CATHETER-RELATED BLOODSTREAM INFECTION AMONG HEMODIALYSIS PATIENTS: INCIDENCE AND MICROBIOLOGICAL PROFILE

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ABSTRACT

Background

Catheter-related bloodstream infections are the most serious infection complication among hemodialysis patients.

Objectives

To identify the incidence of catheter-related bloodstream infections among hemodialysis patients in Sulaimani city. Also to find the relationship of infection with the catheter type, site, and duration, and to identify the causative organisms and their antimicrobial susceptibility.

Methods

A cross-sectional observational study done in hemodialysis patients suspected to have catheter-related bloodstream infections. Two blood samples (from peripheral vein and catheter lumen) were cultured aerobically on blood culture media. Removed catheters were also cultured aerobically to detect catheter colonization. Isolates were identified based on cultural characteristic, microscopy, biochemical profile and Vitek® 2 system. Antimicrobial susceptibilities test done using Kirby-Bauer method.

Results

A total 117 patients suspected to have catheter-related bloodstream infections were included from two dialysis centers (49 from Shar center and 68 from Qirga center). These patients experienced 164 suspected infection episodes, of these, 146 (89%) yielded bacterial growth giving infection incidence of 24.95 per 1000 dialysis-sessions through different catheters. Coagulase-negative staphylococci were the commonest isolates in both centers, 51.5% and 19.3% in Shar and Qirga center respectively followed by *S. aureus* (25.7%) in Shar and pseudomonas spp. (15.8%) in Qirga center. Catheter colonization was caused by coagulase-negative staphylococci (39.1%) in Shar and Pseudomonas spp. (23.3%) in Qirga. Linezolid, tigecycline and teicoplanin were most effective against most gram-positive bacteria. Likewise, ampicillin-sulbactam and piperacillin-tazobactam were effective against most of the gram-negative isolates. None of the empirically used antibiotics, vancomycin and gentamicin, was fully effective against all the isolates.

Conclusion

Incidence of catheter-related bloodstream infections is high in Sulaimani dialysis centers. The dialysis centers revealed different isolates but mainly staphylococci and pseudomonas spp. Prolong empirical antimicrobial use is not recommended and such infections should be treated according to the antimicrobial susceptibility results. Infection was less with permanent tunneled catheters compared to temporary catheters, however, temporary hemodialysis catheter inserted to internal jugular vein showed less chance of infection than in subclavian and femoral vein catheters.

Keywords: *Hemodialysis, Central venous catheters, Catheter-related bloodstream infection, Sulaimani.*

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INTRODUCTION

Patients undergoing hemodialysis are commonly prone to infections due to their frequent hospitalization and inserted catheters that overcome local immunity and this result in an increase in morbidity and mortality of hemodialysis patients [1]. For hemodialysis, the international guidelines recommends arteriovenous fistula (AVF) as a vascular access; however, when a functioning AVF cannot be established, a hemodialysis (HD) catheters are opted for hemodialysis [2] . Despite all the preventive measures and applied guidelines, the incidence of infection is highest in patients with HD catheter compared to those who have AVF [3, 4] .

Hemodialysis catheter-related-infections include catheter exit site infections (ESI), tunnel infections, and catheter-related bloodstream infections (CR-BSI), which is the most serious infection complication. Patients with CR-BSI usually present with a sudden onset of fever and/or chills with or without signs and symptoms of sepsis such as hypotension and without a clear infection source apart from the HD catheter [5, 6]. The Clinical definition of CR-BSI varies according to different international organizations such as Centers for Disease Control and Prevention (CDC), Infectious Diseases Society of America (IDSA), National Kidney Foundation - Kidney Disease Outcomes Quality Initiative (NKF KDOQI), and Public Health Agency of Canada; however CDC defines CR-BSI as " a patient with accompanying symptoms of BSI and no other apparent source of infection apart from the HD catheter plus isolation of the same organism from semi-quantitative or quantitative catheter tip culture and from blood culture (preferably from a peripheral vein) " or " isolation of same organism from simultaneous cultures of blood samples from catheter lumen and peripheral vein with a ratio of ≥3:1 (catheter vs. peripheral) " or " same organism grown from blood cultures of two different lumens of the same catheter " [6] .

The catheter-related bacteremia starts when bacteria access circulation through two main routes: bacteria move from the catheter entry site through the patient's skin and down the external surface of the catheter to the catheter tip, or by migration of the organisms through the catheter hub and along the lumen to the catheter tip [7]. In either way, the organisms may reach the blood stream and may multiply to cause bacteremia and hence bloodstream infections [8]. Possible serious and immediate consequences of presence of microorganisms in the bloodstream are shock, multiple organ failure, disseminated intravascular coagulation, and death [9] .

The incidence of CR-BSI varies in different countries and different centers; it ranges from 0.46 to 30 per 1000 catheter-days, or from 4.3% to 26% of placed catheters [10-13]. The incidence of CR-BSI is related to the type of catheter and the site of vascular access. Temporary (non-tunneled) catheter and permanent (tunneled) catheter carry different risks of infection as different vascular sites such as, subclavian, internal jugular and femoral veins carry different risks [5].

The common causative organisms of CR-BSI are organisms that inhabit the skin of the patients such as coagulase-negative staphylococci (CoNS) especially *Staphylococcus epidermidis* [14]. *Staphylococcus aureus* is also playing an important role in causing CR-BSI; the organism inhabits the anterior nares and the skin of both patients and the medical staff [14, 15]. Organisms with the ability to produce biofilm are most suited for causing CR-BSI [16]. Like other biofilm-related infection, the main problem of mature biofilms in case of catheter-related infection is the ability of biofilm cells to survive antimicrobial agents and the host immune system [17, 18]. Many studies concluded that gram-positive bacteria are responsible of the majority of the CR-BSI, followed by gram-negative bacteria [5, 19], however others pointed that gram-negative bacteria makes a bigger proportion than gram-positives [20, 21]. Causative organisms other than aerobic gram-positives and gram-negatives include anaerobes and fungi [14]. Microorganisms causing CR-BSI are becoming more resistant to antimicrobials. Therefore, timely detection and identification of pathogens in the blood are important for proper management [22]. The choice of empirical antimicrobial treatment of CR-BSI varies among different dialysis centers; therefore, every dialysis center should investigate their own causative organisms of CR-BSI [5, 23].

This study aims to investigate the incidence of CR-BSI among hemodialysis patients, finding the relation between CR-BSI and catheter type, site, and duration of HD catheter, and identify the infecting organisms and their antimicrobial susceptibility pattern.

MATERIALS AND METHODS

This is a cross-sectional observational study on patients receiving hemodialysis in Sulaimani-city Iraqi-Kurdistan. The study was approved by the Ethics and Research Committee of Kurdistan Board of Medical

Specialties (KBMS). The study was conducted from November the 1st 2016 to June the 30th 2017. Patients from two dialysis centers were enrolled, Shar Hospital Dialysis Center and Qirga Dialysis Center. We obtained consents from all patients. Through a detailed question sheet, we recorded demographic and clinical data including duration of dialysis, comorbidity, treatment history, previous and current HD catheter history, and signs and symptoms of CR-BSI.

Inclusion criteria included inpatients or outpatients whom had HD catheters suspected of having CR-BSI with no other apparent source of infection apart from the catheter. HD patients who presented with other source of infection and/or the vascular access at time of presentation were only AVF were excluded from the study.

We obtained two blood samples from patients suspected to have CR-BSI for aerobic blood culture; one from a peripheral vein and another from the catheter hub, both under aseptic conditions. Ten milliliters of blood was used for each culture and was inoculated in blood culture bottle (Atlas Medical, UK) aseptically and the culture bottles were incubated at 37°C for 5 days. We subcultured the incubated blood culture bottles on day 2 and 5 on blood agar (LABM-Limited UK) and MacConkey agar (BIOMARK-Laboratories, INDIA), the agar plates were incubated at 37°C.

For catheter culture, we cut the distal 5 cm part from the catheter and placed it in a sterile 50 mL plastic screw-cupped tube using a sterile forceps. We proceed the catheter tips by two methods: semiquantitative or roll plate method [24] by rolling back and forth the tip on the surface of a blood agar plate (LABM-Limited UK) at least 4 times, the plate was incubated for 24 hr at 35°C with 5% CO_2. Growth of ≥ 15 colony forming unit (CFU) per plate was considered as a significant growth. We also used the 24 hour enriched media method; following the roll-plate, we placed the catheter tip in a sterile tube containing 10 mL thioglycolate broth (LABM-Limited UK), incubated for 24 hr, then we used 10 microliters (µL) from the media and streaking it over blood agar plate and MacConkey agar plates (BIOMARK-Laboratories, INDIA) as mentioned [25], incubated the plates for 24 hr at 35°C with 5% CO_2, Growth of ≥ 1000 CFU was regarded as significant.

We identified the isolates on colonial morphology, gram stain reaction, and biochemical properties [26, 27] and we used Vitek® 2 system (BioMérieux, France) for final identification of some isolates.

We tested the isolate susceptibility to antimicrobial agents using Kirby-Bauer disk diffusion method [28]. We used 0.5 McFarland compatible saline suspension of the isolate on Mueller-Hinton agar (LABM-Limited UK) and 8-12 antibiotic disks per isolate. We used the following antimicrobial disks (Bioanalyse®, Turkey): ampicillin-sulbactam (30 microgram) (µg); piperacillin-tazobactam (30 µg); ticarcillin (10 µg); cloxacillin (10 µg); oxacillin (10 µg); amoxicillin-clavulanic acid (30 µg); gentamicin (10 µg); amikacin (10 µg); tobramycin (10 µg); meropenem (10 µg); imipenem (10 µg); cephalothin (30 µg); cefixime (5 µg); cefotaxime (30 µg); ceftriaxone (10 µg); ceftazidime (30 µg); cefepime (30 µg); vancomycin (30 µg); teicoplanin (30 µg); clindamycin (10 µg); erythromycin (15 µg); ciprofloxacin (10 µg); levofloxacin (15 µg); trimethoprim-sulfamethoxazole (25 µg); tetracycline (30 µg); linezolid (10 µg), tigecycline (15 µg); aztreonam (10 µg). We screened methicillin-resistant *Staphylococcus aureus* (MRSA) using oxacillin (10 µg) disk. We followed criteria provided by CLSI - Performance Standards for Antimicrobial Susceptibility Testing to determine isolates susceptibility and to evaluate the susceptibility results [29].

Other than confirmed definitive CR-BSI, we also identified catheter colonization as significant growth only from catheter tip or blood from the catheter hub and no growth from the peripheral blood, or growth from only one lumen of the catheter and not from the other lumen of the same catheter [23, 30]. A polymicrobial infection was defined when more than one organism was isolated in the same blood culture, or different organisms grown from catheter tip culture and blood culture [14].

RESULTS

A total of 12,240 dialysis sessions were performed during the study period in the two dialysis centers in Sulaimani city; out of these, 5,850 dialysis sessions were done through HD catheters. The study included 117 patients suspected to have CR-BSI, 49 from Shar center and 68 from Qirga center, 66 (56.5%) and 51 (43.5%) were males and females, respectively; the major age group was between 36-55 years old, which included 52 (44.5%) out of the included 117.

Since any patient may have more than one CR-BSI episode, we used the term " episode " for each separate event. The patients experienced 164-suspected CR-

BSI episodes, 64 from Shar and 100 from Qirga. The number of laboratory confirmed CR-BSIs were 146 (89%), 57 (89%) out of 64 in Shar, and 89 (89%) out of 100 in Qirga. Incidence of CR-BSI was calculated as total number of confirmed infection episodes over total number of dialysis sessions performed through HD catheters multiply by 1,000. The total incidence rate (including both centers) was 24.95 CR-BSI per 1,000 dialysis sessions through HD catheters. The total number of confirmed CR-BSI that showed growth is categorized in to: definitive CR-BSI, catheter colonization, and polymicrobial growth (Table 1).

Table 2 shows correlation between type, site of the catheters and its age (duration in place) at which infection suspected. In total, 102 episodes with temporary and 62 episodes with permanent catheters were investigated. Out of 102 infected temporary catheters, nine (9%) of them were in place for less than 2 weeks, 48 (47%) of them were inserted for 2-4 weeks, and 45 (44%) of them when infected were in place between 5-12 weeks. None of the infected temporary catheters were older than 12 weeks in place. Out of the 62 infected permanent catheters, Only 1 (2%) and 10 (16%) of them were at age of 2-4 weeks and 5-12 weeks respectively. Eighty-three percent of the infected permanent catheters were in place more than 12 weeks. None of the permanent catheters were infected up to 2 weeks duration. Comparing the site of the infected temporary catheters at 2 weeks age; only 7 out of 92 (8%) of the internal jugular vein, comparing to 1 out of 5 (20%) of each of subclavian and femoral veins at the same age were identified.

Table 3 shows the relation of different parameters to bacterial growth from patients suspected to have infection. Only the relation to the site of the catheter showed a statistically significant relationship.

The causative organisms of CR-BSI and catheter colonization, excluding polymicrobial isolates were shown in Table 4. In total, gram-positive aerobic bacteria formed 57.44% of the infections, while gram-negative aerobic bacteria formed 41.13%, and *Candida* spp. formed 1.4%. In Shar center, gram-positive bacteria represents 90.3% of CR-BSI and 78.3% of catheter colonization, while in Qirga center, gram-negative bacteria was the major causative agent by 56.1% of CR-BSI and 60% of catheter colonization. The commonest causative organism in Shar was CoNS (including *S. epidermidis*) and was isolated in 51.5% of CR-BSI and 39.1% in catheter colonization; this was followed by *S. aureus* (including MRSA) as second commonest causative organism of CR-BSI (25.7%) and catheter colonization (30.4%). *Pseudomonas* spp. in Shar center made only 3.2% and 0.0% of CR-BSI and catheter colonization, respectively. In Qirga, the commonest organism of CR-BSI was again CoNS (including *S. epidermidis*) by 19.3%, while the commonest causative organism of catheter colonization was *Pseudomonas* spp. (including *P. aeruginosa*) by 23.3%, which also represented the second commonest cause of CR-BSI in Qirga by 15.8%. Extended-spectrum beta-lactamases (ESBL) enzyme-producing isolates, identified by Vitek® 2 constituted 3 out of 8 isolated *E. coli*. Uncommon identified gram-positive and gram-negative isolates were: *Kocuria kristinae, Aerococcus viridans, Enterobacter cloacae, Stenotrophomonas maltophilia, Sphingomonas paucimobilis, Serratia marcescens, Morganella morganii, Citrobacter freundii,* and *Rhizobium radiobacter.*

Tables 5 and 6 show the antimicrobial susceptibility results (only susceptible) of the isolates in both centers. Only linezolid and tigecycline were most effective against all gram-positive bacteria. Neither vancomycin nor gentamicin was fully effective against all gram-positive bacteria. Sixteen *S. aureus* isolates were tested for oxacillin disks, 8 isolates showed resistance and regarded as MRSA. Sixteen out of 18 tested CoNS (including *S. epidermidis*) were resistant to oxacillin. Teicoplanin showed to be effective against all gram-positive bacteria but still not against all gram-positive isolates.

As a wide range of gram-negative species was isolated, none of the antibiotics showed entire effectiveness against all the gram-negative isolates. Ampicillin-sulbactam and piperacillin-tazobactam were effective against the majority of the gram-negative isolates. Gentamicin was good but not against *E. coli* and *Stenotrophomonas maltophilia*. Ciprofloxacin was shown to be effective against the majority of the isolates but not against *Sphingomonas paucimobilis* and *Morganella morganii*. In general, many isolates showed multidrug resistant MDR, as they were resistant to at least one agent in three or more categories.

Table 1. Number of dialysis sessions, included patients, sex and age groups, infection episodes, categories of infections, and incidence rate of CR-BSI.

	Shar center	Qirga center	Both centers
Total no. of dialysis sessions performed through all types of vascular accesses during the study (8 months)	4072	8168	12240
Total no. of dialysis sessions performed through CVC/HD catheters during the study (8 months)	2315	3535	5850
No. of patients included in the study	49	68	117
Sex of the study patients			
Male, no. (%)	28 (57)	38 (56)	66 (56.5)
Female, no. (%)	21 (43)	30 (44)	51 (43.5)
Age group (in years) of included patients			
<18	1 (2)	2 (3)	3 (2.5)
18-35	6 (12.5)	16 (23)	22 (19)
36-55	29 (59)	23 (34)	52 (44.5)
56-65	9 (18.5)	23 (34)	32 (27)
>65	4 (8)	4 (6)	8 (7)
No. of episodes of suspected CR-BSI			
Total no.	64	100	164
Growth, no. (%)	57 (89)	89 (89)	146 (89)
No growth, no. (%)	7 (11)	11 (11)	18 (11)
Incidence rate			
Infection episodes (growth) per 1000 dialysis-sessions through HD catheters	24.62	25.17	24.95
Categories of growth, No. (%)			
Definitive CR-BSI	31 (48.5)	57 (57)	88 (53.5)
Catheter colonization	23 (36)	30 (30)	53 (32.5)
Polymicrobial growth	3 (4.5)	2 (2)	5 (3)

Table 2. Type, site in relation of infected to the duration of catheters (*n*=164) in both Shar and Qirga dialysis centers.

Types and sites of infected catheters	no.	Duration at time of infection: no. (%)				
		<2 wks	2-4 wks	5-12 wks	13-24 wks	>24 wks
Temporary (non-tunneled)						
Internal jugular	92	7 (8)	44 (48)	41 (44)		
Femoral	5	1 (20)	2 (40)	2 (40)		
Subclavian	5	1 (20)	2 (40)	2 (40)		
All temporary	102	9 (9)	48 (47)	45 (44)		
Permanent (tunneled)						
Internal jugular	61	0 (0)	1 (2)	9 (15)	21 (35)	30 (49)
Femoral	1	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
All permanents	62	0 (0)	1 (2)	10 (16)	21 (35)	30 (48)

Table 3. Contingency table showing the relation of different parameters to bacterial growth among patients with suspected CR-BSI.

	Growth n=146	No growth n=18	P-value
Center			
Shar	57	7	0.807
Qirga	89	11	
Sex			
Male	83	7	0.2326
Female	63	11	
Patient stay			
In-patient	116	13	0.688
Out-patient	30	5	
Dialysis sessions/week			
Once	2	0	0.283
Twice	63	8	
Three times	80	9	
Four times	1	1	
Type of catheter			
Temporary	93	8	0.182
Permanent	53	10	
Site of catheter (Temporary and Permanent)			
Internal jugular	135	17	0.002
Femoral	5	1	
Subclavian	6	0	
Duration of catheter (Temporary and Permanent)			
<2 weeks	8	1	0.7676
2-4 weeks	45	4	
5-12 weeks	50	5	
13-24 weeks	18	3	
>24 weeks	25	5	

Table 4. Isolated bacteria of CR-BSI and catheter colonization.

Isolate name	**CR-BSI**		**Catheter colonization**		**CR-BSI and colonization in both centers: 141**
	Shar: 31	**Qirga: 57**	**Shar: 23**	**Qirga: 30**	
Staphylococcus epidermidis	9 (29.0)	7 (12.3)	7 (30.4)	2 (6.6)	25 (20.56)
Other *Coagulase-negative* Staphylococci	7 (22.5)	4 (7.0)	2 (8.7)	3 (10.0)	16 (11.34)
Methicillin Sensitive *Staphylococcus aureus*	6 (19.3)	3 (5.3)	7 (30.4)	2 (6.6)	18 (12.76)
Methicillin Resistant *Staphylococcus aureus*	2 (6.4)	5 (8.8)	0 (0)	1 (3.3)	8 (5.67)
Enterococcus spp.	3 (9.7)	4 (7.0)	2 (8.7)	2 (6.6)	11 (7.80)
Kocuria kristinae	0 (0)	2 (3.5)	0 (0)	0 (0)	2 (1.40)
Aerococcus viridans	1 (3.2)	0 (0)	0 (0)	0 (0)	1 (0.70)
Total gram-positive spp.	**28 (90.3)**	**25 (43.9)**	**18 (78.3)**	**10 (33.3)**	**81 (57.44)**
Pseudomonas aeruginosa	0 (0)	4 (7.0)	0 (0)	1 (3.3)	5 (3.54)
Other *Pseudomonas* spp.	1 (3.2)	5 (8.8)	0 (0)	6 (20.0)	12 (8.51)
Acinetobacter baumanii	0 (0)	4 (7.0)	2 (8.7)	2 (6.6)	8 (5.67)
Other *Acinetobacter* spp.	0 (0)	2 (3.5)	1 (4.3)	1 (3.3)	4 (2.83)
Enterobacter cloacae	0 (0)	5 (8.8)	1 (4.3)	1 (3.3)	7 (4.96)
Escherichia coli	0 (0)	5 (8.8)	1 (4.3)	2 (6.6)	8 (5.67)
Sphingomonas paucimobilis	0 (0)	2 (3.5)	0 (0)	2 (6.6)	4 (2.83)
Serratia marcescens	0 (0)	1 (1.75)	0 (0)	2 (6.6)	3 (2.12)
Klebsiella pneumoniae	1 (3.2)	1 (1.75)	0 (0)	0 (0)	2 (1.40)
Stenotrophomonas maltophilia	0 (0)	1 (1.75)	0 (0)	1 (3.3)	2 (1.40)
Morganella morganii	0 (0)	1 (1.75)	0 (0)	0 (0)	1 (0.70)
Rhizobium radiobacter	1 (3.2)	0 (0)	0 (0)	0 (0)	1 (0.70)
Citrobacter freundii	0 (0)	1 (1.75)	0 (0)	0 (0)	1 (0.70)
Total gram-negative spp.	**3 (9.7)**	**32 (56.1)**	**5 (21.7)**	**18 (60.0)**	**58 (41.13)**
Candida spp.	0 (0)	0 (0)	0 (0)	2 (6.6)	2 (1.40)

Table 5. Antimicrobial susceptibility of isolated gram-positive bacteria.

	Staphylococcus epidermidis	Other CoNS	MSSA	MRSA	Enterococcus spp.	Kocuria kristinae	Aerococcus viridans
	n= 25	n=16	n=18	n=8	n=11	n=2	n=1
	No. and % of isolates susceptible to						
Cloxacillin	7 (57)		2 (100)		3 (100)		
Oxacillin	12 (16)	6 (0)	8 (100)	8 (0)	4 (0)		
Amoxicillin-clavulanic acid	7 (57)	3 (33)	6 (33)	4 (75)	2 (0)	2 (100)	1 (100)
Gentamicin	21 (57)	12 (50)	18 (94)	7 (28)	3 (67)	2 (100)	1 (100)
Amikacin	4 (100)	3 (66)	4 (100)		3 (33)		
Meropenem	10 (90)	7 (57)	10 (90)	7 (71)	6 (33)	2 (100)	1 (100)
Imipenem	4 (50)	4 (100)	8 (100)	4 (50)		2 (100)	1 (100)
Cephalothin	7 (100)	4 (25)	2 (100)	1 (0)	4 (25)		
Cefixime	4 (25)	4 (0)	7 (14)	3 (33)			
Cefotaxime	7 (57)	6 (0)	7 (71)	4 (75)	2 (100)	1 (0)	1 (0)
Ceftriaxone	5 (40)	2 (0)		1 (0)	2 (0)		
Ceftazidime	7 (28)	3 (0)	3 (0)	4 (0)	6 (0)	2 (50)	1 (0)
Vancomycin	23 (91)	15 (100)	17 (100)	8 (87)	8 (89)	2 (100)	1 (100)
Teicoplanin	7 (100)	6 (83)	2 (100)		6 (100)		
Clindamycin	13 (61)	11 (81)	9 (77)	4 (50)			
Erythromycin	7 (28)	6 (0)	4 (25)	3 (67)	7 (0)		
Ciprofloxacin	16 (81)	7 (42)	11 (72)	5 (80)	6 (33)	2 (100)	1 (100)
Levofloxacin	15 (80)	9 (10)	7 (87)	1 (100)	8 (37)		
Trimethoprim-sulfamethoxazole	9 (67)	10 (50)	10 (50)		6 (33)	1 (100)	1 (100)
Tetracycline	6 (16)	5 (80)	2 (50)		5 (0)		
Linezolid	7 (100)	5 (100)	3 (100)		6 (100)		
Tigecycline	7 (100)	5 (100)	3 (100)		6 (100)		

Table 6. Antimicrobial susceptibility of isolated gram-negative bacteria.

	Pseudomonas aeruginosa	Other Pseudomonas Spp.	Acinetobacter baumanii	Other Acinetobacter spp.	E. coli	Enterobacter cloacae	Sphingomonas paucimobilis	Serratia marcescens	Klebsiella pneumoniae	Stenotrophomonas maltophilia	Morganella morganii	Rhizobium radiobacter	Citrobacter freundii
	n=5	n=12	n=8	n=4	n=8	n=7	n=4	n=3	n=2	n=2	n=1	n=1	n=1
	No. and % of isolates susceptible to												
Ampicillin-sulbactam		3 (100)	4 (100)	3 (67)			1 (100)		2 (100)				
Piperacillin-tazobactam	2 (100)		5 (100)	4 (100)	3 (100)	5 (60)	4 (100)	2 (100)	2 (100)		1 (100)	1 (100)	
Ticarcillin	2 (100)	3 (100)			3 (0)	3 (100)	3 (33)	2 (100)			1 (100)	1 (100)	1 (100)
Amoxicillin-clavulanic acid			4 (0)				2 (100)			2 (0)			
Gentamicin	5 (100)	12 (100)	6 (100)	4 (75)	8 (50)	7 (71)	3 (100)	3 (100)	2 (100)	2 (0)	1 (100)	1 (100)	1 (100)
Amikacin	3 (100)	9 (77)	3 (100)	4 (75)	7 (71)	7 (71)	3 (100)	3 (100)	2 (100)	2 (0)	1 (100)	1 (100)	1 (100)
Tobramycin	4 (75)	11 (90)	4 (100)		4 (0)	5 (60)	3 (67)	2 (50)					
Meropenem	5 (100)	11 (100)	7 (100)	4 (75)	6 (83)	7 (71)	3 (67)	3 (100)	2 (100)	2 (0)	1 (100)	1 (100)	1 (100)
Imipenem	3 (100)	8 (100)	7 (100)	4 (75)	6 (83)	7 (71)	4 (100)	3 (100)	2 (100)	2 (50)	1 (100)	1 (100)	1 (100)
Cephalothin	2 (0)	2 (0)	4 (0)	2 (50)	5 (0)		2 (0)	2 (50)	2 (100)				
Cefixime	2 (0)	4 (25)			4 (50)		4 (25)		2 (100)		1 (0)		1 (0)
Cefotaxime	5 (40)	4 (25)	4 (50)	3 (67)	4 (25)	4 (100)	2 (50)		2 (100)		1 (100)		1 (0)
Ceftriaxone	4 (25)	2 (100)	5 (60)	3 (67)	4 (25)	7 (71)	2 (0)		2 (100)				
Ceftazidime	4 (25)	8 (75)	6 (67)	4 (50)	5 (40)	7 (71)	4 (25)	3 (67)	2 (100)		1 (100)	1 (100)	1 (100)
Cefepime									2 (100)		1 (100)	1 (100)	1 (100)
Ciprofloxacin	3 (67)	12 (100)	7 (100)	4 (100)	7 (71)		4 (25)	3 (100)	2 (100)	2 (100)	1 (0)	1 (100)	1 (100)
Levofloxacin	1 (100)	3 (100)	4 (100)	3 (67)		2 (0)	2 (50)		2 (100)	1 (0)			
Trimethoprim-sulfamethoxazole	3 (0)	11 (90)	6 (100)	3 (67)	5 (60)	5 (100)	4 (25)	3 (67)	2 (100)	2 (50)	1 (0)	1 (100)	1 (0)
Tigecycline		2 (100)	2 (100)	3 (100)		5 (100)	2 (50)						
Aztreonam					3 (0)	5 (60)	2 (50)						

DISCUSSION

In this study, the incidence of CR-BSI among inpatients and outpatients receiving hemodialysis through HD catheters in both centers was 24.95 CR-BSI per 1000 dialysis-sessions through HD catheters, this incidence is higher than that in a neighboring country, Turkey, which showed 19.4 CR-BSI per 1000 dialysis-sessions done using temporary HD catheter [(31)]. Other studies showed variable rates of CR-BSI, ranging from 0.46 to 30 per 1000 catheter-days [(10-13)]. However, the incidence in this study is not precisely comparable with other studies as we calculated the incidence rate per 1000 dialysis-sessions performed through HD catheters rather than per 1000 catheter-days followed by other studies. This is due to the fact that we included both inpatients and outpatients suspected of having CR-BSI, whether the catheter been inserted before or after the start date of the study, hence it was difficult to calculate exact catheter-days being in place, and we used performed dialysis-sessions instead. Therefore, we implemented the study in a cross-sectional rather than prospective way. Comparing the incidence rates of CR-BSIs between the two-dialysis centers, Shar and Qirga, were nearly the same.

Weijmer M.C. compared tunneled cuffed (permanent) hemodialysis catheters to temporary un-tunneled catheters with regard of complications within 2 weeks of use and found that the risk of BSI increased by 4 folds with temporary catheters [(32)]. In this study we founded that 9% of the infected temporary catheters were in place for less than 2 weeks, while none of the infected permanent catheters were in for less than 2 weeks. Furthermore, up to 4 weeks in place, the risk of BSI will significantly increase for temporary catheters, as cumulatively reaches 56% of the infected temporary catheters, while at the same age of use, the infected permanent tunneled catheters is only 2% that is nearly 28 times less. However, even with permanent tunneled catheters, the risk of BSI will rise critically with longer duration in place, as cumulatively 53% of the infected permanent catheters were at 24 weeks age. Moretti et al. [(33)] and Oliver et al. [(34)] also showed statistically significant increasing colonization and bacteremia with increasing duration of HD catheters.

In this study, comparing the site of catheters at 2 weeks in place; only 8% of the infected temporary internal jugular catheters, comparing to 20% of each of subclavian and femoral sites at the same age were detected, this was 2.5 times less in favor of internal jugular temporary catheters. This is similar to the results of Oliver et al. that showed infection rate at 2 weeks of 4.6% and 10.7% of internal jugular and femoral temporary catheters, respectively. However, this result contrasting that of Moretti et al., in which the colonization rate of both internal jugular and femoral catheters were nearly the same but were both higher than subclavian [(33)].

Infection rate of all sites of temporary catheters at the age of 4 weeks were the same, which reveals that the rate of infection of temporary catheters significantly and equally increasing after 2 weeks regardless of the site of insertion. Regarding the permanent tunneled catheters, very few permanent subclavian and femoral catheters were used and statistically incomparable to the permanent internal jugular catheters. It is worth knowing that only half of the removed catheter tips were cultured by both methods, the 24 hr enriched media and the rolling plate method, the rest are cultured only by the first method, this is due to late (out of day work time) removal of the catheter when the skilled laboratory staff unavailable to perform the semiquantitative method. However, growth by either method was regarded as significant.

The main causative organism (CR-BSI and catheter colonization) in both centers were gram-positive aerobes, it constituted 57.44% of infections. This was very obvious in Shar center as gram-positive organisms formed 90.3% and 78.3% of CR-BSI and catheter colonization, respectively. Similar results were found in most related studies [(5, 14, 19, 35)], indicating the ability of these organisms to cause such infections. CoNS including *S. epidermidis* were the most common agents in Shar center, followed by *S. aureus* including MRSA. These organisms are found to be the main causative organisms of CR-BSI from many researches [(11, 14, 15, 19, 35-38)].

In our study, Qirga center showed different trend; gram-negative organisms were more common than gram-positives, and they constituted 56.1% of CR-BSI and 60% of catheter colonization. There are similar studies also showed increased incidence of gram-negative bacteria causing CR-BSI and catheter colonization [(36, 39-41)]. The increase incidence of gram-negatives is related to, as also explained by other studies by the chronicity of the cases, longer hospital stay, increasing complexity of patient care, which determines more catheters placed for longer periods, wider use of antibiotics and increase in MDR strains [(21)]. Comorbidity such as diabetes mellitus and immunosuppression also play role in increasing the incidence of gram-negative infection [42]. Among the gram-negatives, *Pseudomonas* spp. including *P. aeruginosa,* in Qirga center, was the most common isolate from CR-BSI and catheter colonization, followed by *Acinetobacter* spp. Almuneef, showed that *Klebsiella pneumoniae* (16.4%) is more common than *P. aeruginosa* (11.0%) in causing CR-BSI, this is contrasting our result, as in our results *P. aeruginosa* constituted (7%) of CR-BSI compared to (1.75%) of *K. pneumoniae.* However, their study population was children in ICU compared to all age groups under hemodialysis in our study, this might have impact on the difference.

In this research we identified many uncommon organisms, these were reported from other studies as rare causes of CR-BSI especially in immunocompromised and end-stage patients [39, 43-46]. One of the limitations of this study is that we have not included anaerobic blood culture, which might have resulted in missing anaerobic organisms, although anaerobes recognized as insignificant cause of hemodialysis CR-BSI.

Organisms causing hemodialysis CR-BSI are often resistant bacteria due to repeated hospital admissions and frequent antibiotic use [47, 48]. In both centers, the routine empirical antibiotics are vancomycin alone or plus gentamicin; although vancomycin showed good effect against most gram-positives but still it is not very effective against all gram-positive bacteria. Likewise, teicoplanin showed very good effect but not against all isolates.

Linezolid and tigecycline were very effective against all gram-positive bacteria, but these antibiotics are expensive and not available all the times. Eight out of 16 *S. aureus* and 16 out of 18 CoNS (including *S. epidermidis*) were resistant to oxacillin disks; according to the IDSA guidelines, knowing this resistance is entirely required to prescribe the antimicrobial management [23]. Gentamicin showed weak effect against gram-positives. Although ampicillin-sulbactam and piperacillin-tazobactam showed good effect against the majority of the gram-negatives but they are also not easily available. However, ciprofloxacin, which is inexpensive, almost available, and orally administered, showed to be effective against the majority of the gram-negative isolates, this could replace gentamicin in case of resistance.

In conclusion, our study revealed high incidence of CR-BSI in the dialysis centers. Permanent tunneled catheters were less susceptible to BSI compared to temporary catheters. Within two weeks of temporary HD catheters, internal jugular vein has 2.5 times less chance of BSI than subclavian and femoral veins. However, with longer duration the rate of BSI will be equal for all the three sites. The dialysis centers showed different isolates but mainly were staphylococci and *Pseudomonas* spp. Neither vancomycin nor gentamicin, which are prescribed empirically in these dialysis centers, and none of the other used antimicrobial agents were effective against all gram-positives and/or gram-negatives. Therefore, it is recommended to perform laboratory investigation for all suspected CR-BSI and use antimicrobials only according to the antimicrobial susceptibility results.

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REFERENCES

1. Leone S, Suter F. Severe bacterial infections in haemodialysis patients. Infez Med. 2010;18(2):79-85.

2. Gilmore J. KDOQI clinical practice guidelines and clinical practice recommendations--2006 updates. Nephrol Nurs J. 2006;33(5):487-8.

3. Lata C, Girard L, Parkins M, James MT. Catheter-related bloodstream infection in end-stage kidney disease: a Canadian narrative review. Can J Kidney Health Dis. 2016;3:24.

4. Dhingra RK, Young EW, Hulbert-Shearon TE, Leavey SF, Port FK. Type of vascular access and mortality in U.S. hemodialysis patients. Kidney Int. 2001;60(4):1443-51.

5. Bohlke M, Uliano G, Barcellos FC. Hemodialysis catheter-related infection: prophylaxis, diagnosis and treatment. J Vasc Access. 2015;16(5):347-55.

6. Miller LM, Clark E, Dipchand C, Hiremath S, Kappel J, Kiaii M, et al. Hemodialysis Tunneled Catheter-Related Infections. Can J Kidney Health Dis. 2016;3:1-11.

7. Safdar N, Maki DG. The pathogenesis of catheter-related bloodstream infection with noncuffed short-term central venous catheters. Intensive Care Med. 2004;30(1):62-7.

8. Gahlot R, Nigam C, Kumar V, Yadav G, Anupurba S. Catheter-related bloodstream infections. Int J Crit Illn Inj Sci. 2014;4(2):162-7.

9. Bates DW, Pruess KE, Lee TH. How bad are bacteremia and sepsis? Outcomes in a cohort with suspected bacteremia. Arch Intern Med. 1995;155(6):593-8.

10. Napalkov P, Felici DM, Chu LK, Jacobs JR, Begelman SM. Incidence of catheter-related complications in patients with central venous or hemodialysis catheters: a health care claims database analysis. BMC Cardiovasc Disord. 2013;13:86.

11. Hammarskjold F, Wallen G, Malmvall BE. Central venous catheter infections at a county hospital in Sweden: a prospective analysis of colonization, incidence of infection and risk factors. Acta Anaesthesiol Scand. 2006;50(4):451-60.

12. McGee DC, Gould MK. Preventing complications of central venous catheterization. N Engl J Med. 2003;348(12):1123-33.

13. Pinon M, Bezzio S, Tovo PA, Fagioli F, Farinasso L, Calabrese R, et al. A prospective 7-year survey on central venous catheter-related complications at a single pediatric hospital. Eur J Pediatr. 2009;168(12):1505-12.

14. Fysaraki M, Samonis G, Valachis A, Daphnis E, Karageorgopoulos DE, Falagas ME, et al. Incidence, clinical, microbiological features and outcome of bloodstream infections in patients undergoing hemodialysis. Int J Med Sci. 2013;10(12):1632-8.

15. Vandecasteele SJ, Boelaert JR, De Vriese AS. Staphylococcus aureus infections in hemodialysis: what a nephrologist should know. Clin J Am Soc Nephrol. 2009;4(8):1388-400.

16. Morales M, Mendez-Alvarez S, Martin-Lopez JV, Marrero C, Freytes CO. Biofilm: the microbial "bunker" for intravascular catheter-related infection. Support Care Cancer. 2004;12(10):701-7.

17. Donlan RM. Biofilms: microbial life on surfaces. Emerg Infect Dis. 2002;8(9):881-90.

18. Gominet M, Compain F, Beloin C, Lebeaux D. Central venous catheters and biofilms: where do we stand in 2017? APMIS. 2017;125(4):365-75.

19. Nabi Z, Anwar S, Barhamein M, Al Mukdad H, El Nassri A. Catheter related infection in hemodialysis patients. Saudi J Kidney Dis Transpl. 2009;20(6):1091-5.

20. Gupta S, Mallya SP, Bhat A, Baliga S. Microbiology of Non-Tunnelled Catheter-Related Infections. J Clin Diagn Res. 2016;10(7):DC24-8.

21. Marcos M, Soriano A, Inurrieta A, Martinez JA, Romero A, Cobos N, et al. Changing epidemiology of central venous catheter-related bloodstream infections: increasing prevalence of Gram-negative pathogens. J Antimicrob Chemother. 2011;66(9):2119-25.

22. Tille PM. Bloodstream Infections. Bailey & Scott's DIAGNOSTIC MICROBIOLOGY. Fourteenth ed. Canada: ELSEVIER; 2017. p. 924-41.

23. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1-45.

24. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. N Engl J Med. 1977;296(23):1305-9.

25. England PH. UK Standards for Microbology Investigations. Investigation of Intravascular cannulae and associated specimens2015. p. 1-24.

26. PM C. Identification of Gram-Positive Organisms. In: Emanuel Goldman LHG, editor. Practical Handbook of Microbiology. Second ed: Boca Raton CRC Press; 2009. p. 53-66.

27. Donna J. Kohlerschmidt KAM, Dumas NB. Identification of Gram-Negative Organisms In: Emanuel Goldman LHG, editor. Practical Handbook of Microbiology. Second ed: Boca Raton: CRC Press; 2009. p. 67-79.

28. Bauer AW, Kirby WM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized single disk method. Am J Clin Pathol. 1966;45(4):493-6.

29. CLSI CALSI. M100-S24 Performance Standards for Antimicrobial Susceptibility Testing; Twenty Fourth Informational Supplement. USA2014.

30. de Freitas LW, Neto MM, Nascimento MM, Figueiredo JF. Bacterial colonization in hemodialysis temporary dual lumen catheters: a prospective study. Ren Fail. 2008;30(1):31-5.

31. CAYLAN R. YG, SOZEN E.E., AYDIN K., KOKSAL I. Incidence and risk factors for bloodstream infections

stemming from temporary hemodialysis catheters. Turk J Med Sci. 2010;40(6):835-41.

32. Weijmer MC, Vervloet MG, ter Wee PM. Compared to tunnelled cuffed haemodialysis catheters, temporary untunnelled catheters are associated with more complications already within 2 weeks of use. Nephrol Dial Transplant. 2004;19(3):670-7.

33. Moretti EW, Ofstead CL, Kristy RM, Wetzler HP. Impact of central venous catheter type and methods on catheter-related colonization and bacteraemia. J Hosp Infect. 2005;61(2):139-45.

34. Oliver MJ, Callery SM, Thorpe KE, Schwab SJ, Churchill DN. Risk of bacteremia from temporary hemodialysis catheters by site of insertion and duration of use: a prospective study. Kidney Int. 2000;58(6):2543-5.

35. Grothe C, da Silva Belasco AG, de Cassia Bittencourt AR, Vianna LA, de Castro Cintra Sesso R, Barbosa DA. Incidence of bloodstream infection among patients on hemodialysis by central venous catheter. Rev Lat Am Enfermagem. 2010;18(1):73-80.

36. Gauna TT, Oshiro E, Luzio YC, Paniago AM, Pontes ER, Chang MR. Bloodstream infection in patients with end-stage renal disease in a teaching hospital in central-western Brazil. Rev Soc Bras Med Trop. 2013;46(4):426-32.

37. Lai CF, Liao CH, Pai MF, Chu FY, Hsu SP, Chen HY, et al. Nasal carriage of methicillin-resistant Staphylococcus aureus is associated with higher all-cause mortality in hemodialysis patients. Clin J Am Soc Nephrol. 2011;6(1):167-74.

38. Rodriguez-Aranda A, Alcazar JM, Sanz F, Garcia-Martin F, Otero JR, Aguado JM, et al. Endoluminal colonization as a risk factor for coagulase-negative staphylococcal catheter-related bloodstream infections in haemodialysis patients. Nephrol Dial Transplant. 2011;26(3):948-55.

39. Abdul Gafor AH, Cheong Ping P, Zainal Abidin AF, Saruddin MZ, Kah Yan N, Adam SQ, et al. Antibiogram for haemodialysis catheter-related bloodstream infections. Int J Nephrol. 2014; 629459.

40. Almuneef MA, Memish ZA, Balkhy HH, Hijazi O, Cunningham G, Francis C. Rate, risk factors and outcomes of catheter-related bloodstream infection in a paediatric intensive care unit in Saudi Arabia. J Hosp Infect. 2006;62(2):207-13.

41. Braun E, Hussein K, Geffen Y, Rabino G, Bar-Lavie Y, Paul M. Predominance of Gram-negative bacilli among patients with catheter-related bloodstream infections. Clin Microbiol Infect. 2014;20(10):O627-9.

42. Murray EC, Marek A, Thomson PC, Coia JE. Gram-negative bacteraemia in haemodialysis. Nephrol Dial Transplant. 2015;30(7):1202-8.

43. Merino JL, Bouarich H, Pita MJ, Martinez P, Bueno B, Caldes S, et al. Serratia marcescens bacteraemia outbreak in haemodialysis patients with tunnelled catheters due to colonisation of antiseptic solution. Experience at 4 hospitals. Nefrologia. 2016;36(6):667-73.

44. Kimura M, Kawai E, Yaoita H, Ichinoi N, Sakamoto O, Kure S. Central Venous Catheter-Related Bloodstream Infection with Kocuria kristinae in a Patient with Propionic Acidemia. Case Rep Infect Dis. 2017; 1254175.

45. Cunha BA, Theodoris AC, Yannelli B. Enterobacter cloacae graft infection/bacteremia in a hemodialysis patient. Am J Infect Control. 2000;28(2):181-3.

46. Kataria A, Lata S, Khillan V. Hemodialysis catheter-related bacteremia caused by Stenotrophomonas maltophilia. Indian J Nephrol. 2015;25(5):318-9.

47. Calfee DP. Multidrug-resistant organisms in dialysis patients. Semin Dial. 2013;26(4):447-56.

48. Snyder GM, D'Agata EM. Novel antimicrobial-resistant bacteria among patients requiring chronic hemodialysis. Curr Opin Nephrol Hypertens. 2012;21(2):211-5.