination, laboratory, and radiological examinations as indicated, patients who had hemodialysis catheters installed in the femoral region, and patients who had received antibiotics before the CLABSI diagnosis was established. All subjects of the study were subjected to the following: full history taking and clinical examination, chest x-ray, and laboratory test which included: complete blood count, serum albumin, blood glucose, blood culture, and bacterial sensitivity from peripheral samples.

One set of blood cultures peripheral vein were taken from each patient. The peripheral blood culture was

taken from a vein in the median cubital fossa or the flexor aspect of the forearm. A sterile zone was then demarcated by draping the area with a sterile sheet. The sterile zone was created by cleaning the area with 70% alcohol, followed by 10% povidone-iodine in a circular motion starting from the center and moving outwards, and the site was left to dry. All operators wore plastic gowns, face masks, and sterile gloves to prevent contamination of the blood culture. The blood cultures were then sent to our microbiology laboratory for culture and antibiotic sensitivity tests. All cultures isolated were tested using the Clinical and Laboratory Standards Institute (CLSI) 2013 protocol.

The diagnosis of CLABSI was based on two criteria of CDC 2017 guidelines⁵

1. The central line was in place for >2 calendar days on the date of the event, with the day of device placement being Day 1.
2. Any of the following Laboratory-Confirmed Bloodstream Infection (LCBI) criteria
 - a. Patient of any age has a recognized pathogen identified (i.e., an organism which is not on the NHSN common commensal list) from one or more blood specimens by culture or non-culture based microbiologic testing method AND Organism(s) identified in the blood is not related to an infection at another site.
 - b. Patient of any age has at least one of the following signs or symptoms: fever (>38.0oC), chills, or hypotension AND Organism(s) identified from blood is not related to an infection at another site, AND the same NHSN common commensal is identified from two or more blood specimens drawn on separate occasions, by culture or non-culture based microbiologic testing method.

Data were analyzed statistically using SPSS 22nd version. Qualitative data were presented in the form of sums and percentages, whereas quantitative data were presented as mean values and standard deviation. The chi-square test was performed to compare independent variables (diabetes mellitus and hypoalbuminemia) between the groups of patients with and without CLABSI. Threshold for significant p-value is < 0,05 with 95 % confidence interval.

RESULT

The number of research subjects was 42 HD patients in the inpatient installation of RSUD dr. Soetomo in the period August 2018 - January 2019 and fulfilled the inclusion and exclusion criteria. General characteristics data are summarized in table 1. In this study, the number of male samples was 24 people (57.1%), and female samples were 18 people (42.9%). The median age in CLABSI patients was 49.6 years with an age range of 20-60 years, whereas in patients without CLABSI it was 48.7 years with an age range of 32-60 years. The mean length of CLABSI patients undergoing HD in 13.64 weeks, and patients without CLABSI, it is 6.47 weeks.

Table 1. General Characteristics of the patients

Category	Frequency	
	CLABSI n= 25	No CLABSI n= 17
Gender		
Male	13	11
Female	12	6
Age (years)		
Median ± SD	50.76 ± 12.35	48.71 ± 10.99
Range (Min-Max)	(20-60 years)	(32- 60 years)
Double lumen catheter location		
Right Subclavian	22 (88%)	17 (100 %)
Right Jugular	3 (12%)	0 (0 %)
Duration of undergoing HD		
Mean ± SD (weeks)	13.64 ± 9.69	6.47 ± 3.93
Duration of double lumen catheter		
Mean ± SD (weeks)	12.6 ± 6.86	6,71 ± 3.90

The results of blood culture were dominated by gram-negative bacteria at 51.86%, while gram-positive bacteria at 48.14%. *S.aureus* is the most frequent bacterial cause of CLABSI of 25.9% and in the gram-positive group of 53.84%. *E. cloacae* is a bacterium that causes CLABSI in the gram-negative group

of 42.85%. The organisms isolated are shown in Table 2.

Table 2. Bacterial isolates from 25 blood cultures

	Count (%)
Gram-positive organism	
<i>Staphylococcus aureus</i>	7 (53.84 %)
<i>Staphylococcus haemolyticus</i>	2 (15.38 %)
<i>Enterococcus faecalis</i>	1 (15.38 %)
<i>Methicillin-resistant staphylococcus aureus</i>	1 (7.69 %)
<i>Corynebacterium matruchotti</i>	1 (7.69 %)
Total	13 (48.14%)
Gram-negative organism	6 (42.85%)
<i>Enterobacter cloacae</i>	2 (14.28 %)
<i>Acinetobacter baumannii</i>	2 (14.28 %)
<i>Escherichia coli</i>	2 (14.28 %)
<i>Stenotrophomonas maltophilia</i>	1 (7.14 %)
<i>Pseudomonas aeruginosa</i>	1 (7.14 %)
<i>Pantoea agglomerans</i>	1 (7.14 %)
Total	14 (51.86 %)
Total for organism	27 (100 %)

In this study, the results were that the incidence of CLABSI with comorbid DM was 17 people (68%) and non-DM patients were eight people (32%). While in the group of patients without CLABSI who had DM comorbidities of 6 people (35.3%) and non-DM patients, 11 people (64.7%). Table 5 shows the distribution of the incidence of CLABSI in HD patients with and without DM.

Table 3 Antibiotic Sensitivity Test Results against Gram-positive Bacteria

Antibiotic	Sensitive	Intermediate	Resistant
Amikacin	-	-	-
Tobramycin	-	-	-
Gentamycin	7/12 (58.33%)	-	5/12 (41.66%)
Aztreonam	-	-	-
Amoxicillin clavulanic acid	7/9 (77.78%)	-	2/9 (22.22%)
Ampicillin	2/11 (18.18 %)	-	9/11(81.82%)
Ampicillin-Sulbactam	-	-	-
Penicillin G		-	
	2/12 (16.67 %)		10/12 (83.33%)
Pepiracillin tazobactam	-	-	-
Oxacillin		-	
	7/10 (70%)		3/10 (30 %)
Cephazolin	-	-	-
Ceftazidime	-	-	-
Cefotaxime	-	-	-
Ceftriaxone	-	-	-
Cefoperazone-Sulbactam	-	-	-
Cotrimoxazole	7/12 (58.33)	-	5/12 (41.67%)
Tetracyclin	6/9	-	3/9
	(66.67 %)		(33.33 %)
Chloramphenicol	9/10(90%)	-	1/10 (10 %)
Erythromycin	8/12 (66.67%)	1/12 (8,33 %)	3/12 (25%)
	8/12 (66.67 %)	-	
Clindamycin	7/8	-	4/8 (33.33 %)
	(87.5 %)		
Quiniopristin-dalfopristin			1/8 (12.5 %)
Ciprofloxacin	6/8 (75 %)	-	2/8 (25 %)
Levofloxacin	6/9	1/9 (11,11 %)	2/9 (22.22%)
	(60.6 %)		
Moxifloxacin	9/11 (81.82 %)	-	2/11
			(18.18 %)
Fosfomycin	11/11	-	-
	(100 %)		
Teicoplanin	10/11 (90.9%)	-	1/11 (9.1 %)
Imipenem	-	-	-
Meropenem	-	-	-
Ertapenem	-	-	-

Table 4. Antibiotic Sensitivity Test Results Against Gram-negative Bacteria

Antibiotic	Sensitive	Intermediate	Resisten
Amikacin	12/13 (92.3%)	-	1/13 (7.6 %)
Tobramycin	-	-	-
Gentamycin	9/12 (75 %)	-	3/12 (25 %)
Astreonam	5/13 (38.46%)	-	8/13 (61.54%)
Amoxicillin clavulanic acid	1/13 (7.7%)	-	12/13 (92.3%)
Ampicillin	1/13 (7.7%)	-	12/13 (92.3%)
Ampicillin-Sulbactam	2/13 (15.38%)	1/13 (7.7%)	10/13 (76.92%)
Pepiracillin tazobactam	9/12 (75 %)	1/12 (8.33 %)	2/12 (16,67 %)
Cephazolin	1/13 (7.7%)	-	12/13 (92.3 %)
Ceftazidime	9/14 (64.28%)	-	5/14 (35.71 %)
Cefotaxime	6/13 (46.15%)	1/13 (7.7%)	6/13 (46.15 %)
Ceftriaxone	7/13 (53.84 %)	1/13 (7.7%)	5/13 (38.46 %)
Cefoperazone-Sulbactam	11/12 (91.67%)	-	1/12 (8.33%)
Cotrimoxazol	11/14 (78.57%)	-	7/9 (21.42%)
Tetracyclin	7/12 (58.33%)	-	5/12 (41.67%)
Chloramphenicol	7/12 (58.33%)	-	5/12 (41.67%)
Ciprofloxacin	9/13 (69.23%)	-	4/13 (30.77%)
Levofloxacin	10/14 (71.42%)	1/14 (7.14%)	3/14 (21.42%)
Fosfomycin	5/12 (41.67%)	1/12 (8.33%)	6/12 (50 %)
Imipenem	11/12 (91.67%)	-	1/12 (8.33%)
Meropenem	11/12 (91.67%)	-	1/12 (8.33%)
Ertapenem	-	-	-

Table 5. Distribution of CLABSI patients with and without DM

	CLABSI	
	Yes	No
With DM	17 (68%)	6 (35.3%)
Without DM	8 (16%)	11 (64.7%)

In this study, antibiotics that had the highest sensitivity to gram-positive bacteria were Fosfomycin (100%), Teicoplanin (90.9%), and Chloramphenicol (90%). While antibiotics that have the highest resistance to gram-positive bacteria are Penicillin G (83.33%) and Ampicillin (81.82%). The results of the test results for antibiotic sensitivity to gram-positive are summarized in Table 3.

In this study, antibiotics that had the highest sensitivity to gram-negative bacteria were Sulbactam Cefoperazone (91.67%), Imipenem (91.67%), and Meropenem (91.67%). In this study, there was 1 CLABSI event with the bacterium *Acinetobacter baumannii*, which was resistant to all antibiotics. While antibiotics that have the highest resistance to gram-negative bacteria are Amoxicillin-clavulanic acid (92.3%), Ampicillin (92.3%), and Cephazolin (92.3%). Ceftriaxone antibiotics that are used as empirical therapy at this time for CLABSI events only have a sensitivity of 53.84%. The data from the test results for antibiotic sensitivity to gram-negative are summarized in Table 4.

The results of the comparison test with chi-square obtained a p-value of 0.037 which is less than the significance level of 0.05 (5%), so it can be concluded that there are significant differences in CLABSI patients with and without DM. The results of OR 3.896 means that patients with a DM have a risk of 3.896 times higher for the CLABSI compared with patients without DM.

In this study, albumin levels in the CLABSI group were divided into two groups, namely the group ≤ 3.5 g / dL as many as 19 people (76%) and > 3.5 g / dL as many as six people (24%). The albumin level in the patients without the CLABSI group was divided into two groups, namely the group ≤ 3.5 g / dL as many as six people (35.3%) and > 3.5 g / dL as many as 11

people (64.7%). Table 6 shows the distribution of the incidence of CLABSI in HD patients with and without hypoalbuminemia.

Table 6. Distribution of CLABSI patients with and without hypoalbuminemia

	CLABSI	
	Yes	No
$\leq 3,5$ g/ dL	19 (76 %)	6 (35.3%)
$> 3,5$ g/ dL	6 (24 %)	11 (64.7%)

The results of the comparison test with chi-square obtained a p-value of 0.023 which is less than the significance level of 0.05 (5%), so it can be concluded that there are significant differences in CLABSI patients with and without hypoalbuminemia. The results of OR 4.524 means that patients with hypoalbuminemia have a risk of 4.524 times higher for the CLABSI compared with patients without hypoalbuminemia.

DISCUSSION

The results of this study found the CLABSI incidence rate of 11.3 per 1000 catheter-days. This result is consistent with the research of Abdulrahman et al., where the incidence of CLABSI was 11.3 per 1000 catheter-days.⁶ Sahli et al. study showed different results where a higher incidence of CLABSI was obtained, namely 16.6 per 1000 catheter days.⁷ This is because, in the Sahli et al. study, the insertion of HD catheters in the femoral area was 79.6%. Femoral insertions have a higher risk of infection than insertions in the internal and subclavian jugular.¹

S. aureus was the most common cause of CLABSI in this study. This is consistent with the research analysis by Saxena et al. in 7 HD centers, which stated *S. aureus* as the cause of 21.9 - 60% of CLABSI. A class of cell surface adhesins – MSCRAMMs specifically interacts with extracellular matrix components and plays an important role in host tissue colonization, invasion, and as a key factor for *S. aureus* virulence.¹ Additionally, *S. aureus* elaborates glycocalyxes which promote the bacterial colonization and spread of infection even further.⁸

Our study was unusual as a high prevalence of gram-negative bacteremia was found in HD patients. As compared to previous studies, our study showed an increasing trend of gram-negative bacteremia. Alexandraki et al. investigated the five-year pattern of organisms isolated from HD patients with catheter infection, which showed a significant increase in the incidence of single gram-negative organisms and polymicrobial bacteraemias.⁹ This trend was consistent with the pattern of catheter infection in nondialysis patients. The high prevalence of gram-negative bacteria may be due to the immunocompromised state of patients, contaminated infusate, and misuse of antibiotics.¹⁰

In this study, antibiotics that had the highest sensitivity to gram-negative bacteria were Sulbactam Cefoperazone (91.67%), Imipenem (91.67%), and Meropenem (91.67%). In this study, there was 1 CLABSI occurrence with the bacterium *Acinetobacter baumannii*, which was resistant to all antibiotics. The study by Chandra et al. the 42 CLABSI events showed a phenomenon of increased resistance to the cephalosporin and carbapenem groups namely Imipenem (77%), Ampicillin Sulbactam (75%), and Ceftazidime (60%). This is due to the research of Chandra et al. 27% of the causes of CLABSI were obtained in the gram-negative group, *Acinetobacter baumannii*.¹¹

In this study, it was found that in HD patients with DM, there was an increase in risk factors for CLABSI with OR 3.896. This supports the research report by Lamaire et al., a multicenter retrospective cohort study with multivariate analysis involving four dialysis installations in 1749 research subjects, showing DM was a significant risk factor for CLABSI (OR 2.37; 95% CI 1.65 - 3.39).¹² In the study of Sahli et al. on 104 research subjects showed DM was an independent risk factor for the incidence of CLABSI with a value of $p < 0.01$.⁷ Ghonemy et al. also reported in his study with 119 study subjects showing DM was a risk factor for CLABSI with a value of $p < 0.001$.¹³

Diabetes mellitus is a risk factor for infection due to various disorders of the immune system, including humoral, cellular, and innate immunity that contributes to the pathogenesis of CLABSI in diabetic patients. In patients with DM, there is a decrease in the ability of

mobilization, chemotaxis, phagocytosis, and impaired adherence function, from PMN.¹⁴ Diabetes mellitus, which is also associated with a decrease in cell-mediated immunity (CMI) function. Diabetes causes a decrease in lymphocyte transformation against excitatory PHA (phytohemagglutinin) in uncontrolled people with diabetes mellitus. T lymphocyte counts decrease, especially CD4, which results in decreased CD4: CD8 ratio due to reduced insulin levels or decreased insulin activity.¹⁵

In this study, it was found that in HD patients with hypoalbuminemia, there was an increase in risk factors for CLABSI with OR 4.524. Ghonemy et al. also reported in his study with 119 study subjects that hypoalbuminemia was a risk factor for CLABSI with a value of $p < 0.008$.¹³ A retrospective study with multivariable logistic regression analysis by Fysaraki et al. of 142 episodes of bloodstream infection in hemodialysis patients showing hypoalbuminemia was a risk factor for CLABSI (OR 1.976; 95% CI).¹⁶

The risk of hypoalbuminemia in HD patients is related to malnutrition, loss of nutrients through the dialysis process, increased protein catabolism, and blood contact with the dialyzer membrane which activates the complement system and monocytes thereby releasing catabolic proinflammatory cytokines.¹⁷ Serum albumin is a marker of nutrition, inflammation, and predictor of death in hemodialysis patients.¹⁸

This study has limitations due to not having the data on what could be the cause of these infections. Future studies should include analysis between risk factors such as hand hygiene practices, water sources, and the incidence and prevalence of CLABSI.

CONCLUSION

This study found *S. aureus* was the most common cause of CRBSI. Our study was unusual as a high prevalence of gram-negative bacteremia was found in HD patients. Diabetes mellitus and hypoalbuminemia increase the risk of CRBSI in hemodialysis patients.

ETHICAL CLEARANCE

This research had been approved by the Ethics Committee before the study conducted.

CONFLICT OF INTEREST STATEMENT

The authors declare that there was no conflict of interest in this research.

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AUTHOR CONTRIBUTION

All authors have contributed to all process in this research, preparation, drafting, review, and approval of this manuscript

DISCLOSURE

The author reports no conflicts of interest in this research.

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