

## Frequency and Microbiological Profile of Catheter-Related Infections in Hemodialysis Patients Receiving Gentamicin as Antimicrobial Lock Therapy for Prophylaxis

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### Abstract

**Background and Objective:** Use of Tunneled cuffed catheters (TCC) and non tunneled catheters are commonly used as an access for hemodialysis (HD). They remain a source of infection in this patient population and results in significant morbidity and mortality, and poses a great financial burden on health care system.

Antibiotic lock solution (ALS) in the lumen of catheter is a mean to decrease the possibility of catheter related blood stream infection (CRBSI). We conducted this study using Gentamicin as ALS to observe the frequency of catheter related infections (CRI) including CRBSI and exit site infection in this hemodialysis patients being dialyzed through tunneled and temporary hemodialysis catheters.

**Methods** This descriptive, cross sectional study was conducted at Dr. Ziauddin Hospital, North Campus between January 2017-December 2017.

Symptomatic patients for CRBSI were included in this study. Blood culture from the catheter ports and periphery and exit site swab if pus visible were sent for culture sensitivity. Actual frequencies and comorbid conditions effect was analyzed.

**Results** Total 138 patients of either gender with age more than 18 years to less than 80 years were evaluated. 44.9% were male and mean age of patients was 58.79±14.05 years. 70.3% patients were diabetic for 15.61±4.61 years and 11.6% were using immunosuppressive drugs.

The overall mean catheter duration was 22.27±14.39 days and mean hemodialysis duration was 25.32±44.31 weeks. Tunneled catheter was placed in 40.6% and 46.4% had femoral temporary catheters. Blood culture was done for 51 cases and 21.5% were positive. Tip culture was positive in 33.3% patients. No significant association of catheter related infections with gender, age, catheter duration, catheter type, catheter site and diabetes mellitus was found,  $p>0.05$ . Microbiological profile data showed a predominance of Gram-positive organisms. In our study, 23.18% patients were found to have catheter related infections, out of which 61.5% were found with gentamicin resistance including colonization.

**Conclusion** We report a high frequency of catheter related infections despite using ALS as prophylaxis, with predominant organisms being gram positives and a high incidence of gentamycin resistance.

**Keywords:** Catheter related infections, antibiotic lock solution , Gentamycin, Hemodialysis, frequency

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### Introduction:

Use of double lumen catheters (both tunneled and non-tunneled) as an access for hemodialysis (HD) remains common worldwide. Despite multiple guidelines to avoid its use in patients anticipated to start HD non cuffed catheters remain the main source of vascular access in patients requiring acute HD, and hence are indispensable. Latest data in US reported about 80% of patients initiate chronic HD via a tunneled cuff dual lumen catheter.<sup>1,2</sup>

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These catheters can be used for short term basis as a bridge for maturity of arteriovenous fistula (AVF) or may be used as permanent access in those who do not have alternative options, like those with low ejection fraction or poor vessels in which AVF or AV grafts are not possible.<sup>3</sup>

Both tunneled cuffed catheters (TCC) and non-cuffed catheters have complications, with infections being the most prevalent that include exit site infection, tunnel infections and catheter related blood stream infection (CRBSI).<sup>4,7</sup> Other infectious complications that are life threatening include endocarditis, lung abscess, osteomyelitis and endophthalmitis.<sup>8</sup> Non infectious complications include central venous stenosis and catheter thrombosis.

Since catheter related infections (CRI) poses a great risk both in terms of morbidity and mortality it also has a substantial burden on cost to the health care system. According to US renal data system, infection is the most leading cause of death on patients with end stage renal disease (ESRD) and leading cause of catheter removal and morbidity in dialysis patients.<sup>9-12</sup>

Several modalities including intraluminal and extraluminal approaches have been assessed as a means to prevent CRI, one of which is to instill an antimicrobial solution (ALS) into the lumen of catheter to avoid intra luminal source of infection, as these solutions can prevent biofilm formation which constitutes a permanent source of bacteremia.<sup>13</sup>

Jaffer et al. meta analyzed several RCT in patients with HD with catheters and showed that ALS had a positive trend in reducing frequency of CRI without producing significant side effects.<sup>14</sup> The available ALS include Gentamycin, Vancomycin, Cefotaxime and Cefazolin beside others, in combination with citrate or heparin. Clinical practice guidelines recommend ALS therapy for better prevention and treatment of CRI.<sup>15,16</sup>

### Objective:

We conducted this descriptive, cross sectional study to a) see the frequency of CRI including CRBSI, exit site infection and catheter tip infections in patients undergoing HD via tunneled or non-tunneled catheters receiving Gentamycin as ALS as prophylaxis and b). the microbiological profiles of patients developing these infections. In addition, incidence of gentamycin resistance was also observed.

### Methods

This descriptive, cross sectional study was conducted at Dr. Ziauddin Hospital, North Campus between January 2017- December 2017.

**Inclusion Criteria.** All adult patients more than 18 years and less than 80 years of age, both males and females undergoing HD via tunneled catheter inserted as a bridge for maturity of AVF or via non tunneled temporary HD catheter inserted for acute HD after informed consent were enrolled in the study.

**Exclusion Criteria:** Refusal to participate in the study, those with bacteremia from known alternate sites and patients with previous history of intravenous drug abuse, chronic skin wounds, endocarditis and HIV infection were excluded. Patients who had tunneled catheters inserted as permanent access were also excluded.

All patients received gentamycin as ALS on Day 1 of insertion of catheter and after every HD session in the following manner in tunneled-catheters: 5,000 international units of heparin with 10mg gentamicin in 1ml 0.9% saline.

In non-tunneled catheters: 10,000 international units of heparin with 20mg gentamicin in 2ml 0.9% saline.

Data was collected for signs of infection if patients developed fever (temperature more than 100

<sup>o</sup>F), shivering, unexplained tachycardia or hypotension (mean arterial blood pressure <65 mmHg), and blood culture both from periphery and catheter port was taken. In addition, culture of the catheter tip was sent if catheter was removed either because of persistent infective signs or routine removal of catheter once indication of HD via catheter was terminated. CRBSI was defined as any positive blood or catheter tip growing an organism, with colony counts of >10<sup>5</sup> colony forming units/ml along with symptoms of infection.

Colonization was defined as any catheter tip growing significant organisms without clinical signs of infection.

Exit site infection was defined as positive pus culture taken from insertion site of catheter.

Data was recorded for age, gender, type of catheter (tunnelled or non-tunnelled), duration of the use of catheter, site of catheter placement (femoral, internal jugular or subclavian), duration on hemodialysis, diabetes mellitus, immunosuppressive drugs, duration of use of immunosuppressive drugs, and any other source of infection.

Culture was performed using MacConkey agar and Antibiotic Disc Diffusion method was used for testing for antibiotic sensitivity. Catheter tips, in cases where they were removed, were cultured using Mannitol Salt Agar (MSA) or Sheep Blood Agar (SBA). In patients with exit-site purulent discharge, pus culture was taken using a sterile swab and culture was performed using MacConkey agar and Antibiotic Disc Diffusion method was used for testing for antibiotic sensitivity.

### Statistical Analysis:

Data was analyzed using SPSS version 23.0 (Armonk, New York, USA).

Mean and standard deviation was calculated for quantitative variables like age, duration of use of catheter. Frequency and percentage were calculated for qualitative variables like gender, catheter-related infection, and diabetes mellitus.

Effect modifiers like age, gender, duration of use of catheter, duration of diabetes, duration of immunosuppressive drugs, site of catheter and type of catheter was controlled through stratification. Post-stratification Chi-square test was applied by taking p-value less than 0.05 as significant

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### Results

Total 138 patients of either gender with age more than 18 years to less than 80 years meeting inclusion criteria of study were evaluated. Demographic data is presented in Table 1. Mean age of patients was 58.79±14.05 years .

**Table – 1:** Baseline characteristics of 138 patients undergoing hemodialysis using temporary and tunneled hemodialysis catheter.

Characteristics	Frequency (%)
Age	58.79+/- 14.05
Age >60 years	67(49)
Age <60 years	71(51)
Male / Female	62 (44.9) /76 (55.1)
Diabetics Mellitus & Duration (Years)	97(70.3) /15.61+/- 4.61
Immunosuppression	16 (11.6)
Catheter Duration (Days)	22.27 +/- 14.39
Hemodialysis Duration (Days)	25.32 +/- 44.31

Majority of the patients 70.3% patients were diabetic with mean duration 15.61±4.61 years Among diabetic patients, 36.1% had good control of DM with HbA1c<7. Immunosuppressive drugs were found positive for 11.6% patients with mean usage duration 26.25±21.56 days.

The overall mean catheter duration was 22.27±14.39 days and mean hemodialysis duration was 25.32±44.31 weeks as shown in Table 1 and Table 2 describes details of catheter characteristics.

**Table 2:** Type of hemodialysis catheters and its duration among 138 patients undergoing hemodialysis.

Catheter Characteristics	Frequency (%)
Catheter type Tunneled / Non-Tunneled	56 (40.6) / 82 (59.4)
Duration of Catheter (Days) <14 / >14	62 (45*) / 76 (55*)
Site Femoral / Internal Jugular	64 (46.4) / 74 (53.6)

\*Days

Blood culture was done for 51 cases, out of which 21.5% were found positive. Tip culture was done for 90 cases, out of which 33.3% were found positive. Further evaluation of data found that out of 30 cases positive for tip culture only 10 (11.1%) were positive in symptomatic patients and the rest 20 (22.2%) were positive in patients in which tip was sent as routine once the catheter was removed and hence was considered colonization.

Microbiological profile data showed a predominance of Gram-positive organisms with 36/52 (69.23%) being gram positive and 16/52 (30.76%) gram negative organisms. Details of the organisms are reported in Table 3. In our study, 23.18% patients were found to have catheter related infections, out of which 61.5% were found with gentamicin resistance including colonization. (Table 3). Pus culture was done for 11 cases and all were found positive as described in Table 4.

Stratification with respect to gender, age, catheter duration, catheter type, catheter site and diabetes mellitus was done to observe effect of these modifiers on catheter related infections. P-value ≤0.05 was considered as significant.

**Table 3:** Microbiological profile of organisms isolated in 52 of 138 patients undergoing hemodialysis via temporary or permanent catheter.

Microorganism	Blood Culture	Exit site	Catheter tip(symptomatic)	Catheter tip (asymptomatic)	Resistance to Gentamycin
Coagulase negative Staph	5	3	4	8	14
MRSA	2	3	3	6	8
Klebsiella	1	2	2	3	5
VRE	2	0	0	0	1
Pseudomonas	0	3	0	2	3
Acinetobacter	1	0	0	0	1
E. coli	0	0	1	1	0
TOTAL	11	11	10	20	32

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The results showed insignificant association of catheter related infections with gender ( $p=0.404$ ), age ( $p=0.187$ ), catheter duration ( $p=0.630$ ), catheter type ( $p=0.748$ ), catheter site ( $p=0.147$ ) and diabetes mellitus ( $p=0.551$ ) as shown in Table 5

**Table 4:** Frequency distribution of cultures obtained for suspected infections in 138 patients undergoing maintenance hemodialysis via tunneled and temporary venous catheters.

Source		Positive	Negative	Total
Blood		11	40	11/51(21.5)
Pus		11	0	11/11(100)
Catheter Tip	Symptomatic	10	60	10/90(11.1)
	Asymptomatic	20		20/90(22.2)

### Discussion

To our knowledge this is the third study from Pakistan to obtain frequency of catheter related infections and only study to detail their microbiological profiles in patients receiving ALS. We did not find any significant association of catheter related infections with gender, age, catheter duration, catheter type, catheter site, and diabetes mellitus.

The earlier two studies using Gentamicin similar to our study however found a significant prevention of CRI with ALS.<sup>17,18</sup> The earlier studies were comparative studies whereas we here report the frequency of CRI as a cross sectional study. We have reported the microbiological profile whereas the other studies by Kashif et.al. and Shabaz et.al., only reported being positive or negative.<sup>17,18</sup> We have also shown a higher rate of Gentamicin resistance in 32/52 (61%) of CRI. Furthermore, 18/52 (35%) had culture positive for gram negative organisms and VRE.

**Table 5:** Chi Square test applied on Patient and catheter characteristics influence on CRI in 138 hemodialysis patients,

Patient and catheter characteristics		Catheter related infection		Total	P-Value
		Yes	No		
Gender	Male	21 (33.9)	41 (66.1)	62	0.404**
	Female	31 (40.8)	45 (59.2)	76	
	Total	52	86	138	
Age	<60	23 (32.4)	48 (67.6)	71	0.187**
	>60	29 (43.3)	38 (56.7)	67	
	Total	52	86	138	
Catheter duration	<14 days	22 (35.5)	40 (64.5)	62	0.630**
	>14 Days	30 (39.5)	46 (60.5)	76	
	Total	52	86	138	
Catheter type	Tunneled	22 (39.3)	34 (60.7)	56	0.748**
	Non-Tunneled	30 (36.6)	52 (63.4)	82	
	Total	52	86	138	
Catheter site	Femoral	20 (31.3)	44 (68.8)	64	0.147**
	Internal jugular	32 (43.2)	42 (56.8)	74	
	Total	52	86	138	

\*\*Not Significant at p value of < 0.05 levels

Our study did not find any correlation to catheter duration and diabetes which is contradictory to published data in which these two variables have been associated with risks of CRBSI as reported by F. Sahli et al and Lemaire et al., however their study was in patients who did not receive any ALS, whether ALS is helpful in these groups cannot be commented as we do not have controls and our study population is limited study.<sup>19,20</sup>

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Our study is in accordance with data provided by Nabi et al, and others where catheter site whether femoral or internal jugular had no correlation to catheter related infections.<sup>21-22</sup>

We report a high frequency of gram-positive organisms in our study with Coagulase negative *Staphylococcus* and Methicillin Resistant *Staph. Aureus* dominating the profile as well as a high incidence of gentamycin resistance with nearly 70% of organisms were resistant to it.

A similar study by Landry et al. was conducted which aimed at assessment of the long-term consequences of a gentamicin and heparin lock (GHL) protocol in maintenance hemodialysis patients using a TCC and to document the associated emergence of gentamicin-resistant bacteremia in these patients.<sup>23</sup> For all patients receiving hemodialysis during the 4-year study period (TCC and AV access), there were 131 episodes of bacteremia in 113 patients. In their study, a total of 121 Gram-positive bacteria (including 48 *Staphylococcus aureus*, 37 coagulase-negative *Staphylococcus*, and 17 *Enterococcus faecalis*) and 17 Gram-negative organisms (most common being *E. coli*) were identified by blood culture. In terms of Gentamicin resistance, the Gram-positive group had 24 instances of resistance organisms with the most common being coagulase-negative *Staphylococcus* followed by *Faecalis*.<sup>7,13</sup> In the gram-negative group, no incidence of gentamicin resistance was observed in this study.

A single-center observational study from New Zealand found a trend toward increasing gentamicin resistance among coagulase-negative *Staphylococci* isolated from hemodialysis patients with a TCC receiving a GHL.<sup>24</sup>

There are no RCTs comparing the frequency of catheter related bacteremia with tunneled or non-tunneled HD catheters; although some previous prospective nonrandomized studies of HD patients observed a catheter-related bacteremia rate that was 2- to 3-fold greater for non-tunneled compared with tunneled CVC.<sup>25</sup> A latest multicenter study of incident HD patients found that, compared with patients with AVFs, the age-adjusted relative risk for developing a bloodstream infection in patients with arteriovenous grafts was 1.69 (95% CI, 0.42-6.79); with tunneled CVC, 9.78 (95% CI, 3.53-27.11) and with no tunneled CVC, 10.54 (95% CI, 3.69-28.20).<sup>26</sup> Therefore, using tunneled or no tunneled dialysis catheters, skin flora can be introduced into the lumen during manipulation of the catheter and form a biofilm, which serves as a nidus for catheter related bacteremia. These results are almost similar to our study where we are seeing an overall nearly 20% infection rate with these catheters. Having a tunneled catheter in 41% of our patients had an impact on microbiological profile is speculative. The handling of tunneled catheters in our local circumstances need further evaluation and lack of strict protocol implementation is speculative. A separate study in tunneled hemodialysis catheters for evaluation of these factors and frequency of CRI is needed since more of our patients with tunneled catheter had CRI 39% vs 36.6%, Table 5.

The use of an alternative, nonantibiotic, catheter lock is a possible solution to prevent CRI in chronic hemodialysis patients with a TCC. Unfortunately, currently available alternative locks all have ongoing questions and concerns beyond their rather limited study data. Taurolidine with 4% sodium citrate has been shown to be effective in several studies but may be associated with an increase in catheter thrombosis and is not currently available in the United States.<sup>27,28</sup> High-dose citrate (30 to 47%) has been well studied but is complicated by the rare but fatal risk of hypocalcemia that led to the FDA's recall of 47% citrate in 2000.<sup>29</sup>

In a recent Cochrane review by Arechabal et.al. noted a significant benefit of ALS compared to the non-antibiotic lock solution or standard catheter lock with Heparin.<sup>30</sup> Our study in comparison to this and other studies have shown a high frequency of CRI even with ALS possibly due to large number of gentamicin resistance in our patients. A detailed analysis and further local studies are needed to document the actual prevalence of antibiotic resistance among our maintenance hemodialysis patients.

The major limitation of our study is the small sample size and lack of control group so whether ALS is helpful in reducing infection rates cannot be commented.

## Conclusion

Our study showed high frequency of catheter related infection and colonization. A high rate of gentamicin resistance was also noted among our patients. We suggest a randomized controlled study comparing ALS and standard catheter lock solution in MHD patients. Furthermore, local data on antimicrobial resistance patterns are needed to plan such studies.

**Conflict of Interest :** The authors do not report any conflict of interest or source of funding.

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