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Central Line Associated Blood Stream Infection with Gram Negative Organisms: Clinical Features, Risk Factors and Mortality

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Abstract

Background
Gram negative (GN) central line associated blood stream infection (CLABSI) has high mortality. Sindh Institute of Urology and Transplantation (SIUT) have a large dialysis unit and CLABSI is a major source of bacteremia. The aim of this study is to determine the clinical and microbiological characteristics, risk factors, antibiotics usage and mortality between CLABSI and non-CLABSI patients.

Methods
It is a cross sectional study done at SIUT from May 2017 to March 2018. Patients >18 years, with GN bacteremia were included. Patients were divided into CLABSI and non-CLABSI groups. Age, ICU stay, mechanical ventilation, Pittsburgh (PITT) bacteremia score, comorbidities (diabetes mellitus, end stage renal diseases, hemodialysis, urinary catheters, recent surgery, stone disease etc.), clinical features (fever, hypotension, altered level of consciousness, leukocytosis, leucopenia, thrombocytopenia), appropriate antibiotic use were noted. Patients were followed till day 30.

Results
Out of 137, 78 (56.9%) were CLABSI and 59 (43%) non-CLABSI. The significant risk factors for CLABSI were end stage renal disease (ESRD) [71.8% vs 15.3% p=<0.001 CI 14.14(5.97-33.56)] and hemodialysis [88.5% vs 30.5% p=<0.001 CI 17.46(7.18-42.46)]. *Klebsiella species* was commonly found in CLABSI (p=0.007) and *Escherichia coli* in non-CLABSI (p<0.001). Only 31% received appropriate empirical antibiotics. Mortality in CLABSI group was significantly associated with PITT bacteremia score (p=0.004), mechanical ventilation (p=0.007) and acute renal failure (p=0.008).

Conclusion
ARF is major risk factor for CLABSI. Arterio-venous (AV) fistula formation should be expedited to prevent CLABSI associated bacteremia. Empirical antibiotics should be according to local antibiogram to avoid inappropriate use.

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Introduction

Central line associated blood stream infection (CLABSI) is the one of most common hospital acquired infection worldwide.[1]

Patients undergoing renal replacement therapy need temporary angioaccess till arteriovenous fistulas are created. It has been observed that the risk of infections due to dialysis catheters is 15 fold greater than arteriovenous fistulas.[2] CLABSI is found to be more common in middle to low income countries ranging from 7.4 to 12.2 per 1000 central line days as compared to 1.3-2.1 per 1000 central line days in high income countries.[3]

The most common organisms causing CLABSI are gram positives, however over the last decade infections with gram negative organisms have become more prominent. According to a study from Spain there is an increase incidence of gram negative (GNR) CLABSI from 4% to 40% over a period of 18 years.[4] Another study from Israel reported increase in the trend of GNR CLABSI over 15 years.[5] In patients on hemodialysis, an increased frequency of gram negative CLABSI has been reported from Saudi Arabia.[6]

Solid organ transplantation, prior use of penicillin and hospital stay longer than 11 days are found to be independent risk factors for GNR CLABSI.[4] GNR bacteremia in patients with central lines are associated with very high mortality.[5,7] Kiran et al studied gram negative bacteremia from our center, 50% of which were CLABSI, they reported infection with a multi drug resistant organisms, prolonged ICU stay of >48 hours and more than one positive blood culture for that organism as risk factors for mortality.[8]

The data on GNR CLABSI is sparse. There are limited comparative reports in terms of clinical and microbiological features and outcome between CLABSI and non- CLABSI. Cairo et al compared GNR CLABSI with non-CLABSI in cancer patients and concluded polymicrobial infections, stenotrophomonas bacteremia and high colony counts on blood cultures are strong predictors of CLABSI which should prompt physicians to remove the line.[9]

To the best of our knowledge, little work has been done on GNR CLABSI in our part of the world especially from Pakistan. Our aim is to determine the clinical characteristics, risk factors, microbiological characteristics, antibiotics used and mortality in gram negative central line blood stream infections.

Material and Methods

This is cross sectional study, conducted at Sindh Institute of Urology and Transplantation (SIUT) Karachi, Pakistan, from May 2017 to March 2018. SIUT is a 700 bedded tertiary care public sector hospital; it mainly caters to nephrology, urology, gastroenterology, oncology and solid organ transplantation. The hospital provides a large number of inpatient and outpatient renal replacement therapy.

The study included all patients >18 years of age, who were admitted at SIUT with documented bacteremia due to *E.coli, Klebsiella species, Psuedomonas aeruginosa, Psuedomonas species, Enterobacter* and *Acinetobacter baumanni*. Patients <18 years, solid organ transplant recipients, patients on out-patient hemodialysis and bacteremia due to organisms other than mentioned above were excluded.

We divided the patients into two groups based on source of bacteremia whether originating from central line (CLABSI) or originating from source other than central line (non-CLABSI). Data was collected after taking informed consent. Demographics, clinical features, co-morbid conditions, on hemodialysis or not, recent antibiotics exposure, ICU stay, on mechanical ventilation, recent surgery, causative microorganisms, antibiotics used were noted. Patients were again followed on day 30 to note whether alive or dead.

Definitions

Central line associated blood stream infection (CLABSI): is defined as when a patient had 1 or more blood cultures growing gram negative bacteria with clinical signs and symptoms consistent with infection and no other site of infection other than central line identified. [10]

Non-central line associated blood stream infection (non-CLABSI): is defined as when a patient had 1 or more blood cultures growing gram negative bacteria with clinical signs and symptoms consistent with infection and central line is not the cause of infection.

Acute renal failure (ARF): acute derangement of renal failure diagnosed and labeled by nephrologists at presentation on basis of KDIGO criteria.[11]

End-stage renal disease (ESRD): Chronic kidney disease (CKD) is defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 mt2, persisting for 3 months or more, irrespective of the cause.[12]

Fever: having an axillary temperature above 101^0F. Altered level of consciousness: defined as any measure of arousal other than full orientation in time, place and person.

Hypotension: It is defined as systolic blood pressure ≤90 mmHg and diastolic blood pressure ≤60 mmHg on 2 different occasions and/or requirement of vasopressor agents within 48 hours of onset of bacteremia.

Leukocytosis/ leucopenia: Leukocytosis is defined as total leukocyte count ≥ 12000 cells/mm^3 and leucopenia as count ≤4500 cells/mm^3 within 48 hours of onset of bacteremia.

Thrombocytopenia: platelets count ≤$100*10^9$/L within 48 hours of onset of bacteremia.

Complications of bacteremia: gram negative bacteremia disseminate to different organs resulting to meningitis, brain abscess, empyema, hydropneumothorax etc.

PITTs bacteremia score: Includes clinical variables (range 0–14 points): temperature of 35.1?36.0°C or 39.0?39.9°C (1 point), temperature of ≤35°C or ≥40°C (2 points), mental status (alert, 0 points; disoriented, 1 point; stuporous, 2 points; comatose, 4 points), hypotension (2 points), receipt of mechanical ventilation (2 points) and cardiac arrest (4 points).

Appropriate antibiotics: Antibiotics which has been started before culture report and later found to be appropriate according to culture and then continued.

The study has been approved by ethical review committee of SIUT.

Statistical analysis: SPSS version 20 was used to analyze the data. Continues variables were reported as mean + SD and categorical variables were presented as frequencies and percentages.

To compare the mean difference between groups for continues variables two sample t-test was used whereas chi square independent test or fisher exact test was used to determine proportion difference between groups. P value <0.05 was considered as significant for categorical variables.

Results

A total of 137 cases with gram-negative bacteremia were included. 78 (56.9%) had CLABSI and 59 (43%) had non-CLABSI.

The age and sex distribution were similar. Significantly more patients with CLABSI presented with high grade fever as compared to non-CLABSI [n=66(84.6%) vs n=31 (52.9%) p=0.001 CI 4.97(2.23-11.05)]. Acute renal failure was seen

more in non-CLABSI patients. Regarding risk factors, CLABSI was found to be significantly associated with ESRD and hemodialysis. However, there is no difference regarding ICU stay [43.6% vs 35.6% p=0.34 CI 1.40 (0.69-2.80)], previous antibiotics exposure [55.1% vs 49.2% p=0.49 CI 1.27(0.64-2.50)], being on mechanical ventilation [17.9% vs 11.9% p=0.33 CI 1.62(0.61-4.32)] and diabetes [17.9% vs 15.3% p=0.68 CI 1.22(0.49-3.04)]. (table1)

Source of bacteremia in non-CLABSI patients are: urinary tract infection 35/59 (59%), pneumonia 5/59 (8.4%), cholangitis 7/59 (11.8%) and others 12/59 (20.33%).

Polymicrobial bacteremia is more seen in CLABSI (20.5% vs 13.6% p=0.29), however not statistically significant. Regarding individual organisms, *Klebsiella spp.* was found more frequently in CLABSI than in non-CLABSI (p=0.007) and *Escherichia coli* was found more commonly in non-CLABSI (p<0.001). Carbapenem resistant organisms were isolated in 38.5% of CLABSI and 49% of non-CLABSI bacteremia. (Table 2)

Overall empirical antibiotics were started in 124/137 (90.5%) of patients (Table 2). Piperacillin-tazobactam was the most commonly used antibiotic 83/124 (67%), 37/68 (54%) in CLABSI group and 46/56 (82%) in non-CLABSI group. Around

Table 1: Comparison of demographics, clinical characteristics, risk factors and mortality between CLABSI and non-CLABSI gram negative bacteremia. n=137

	CLABSI n=78	non-CLABSI n=59	p-value	OR (95%CI)
Age	42.5 (±16.1)	45.6 (±16.3)	0.277	NA
Male	54(69.2%)	41(69.5%)	0.97	0.98 (0.47 – 2.05)
Risk factors				
ICU stay >48hrs	34 (43.6%)	21 (35.6%)	0.34	1.40 (0.69-2.80)
Mechanical ventilation	14(17.9%)	7(11.9%)	0.33	1.62(0.61-4.32)
Diabetes Mellitus	14(17.9%)	9(15.3%)	0.68	1.22(0.49-3.04)
ESRD56	(71.8%)	9(15.3%)	<0.001	14.14(5.97-33.56)
Hemodialysis	69(88.5%)	18(30.5%)	<0.001	17.46(7.18-42.46)
Recent Antibiotics exposure	43(55.1%)	29(49.2%)	0.49	1.27(0.64-2.50)
Surgery	6(7.7%)	12(20.3%)	0.03	0.33(0.12-0.93)
Malignancy	2 (2.6%)	8 (13.6%)	0.02	0.17(0.03-0.82)
Stone diseases	8(10.3%)	12(20.3%)	0.09	0.45(0.17-1.18)
PCN	5(6.4%)	10(16.9%)	<0.001	0.34(0.11-1.04)
Foleys	29(37.2%)	40(67.8%)	<0.001	0.28(0.14-0.57)
Clinical features				
Fever	66 (84.6%)	31 (52.9%)	<0.001	4.97(2.23-11.05)
Hypotension	23 (29.5%)	14 (23.7%)	0.45	1.34(0.62-2.91)
ALOC	29 (37.2%)	17 (28.8%)	0.31	1.46(0.71-3.03)
Leukocytosis	55 (70.5%)	45 (76.3%)	0.45	0.74(0.34-1.61)
Leucopenia	5(6.4%)	2(3.4%)	0.35	1.95(0.37-10.43)
Thrombocytopenia ($<100*10^9$/L)	16(20.5%)	13(22.0%)	0.83	0.91(0.40-2.08)
Cardiac arrest	6 (7.7%)	1 (1.7%)	0.15	4.8(0.56-41.3)
PITT bacteremia score >4	14 (17.9%)	7 (11.9%)	0.32	1.62(0.61-4.32)
Complications	3(3.8%)	4(6.8%)	0.35	0.55(0.12-2.56)
Acute renal failure	20(25.6%)	44(74.6%)	<0.001	0.12(0.05-0.25)
Mortality				
30 Day mortality	24 (30.8%)	13 (22%)	0.25	0.63(0.29-1.39)

ICU=Intensive Care Unit, PITTs =Pittsburgh ESRD=End stage renal disease PCN= Percutanous nephrostomy ALOC= Altered level of consciousness

Table 2: Comparison of empirical antibiotics used and microorganisms isolated between CLABSI and non-CLABSI gram negative bacteremia

	CLABSI N=78	non-CLABSI N=59	p-value	OR (CI)
Empiric antibiotics	68(87.17%)	56 (94.9%)	0.13	0.36 (0.9-1.39)
Appropriate antibiotics received empirically	21(31%)	22(39%)	0.19	0.62 (0.29 – 1.28)
Micro-organisms isolated				
Polymicrobial	16 (20.5%)	8 (13.6%)	0.29	0.61(0.24-1.53)
Pseudomonas aeruginosa	11(14.1%)	8(13.6%)	0.93	1.05(0.39-2.79)
Acinetobacter	14(17.9%)	11(18.6%)	0.92	0.95(0.40-2.29)
Klebsiella species	36(46.2%)	14(23.7%)	0.007	2.75(1.30-5.81)
E.coli	11(14.1%)	25(42.4%)	<0.001	0.22(0.10-0.50)
others	6(7.7%)	1(1.7%)	0.12	4.83(0.57-41.29)
Carbapenem resistant organisms	30 (38.5%)	29 (49.2%)	0.21	0.65 (0.33-1.29)

43(31%) received appropriate antibiotics and 94(68.6%) received inappropriate antibiotics empirically.

Out of a total of 137 patients, 24 (30.8%) in CLABSI and 13 (22%) in non-CLABSI were died. There was no significant difference in 30 days' mortality between CLABSI and non-CLABSI patients. When clinical features and risk factors were compared, the PITT bacteremia score ≥4 was found to be significantly associated with mortality in CLABSI group as compared to non-CLABSI group (10/14 vs. 0/7, p value= 0.004). There is also a significantly high mortality in patients with CLABSI who had altered level of consciousness (p=0.07), on mechanical ventilation (p=0.007) and had acute renal failure (p=0.008). Regarding bacteria isolated, *Klebsiella* bacteremia in non-CLABSI patients is more fatal than in CLABSI patients however not statistically significant (p=0.089) (Table 3). Overall out of 37 patients who died, 28 (76%) patients were on inappropriate antibiotics and 9 (24%) were on appropriate antibiotics, however the difference was not statistically significant (p=0.27).

Discussion

SIUT mainly caters to renal and urological diseases with a large hemodialysis unit and a busy urology surgical service. We compared GNR CLABSI with non-CLABSI. The age and gender were comparable. When we looked into the risk factors, CLABSI is significantly associated with ESRD. It has been observed that around 80% of patients initiated dialysis via temporary central venous catheter access worldwide and there is three to fourfold higher risk of catheter related infections compared with either fistula or graft.[13] Mehmood *et al* from Pakistan also reported around 80% of patients presented with ESRD with acute need for hemodialysis through temporary access lines.[14] This patient population should have the arterio-venous (AV) fistula prepared in advance when they are in their stage 4 or 5 kidney disease in order to avoid dialysis lines. It has been observed that AV fistula is the best modality for hemodialysis with least infections.[13] Early diagnosis of chronic kidney disease (CKD) with prompt fistula formation has been associated with avoidance of central lines and hence infections.[15] The reason of late presentation may be the fact that majority of our patients come from low socioeconomic group with reduce access to diagnosis and management of CKD. Bokhari *et al* reported late diagnosis of CKD and lack of awareness among patients about seeking medical care for early fistula formation as the most frequent reasons of unavailability of AV fistula.[16]

At our center the central line infection rates in the dialysis unit are very high; around 40 per 100 patient months, according to our recent surveillance data. We observed the same trend in our study; CLABSI bacteremia is significantly more common in patients on hemodialysis than in non-CLABSI bacteremia. More focus has to be placed on stringent infection control measures in hemodialysis unit during insertion as well as handling of dialysis lines for the prevention of catheter infections.

In non-CLABSI patients bacteremia is significantly associated with foley's catheter or percutaneous nephrostomy tubes. It reflects our patient population, admitted mostly with urological problems including malignancies and urological surgeries. These patients require multiple urological interventions and requirement of indwelling catheters for long time posing them high risk of developing urinary tract infections and urosepsis.

We have found significant difference in microbiological characteristics of CLABSI and non CLABSI bacteremia. *Klebsiella spp*. infection is more common in CLABSI patients. Kiran *et al* from our center also reported *Klebsiella* bacteremia to be the most common organism among gram negative

Table 3: Comparison of clinical features, risk factors and microorganisms isolated with mortality between CLABSI and non-CLABSI gram negative bacteremia.

	30 day Mortality`` in CLABSI No/total no (%)	30 day Mortality in non- CLABSI No/total no (%)	p-value
Clinical features			
Pitt bacteremia score ≥4	10/14 (71.42%)	0/7	0.004
ICU 48 hrs.	13/34 (38.23%)	4/21 (19.04%)	0.229
Hypotension	11/23 (47.82%)	3/14 (21.42%)	0.166
Altered level of consciousness	15/29 (51.72%)	4/17 (23.52%)	0.073
Mechanical ventilation	9/14 (64.28%)	0/7	0.007
Cardiac arrest	5/6 (83.33%)	0/1	0.286
Complications	2/3 (66.66%)	2/4 (50%)	1.000
Acute renal failure	8/20 (40%)	5/44 (11.36%)	0.008
ESRD	14/56 (25%)	5/9 (55.55%)	0.108
Hemodialysis	21/69 (30.43%)	4/18 (22.22%)	0.572
Organisms			
Pseudomonas aeruginosa	5/11 (45.45%)	1/8 (12.5%)	0.177
Acinetobacter species	6/14 (42.85%)	2/11 (18.18%)	0.234
Klebsiella species	9/36 (25%)	7/14 (50%)	0.089
E.coli	4/11 (36.36%)	3/25 (12.0%)	0.167
Polymicrobial	4/16 (25%)	4/8 (50%)	0.363
Carbapenem resistant organisms	8/30 (26.66%)	6/29 (20.68%)	0.590
Inappropriate antibiotics	18/57 (31.5%)	10/37 (27%)	0.637

infections.[8] This finding is consistent with other studies done recently which report increase frequency of Klebsiella as the causative organism in CLABSI with high mortality.[4,5,6] *Klebsiella spp* has been reported as the third most common pathogen in hospital settings.[17] The possible reasons behind the rising trend of nosocomial *Klebsiella* infection are high rates of colonization in gastrointestinal tract of patients and increase propensity of biofilm formation by this organism.[18] Infection control measures with environmental cleaning and hand hygiene are the best possible way to prevent this pathogen to cause infections.

When we looked into antibiotic usage we found that around 90% of our patients received empirical antibiotics with more than half received pipracillin/tazobactam. However, if we assess the appropriateness of empirical therapy, only one third of the patients received appropriate antibiotics at the time of admission. Triffi *et al* reported empiric appropriate antibiotics is associated with early reduction of vasopressor requirement and hence reduce mortality.[19] The possible cause of inappropriate antibiotic can be explained by the increase prevalence of resistant organisms in our center. Around 40% of our patients in both CLABSI and non-CLABSI group had carbapenem resistant bacteremia. Kalam *et al* from our institute also reported the frequency of carbapenem resistant bacteremia as 42%.[8] We found a high mortality in patients who received inappropriate antibiotics, although not statistically significant. A regular communication between microbiologists and treating physicians regarding local susceptibility patterns may improve the prescription of appropriate empirical antibiotics.

There was no difference in all-cause mortality at 30 days, between CLABSI and non-CLABSI. However, in patients with CLABSI, mortality is significantly associated with high PITTs bacteremia score, being on mechanical ventilator and having renal failure. According to Cairo *et al* high bacterial load in blood culture is predictive of CLABSI.[9] We can infer that since CLABSI is associated with high bacterial load, it presents with more severe disease associated with high PITTs bacteremia score and more complicated clinical course before death.

The limitations of our study are the number of patients in non-CLABSI group is less than in the study arm, which may not represent the true associations. However, it is the first study to compare the CLABSI with non-CLABSI in Pakistan.

In conclusion CLABSI is a severe disease. We need to expedite

AV fistula formation in order to avoid central line infections. Good infection control practices in handling central lines as well as other devices should be emphasized. Empirical antibiotics in gram negative bacteremia should be according to the local antibiogram of each unit.

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