

## Original Research Article

# Haemodialysis catheter-related blood stream infection in ESRD patients: incidence, outcome and antibiogram of the isolated organisms

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### ABSTRACT

**Background:** Catheters are used in roughly between 60- 80% of patients at the time of initiation and 25-30% of all prevalent patients as a bridge to permanent vascular access. Relative risk of mortality due to the dreaded complication of bacteraemia is multiple folds higher with the use of haemodialysis (HD) catheters compared to AV fistulas. In the present study we investigate the incidence, causative organisms and the final outcome of catheter related blood stream infections (CRBSI) in haemodialysis patients.

**Methods:** It was a retrospective cross-sectional study carried in a tertiary care hospital in north India which included adult (>18 years) ESRD patients with the diagnosis of HD CRBSIs in a duration of 2 years.

**Results:** Forty two cases of infection were reported in 39 subjects. In the temporary uncuffed catheter (TUC) group expired patients were older, had lower haemoglobin levels and longer hospital stay although none was significant. In the permanent cuffed catheter group expired patients had longer hospital stay, lower haemoglobin levels. Catheter removal was significantly more in TUCs and salvageability was significantly more in PUCs ( $p = 0.0035$ ). The rise in *Acinetobacter* and *Citrobacter* positive cases and the growing resistance against third generation cephalosporin, carbapenems was a notable phenomenon amongst gram negative organisms.

**Conclusions:** Hemodialysis patients with catheter as vascular access presenting with fever, the first differential diagnosis is CRBSI. They can be managed on an outpatient basis barring those with evidence of severe sepsis. Early removal of temporary uncuffed catheters can give good results in selected patients.

**Keywords:** Antibiogram, CRBSI, Haemodialysis

### INTRODUCTION

A sizeable percentage of patients resort to temporary/permanent central venous catheters for vascular access at the time of initiation of hemodialysis in ESRD patients. The mean incidence of uncuffed temporary catheters is around 5/1000 catheter days and for permanent cuffed catheters 3.5 /1000 catheter days.<sup>1-3</sup> The elderly population, females and diabetics are less

likely to have functional native av fistula at the time of initiation of hemodialysis which puts this high risk group more likely to have prolonged catheter usage.<sup>4-6</sup>

The risk of bacteremia increases tremendously with duration of the catheter use.<sup>7</sup> The relative risk of bacteremia is nearly 7 times in dialysis catheter use compared to native arteriovenous fistulas.<sup>8</sup> It is also reflected in the increase in mortality by upto 50%.<sup>9</sup>

Despite this dismal outlook central venous catheters remain an irreplaceable tool for immediate vascular access. Although the risk of CRBSI they carry adds to the cost and increases the mortality rates.<sup>10, 11</sup> Antibiograms are needed as a guide to manage these infections. However, reported antibiograms in this group of patients are scarce.<sup>2,3</sup>

## METHODS

It was a retrospective cross-sectional study carried in a tertiary care hospital, in northern India which included adult (>18 years) ESRD patients with the diagnosis of HD catheter related blood stream infections (CRBSIs) in a duration of 2 years from September 2013 to August 2015. The diagnosis of CRBSI was based on the clinical presentation of fever, chills and/or hypotension and any of the following two criteria:<sup>12-15</sup>

- Same organism recovered from percutaneous blood culture and from semi-quantitative roll-plate culture (>15 colony forming units) of the catheter tip
- Same organism recovered from a percutaneous and a catheter lumen blood culture, with growth detected 2 hours earlier (i.e. 2 hours less incubation period) in the blood collected through catheter than the blood collected percutaneously.

HD patients who presented with any other source of infection were excluded from the study. Only internal jugular catheters were included in the present study. Salvageable catheters included those which were either retained or exchanged over guidewire. Catheters removed within three days of clinical recognition of bacteremia were considered to be removed immediately beyond which they were considered to have had attempted salvage. Collection and analysis of the data was completely anonymous. All statistical analysis was carried out using SPSS version 16. Mann Whitney test was used for parametric variables. Chi square test and

Fisher exact test were used for qualitative variables. P = 0.05 was taken as statistically significant.

## RESULTS

In 69 cases of suspected CRBSI, forty two cases of catheter related bacteremia (CRB) were reported in 39 subjects. Among rest of the cases, 6 were detected to have pneumonia, 2 had UTI, 1 had gastrointestinal infection were as cultures were negative in 18 of them with no identifiable source of infection. In the 42 reported cases three subjects had two episodes each. Three had polymicrobial infection, all comprising of gram positive and gram negative bacteria. One had infection by *Candida nonalbicans*, successfully treated with removal of the TUC and antifungals. Thirty four subjects had uncuffed temporary catheter in place while eight subjects had permanent cuffed catheter.

### Temporary uncuffed catheter (TUC) group

As it is clear from Table 1, expired patients were older compared to the survived ones but not significantly. Expired patients had a lower haemoglobin, albumin and higher total leucocyte count but none was found to be significant. Expired patients stayed in the hospital for a longer time which possibly is explained by the poor general condition of the individual subjects. Survival was uninfluenced by the gender of the subjects. Hypertension was the dominant comorbidity, present in 76.7% of patients. This was followed by Type 2 diabetes mellitus (26.4%).

### Permanent cuffed catheters (PCCs) group

Table 2 shows that expired patients had longer duration of catheter in situ compared to the survived ones. They also had lower haemoglobin and higher serum ferritin levels although none was found to be significant. Hypertension was present in all the patients followed by type 2 diabetes mellitus (33.3%).

**Table 1: Comparison of demographic variables of subgroups of outcome in temporary uncuffed catheter (TUC) group.**

Variables	Survived (n = 30), mean± SD	Expired (n = 4) mean± SD	p value
Age (years)	39 ± 16.09	45.25±15.43	0.54
Sex	M-17 (56.7%), F-13 (43.3%)	M-2 (50%), F-2 (50%)	1.0
Comorbidity	T2DM-7 (23.3%) HTN- 23 (76.7%)	T2DM-2 (50%) HTN- 3 (75%)	0.24
Duration of catheter in situ (days)	28.8± 19.13	27.5±14.52	0.52
Hemoglobin (g/dl)	7.51±1.42	6.85±0.34	0.18
Albumin (mg/dl)	3.46±0.77	3.26±0.30	0.58
TLC per cumm	11.21±4.58	14.30±4.12	0.14
Iron (µg/dl)	44.92±21.85	44.50±28.21	0.93
Transferrin saturation (%)	29.59±39.37	19.45±10.74	0.82
Ferritin (ng/ml)	467.18±348.37	350.57±198.71	0.73
Duration of hospital stay (days)	14.10±8.63 (in 14 pts.)	20.66±7.02 (in 3 pts.)	0.21

T2DM = type 2 Diabetes Mellitus, HTN= hypertension

**Table 2: Comparison of demographic variables in two subgroups of permanent cuffed catheters (PCC).**

Variables	Survived (n = 6) mean±SD	Expired (n = 2) mean±SD	p value
Age (years)	45.3±12.13	39±8.45	0.42
Sex	M-5(62.5%), F-1(12.5%)	M-0, F-2(100%)	0.37
Comorbidity	T2DM-2(33.3%) HTN- 6(100%)	T2DM-0 HTN- 2(100%)	1.0
Duration of catheter in situ (days)	57.83±42.48	82.5±53.0	0.42
Hemoglobin (g/dl)	8.61±1.63	7.35±1.62	0.42
Albumin(mg/dl)	3.36±0.54	3.21±1.06	0.87
TLC per cumm	12.87±6.97	13.92±5.76	0.85
Iron (µg/dl)	45.50±16.92	52±18.38	1.0
Transferrin saturation (%)	28.04±10.33	30.41±4.95	0.73
Ferritin (ng/ml)	674.50±198.15	866.5±259.57	0.28
Duration of hospital stay (days)	7.33±4.51(n-3)	7.0±0(n-1)	

T2DM- type 2 Diabetes Mellitus, HTN- hypertension

**Table 3: Antibigram for gram-positive bacteria. Percentage susceptibility. Number in parenthesis is the number of isolates tested for that particular bacteria.**

Bacteria No.of isolates against tested drug	CONS (16)	MSSA (3)	MRSA (5)	Enterococcus (2)
Amikacin	80 (5)	100 (2)	50 (2)	
Cefoperazone sulbactam	100 (3)	100 (2)	0 (1)	
Ceftriaxone sulbactam	100 (2)			
Cefoxitin			0 (1)	
Chloramphenicol	83.3 (6)	100 (2)	100 (1)	100 (1)
Ciprofloxacin	61.5 (13)	33.3 (3)	0 (3)	0 (1)
Clindamycin	76.9 (13)	66.7 (3)	50 (2)	
Doxycycline	84.6 (13)	100 (2)	6.7 (3)	100 (1)
Erythromycin	69.2 (13)	66.7 (3)	50 (2)	0 (1)
Gentamicin	54.5 (11)	50 (2)	0 (2)	0 (1)
Levofloxacin	60 (5)	50 (2)		0 (1)
Linezolid	100 (6)	100 (1)	100 (1)	100 (1)
Netilmycin	83.3 (6)	100 (2)	100 (1)	
Ofloxacin	33.3 (3)	0 (2)	0 (1)	
Oxacillin	41.7 (12)	100 (3)	0 (2)	100 (1)
Penicillin	23.1 (13)	0 (3)	0 (3)	0 (1)
Teicoplanin	100 (13)	100 (3)	100 (3)	0 (1)
Tetracycline	84.6 (13)	50 (2)	0 (2)	100 (1)
Tobramycin	75 (4)	100 (2)	0 (1)	
Vancomycin			100 (1)	

CONS-coagulase negative *Staphylococci aureus*, MSSA- methicillin sensitive *Staphylococci aureus*, MRSA- methicillin resistant *Staphylococcus aureus*, HD- haemodialysis.

### Treatment

Referring to Figure 1, salvage was initially attempted in 16 TUCs and 7 PCCs. It failed in 11 TUCs as the patients continued to have fever with two of them growing same initial organism in repeated blood culture forcing the ultimate removal of the catheter. Out of the five (31.25%) successfully salvaged TUCs catheters three underwent exchange and two continued on the same catheter, treated with antibiotics. Amongst PCCs, five (71.42%) were successfully salvaged with antibiotics alone.

In 18 (52.9%) cases of the TUCs, catheter was removed within three days (immediate) of presentation. Out of these four patients died. The prime reason for the removal of the catheter was the degree of severity of infection with on-going sepsis. All cases undergoing late removal survived. Catheter removal was significantly more in TUCs and salvageability was significantly more in PCCs. ( $p = 0.0035$ ). Comorbidity had no influence on the likelihood of salvageability of the catheters. Only one patient (with TUC) had evidence of metastatic complication in the form of endocarditis in which the catheter was ultimately removed and successfully treated with prolonged course of antibiotics. Type of organism

did not significantly influence the salvageability or the ultimate outcome.

Table 3 and 4 shows the antibiogram of the gram positive and negative organisms. Gram positive organisms were more as compared to gram negative ones (57.8% versus

40%). Gram positive organisms had 100 % sensitivity to linezolid. Teicoplanin was also effective against most of them except *Enterococcus*. The rise in *Acinetobacter* and *Citrobacter* positive cases and the growing resistance against third generation cephalosporins, carbapenems was a notable phenomenon amongst gram negative organism.

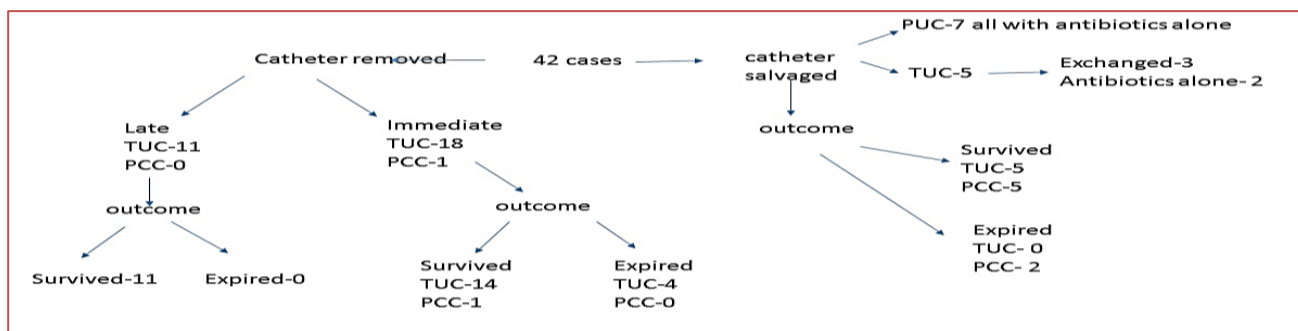


Figure 1: Flow chart for treatment schedule.

Table 4: Antibiogram for gram-negative bacteria. Percentage susceptibility. Number in parenthesis is the number of isolates tested for that particular bacteria.

Bacteria with No of isolates against tested drug	<i>Acinetobacter</i> (5)	<i>Klebsiella</i> (4)	<i>E. coli</i> (1)	<i>Pseudomonas</i> (2)	<i>Citrobacter</i> (3)	<i>Enterobacter</i> (3)
Amikacin	33.3 (3)	66.7 (3)		100 (2)	0 (2)	100 (2)
Ampicillin sulbactam	50 (4)	50 (4)			0 (2)	50 (2)
Aztreonam	50 (2)	33.3 (3)	0 (1)	50 (2)	50 (2)	66.7 (3)
Cefepime	33.3 (3)	66.7(3)	0 (1)	0 (1)	66.7 (3)	100 (2)
Cefoperazone sulbactam	66.7 (3)	66.7(3)		100 (1)	50 (2)	100 (1)
Cefotaxime	100 (1)	50 (2)			50 (2)	50 (2)
Ceftazidime	25 (4)	50 (2)	0 (1)	100 (2)	0 (1)	
Ceftriaxone sulbactam	100 (1)				100 (1)	
Chloramphenicol						100 (1)
Ciprofloxacin	80 (5)	75 (4)	100 (1)	100 (2)	100 (2)	100 (3)
Colistin	100 (2)				100 (1)	100 (1)
Doripenem	33.3 (3)				100 (1)	
Doxycycline	100 (4)	75 (4)	100 (1)	100 (1)	66.7 (3)	100 (2)
Ertapenem	50 (2)	66.7 (3)	100 (1)		50 (2)	100 (3)
Gentamicin	80 (5)	50 (2)	0 (1)	100 (1)	66.7 (3)	100 (2)
Imipenem	25 (25)	66.7 (3)		100 (1)	50 (2)	100 (3)
Levofloxacin	75 (4)	100 (3)		100 (1)	100 (1)	
Meropenem	75 (4)	75 (4)			50 (2)	100(2)
Netilmicin	33.3 (3)	50 (4)		100 (1)	0 (1)	
Ofloxacin	100 (1)					
Piperacillin-tazobactam	100 (4)	50 (4)	100 (1)	100 (2)	50 (3)	100 (2)
Tetracycline	4 (100)	33.3 (3)			100 (2)	100 (2)
Tigecycline	100 (1)	100 (2)			0 (1)	
Tobramycin	66.7 (3)	50 (4)		100 (1)	0 (2)	100 (1)
Trimethoprim-sulfamethoxazole	0 (1)					100 (1)

## DISCUSSION

In our study, incidence of CRB in TUCs was 5.37 episodes per 1000 catheter days and 6.5 episodes per 1000 catheter days in case of PCCs. It is higher as compared to other studies.<sup>3, 16</sup> KDOQI guidelines suggest that incidence of CRB should be less than 10% at 3 months and 50% at 1 year.<sup>17</sup>

The paucity of diabetic cases in our study (27.7%) seen in our study stands in contrast to the study done by Jean et al.<sup>18</sup> The demographic data of survived and expired subjects did show some difference albeit none was significant. This can be explained by the small number of subjects included in the study.

The dominance of gram positive organisms in HD CRBSI has been shown in a number of studies. Our study results follow the trend with gram positive organisms outnumbering others (57.8%). Gram negatives are the ones to follow next with polymicrobials and fungal species being amongst the lesser common ones.<sup>19-22</sup> Gram negative bacteria are isolated in 27-36% of cases with fungal isolates reported in <10% of cases.<sup>23,24</sup>

However, this trend is not universal with Alexandraki et al. reporting a significant increase in the incidence of gram-negative organisms (43.3%) and polymicrobial (28.1%) bacteraemias.<sup>25</sup> We also found a high incidence of gram negative organisms at 40%. Growing prevalence of gram-negative bacteria has been related to the immunocompromised state of patients, contaminated infusate and overexposure of antibiotics.<sup>26-29</sup> The dominance of *Acinetobacter* in our study is a worrying phenomenon as it is a potential ESBL.

In our study there were only two episodes of infection occurring within eight days of catheter insertion which possibly indicates a lesser chance of procedural lapses during catheter insertion. Hence the likely reasons could have been the migration of the skin organism to catheter tip or through the catheter hub. Nurses/technician to patient ratio of 1:3 was followed during the entire period of study which is usually the recommended ratio. With no significant care limitations based on time, cost, or other consumables it is possible that some lapses in the handling of the catheters might have occurred. Onset of contamination of catheters occurs mainly through four routes: 1) skin organisms migrating through catheter insertion site colonizing the catheter tip; 2) direct contact with hand, contaminated fluid; 3) another source of infection seeding the catheter through haematogenous route.<sup>30-32</sup> This highlights the importance of following the sterile procedure carefully and time to time reassessment of the practice.

Thrombogenicity of the catheter material also promotes thrombus formation leading to catheter colonization.<sup>33, 34</sup> Although poor functionality due to thrombus formation was rarely (1 case) seen in our study. Membrane reuse

has been regarded as an independent risk factor for septicaemia.<sup>7</sup> In our centre the average reuse of the dialyser was around eight times.

Nasal carriers of *S. aureus* are predisposed to CRBSI as it gets disseminated to catheter site through hands.<sup>35-37</sup> The rate of nasal carriage of *S. aureus* varies from 11-60%.<sup>36,37</sup> In our centre of hemodialysis, a higher prevalence of 75% was found (not shown).

Poor immune status of ESRD patients with multiple comorbidities has made the scenario worse. A sizable proportion of subjects in our study were hypertensive and had low albumin levels perhaps suffering from malnutrition.<sup>38,39</sup> Hypoalbuminemia (<3.5) has been reported to be a risk factor for recurrent bacteraemia.<sup>40</sup> Oxidative stress can further lead to defective T cell mediated immunity.<sup>41,42</sup> High ferritin levels in the expired patients in our study point in this direction.

Complications like endocarditis, osteomyelitis, septic arthritis, septic emboli, and atrial thrombi occur in a number of patients with incidence ranging from 22-44%.<sup>21, 22, 43-45</sup>

This is in contrast to our study as we could detect only one complication in the form of endocarditis. The rarity of metastatic complication can be explained by the fact that most patients presented early (within seven days) and aggressiveness in the management with low threshold for removal of the temporary catheters (85.29%). Other reason for this could also be the fact that patients were subjected to thorough investigations only when they failed to clear CAB in the expected time duration. The incidence of infectious complications has been reported higher in cases of catheter salvage.<sup>46</sup>

Approach to management of CRBSI varies to some extent from centre to centre. Marr et al were able to salvage 32% of catheters (PCCs) by treating them with antibiotics and catheter in place.<sup>16</sup> 56% salvageability was reported in one of the studies with an empirical therapy of amikacin and vancomycin.<sup>47</sup> In our centre salvageability was particularly low for TUCs (31.25%) compared to that of PCCs (71.42%).

Usual indications for removal of HD catheter are: persistence of fever and positive blood culture while on systemic antibiotics for 36-48 hours, recurrence of fever and bacteraemia despite adequate dosage and duration of systemic antibiotics, exit site of infection with catheter tunnel involvement, hypotension and metastatic complications.<sup>48</sup>

In our study early removal of the catheter was primarily based on the clinical presentation although long duration of the catheter use beyond the recommended period could also have shifted the balance of decision in favour of its removal. Fever is usually the most common presenting sign with CRBSI which was universal in our study.<sup>47</sup>

Need of hospitalisation is affected by the type of organism isolated, highest being for *S. aureus* followed by enterococcus and gram negative bacteria.<sup>47</sup> Our study did not show any such association.

Our study is limited by its observational design. Secondly, there was no control on the length of time the catheters were in place as most patients exceeded the time period advised for the temporary catheters to be in place. The lack of alternate vascular access might have influenced the decision to salvage the catheter particularly in the case of permcaths. Future larger prospective studies are warranted to study the various aspects pertaining to catheter salvageability.

## CONCLUSION

To summarize, haemodialysis patients with catheter as vascular access presenting with fever, the first differential diagnosis is CRBSI. They need to be investigated accordingly, simultaneously ruling out any other source of infection.

There is a growing incidence of gram negative infections highlighted in this study. Resistance to third generation cephalosporins and carbapenems amongst gram negatives is also a worrying phenomenon. Hospitals need to formulate their own antibiotic protocol based on antibiograms.

This study provides vital information in the form of antibiogram to be used in this part of the country. In both TUCs and PCCs, catheters salvage can be attempted in those without evidence of severe sepsis.

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