ORIGINAL ARTICLE

PATTERN OF CAUSATIVE MICRO-ORGANISMS IN CATHETER RELATED BLOOD STREAM INFECTIONS IN DIALYSIS PATIENTS: EXPERIENCE FROM SAUDI ARABIA

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Background: Catheter related blood stream infections (CRBSI) are the leading cause of morbidity in HD patients. The majority of these infections relate to haemodialysis catheters. There is a paucity of local data on microbial agents responsible for CRBSI in our region. This prompted our study. **Methods:** This Prospective observatory survey was conducted in Department of Nephrology, King Fahd Hospital, Hofuf KSA from Nov 2014 to Jan 2017 (26 months). It was performed on dialysis patients with HD catheters who developed features of CRBSI. Blood cultures were taken from the patient and cultured microorganisms were observed and stratified according to type and prevalence in relation to age gender and comorbidities. **Results:** There were 210 distinct episodes of CRBSI. 61.5% (n=129) were due to gram negative microorganisms and 38.5% (n=81) were due to Gram positive microorganism. Fifty-three events were due to Coagulase Negative *Staphylococcus aureus*. *Enterobacter cloachae* accounted for 28 events. *Pseudomonas* 19 events, *Enterococcus faecalis* 13, *Klebsiella* 11, *Acinitobacter* accounted for 8 events. CRBSI was observed more frequently in males (n=136), diabetics (n=113) and in age 40 years±19 years(n=97). **Conclusion:** Gram negative microorganisms were more commonly responsible for CRBSI in our settings. *Enterobacter cloachae* was most common gram-negative microorganism responsible for CRBSI, a finding not observed in other studies. There was significant predisposition to diabetics, male gender and middle age group. We need further studies to observe antibiotics sensitivity of microorganisms so that we can standardize empirical antibiotics in cases of CRBSI.

Keywords: CRBSI; Haemodialysis; *Enterobacter cloachae; Staphylococcus spp*

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INTRODUCTION

A good working vascular access is an essential component of haemodialysis.[1] Haemodialysis catheters are a significant component of renal replacement therapy. They are relatively easy to be inserted and can be used immediately in wide range of kidney failure patients. Unfortunately, HD catheters have their own problems.[2] There is an increased risk of blood stream infections associated with the use of these catheters leading to increased morbidity and mortality.[3]

In one study, mortality attributed from HD catheter related infection was estimated between 12–25% and the estimated cost to the health care system was $25000 per episode.[4] Temporary HD catheters account for an average of about five episodes/1 000 days, while there is an infection rate of roughly 3.5 episodes/1 000 days with permanent or tunnelled catheters.[5] The factors that increase the risk for catheter infection include prolonged duration of usage, past history of HD catheter-related infection, recent surgery, diabetes mellitus, *Staphylococcus aureus* nasal colonization, old age, low haemoglobin and serum albumin levels.[6]

Other risk factors for HD catheter infections include contamination of dialysate or equipment, inadequate water treatment, reuse of dialyzer, higher dose of and recombinant human erythropoietin, peripheral vascular disease, and recent hospitalization.[7]

A diagnosis of a CRBSI is occasionally difficult to establish in the haemodialysis patient. The physician should suspect CRBSI in any patient with an indwelling haemodialysis catheter who presents with the symptoms and signs of infection. Some patients may present atypically with hemodynamic instability, hypothermia, acidosis, delirium or a poorly functioning catheter.[8] Various causative organisms have been described in different studies worldwide. The spectrum varies between different regions and centres ranging from gram positive microorganism responsible for most of the occurrence in the Indian and American studies and gram-negative microorganism responsible pre-dominantly in European studies.[9–15]

It is necessary for each dialysis unit to have a database of suspected and proven cases of HD catheter related infections, with details on the causative microorganisms, their antibiotic sensitivity and therapeutic outcome.[16]

However, there is a paucity of local data on this subject. This prompted our study. Recent local data are needed to find out the causative microorganisms for haemodialysis CRBSI, and to detect the emergence of new organisms. This study aimed to describe the microorganisms that cause bloodstream infections in

haemodialysis patients with indwelling haemodialysis catheters and to find their distribution according to gender age and diabetes mellitus.

MATERIAL AND METHODS

A prospective observatory survey was performed of cultured organisms from patients with indwelling haemodialysis catheters with suspected blood stream infection in the Dialysis unit of King Fahd Hospital, Hofuf, Saudi Arabia. Duration of study was 26 months from November 2014 to January 2017. 313 patients were undergoing regular haemodialysis in our centre at the time of study, three to four times per week. 172 patients were male and 141 were female. Elective number of Dialysis sessions was 1562 per month and around 305 patients were dialyzed in ER setting every month for 26 months. Patients who were dialyzed via tunnelled haemodialysis catheters with documented bloodstream infections between November 2014 and January 2017 were included in the study. Duplicate blood cultures from the same patient were excluded from the study. Every event was treated as a single event despite repeated infections in the same patient. Patients with flagged positive blood culture with no growth were excluded. An electronic database was used to select the patient population and to collect the demographic details and clinical information. A paper datasheet was used to capture the demographic details, co-morbidities, and the organisms cultured.

Four-hundred and ninety-two blood cultures from haemodialysis patients suspected to have a CRBSI were sent for analysis. Two hundred and eighty-one of those were positive. Fifty blood cultures were duplicate and were excluded. After the exclusion of the patients who did not meet the inclusion criteria, 210 distinct episodes of CRBSI were included in this study.

Descriptive statistical analysis was performed using SPSS version 22. Frequency and percentages were computed to present categorical variables such as catheter related infection, causative microorganisms, gender, age, diabetes mellitus.

All continuous response variables such as patient's age, biochemical parameters were presented as the mean±SD. Statistical significance was considered as $p \leq 0.05$. In our unit, informed consent is taken from the patients for possibility of use of clinical and demographic information for research purpose at the initiation of haemodialysis. Formal consent for the study was taken from Research Ethical committee and the Head of division of Nephrology and Director of Internal Medicine and Allied Specialties.

CRBSIs were defined as bacteraemia and fungemia in a patient with an intravascular catheter with at least one positive blood culture obtained from a peripheral vein, the clinical manifestation of infection (i.e., fever, chills and/or hypotension), and no apparent source of bloodstream infection, except the central venous catheter (in this case, the haemodialysis catheter).[17]

RESULTS

In the study period, 492 times patients presented with symptoms suggestive of CRBSI necessitating blood culture. Blood culture was positive in 57% of the events (n=281). After excluding duplicate blood cultures and other sources of blood stream infection 210 cases of HD catheter related blood stream infection were identified.

Gram negative microorganisms accounted for 61.5% of the events (n=129). *Enterobacter spp.* Accounted for 19% (n=39) events out of which 28 were *Enterobacter cloachae* (Table-2). *Pseudomonas* accounted for 9% (n=19) of the events, *Enterococcus spp*. 6% (n=13), *klebsiella* and S*tenotrophomonas* 5% each (n=11). *Acinetobacter spp.* accounted for 5% events (n=10) out of which 4 were MDR. *Proteus, Serratia*, *E coli*, Citrobacter, non- fermenting Gram-Negative Rods accounted for 4 events or less. One case each was reported for *Xanthomonas maltofilia*, *Morganella morgagni*, *Candida* and Group B *streptococcus* (Table-3)

Gram positive microorganism accounted for 38.5% of events (n=81). Out of these gram-positive microorganisms, 53 were Coagulase Negative *Staphylococcus aureus,* 11 were MSSA, 8 were MRSA, 7 were *Staph epidermidis*, and 2 were *Staphylococcus lugdonesis*. (Table-1) There was a significant male predominance. 64.7 % of incidences (n=136) were documented in male population. 35.3% cases were female (n=74). Coagulase negative *Staphylococcus aureus* was the most common microorganism in males (n=36). *Enterobactercloachae* was the second most common (n=22) followed by *Enterococcus faecalis* (n=10), *Pseudomonas* and *Klebsiella* 9 cases each.

In females, most common microorganism was coagulase negative *Staphylococcus aureus* (n=17), followed by *Pseudomonas* (n=10) and *Stenotrophomonas* (n=8). Detailed distribution of microorganism according to gender is shown in table-4. Mean age of the patients having CRBSI was 40 years ± 19 years. 46% of the patients were aged 31–60 years (n=97). 37% of the patients were 61 years and above (n=78). 17% of the patients were 30 years or below. Table-5 shows distribution of microorganisms according to age. Most common microorganism in all three age groups was Coagulase Negative *Staphylococcus aureus*. Second most common microorganism in age less than 30 years was *Klebsiella* (n=5) and *Enterococcus faecalis* (n=5). In age group 31–60 years, the second most common microorganism was *Enterobacter cloachae* (n=12). It accounted for 12% of events in this age group. In age

61 years and above the second most common microorganism was *Enterobacter cloachae*. It accounted for 15% of events (n=12). Further distribution of microorganism is shown the table 5. One hundred and thirteen patients were having Diabetes Mellitus whereas 97 patients were non- diabetic. In Diabetic patients, Coagulase Negative *Staphylococcus aureus* was the most common microorganism (n=24) followed by *Enterobacter cloachae* (n=16). In Non-diabetic patients, Coagulase Negative *Staphylococcus aureus* was the most common microorganism (n=29) followed by *Enterobacter cloachae* (n=12). Pseudomonas was the third common microorganism in both groups accounting for 9 events in Diabetic Patients and 10 patients in Nondiabetic patients. Further distribution of cases is shown in table-6.

Table-1: *Staphylococcus*: Distribution according to type, gender, DM and age

Microorganism	DM	Non- DM	Male	Female	Total	30 yrs or Less	31–60	61 and above
Coagulase negative *Staph aureus*	24	29	36	17	53	8	31	14
Methicillin sensitive *Staph aureus*	4	7	9	2	11	1	8	2
Methicillin resistant *Staph aureus*	5	3	4	4	8	1	6	1
Staph epidermidis	7	0	3	4	7	0	4	3
Staph lugdonesis	2	0	2	0	2	0	2	0

Table-2: Enterobacter: Distribution according to type, gender, DM and Age

Microorganism	DM	Non- DM	Male	Female	Total	30 yrs or Less	31–60	61 and above
Enterobacter cloachae	16	12	22	6	28	4	12	12
Enterobacter species	6	5	5	6	11	1	4	6

Table-3: Frequency of different microorganisms leading to CRBSI

Microorganism	Total (n)
Coagulase negative *Staph aureus*	53
Methicillin sensitive *Staph aureus*	11
Methicillin resistant *Staph aureus*	8
Staph epidermidis	7
Staph lugdonesis	2
Enterobacter Cloachae	28
Enterobacter species	11
Stenotrophomonas maltophilia	11
Pseudomonas	19
Klebsiella	11
E coli	2
E coli esbl	2
Acinito bacter senssitive	6
Acinitobacter mdr	4
Nf gram negative rods	4
Proteus	4
Enterococcus faecalis	13
Serratia ficarna	3
Citrobacter	3
Candida	2
Miscellaneous	6
Total	210

Table-4: Distribution of microorganisms according to gender

Microorganism	Male	Female
Coagulase negative *Staph aureus*	36	17
Methicillin sensitive *Staph aureus*	9	2
Methicillin resistant *Staph aureus*	4	4
Staph epidermidis	3	4
Staph lugdonesis	2	0
Enterobacter Cloachae	22	6
Enterobacter species	5	6
Stenotrophomonas maltophilia	3	8
Pseudomonas	9	10
Klebsiella	9	2
E coli	2	0
E coli esbl	1	1
Acinito bacter senssitive	5	1
Acinitobacter mdr	2	2
Nf gram negative rods	4	0
Proteus	2	2
Enterococcus faecalis	10	3
Serratia ficarna	3	0
Citrobacter	0	3
Candida	1	1
Miscellaneous	4	2
Total	136	74

Table-5: Microorganisms according to age

Microorganism	30 yrs or Less	31 to 60	61 and above
Coagulase negative staph aureus	8	31	14
Methicillin sensitive staph aureus	1	8	2
Methicillin resistant staph aureus	1	6	1
Staph epidermidis	0	4	3
Staph lugdonesis	0	2	0
Enterobacter Cloachae	4	12	12
Enterobacter species	1	4	6
Stenotrophomonas maltophilia	3	5	3
Pseudomonas	3	9	7
Klebsiella	5	3	3
E coli	0	0	2
E coli esbl	0	0	2
Acinito bacter senssitive	0	3	3
Acinitobacter mdr	0	1	3
Nf gram negative rods	0	2	2
Proteus	1	1	2
Enterococcus faecalis	5	2	6
Serratia ficarna	0	2	1
Citrobacter	1	0	2
Candida	1	0	1
Miscellaneous	1	2	3
Total (n)	35	97	78

Table-6: Distribution of microorganisms in diabetic and nondiabetic patients

Microorganism	DM	Non-DM
Coagulase negative *Staph aureus*	24	29
Methicillin sensitive *Staph aureus*	4	7
Methicillin resistant *Staph aureus*	5	3
Staph epidermidis	7	0
Staph lugdonesis	2	0
EnterobacterCloachae	16	12
Enterobacter species	6	5
Stenotrophomonas maltophilia	8	3
Pseudomonas	9	10
Klebsiella	4	7
E coli	2	0
E coli esbl	1	1
Acinito bacter senssitive	2	4
Acinitobacter mdr	4	0
Nf gram negative rods	4	0
Proteus	2	2
Enterococcus faecalis	5	8
Serratia ficarna	2	1
Citrobacter	2	1
Candida	1	1
Miscellaneous	3	3
Total	113	97

DISCUSSION

The causative organisms in CRBSI in haemodialysis patients and their pattern of distribution as related to gender, age, and comorbidities in a given population must be audited to find out differences, if any, from other dialysis patients population all over the world.

Gram negative microorganisms accounted for 61.5% of events in our study (n=129). Out of this *Enterobacter cloachae* was the most common accounting for (n=28) 13%, *Pseudomonas* (n=19) 9%, *Enterococcus faecalis* n=13 (6%); *Strephomonas, Klebsiella* and Enterobacter spp. accounted for 5% of cases each (n=11 each). Acinitobacter was observed in 4.7% (n=10) events. Serratia and Citrobacter (n=3 each) *Proteus* (n=4), and *Candida* (n=2) were also observed in our study. *Xanthomonas maltophilia* was observed in one event of CRBSI.

Our spectrum was found significantly different from other studies. In the study of Ramanathan Parameswaran *et al*., 64% of the pathogens causing CRBSI were Gram-positive and 36% were Gram-negative. The commonest pathogen causing CRBSI was *S. aureus* 40%, *Pseudomonas aeruginosa* 16%, co-agulase negative staphylococci 8%, *E. coli* 8%, *Klebsiellapneumoniae* 8%, and *Acinetobacterbaumanii* 4%.[9] This was significantly different from our findings. In our study 61.5% of events were due to gram negative bacteria. Enterobacter cloachae, *Stenotrophomonas*, *Xanthotrophomonas*, *Enterococcus faecalis*, *Proteus, Citrobacter* were not observed in study by Ramanathan Parameswaran *et al*. In the study of Almuneef *et al*. of total 50 CRBSI episodes, 48% were polymicrobial, 32% were due to Gram-negative bacilli, and 10% were due to Gram-positive organisms. The most common gram-negative organisms isolated were *Klebsiella pneumonia,*

16%, as compared to our study in which *Enterobacter cloachae* was the most common gram-negative microorganism followed by *Pseudomonas*.[10]

In western studies and other studies in US[11–15], the microbial spectrum was different from our findings. In our study, *Staphylococcus* spp. was the predominant gram-positive microorganism responsible for CRBSI in our setting (n=81) a finding which was in keeping with the regional[6] and international studies.[9–15] In a study by Zahid N *et al*[6] *Staphylococcus spp.* was the most common microorganism isolated in CRBSI. Incidence of Staphylococcus infection was higher, 59%, than our study 38.5%. Coagulase negative *Staphylococcus aureus* was most common microorganism in the *Staphylococcus* Spp. which is a comparable to our study. Coagulase negative *Staphylococcus hemolyticus* was observed in their study and not with our study. In our study out of *Staphylococcus* Spp. 65% of infections were caused by Coagulase Negative *Staphylococcus aureus*, 13% by Methicillin Sensitive *Staphylococcus aureus* and 9 % by Methicillin Resistant *Staphylococcus aureus*. Seven cases were observed for *Staphylococcus epidermidis* and two cases were observed of *Staphylococcus lugdonesis* which were not observed in study by Zahid N *et al*.[6] Similar findings have been documented in a study in India by Parameswaran R[9] in which 40% of incidences of CRBSI were due to *Staphylococuss spp*. as compared to 38.5% in our study. Seifert *et al*., showed coagulase-negative *Staphylococci* were present in 50% cases of CRBSI in their study as compared to 25% in our study.[10] Similar distribution of gram positive microorganism was noted in a study in USA.[11] It is also comparable to the prospective trial performed by Dopairak *et al*, Kairaitisetal and Blakestijin.[13–15]

The most significant finding in our study was the presence of Enterobacter Species especially *Enterobacter cloachae* as a cause of CRBSI. Enterobacter Cloachae is uncommon cause of CRBSI worldwide.[9–15] It was the second most common microorganism responsible for CRBSI in our study responsible for 18.5% of events (n=28). There was significant male gender predisposition for this microorganism with 78% (n=22) events observed in male patients and 22% (n=6) observed in females. 57% (n=16) patients with *Enterobacter cloachae* were diabetic and 43 % (n=16) were nondiabetic so Diabetics were seen to be a more prone to have CRBSI with *Enterobacter loachae*.

It was found to be more prevalent in age 31 years and above in our population of patients (n=24) with only 4 events in age less than 30 years. In the regional study by Zahid N *et al*[6] this microbial spectrum was not observed. This could be due to comparatively shorter duration of study (one month) or the use of temporary HD cathetcers as compared to our patient population with cuffed tunnelled HD catheters. It can also represent regional variation in microbial spectrum for causative microorganisms. Similarly, in a study by Parameswaran R *et al*[9] which was done in India no case was reported for *Enterobacter cloachae*. Studies on similar patient populations done in Europe[13–15] have shown infections with Enterobacter spp. but not with *Enterobacter cloachae*. Enterobacter accounted for 10% of events in studies in Europeas compared to 18.5% of cases in our study. This finding is significant to our study which is not observed in studies done on similar patient populations worldwide.

Strenotrophomonas accounted for 11 events and was not observed is other regional[6] and International studies[9–15] as a cause of CRBSI. *Acinitobacter* accounted for 10 events with no predisposition to gender age or DM. It was observed on middle age ambulatory patients which was a finding in contrast to other studies[9–15] in which it was found in geriatric age group and with multiple comorbidities and bed ridden patients.

The distribution of other microorganism did not reveal any significant difference than the available data worldwide. There was significant gender predisposition to CRBSI in our study with 64% (n=136) of events recorded with male patient and 36% (n=74) of events recorded in females. This is in contrast to regional study by Zahid N *et al*[6] in which 45% of patients were male and 55% of patients were female. This difference may be due to small sample size of events in their study (n=11) as compared to our study with events (n=210). It may also be related to shorter duration of study and type of HD catheter. In other international studies[9–15] there is no significant gender predisposition to CRBSI. We need to further study this finding in relation to *Enterobacter cloachae* which was found to be present significantly in male patients (n=22) than females (n=6). Diabetic patients were found to be more prone to CRBSI. 54% of events were noted in patients who were diabetic. This finding is consistent with other studies worldwide.[9-15]

The mean age of CRBSI in our study was 40 years ± 19 years. It was consistent with study by Zahid N et al[6] and Ramanathan Parameswaran *et al*[9] and other studies[10–14]. *Enterobacter cloachae* and *Acinitobacter* were also seen commonly in the same age group.

All the events were reported with Tunnelled cuffed HD catheters as we did not have patients with temporary HD catheters receiving haemodialysis.

Our study had a few limitations. We had paucity of data available regarding time of insertion of the tunnelled catheter and its site. This limited us from comparison of the life of the tunnelled catheter to CRBSI. We did not have documentation of the site of the tunnelled catheter so we could not compare the frequency of infection as related to site and any difference in causative microorganism.

CONCLUSION

We conclude from our study that pattern of microorganism in our region responsible for CRBSI is significantly different from other regions and countries. Gram negative microorganisms were found to be more prevalent than gram positive microorganisms. *Staphylococcus* species was the leading cause of CRBSI in our patients. *Enterobacter cloachae* was the second most common microorganism responsible for CRBSI, a finding which is significant but uncommon in dialysis patients with CRBSI in other regions and countries.

We recommend a multicentric research study within the region to compare our findings with other regions so that we can study our spectrum of microorganism in a better way. We recommend a retrospective analysis of antibiotic sensitivities of microorganism observed in our study so that we can observe the pattern of antimicrobial resistance in our region.

We also recommend further study into the finding of *Enterobacter claochae* as a cause of CBSI in our population. We need to extend our study to find out the sensitivity of microorganisms, especially *Enterobacter cloachae* to antibiotics in our region so that we can standardize empirical antibiotic treatment is suspected cases of CRBSI.

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