BACTERIAL SPECTRUM AND ANTIMICROBIAL PATTERN OF BLOOD STREAM INFECTIONS ASSOCIATED WITH NON-TUNNELED DOUBLE LUMEN CATHETER IN HEMODIALYSIS PATIENTS

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ABSTRACT

Objective: To assess Bacterial spectrum and antimicrobial pattern of Blood Stream Infections associated with non-tunneled double lumen catheter in hemodialysis patients.

Study Design: Prospective observational study.

Place and Duration of Study: Department of Nephrology, Pakistan Emirates Military Hospital Rawalpindi Pakistan; Armed Forces Institute of Pathology Rawalpindi, Pakistan, from May 2019 to Apr 2020.

Methodology: A total of 753 patients underwent placement of non-tunneled double lumen catheter (457 femoral, 296 Internal Jugular). Patients with clinically suspected bloodstream infections had their catheters removed with tips being sent for culture along with 2 sets of peripheral blood cultures. Patients were labelled as having bloodstream infection if growth of organism was detected in catheter tip and at least one peripheral blood culture. Susceptibility testing was done for available antimicrobials.

Results: One hundred and thirty six (18.06%) incidences or 5.48 bloodstream infections per 1000 catheter days, with confirmed growth on blood cultures were identified. Gram positive infections were seen in 76 (55.88%) individuals with most common organism being coagulase-negative Staphylococcus (28.68%), followed by Staphylococcus aureus (21.32%). These organisms had low resistance rates to Vancomycin (0%), Tigecycline (0%), Doxycycline (6.6%) and Linezolid (9.5%). Gram negative infections were seen in 60 (44.11%) patients with Klebsiella pneumoniae (13.24%) being the most commonly identified pathogen followed by Acinetobacter baumannii (12.50%) and had relatively higher degree of antimicrobial resistance.

Conclusion: Gram positive organisms were the most common cause of bloodstream infection in this study and were found susceptible to vancomycin and doxycycline whereas gram-negative organisms had high rates of antimicrobial resistance.

Keywords: Blood stream infection, Coagulase negative staphylococcus, Double lumen catheter, Hemodialysis.

INTRODUCTION

Catheter related blood stream infections (CRBSI) can be defined as "positive culture of the catheter (on removal), or paired blood cultures from a peripheral vein and the catheter (when left in place) with isolation of identical organisms (both species and antibiograms) from cultures of catheter segments and blood drawn from a peripheral vein in a patient with clinical symptoms of sepsis and the absence of another source of infection"[1]. Non-tunneled hemodialysis catheter is a fast and easily accessible method to initiate dialysis in most patients. United States Renal Data System reveals that as many as 80.1% of individuals start hemodialysis via central catheter and up to 35% continue dialysis via central catheter beyond 12 months[2]. Even though catheter access has some benefits, a high rate of complications makes it a less preferred option. CRBSI in this subset of population is both common and feared complication as it leads to increased morbidity and mortality[3]. It can result in life threatening complications including septic shock, endocarditis, lung abscess, osteomyelitis or septic arthritis[3,4]. In a study conducted in Pakistan, prevalence of hemodialysis catheter colonization was seen in 51.6% individuals and bacteremia in 25%[5]. Worldwide incidence of dialysis related CRBSI is between 2.5-5-5 cases per 1,000 catheter days, or 0.9-2.0 episodes per patient year[6].

Due to this high prevalence, bacteremia is the second most common cause of mortality after cardiovascular disease in Chronic Kidney Disease (CKD) in US[7], and most common cause in CKD patients undergoing dialysis via dialysis catheter in some studies[8]. Previous studies have shown gram positive cocci especially skin colonizers such as coagulase negative *Staphylococci* and *S. aureus* to be the most commonly involved pathogens[6,9]. Other common organisms include Gram negative rods (GNRs) and *Enterococci*[6,9]. As these patients commonly receive broad spectrum antibiotics empirically, antibiotic resistance is common. It is therefore, necessary to recognize the local microbiology and susceptibility pattern to provide effective empiric ther-

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apy in order to decrease both mortality and emergence of antimicrobial resistance. This study was directed to learn incidence, bacteriological spectrum and microbiological characteristics of BSI in local population.

METHODOLOGY

This prospective observational study was conducted at the department of Nephrology of Pak Emirates Military Hospital and Armed Forces Institute of Pathology, Rawalpindi Pakistan, from May 2019 to April 2020 after approval from Ethics Review Board of same hospital via letter no Ex/FC-18/READ-IRB/19/406. Using a previously reported prevalence of 25% of catheter related bacteremia in our population and estimated 5% margin of error with 99% confidence interval, an estimated sample size of 498 was calculated using WHO sample size calculator[5].

Patients included in study were undergoing dialysis via non-tunneled hemodialysis catheter and between ages of 18-80 years. Patients who were undergoing hemodialysis via either tunneled catheter or AV Fistula or had established septicemia were excluded. Non-probability consecutive sampling technique was utilized and informed consent was taken. If a patient required more than one catheter during observational period then each catheter insertion was taken as a separate incidence. A total of 753 incidences of catheter insertion were included in the analysis. Catheters were inserted by a physician with strict antiseptic measures using Seldinger's technique under ultrasound guidance in either Femoral Vein or Internal Jugular Vein (IJV) and sutured to skin. Insertion point was then covered by sterile occlusive dressing which was changed on each dialysis session or sooner if contaminated. During each dialysis session, entry site of catheter was seen for any presence of local inflammation and purulent discharge by trained nursing staff.

Catheters were removed if they were no longer needed, blocked, or in case of any local or systemic complication. Duration of catheter placement was noted. Patients were observed for signs of local or systemic infections. In patients who had signs of local or systemic infections that included fever with chills, pain or purulent discharge, early signs of sepsis (tachycardia, hypotension or altered mental state), systemic involvement (Endocarditis, Thrombophlebitis, Septic Arthritis or Abscess) or raised inflammatory markers (TLC, CRP, Procalcitonin), their dialysis catheter was removed and distal 3-5 cm tip along with two samples from peripheral vein were taken for culture as per Clinical and Laboratory Standards Institute (CLSI) guidelines[10]. CRBSI was defined as growth of same organism from at least 1 percutaneous blood culture and from a culture of catheter tip as per Infection disease society of America (IDSA) guidelines[11]. All pathogens recovered from cultures were identified by standard microbiological procedure and susceptibility testing was done for available antibiotics.

All data was initially recorded in written form and was later transferred to Microsoft Excel 2016. Statistical analysis was done using Microsoft Excel 2016. Continuous variables such as age were expressed as age ± SD. Categorical variables were expressed as relative or absolute frequencies and percentages.

RESULTS

A total of 753 individuals were included in the study with mean age of 57.06 ± 11.82 years. Males constituted 501 (66.53%) while females were 252 (33.47%) of study population. Common risk factors in this group included hypertension (79.81%), diabetes (42.9%), cardiovascular diseases (24.83%), autoimmune disease (18.86%) and liver disease (15%). Among 407 (54.05%) catheters were femoral and 346 (45.95%) were placed in IJV with average catheter time across population was 32.95 days. Among 753 individuals, 228 (30.28%) patients showed one or more symptom or sign of bloodstream infection (BSI) and hence their catheter tips along with peripheral blood samples were sent for culture and sensitivity. Common symptoms in this subgroup were fever (88.60%), chills (65.78%), local inflammation (38.16%), pus discharge from catheter site (12.28%), septic shock (8.77%) and misc systemic complication (9.65%) including Septic Arthritis, abscess and pneumonia.

Among 228 patients, definite evidence of CRBSI as per IDSA criteria was seen in 136 patients (18.06%). Average age in this subset was 57.88 ± 12.78 years with 86 (63.24%) being males and females accounting for 50 (36.76%) of the cases. Femoral catheters had a higher risk of causing CRBSI (100 out of 407 or 24.5%) as compared to IJV catheters (36 out of 346 or 10.40%) with relative risk of 2.36. Average time to infection after catheter insertion was 21.66 ± 7.27 days with shorter time to infection seen in femoral catheters (20.11 ± 6.91 days) compared to IJV catheters (25.97 ± 6.56 days). This translates to about 5.48 incidences of CRBSI per 1000 catheter days overall (Infection per 1000 days = Total incidences of CRBSI/Total Catheter days x 1000). Rate of infection per week are shown in fig-1A.

In this study 55.88% of CRBSI were caused by gram positive organisms coagulase negative *Staphylo-*

cocci being the most common causing 28.68% of infections, followed by *Staphylococcus aureus* and *Klebsiella pneumoniae* at 21.32% and 13.24% respectively. Detailed distribution of organisms is shown in fig-1B.

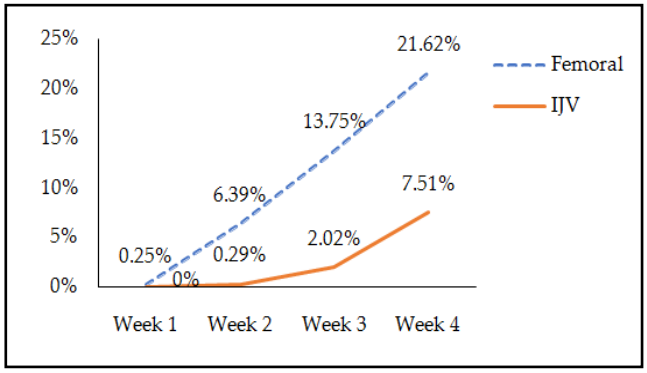

Figure- 1A: Weekly rate of infection.

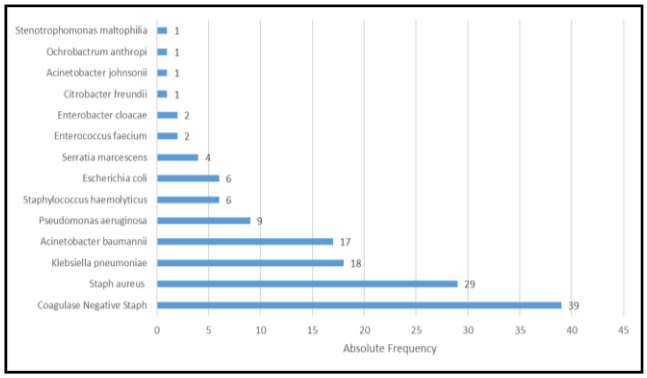

Figure-1B: Absolute frequency of organisms causing CRBSI.

Susceptibility patterns of the isolated gram positive and negative pathogens has been shown in table-I & II respectively. All gram-positive pathogens were susceptible to vancomycin and tigecycline and had low rates of resistance to doxycycline and linezolid. Among *S. aureus*, 58.6% were methicillin-resistant. Gram negative organisms had high rates of resistance to ampicillin, ceftriaxone and ciprofloxacin (94.23%, 96.77% & 74% respectively) (table-III). Co-morbidities associated with CRBSI in this population with Relative Risk are described in table-IV.

DISCUSSION

Temporary non-tunneled catheters, unlike other modalities (Tunneled Double Lumen, AV Fistula, AV Graft) provide a rapid access for hemodialysis in acute kidney injury (AKI) acute on chronic kidney disease (CKD) and when emergency dialysis is required[2]. In US, CRBSI form third commonest cause of hospital acquired infections with an attributable mortality rate of 12-25%[2]. Each incident of infection can cost an average of $20,000 to $25,000 US dollars[12].

In this study, hypertension, diabetes and cardiovascular disease were the most common underlying comorbidities in patients undergoing hemodialysis. These comorbidities were even more common in subset of patients developing CRBSI with especially high relative risk for diabetes, autoimmune disease and hypertension. Similar findings were reported by Allon *et al*[3], and Nasser *et al*[9].

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Table-I: Antibiotic resistant rates among gram positive pathogens from study population.

Antimicrobial Drug	Coagulase Negative Staphylococci (n=39)	Staphylococcus Aureus (n=29)	Staphylococcus Haemolyticus (n=6)	Enterococcus Faecium (n=2)
Penicillin	91.9	96.6	100	100
Ampicillin	91.9	95.8	100	100
Co-Amoxiclav	84.2	78.6	100	100
Cloxacillin	61.1	58.6	83.3	100
Piperacillin-Tazobactam	56.4	58.6	100	100
Cephradine	80.8	72	100	100
Cefepime	33.3	16.7	100	100
Vancomycin	-	-	0	-
Linezolid	10.3	6.9	16.67	-
Tigecycline	-	-	-	-
Co-Trimoxazole	65.7	25.9	66.7	100
Erythromycin	85.7	86.2	100	100
Clindamycin	48.7	40.7	50	100
Doxycycline	7.7	3.6	-	50
Gentamicin	69.7	61.5	66.7	Not Done
Amikacin	13.9	30.8	33.3	Not Done
Ciprofloxacin	75	79.2	83.3	100
Fusidic Acid	83.3	50	75	Not Done

sortium surveillance data reported a CRBSI rate of 4.1 per 1000 catheter days 13 while in this sample CRBSI was seen in 5.48 cases per 1000 catheter days which was within the described range available in previous studies (table-IV). Most common isolated organisms were also found to be similar across the board with Gram-positive organisms in 2 of top 3 positions in almost all similar studies.

Studies have reported fever with chills to be most common symptom associated with CRBSI which was seen in about 65% of our patients[3,9,18,19]. It has high sensitivity but low specificity as other infective etiologies may present with similar features[3,20,21].

In our population high rates of antimicrobial resistance were seen in both gram positive and negative organisms. In gram positive organisms 61.1% of coagulase-negative *Staphylococci*, 58.6% of *S. aureus* and 83.3% of *Staphylococcus* haemolyticus isolates were found to be methicillin (cloxacillin) resistant. However, all gram-positive organisms were found to be sensitive to vancomycin and tigecycline. doxycycline sensitivity was also surprisingly high at 93.24% across all Gram-

Table-II: Antibiotic resistant rates among gram negative pathogens from study population.

Antimicrobial Drug	Klebsiella Pneumoniae (n=18)	Acinetobacter Baumanii (n=17)	Pseudomonas Aeruginosa (n=9)	Escherichia Coli (n=6)	Serratia Marcescens (n=4)
Penicillin	100	100	100	100	100
Ampicillin	100	100	100	100	100
Piperacillin-Tazobactam	33.33	71.4	22.2	25	25
Ceftriaxone	83.3	100	100	100	66.7
Sulzone	66.7	85.7	100	100	100
Ceftazidime	ND	ND	44.4	Not Done	Not Done
Cefepime	75	100	ND	100	66.7
Meropenem	27.8	29.2	33.3	16.67	-
Tigecycline	12.5	18.7	Not Done	-	-
Co-Trimoxazole	85.7	92.8	100	100	50
Doxycycline	62.5	50	Not Done	25	33.33
Gentamicin	80	93.33	66.6	75	50
Amikacin	75	92.85	55.5	60	25
Ciprofloxacin	88.9	75	55.5	80	33.33
Polymyxin B	11.8	-	11.1	-	-

Table-III: Frequency, relative frequency and relative risk of comorbid associated.

Disease	Frequency (n)	Relative Frequency (n/136)	Relative Risk
Diabetes	88	0.65	2.16
Hypertension	115	0.84	1.37
Cardiovascular Disease	41	0.30	1.31
Autoimmune Disease	39	0.28	1.72
Liver Disease	23	0.16	1.15
Misc	53	0.39	1.03

Table-IV: Rates of BSI with common organisms in similar studies.

Data	Incidence of BSI (per 1000 patient days)	1st Commonest Organism	2nd Commonest Organism	3rd Commonest Organism
Our Data	5.48	Coagulase negative Staphylococci	Staphylococcus aureus	Klebsiella pneumoniae
Zhang *et al*, 2019[14]	0.84	Staphylococcus aureus	Enterobacter spp	Coagulase negative Staphylococci
Sahli *et al*, 2017[15]	10.8	Klebsiella pneumoniae	Coagulase negative Staphylococci	Staphylococcus aureus
Menegueti *et al*, 2017[16]	6.1	Coagulase negative Staphylococci	Staphylococcus aureus	Pseudomonas aeruginosa
Chandra *et al,* 2016[17]	ND	Coagulase negative Staphylococci	Staphylococcus aureus	Acinetobacter baumanii
Fysaraki *et al,* 2013[18]	3.18	Staphylococcus aureus	Coagulase negative Staphylococci	Escherichia coli

positive organisms which has not been demonstrated in similar studies like Pandit *et al*[22], and Gafor *et al*[23]. Gram negative infections were found to have polymicrobial resistance. Antibiotics with relatively high sensitivity (>50%) in descending order were Polymyxin B, Tigecycline, Meropenem and Piperacillin-Tazobactam (Pip-Tazo). Among 47.2% of gram-negative isolates were susceptible to doxycycline. High degree of penicillin, cephalosporin, quinolone and aminoglycoside resistance were noted in these isolates. Based on above data empiric therapy for all severe CRBSI patients must include vancomycin for gram-positive coverage and either a carbapenem or Pip-Tazo for gram negative coverage.

Another highlighted aspect in this study was high rates of CRBSI secondary to femoral vein catheterization as compared to IJV catheterization. Femoral catheters were used for temporary access in patients undergoing emergency hemodialysis or those awaiting definite procedures for permanent access. Oliver *et al*[24], reports high rates of bacteremia secondary to femoral catheters 27 with relative risk of 3.1 vs 2.36 in this study. Therefore, IJV catheterization should be preferred over femoral.

As this study was only observational in nature, we did not compare use of described antimicrobial drug in these patients, which can be subject of future study in our population.

CONCLUSION

More than 80% of CKD patients require hemodialysis via non-tunneled catheter at least once[2]. Although necessary, this intervention puts patient at risk of CRBSI which has a mortality rate of up to 25% in patients undergoing hemodialysis. Early control of CRBSI requires knowledge of effective empirical therapy which further requires knowledge of local antibio-gram. This study has highlighted antibiogram in this selected population. Gram positive organisms were seen more commonly which were fully susceptible to Vancomycin. Gram negative organisms, on the other hand were relatively more resistant and no single antimicrobial was found to be 100% effective. However, on this data, empiric therapy in these infections should include vancomycin with either a carbapenem or piperacillin-tazobactam. Furthermore, IJV catheters due to low infection rates should be preferred to reduce chances of CRBSI.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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