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Research Article

Evaluation of catheter related bacteremia in patients with end stage renal disease on hemodialysis

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Introduction

Infections are common complications among patients on chronic hemodialysis. Hemodialysis patients with a catheter have a 2- to 3-fold increased risk of hospitalization for infection and death compared with patients with an arteriovenous fistula or graft [1].

Infection is second only to cardiovascular disease as a cause of death in end-stage renal disease. Septicemia accounts for more than 75% of infection-associated death. The arteriovenous fistula is the preferred vascular access for HD because of reduced infections rate and improved delivery of adequate dialysis, unlike cardiovascular catheter (CVC) that has lower patency rate, high infection rate, hospitalization and mortality mainly due to catheter related blood stream infection [2].

The predominant reasons for use of CVCs include: temporary loss of permanent hemodialysis access, late referral for initiation of dialysis, the need to await maturation of Arteriovenous Fistulas (AVFs) and limited access options in patients with severe peripheral vascular disease. On - tunneled CVCs for HD primarily placed in internal jugular, sub-clavian or femoral vein, they are indicated for short-term HD access and their use should be limited to less than three weeks; otherwise if we need it for more than three weeks, a tunneled catheter is the option [3,4].

Types of CVC used for chronic hemodialysis include tunneled cuffed catheters and nontunneled catheters. The risk of developing bacteremia varies with site of CVC insertion, type of device and duration of CVC use. The most common causative pathogens are gram positive bacteria, with Staphylococcus aureus and coagulase- negative staphylococci accounting for 40% to 80% of catheter related blood stream infection (CRBSIs)13) Gram-negative organisms cause 20% to 40% CRBSIs, whereas polymicrobial infections (10% - 20%) and fungal infections (<5%) are less common. Metastatic infectious complications of CRBSIs include endocarditis, osteomyelitis, spinal epidural abscess, septic arthritis, brain abscess, and septic pulmonary emboli [5-13].

Risk Factors for the Occurrence of CRBSIs include: Submaximal barrier precautions at the time of catheter insertion, Nontunneled catheter, Site of insertion—femoral > internal jugular > subclavian, Prolonged duration of catheter use, Previous episode of CRBSI, Staphylococcus aureus nasal carriage, Diabetes, Hypoalbuminemia and Recent surgery.

Clinical Features; Fever and chills are the most sensitive clinical features, associated with positive blood cultures in 60% to 80% of patients [14,15]. Only 5% of patients with CRBSIs will have a concurrent exit-site or tunnel infection [16]. Other clinical manifestations of CRBSIs include hemodynamic instability, altered mental status, catheter dysfunction, hypothermia, nausea/vomiting and generalized malaise [17].

Clinical definitions of CRBSIs are those where other sources of infection are excluded by patient examination and review of patient record and finding of positive catheter tip cultures (if available) with the same organism as that seen on blood cultures [18,19].

Diagnosis without catheter withdrawal; Paired

quantitative blood cultures, both sets are positive for the same microorganism and the set obtained through the catheter has ≥3:1 fold-higher colony count than the peripheral culture [18-20] Diagnosis with catheter withdrawal.

Semiquantitative catheter culture ≥15 CFU The same microorganism in at least one percutaneous blood culture and catheter tip culture [18-20].

Catheter cultures should be performed when a catheter is removed for suspected CRBSI; catheter cultures should not be obtained routinely. For Central Venous Catheters (CVCs), the catheter tip should be cultured, rather than the subcutaneous segment [21-27].

Exit-site infection diagnosed by Hyperemia, induration, and/or tenderness ≤2 cm from catheter exit site. May be associated with fever and purulent drainage from the exit site. It may or may not be associated with bacteremia. If there is purulent drainage, it should be collected and sent for Gram staining and culture. Treatment for 7 to 14 days, depending on the microorganism isolated and local practice [17,20].

Tunnel infection diagnosed by Tenderness, hyperemia, and/or induration that extends >2 cm from the exit site and along the subcutaneous tunnel. It may or may not be associated with bacteremia. If there is purulent drainage, it should be collected and sent for Gram staining and culture [20]. The catheter should always be removed, without exchange over a wire. A new catheter should be inserted at a separate site. Start empiric broad-spectrum antibiotics to cover both gram-positive and gram negative organisms.

Modify antibiotic regimen when culture and sensitivity results are available.

Tunnel infections, in the absence of a concurrent CRBSI, are typically treated for 10 to 14 days, depending on the microorganism isolated and local practice. If a CRBSI is also present, then duration of therapy will be determined by the management of the CRBSI [17].

Catheter-Related Bloodstream Infection Empiric management; Broad-spectrum antibiotics should be initiated to cover both gram-positive and gram-negative organisms. Antibiotics should generally cover methicillin resistant S aureus (MRSA) and Pseudomonas. Following initiation of empiric antibiotic therapy, it is crucial that culture and sensitivity data are followed up in a timely manner, so that the most appropriate antibiotics based on sensitivity results can be used [20].

Definitive management of CRBSIs must be tailored to the clinical presentation of the patient, the microorganism isolated, and vascular access options of the patient. For example, management of the patient with septic shock secondary to MRSA CRBSI will differ from that of hemodynamically stable patient presenting with a fever and found to have coagulase-negative staphylococcus. Treatment can be categorized into 3 groups: systemic antibiotics, antimicrobial locking (instillation) solutions and catheter management [17].

Systemic antibiotics; all patients with a CRBSI should receive systemic antibiotics, which will typically be administered for 2 to 6 weeks depending on the microorganism, clinical presentation and complications. Final decision on specific antibiotic agent(s) is dependent on final blood culture result and sensitivities and whether or not patient has any allergies [28-35].

If Methicillin Sensitive S Aureus (MSSA) infection is isolated, cefazolin is the preferred choice over vancomycin because it is associated with decreased hospitalization and death secondary to infection [21].

Patients and methods

Study settings and design

A cross - sectional observational study, enrolling (300) ESRD patients in whom tunneled and non-tunneled catheters used for hemodialysis in the Dialysis Center of Al Imamain Alkadhumain Medical City from February 2020 to February 2021 under supervision of Nephrologist. (on regular hemodialysis in this center but not of all them complaining bacteremia) [36-43].

Patients assessments

All 300 patients on regular hemodialysis with three or two sessions per week and 4 hours duration for each session using GAMBRO Dialysis system were evaluated in this study.

Patients selection

Initially, three hundred patients were evaluated in this study, but only 122 of them gave signs and symptoms of catheter related infection, all of them more than 18 years old, using tunneled and non tunneld catheter.

178 patients were excluded from this study, including;

68 patients were asymptomatic.

60 patients were having arteriovenous fistula.

14 patients were receiving antibiotics at the time of blood culture or catheter removal.

30 patients with infection other than catheter related infection such as pneumonia and UTI.

4 patients on immunosuppressive treatment or steroids.

2 patients with malignancy.

Baseline assessment

Including history, physical examination and investigations were done for studied patients according to the following: -

age: younger age < 45 years, middle aged group 45 - 65 years and elderly > 65 years old [43], sex, causes of CKD, types of double lumen whether tunneled or non tunneld.

- site of double lumen (internal jugular, femoral, subclavian), duration of hemodialysis and duration of double lumen (less than 4 weeks and more than 4 weeks), presentation: fever, chills, rigor, nausea and vomiting, unexplained hypotension, change in mental status, local signs of exit site infection and catheter dysfunction, duration of symptoms equal or >3 days or <3 days during HD sessions or during HD free period [44,45].

Investigations: WBC (neutrophil), HB, B.urea, s.cr, RBS, s.albumin, blood culture, catheter tip culture, CxR, GUE .

- Hb level: < 8 g/dL (sever), 8 – 10.9 g/dl (moderate) and ≥ 11 g/dL(mild) [46].
- Wbc count: 4 – 11 × 109/L (normal), > 11 × 109/L (leukocytosis) [47].
- Neutrophil count (2 - 8× 109/L (normal), > 8 × 109/dL (neutrophilia) [47].
- Albumin level: normal s. albumin ≥ 3.5 g/dL, hypoalbuminemia < 3.5 g/dl [45].
- Random blood glucose : 11.1 mmol/L (200 mg/dl) or more
- {Hyperglycemia}, <11.1 mmol/L (200mg/dl) {normal} [44]. (all these investigations routinely done for all the patients in dialysis to assessment the health of patients)
- Hx of previously receiving antibiotics and for how long duration, Treatment whether need antibiotics only (systemic antibiotics and antibiotics lock) or removal of catheter plus antibiotics.
- We remove the double lumen and cut nearly 4 cm from the tip and place it in sterile container, then transported to the lab for culture [48].
- We use catheter hub and at least one peripheral venous site for (blood culture and sensitivity).
- Blood culture and sensitivity were done in the device by Minimum Inhibitory Concentration (MIC).

Data collection

A preformed Questionnaire was used to get information from studied population. Blood samples were taken at dialysis units and investigated in Alkadhumain medical city / laboratory department.

Ethical issues

The patients will be informed about the study purpose and its relevance and their verbal consent had been taken to conduct the study. Ethical Approved by Iraq board internal medicine committee.

Statistical analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 22. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent ttest (two tailed) was used to compare the continuous variables among study groups accordingly. Pearson's Chi–square test was used to assess statistical association between categorical variables. Multivariate regression analysis was conducted to identify the significant unconfounded factors associated with the controlled status of DM. A level of p – value < 0.05 was considered significant.

Results

There 300 patients included in this study. The mean age was 56.7 ± 13 years (range 23 – 80). Males and female were represented 49.3% (148), 50.7% (152) respectively. The features shown in Tables 1,2.

The most common bacteria identified in blood culture was staphylococcus epidermidis, which was presented in 30 (24.5%) patients. Then pseudomonas aeruginosa and methicillin sensitive staph. aureus which were presented in 12 (9.8%) patients for each. Then methicillin resistance staph. aureus and proteus mirabilis, which were found in 9 (7.3%) patients for each bacteria [49-55]. Klebsiella pneumonia was presented in 8 (6.2%) patients. There were 42 (34.4%) patients have negative results on blood culture Figures 1-3.

Table 1: Demographic features of patients (No. 300).

Variable	Frequency	Percentage
Age	Mean ± SD - 56.7 ± 13 Years	
Duration of Dialysis	Mean ± SD - 3.2 ± 2 Years	
Sex		
Male	148	49.3%
Female	152	50.7%
Type of vascular access		
Double lumen	240	80.0
Arteriovenous fistula	60	20.0
Site of lumen		
Femoral vein	33	13.7
Internal Jugular vein	202	84.1
Subclavian vein	5	2.9
Type of Double lumen		
Non Tunneled	105	35.0
Tunneled	195	65.0
Duration of Double Lumen		
< 4 weeks	163	54.3
> 4 weeks	137	45.7
Causes of chronic kidney disease		
Diabetic Nephropathy	125	41.7
Hypertention/Diabetis mellitus	54	18.0
Hypertention	50	16.7
Systemic lupus erythmatosus	5	1.7
Polycystic kidney disease	12	4.0
Unknown cause	54	18.0

Table 2: Clinical manifestation among patients.

Symptoms	During HD (n = 122) N. (%)	Free of HD (n = 82)	
		N. (%)	p value*
Fever with/without chills Yes	122 (100)	82 (100)	--
Nausea and vomiting Yes No	31 (25.4) 91 (74.6)	21 (25.6) 61 (74.4)	0.94
Unexplained hypotension Yes No	8 (6.6) 114 (93.4)	8 (9.8) 74 (90.2)	0.041
Change in mental state Yes No	6 (4.9) 116 (95.1)	6 (7.3) 76 (92.7)	0.79
Catheter dysfunction Yes No	10 (8.2) 112 (91.8)	10 (12.2) 72 (87.8)	0.021
Local signs of exit site or tunnel infection Yes No	24 (19.7) 98 (80.3)	14 (17.2) 68 (82.9)	0.31

*Chi-Square test (within Free of HD group only).

Positive blood culture was associated with lower duration of symptoms (p value = 0.043), with higher WBC and neutrophilia (p value < 0.0001), and with lower S.creatinine and s.albumin (p value = 0.01 and 0.008 respectively). The age, Hb, B.urea, and RBS did not showed an association with positive blood culture [56-58].

The analysis of association between the blood culture and causes of CKD shown no association between the causes of CKD and positivity of blood culture, p value = 0.58.

The catheter tip culture was done for 58 (47.5%) patients, it revealed that pseudomonas aeruginosa was the most common bacteria, identified in 14 (11.4%) patients. Methicillin sensitive staph. aureus was presented in 12 (9.8%) patients. MRSA was presented in 9 (7.3%) patients. Negative results were observed in 12 (9.8%) patients.

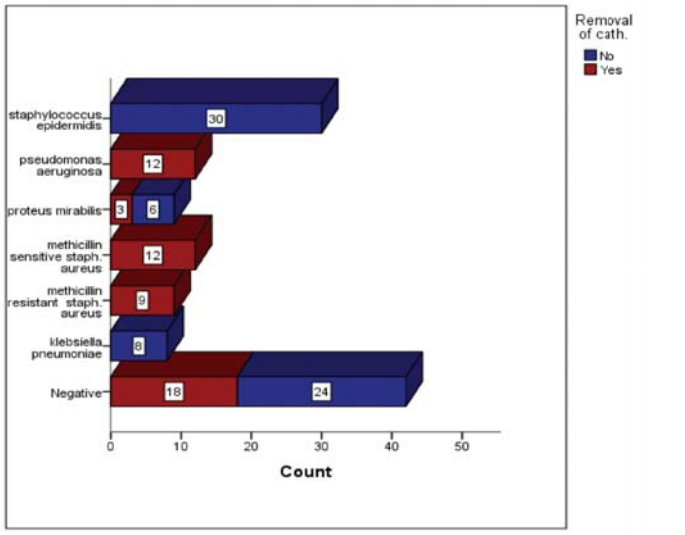

Figure 1: The Distribution of catheter removal across the type of bacteria identified in the blood culture. Chi-Squ = 72.2, p value = 0.0001. Chi-Squ = 113.3, p value = 0.0001

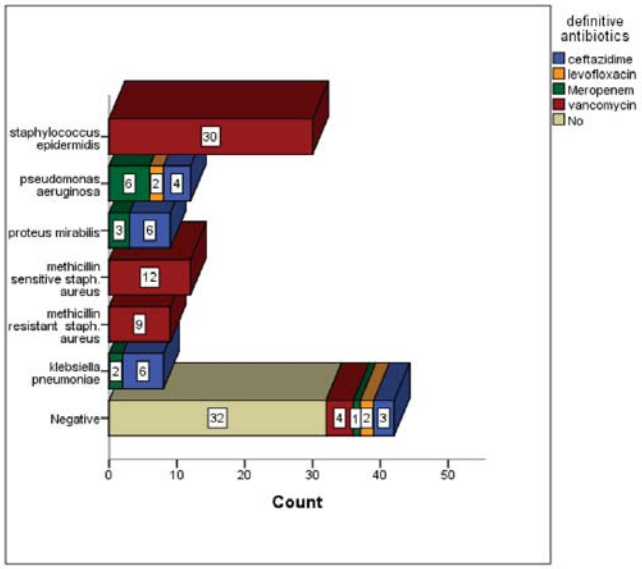

Figure 2: The Distribution of definitive antibiotics across the type of bacteria identified in the blood culture. Chi-Squ = 199.1, p value = 0.0001.

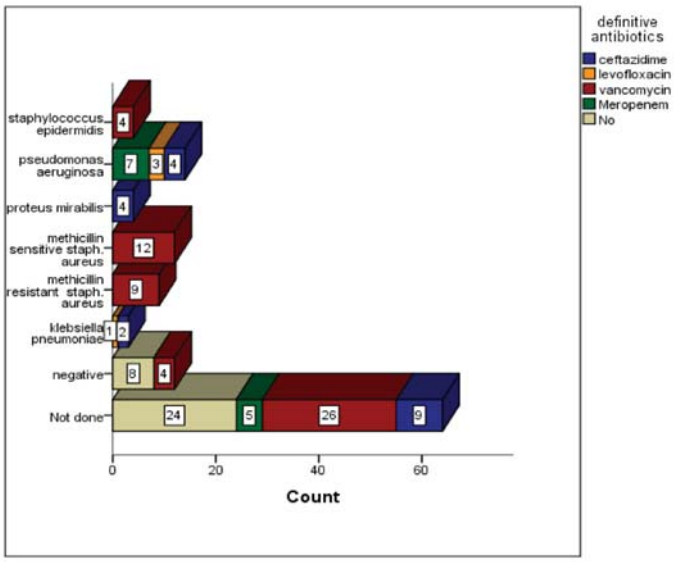

Figure 3: The Distribution of definitive antibiotics across the type of bacteria identified in the catheter tip culture. Chi-Squ = 133.5, p value = 0.0001.

Table 3: The distribution of patients according to blood culture and catheter tip culture bacteria.

Blood Culture	Catheter Tip Culture								
	klebsiella	methicillin resistant	methicillin sensitive	-ve	Not done	proteus mirabilis	aeruginosa	epidermidis	Total
klebsiella pneumoniae	0	0	0	0	8	0	0	0	8
Methicillin resistant	0	9	0	0	0	0	0	0	9
Methicillin sensitive	0	0	12	0	0	0	0	0	12
Negative	3	0	0	8	24	1	2	4	42
proteus mirabilis	0	0	0	0	6	3	0	0	9
pseudomonas aeruginosa	0	0	0	0	0	0	12	0	12
staphylococcus epidermidis	0	0	0	4	26	0	0	0	30
Total	3	9	12	12	64	4	14	4	122

Chi-Square= 391.8, *p* value = 0.001.

The assessment of the factors associated with positive catheter tip culture revealed that, positive catheter tip culture was associated with higher WBC, neutrophilia, and RBS (*p* value < 0.0001). The age, duration of symptoms, Hb, B.urea, s.creatinine and s.albumin did not showed an association with positive catheter tip culture.

The association between patients with blood culture and catheter tip culture bacteria are shown in Table 3. There was a strong association between the blood culture and catheter tip culture bacteria (*p* value = 0.001).

All patients had received anempirical systemic antibiotics (vancomycin + ceftazidime). The definitive antibiotics and duration of antibiotics was given in the Table 4.

Table 4: Duration of systemic antibiotics.

Variable	Incidence	Percentage
1. Definitive Antibiotic		
2. Ceftazidime	19	15.6
3. Levofloxacin	4	3.3
4. Vancomycin	55	45.1
5. Meropenem	12	9.8
6. No antibiotics	32	26.2
Duration		
2 weeks	64	52.5
4 weeks	12	9.8
4 – 6 weeks	14	11.5
No	32	26.2
Removal of Catheter		
Yes	54	44.3
No	68	55.7
Antibiotics lock		
Yes	44	36.1
No	78	63.9

Table 5: Association between blood culture and type of treatment.

Variable	Blood culture		
	Positive No. (%)	Negative No. (%)	*p* value*
Removal of Cath.	36 (66.7)	18 (33.3%)	0.82
Definitive Antibiotics			
Ceftazidime	16 (84.2)	3 (15.8)	
Levofloxacin	2 (50)	2 (50)	
Vancomycin	51 (92.7)	4 (7.3)	0.0001
Meropenem	11 (91.7)	1 (8.3)	
No	0	32 (100)	
D			
2 weeks	54 (84.4)	10 (15.6)	
4 weeks	14 (100)	0	0.0001
4 – 6 weeks	12 (100)	0	
No	0	32 (100)	
Antibiotics lock			
Yes	44 (100)	0	0.0001
No	36 (46.2)	4242 (53.8)	

*Chi-Square Test.

Treatment association with blood culture was given in the below Table 5. There were a strong association between positive culture and definitive antibiotic, duration of antibiotic and antibiotic lock (p value < 0.005).

Discussion

Patients with CKD on hemodialysis are at increased risk for blood stream infection especially those with catheters. In this research, we aimed to investigate the frequency and factors associated with catheter-related bacteremia in patients with CKD on hemodialysis.

The age and sex were comparable to previously published local study by Jaudah and Musa from AlBasra, in which they reported a mean age of 54 years and 55% of their patients were females [56]. The global study from USA at 2019 showed a relatively lower mean age (50 years) in comparison to our study, however, the difference in sample size could contributed to this difference [57].

The most common cause for CKD was diabetic nephropathy followed by hypertension, while the unknown cause was reported in less than 20% of patients, this was comparable to a previous study conducted in Iraq by Awad, in which he studied the causes of CKD [58]. However, in a study conducted among the Iranian population in 2009, they reported that hypertension was relatively higher than DM as a cause for CKD (30.5% and 30.1% respectively) [59]. This difference could rely on the number of patients recruited in their study which was double of our patients, also, ethnicity could play a role too.

Around 40% of recruited patients develop signs/symptoms of infection.

This percentage was comparable to Sanavi's, et al. study, which showed a 41% of their patients developed an infection [60]. Another Samani's, et al. study showed that less than 20% of patients developed an infection [61].

While studies from the USA and Italy reported a higher incidence rate of a catheter-related infection (more than 70%) in comparison to our results [57,62]. This differences in studies could be related to difference in the studies design and the precautions measures taken by different institutes to decrease the infection rate.

The presenting symptoms in the majority of patients were fever and rigors in which the bacterial infections are presented with a fever the most, another study by Farrington CA and Allon M to assess the Complications of hemodialysis catheter blood stream infections: impact of infecting organism also reported that more than 90% of their patients presented with fever and rigors [57]. This gave us the assurance of presenting symptoms during HD or not related to HD should take into consideration for identifying the potential catheter-related infection in HD patients.

Among patients who developed sings/symptoms of infection (122), the blood culture showed that 65% of patients have positive culture. The most common bacteria identified in blood culture was staphylococcus epidermidis, while the staph aureus was reported in 16% of patients. This was comparable to a local study by Jaudah and Musa from AlBasra, which showed the most common blood culture organism was staphylococcus epidermidis [56]. In USA, Farrington CA and Allon M found that the staphylococcus epidermidis was the most common organism identified also [57]. Also, Hadian's et study showed that staphylococcus epidermidis was most common followed by staph aureus [63].

While in study conducted in Canada by Lok CE and Mokrzycki MH, it showed that the staph aureus is the most common identified bacteria across Canada [64].

Also, Sanavi's, et al. from Iran reported that 42% of isolated organisms was staph aureus [5]. Samani's, et al. study also showed that staph aureus was the most identified bacteria by blood culture [62].

In narrative review study in Canada by Lata C, et al. to assess the Catheterrelated bloodstream infection in end-stage kidney disease found that the staph aureus bacteria was reported in 31% of patients in which it was the most common bacteria [65].

The short duration of symptoms, leukocytosis, neutrophilia, lowers creatinine, and albumin have been associated with a positive catheter related blood stream infections incidence rate. The binary logistic analysis revealed that hypotension, catheter dysfunction and local signs of exit site infection have been associated positive blood culture. Jaudah and Musa from AlBasra, showed association with local sign, also the showed an association with males, DM, central venous catheter duration and fever [56]. In USA study, it reported that the fever was significantly associated with staph aureus in comparison to staphylococcus epidermidis [2]. While Italian study showed that age, gender and type of catheter were associated with increased incidence of blood culture infection [63]. In study conducted in Canada, it showed different factors than factors in our study, one of the factors was hypertension [66].

This discrepancy in results between studies for factors associated with catheter-related infection in HD patients showed us the importance of all factors and all potentially could have effect on patients [67].

The catheter tip culture was done for half of patients only, among them, the positive catheter tip culture was observed in 74% of patient, which was higher in comparison to local study by Jaudah and Musa, in which they reported that 51% of patients have positive catheter tip culture [1], and to a study conducted in Pakistan by Mahmood SN, et al. to assess the Frequency and microbiological profile of catheter-related

infections in hemodialysis patients receiving gentamicin as antimicrobial lock therapy for prophylaxis which showed only 33% of patients were have positive catheter tip culture [68].

The catheter tip culture showed that the pseudomonas aeruginosa was the most common bacteria identifies. The local study by Jaudah and Musa from AlBasra, which showed the most common blood culture organism was staphylococcus epidermidis [56].

Binary logistic analysis revealed that gender, duration of dialysis, hypotension, mental involvement, local signs of exit site infection and symptoms during HD free period were have been associated with positive catheter tip culture.

Diabetes acts as an important factor for catheter tip infection, with an increased likelihood of catheter colonization as in Sahli, et al. in 2016 [69]. This result looks accepted by knowing that Diabetes Mellitus will increase the tissue susceptibility to infection [70].

Ghonemy, et al. in 2015 had found a significant relation between hypoalbuminemia and the risk of CTI that was not evident in our study as they take a larger cohort with different comorbidities [71].

In our study, the positive catheter tip culture was associated with leukocytosis as it associated with response to bacterial infection. Jaudah and Musa from AlBasra, did not showed association between the leukocyte count and positive catheter tip culture [56].

The Staphylococcus Aureus (MSSA) and Staphylococcus epidermidis shared approximately the same antibiotic sensitivity for vancomycin and being MDR, comparable to the studies of Katneni and Hedayati [72], Leone and Suter [73], and Sahli, et al. [68]. Unlike the Pseudomonas aeruginosa, Klebsiella and Merabilis that have a different antibiotic sensitivity like that of Gupta, et al. [74].

Regarding the treatment, given the necessity of proper management, we empirically initiate antibiotic therapy as soon as possible, until receiving definite culture results, in hemodialysis patients suspected of bacteremia [63]. In our study, both gram-positive and gram-negative organisms were common. Hence, when initial empirical treatment is indicated, the coverage of both grams positive and gram negative organisms must be considered [75]. The catheter was removed in 44% of patients as a therapeutic intervention, however, with successful antibiotics, the catheter can be preserved [76]. A longer course of tailored antibiotic therapy with catheter removal or exchange is more appropriate in patients with complicated catheter-related bloodstream infections [67]. So patients without complications, we can preserved the catheter.

Antibiotic Lock Therapy (ALT), in conjunction with systemic antibiotics, is recommended by scientific societies as a treatment of uncomplicated catheter-related bloodstream infections in hemodynamically stable hemodialysis patients for whom catheter salvage is the goal.

The rationale for this strategy is the eradication of intraluminal biofilms by the highly concentrated antibiotic used in the lock. In this study, we used the antibiotic lock for 36% of patients.

However, the available evidence supporting this recommendation is scanty and only includes small, short-term, observational studies (most of them single-arm), with different definitions of CRBSI cure and variable follow-up periods. In this editorial we provide a critical view on the available evidence regarding the efficacy of ALT on the treatment of CRBSI in hemodialysis patients, as well as the microbiological issues and technical challenges of this strategy [77,78].

Conclusion

1. Nearly less than half of hemodialysis patients develop signs/symptoms of infection.
2. The blood culture showed nearly 2 third of patients have positive culture.
3. The most common bacteria identified in blood culture was staphylococcus epidermidis, while the staph aureus was reported in 16% of patients.
4. Positive catheter tip culture was observed in 2 third of the patients.
5. The catheter tip culture showed that the pseudomonas aeruginosa was the most common bacteria identified.
6. Methicillin Sensitive Staph (MSSA) and Staphylococcus epidermidis shared approximately the same antibiotic sensitivity for vancomycin.

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