

Procalcitonin levels versus Microbiological profile in Central line associated bloodstream infections (CLABSI) of patients on Hemodialysis



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ABSTRACT

Background: CLABSI is one of the most common forms of hospital acquired systemic infection (sepsis), associated with high mortality. Although Procalcitonin (PCT) is proved to be the earliest and specific marker for the diagnosis of sepsis, there is relatively sparse literature on the usage of this marker in CLABSI with chronic kidney disease (CKD). **Aims and Objective:** To correlate the Procalcitonin levels with microbiological profile of CLABSI CKD patients. **Materials and Methods:** A retrospective case control study was conducted in a tertiary care Nephro-Urology hospital in Bangalore, from January 2019 to December 2019 including all CKD patients (age > 20 years) with central venous catheter undergoing Hemodialysis. Based on blood culture reports of these patients, they were divided into CLABSI (positive growth), and no growth. Procalcitonin was analyzed in both the groups. Statistical analysis was done using SPSS software version 17. **Results:** Sixty-one percentage of the CKD patients of mean age 46 years had CLABSI. Most common isolate in CLABSI CKD was *Staphylococcus aureus* (35%), followed by *Escherichia coli* (19%), *Klebsiella pneumoniae* (10%). Mean PCT was significantly higher (p value 0.001) in CP-CKD (Culture positive-chronic kidney disease) patients (36.1 ± 35.0 ng/ml) compared to CN-CKD (Culture negative-chronic kidney disease) (4.6 ± 10.0 ng/ml). Also mean PCT for Gram positive (GP) isolates (28.7 ± 30.2) was significantly lower (P value 0.0008) than that for gram negative (GN) isolates (53.6 ± 33.7). **Conclusion:** The study highlights higher incidence of CLABSI in CKD patients. Higher PCT values were observed in gram negative bacteria compared to gram positive, indicating its probable role for differentiating CLABSI due to gram-positive and gram-negative bacteria.

Key words: Central line associated bloodstream infections; Procalcitonin; Chronic kidney disease; Blood culture

INTRODUCTION

Sepsis is the systemic inflammatory response developed by the body immune system to the invasion of various infectious pathogens.¹ It affects almost all the organs of the body and hence presence of various markers of human host markers like cytokines, receptor biomarkers, cell markers etc. is evident of sepsis.² Although total leukocyte count and C-reactive protein (CRP) are used as the conventional

markers for the diagnosis of sepsis, absence of these markers will not exclude sepsis, also these markers lack sensitivity and specificity.³ Procalcitonin (PCT) is produced by the thyroid glands for calcium regulation. It gets broken down to calcitonin for the same purpose. Though all tissues in the body have the ability to produce PCT, only the C cells of thyroid gland produce required enzymes to cleave PCT to calcitonin in order to maintain calcium balance. During sepsis, there is a surge of cytokines such as IL-6,

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TNF- α and IL-1 β which stimulate the production of PCT from non-thyroid tissues of the body. Hence, there is an increase in PCT levels during sepsis.

Thus, it serves as an early marker of sepsis as it is increased within four hours of sepsis and reaches its maximum within six hours indicating that PCT is a better biomarker of sepsis than other traditional ones^{4,5} Also, PCT is more indicative of bacterial infections as its values are normal in viral and fungal infections, and other noninfectious inflammatory conditions.^{6,7}

A central line-associated bloodstream infection (CLABSI) is a bloodstream infection mainly confirmed by laboratory investigation, which develops after two calendar days of placement of central venous line, with no evidence of infection at any other site.^{8,9} CLABSI is one of the most common forms of hospital acquired systemic infection (sepsis), which requires a prolonged hospital stay, high risk of mortality and has high cost burden.^{10,11} More than 50% of the nosocomial bacteremia are known to have a source from intravascular access.¹² A recent survey from United states has reported that around 2,50,000 intravascular blood stream infections are detected with a mortality rate of 12%–25% annually.^{13,14} A survey by International Nosocomial Infection Control Consortium (INICC) included intensive care units of 15 developing countries and reported that CLABSI occurs at a rate of 4.1 per 1000 central lines.¹⁵

Hence, earliest diagnosis of CLABSI is very important for the clinician so that an appropriate treatment can be initiated in order to prevent morbidity and mortality associated with that. Although PCT is proved to be the earliest and specific marker for the diagnosis of sepsis, there is relatively sparse literature on the usage of this marker in the diagnosis and management of central line associated blood stream infections. In the present study we focus on detecting the incidence of CLABSI in chronic kidney disease (CKD) patients on hemodialysis (HD), and correlation of procalcitonin with microbiological profile of CLABSI. We also focus on studying antibiotic resistance pattern of CLABSI in CKD patients and its possible correlation with procalcitonin.

MATERIALS AND METHODS

This is a retrospective case control study conducted in a tertiary care Nephro-Urology hospital in Bangalore, Karnataka, South India, from January 2019 to December 2019. CKD patients (age >20 years) with central venous catheter undergoing hemodialysis were enrolled in the study. Blood culture reports of all such patients were collected. As part of hospital policy, blood samples are collected as per standard guidelines and sent for culture and S. PCT

levels prior to initiating empirical antibiotic therapy. As per the culture reports, subjects were divided into 2 groups, group 1 with culture positive cases and group 2 with culture negative cases. Procalcitonin was analyzed in both the groups. Patients who had infection from any source other than central venous catheter were excluded from the study.

Inclusion criteria

All CKD patients (Age >20 years) presenting with signs and symptoms suspicious of CLABSI such as fever, chills, malaise, hypotension with no other localizing signs of infection having central venous catheter (temporary or permanent) in situ for more than two consecutive calendar days.

Exclusion criteria

- 1) CKD patients with other known causes of infection.
- 2) CKD patients with other comorbidities which cause high PCT values.

Sample collection and laboratory analysis of the sample

Blood culture and antimicrobial susceptibility test

Paired blood cultures (one each from the central line and peripheral vein) were collected with strict aseptic precautions, labelled appropriately and incubated in BacT/ALERT 3D Automated Blood Culture system (BioMérieux). When there was difficulty in collecting peripheral blood cultures as in CKD patients, two or more samples were collected from different lumens of a multi-lumen central line catheter¹⁷. When the instrument flagged positive, subcultures were made on to MacConkey agar and 5% defibrinated sheep blood agar and incubated overnight at 37°C after noting the time. The plates were then observed for colony morphology and the isolate identified with standard biochemical tests. Following this, antimicrobial susceptibility was performed by Kirby-Bauer disc diffusion method as per current CLSI guidelines.^{18,19}

Biochemical parameters

After taking all aseptic precautions, 5 ml of venous blood sample was collected from median cubital vein, and was centrifuged for 15 mins. Serum sample thus separated was used for analysis. All the parameters were assayed in our Biochemistry laboratory using Abbott CI 4100, chemistry and immunoassay analyzer. Urea and creatinine were assayed using enzymatic method, urea by Urease method and creatinine by Jaffe's method.

Procalcitonin was measured using chemiluminescent microparticle immunoassay (CMIA), with a measuring range of 0.02-100 ng/ml. C-reactive protein (CRP) was measured using Immunoturbidimetric method, with the reportable range of 0.50 to 30.00 mg/dl.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences software Version 17. Chi square test was used to find the significance among incidence and prevalence rates. Unpaired independent student t test was used to find out significance among independent variables.

RESULTS

One-hundred ten consecutive patients as mentioned in the inclusion criteria. Sixty-eight (61.8%) cases had a positive blood culture. 42(38.2%) cases had no growth on blood culture. 51% of the culture positives were in the age group of 35 to 50 years. There was no statistically significant difference between male and females with respect to culture positivity (Table 1).

Table 2 shows the comparison of clinical data in culture positive (CP)CKD and culture negative (CN) CKD patients. Mean age of the patients in CP-CKD and CN-CKD group was 46 years and 48 years respectively (Table 2).

Mean duration of hemodialysis was 426 days and 397 days in culture positive CKD and culture negative CKD respectively. There was no significant association between

the culture positive growths and duration of hemodialysis (Table 2).

Duration of catherization was significantly higher in culture positive CKD patients (mean 50±30 days) compared to culture negative CKD (mean 15±5 days) with P value of 0.0001 at 95% confidence interval (CI) 44.2-25.7 (Table 2).

Mean PCT was significantly higher in CP-CKD patients (36.1±35. ng/ml) compared to CN CKD (4.6±10.0 ng/ml) with a p value of 0.0001 at 95% CI (20.3-42.6) (Table 2).

Both CP-CKD and CN-CKD patients were divided into 4 subgroups based on the PCT values which were a) PCT <0.5ng/ml, b) 0.5-2.0ng/ml, c) 2.0-10ng/ml and d) >10ng/ml. 37(54%) of the culture positive CKD patients, fell into PCT >10 group(Group d), which was statistically significant compared to culture negative CKD patients (Table 3) (Figure1).

Other markers of inflammation, C-reactive protein (CRP), total leucocyte count (TLC) were also compared, which revealed significantly higher value of CRP (p value: 0.0001) in CP-CKD (24±11 mg/dl) compared to CN-CKD (12±6 mg/dl) and TLC was also significantly high in CP-CKD (P value: 0.0001) (Table 2).

On comparing PCT values between gram positive (28.7±30.2) and gram negative isolates (53.6±33.7) of culture positive patients, there was significantly (P value-0.0008) increased PCT values in gram negative CLABSI compared to gram positive CLABSI (Table 4).

Among a total of 68 culture positive patients, 28 (41%) were gram positive bacteria, 28 (41%) were gram negative bacteria and 5 (7%) were fungal pathogens. Most common

Table 1: Demographic data

Total (n)	Culture positive n (n%)	Culture negative n (n%)	P value (Chi Square value)
Number of HD patients on central line	68(61.8%)	42(38.2%)	
Age group (years)			
20-35	21(30%)	18	0.31
35-50	35(51%)	20	(χ ² value: 2.305)
>50	12(17%)	4	0.808
Sex			
Male(54)	34(62%)	20(38%)	(χ ² value: 0.05)
Female(56)	34(60%)	22(39%)	

Hd- Hemodialysis, χ²- chi square

Table 2 : Distribution of clinical parameters among culture positive and culture negative cases

Parameters	Culture positive (mean±sd)	Culture negative (mean±sd)	P value
Age(Years)	46±16	48±14	0.5
Duration of hemodialysis(Days)	426±237	397±212	0.5
Duration of catheterisation(Days)	50±30	15±5	0.0001
PCT (ng/ml)	36.1±35.7	4.6± 1.3	0.0001
CRP(mg/dl)	24±11	12±6	0.0001
Leucocyte count(cells/cubic mm)	17313±7796	8775±4806	0.0001
Creatinine(mg/dl)	12.3±5.6	8.4±3.6	

Table 3 : Clinical and Biochemical data of the study groups

Inflammatory markers	Culture positive n (n%)	Culture negative n (n%)	P value (Chi Square value)
PCT (ng/ml)			
< 0.5	13(19%)	16(38%)	
0.5- 2	8(11%)	7(16%)	0.00065
2- 10	10(14%)	16(38%)	(χ ² value: 22.1)
> 10	37(54%)	5(11%)	
CRP(mg/dl)			
>32	31(45%)	1(1.4%)	0.00001
<32	37(55%)	41(98.6%)	(χ ² value: 23.4)
Leucocytosis (TLC >11000cells/m ³)	55(80%)	12(17%)	0.0001
Fever	10(14%)	5(11%)	0.67

PCT: Procalcitonin. Pct values: <0.5 - Systemic Infection not Likely, 0.5- 2 - moderate risk systemic infection, 2-10 - High risk systemic infection, >10 - severe sepsis CRP: C-Reactive protien. TLC:total leucocyte count

Table 4: PCT [ng/ml] in GPB and GNB CLABSI

PCT in GPB CLABSI, Mean±SD Median	PCT in GNB CLABSI, Mean±SD Median	P value (std error)	Significance level
28.7±30.2 36.2 (0.11-100)	53.6±33.7 77.3 (1.2-100)	0.0008 (8.428)	Significant

PCT- Procalcitonin, GPB- Gram positive bacteria, GNB- Gram negative bacteria, CLABSI- Central line associated blood stream infection

Table 5: Microbiological data and its correlation with PCT

Pathogen isolated	Number (%)	PCT Median (Range)
Gram positive bacteria		
1. <i>Staphylococcus aureus</i>	24(35%)	52.6(0.11-100)
2. <i>Coagulase negative staphylococci(CONS)</i>	2 (2.9%)	17.5(17- 18)
3. <i>Enterococcus faecalis</i>	2(2.9%)	3.7(3.3-4.2)
Gram negative bacteria		
1. <i>Klebsiella pneumoniae</i>	7(10%)	77.2(39.2-100)
2. <i>Pseudomonas aeruginosa</i>	3(2.9)	53.5(19.8-72.0)
3. <i>Escherichia coli</i>	13(19%)	63.2(0.18-79.7)
4. <i>Acinetobacter species</i>	2(2.9%)	5.5(1.2-9.4)
5. <i>Enterobacter species</i>	3(4.4%)	56(3-100)
Fungal growth		
1. <i>Candida albicans</i>	4(5.8%)	2.85(0.2-3.1)
2. Non <i>Candida albicans</i>	1(1.4%)	2.71
Contaminants (Micrococi)	6(8.8)	23.4(0.32-99.2)
Total	68(100%)	

Table 6: Antibiotic resistance pattern for Gram positive isolates

Antibiotics	N	S	I	R	Resistance %	Efficacy
Vancomycin	28	28	0	0	0%	100%
Tiecoplanin	28	28	0	0	0%	100%
Linezolid	28	28	0	0	0%	100%
Cotrimoxazole	28	4	2	23	82.1%	17.9%
Doxycycline	28	5	1	23	82.1%	17.9%
Clindamycin	28	25	2	1	3.5%	96.5%
Levofloxacin	28	2	2	24	85.7%	14.3%

N- number of susceptibility tests, S-sensitive, I-intermediate, R-resistant, Resistance(%)= R/N x 100%, EFFICACY(%)= S+I/N x 100%.

species that were isolated were *Staphylococcus aureus* 24(35%), followed by *Escherichia coli* 13 (19%), *Klebsiella pneumoniae* 7 (10%) (Table 5) (Figure 2).

Antibiotic susceptibility tests were done for both gram-positive isolates and gram-negative isolates. Antibiotic resistance and efficacy pattern for GP and GN isolates are demonstrated in the Table 6 and 7.

In Gram positive isolates, levofloxacin, cotrimoxazole and doxycycline showed resistance rates of more than 50%, and vancomycin, linezolid, teicoplanin showed zero resistance indicating 100% efficacy (Table 6)(Figure 3).

In Gram negative isolates, aztreonam, cefotaxime, ciprofloxacin, ceftazidime, levofloxacin, amikacin,

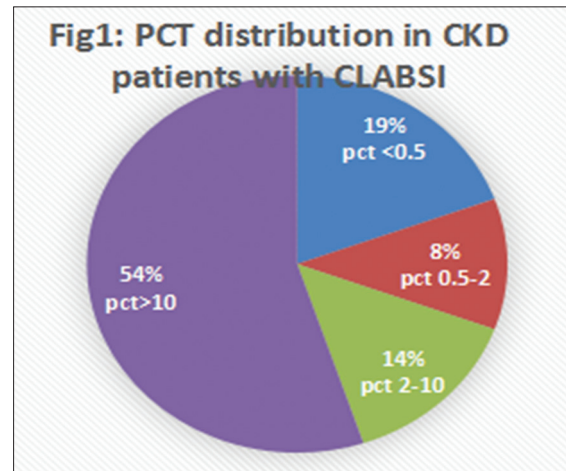


Figure 1: PCT distribution in CKD patients with CLABSI

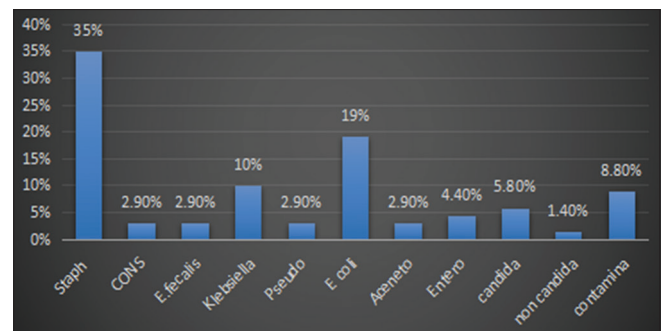


Figure 2: Microbiological profile of CLABSI in CKD patients

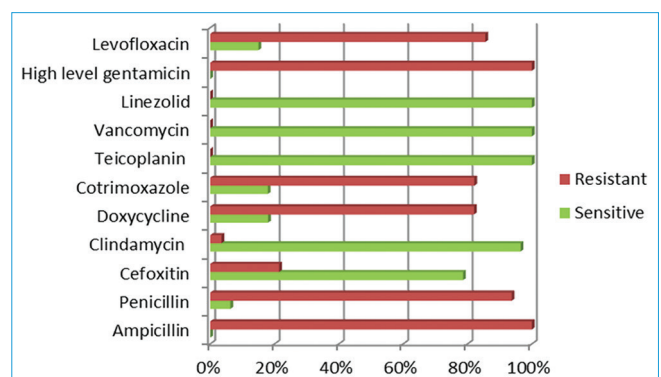


Figure 3: Antibiogram of gram-positive organisms

gentamycin, showed more than 50% resistance, whereas polymyxin B, imipenem, meropenem, cefoperazone-sulbactam showed zero resistance indicating 100% efficacy (Table 7) (Figure 4).

Table 7: Antibiotic resistance pattern for Gram negative isolates

Antibiotics	N	S	I	R	Resistance %	Efficacy
Aztreonam	28	4	1	23	81%	19
Cefotaxime	28	2	1	25	89.2%	10.8
Ciprofloxacin	28	4	1	23	82.1 %	17.9
Colistin	28	28	0	0	0%	100
Ceftazidime	28	5	0	23	82.1%	17.9
Ertapenem	28	1	1	26	92.8%	7.2
Imipenem	28	27	0	1	3.5%	96.5%
Meropenem	28	28	0	0	0%	100
Cefoperazone-Sulbactam	28	28	0	0	0%	100
Piperacillin-Tazobactam	28	6	2	20	71.4%	29.6
Polymyxin-B	28	28	0	0	0%	100
Levofloxacin	28	3	2	23	82.1%	17.9
Tigecycline	28	28	0	0	0%	100
Amikacin	28	14	0	14	50%	50

N- number of susceptibility tests, S-sensitive, I-intermediate, R-resistant, Resistance(%)= R/N x 100%, EFFICACY(%)= S+I/N x 100%.

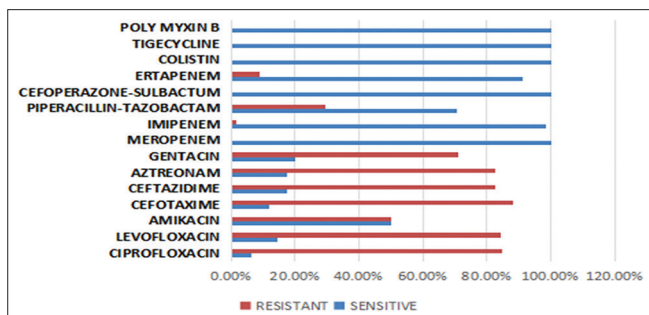


Figure. 4: Antibiogram of Gram-negative organisms

DISCUSSION

Central line associated blood stream infection (CLABSI) is defined by CDC, as recovery of a pathogen from a blood culture of a patient who had central line in place for more than two calendar days, where the infection cannot be related to any source, other than central line.¹⁶

CLABSI is one of the most common forms of hospital acquired infection in patients receiving hemodialysis (HD), with an estimated incidence of 12- 25%.²⁰⁻²²

In the present study, culture positive CLABSI occurred in 61% (68 out of 110) of the CKD patients with central line on HD. All these patients were admitted in ICU. Most common organisms isolated from blood culture of CLABSI patients in our study was *Staphylococcus aureus* (54%), followed by *Escherichia coli*, and *Klebsiella species*. Similar findings were observed in Lata et al study where incidence of CLABSI was around 30% in ESRD patients with predominance of *Staphylococcal* isolates.²³

Procalcitonin is known to be increased in patients with bacteremia as proved in many studies.²⁴⁻²⁶ In the present study PCT levels were significantly higher in Gram negative isolates compared to gram positive isolates. Similar results were seen in Charles et al who demonstrated the ability of PCT to differentiate between the systemic infection by gram positive and gram negative organisms in critically ill patients.²⁷ Another study by St. Yan et al have recently proved that PCT can be used as a marker to distinguish between GNB and GPB infection, as well as between different bacterial species and infection sites.²⁸

The present study is apparently one of very few studies done to correlate the PCT and microbiological profile of CLABSI in CKD patients. In the present study, PCT median values for different microbial growths of CLABSI are compared in order to evaluate the possibility that different PCT values could correspond to different microbial groups. Accordingly, PCT was found to be high in gram negative organisms than in gram positive. Also, *Klebsiella pneumoniae* species was associated with highest median PCT in CLABSI CKD patients in our study.

The process of producing PCT by the host in response to gram negative and gram positive bacterial infection is unclear. This might be attributed to the membrane composition of gram positive and gram negative bacteria. In Gram negative bacteria, the major cell membrane component is lipopolysaccharide (LPS) which is also a major component of endotoxin. Whereas, in gram positive bacteria the major cell membrane component is peptidoglycan (PGN). Both these components which are pathogen associated molecular patterns (PAMPs) are identified by pattern recognition receptors (PRRs) during the innate immune response. These PRRs constitute several families like toll like receptors (TLR) and C-type lectin receptors (CLRS). TLRs play a major role in detecting the bacteria. Proinflammatory cytokines are released when the PAMPs bind to TLRs initiating signaling pathways. TLR-4 identifies LPS as a ligand whereas PGN by TLR2. MyD88 dependent signaling pathway which releases cytokines like TNF- α , IL-6 is activated when LPS binds to TLR4. Comparatively poor cytokine levels (TNF α and IL-6) are observed in gram positive infections due to TLR-3 dependent stimulation. These factors might lead to higher PCT levels in gram negative bacterial infections compared to gram positive ones.²⁹

Different ranges of PCT indicates the different degree of systemic inflammation namely no risk of systemic inflammation(PCT <0.5ng/ml), moderate risk of systemic infection(PCT 0.5- 2ng/m), high risk of systemic infection (PCT 2-10ng/ml), severe systemic infection or bacterial sepsis (PCT values >10ng/ml) Harbart et al.²⁹ The result

of the present study revealed that 54% of the CLABSI-CKD patients had PCT >10ng/ml, corresponding to severe systemic infection with mean PCT of 36.1ng/ml. This gives an indication that PCT cut off value for CLABSI CKD needs to be increased for better management of these patients.

The study also observed that 38% of CKD patients without CLABSI had PCT in the range 2-10ng/ml, corresponding to high risk systemic infection with mean PCT of 4.6 ng/ml. This is in accordance with a few studies which have proved that PCT level can be higher than normal baseline values in CKD patients regardless of whether they have superimposed infection or not.^{30,31}

The pathophysiology of elevated PCT in these patients is due to an increase in pro-inflammatory mediators that stimulate the immune system in CKD patients to cause the release of PCT into the circulation.³²

Also, 19% of the CLABSI CKD patients in our study had a PCT of <0.5, indicating that low or normal PCT does not always exclude the presence of bacterial infection. This might be a cause in early course of bacterial infection, or infection due to a few bacterial species which may not be associated with high PCT.

Development of antibiotic resistance in CKD patients is a major problem which is encountered by the clinicians. In the present study, antibiotic susceptibility tests were done for antibiotics for both gram-positive isolates and gram-negative isolates.

In Gram positive isolates, levofloxacin, cotrimoxazole and doxycycline showed resistance rates of more than 50%, and vancomycin, linezolid, teicoplanin showed zero resistance indicating 100% efficacy. Six isolates (25%) of *Staphylococcus aureus* were methicillin resistant (MRSA).

In Gram negative isolates, aztreonam, cefotaxime, ciprofloxacin, ceftazidime, levofloxacin, amikacin, gentamicin, showed more than 50% resistance, whereas polymyxin B, imipenem, meropenem, cefoperazone-sulbactam showed zero resistance indicating 100% efficacy.

High sensitivity of these antibiotics contributes to their use as an option in empirical antibiotic therapy. Accordingly, our study suggests that vancomycin, linezolid and teicoplanin could be considered for empirical antibiotic therapy for gram positive infections, and imipenem, meropenem, cefoperazone-sulbactam could be used for gram negative infections of CLABSI-CKD patients. Large number of studies are needed in this aspect to arrive at this conclusion.

Early and appropriate administration of antibiotic therapy for serious infections is known to be associated with lower mortality, shorter duration of hospitalization, and reduced cost of health care.³³ Hence, strategies need to be made for the judicious use of antibiotics in order to control the resistance and to improve their rational use. One such strategy is to use PCT guided antibiotic therapy.³⁴⁻³⁶ One of the largest studies conducted in this aspect was the use of procalcitonin to de-escalate antibiotic therapy, in acutely ill patients (PRORATA) trial,³⁷ a randomized controlled trial involving seven ICUs, where the criterion for stopping antibiotics was a decrease of PCT \geq 80% from its peak value. Concluding that PCT guided strategy was effective in reducing antibiotic exposure without any apparent adverse outcomes.

In the present study, though there was positive association between the development of antibiotic resistance and peaked PCT values, the result was not statistically significant. This may be due to smaller study population and shorter duration of the study indicating the requirement of further studies in this aspect. Also the association between PCT and leukopenia was not studied.

CONCLUSION

The study highlights higher incidence of CLABSI in CKD patients. Higher PCT values were observed in gram negative bacteria compared to gram positive, indicating its probable role for differentiating CLABSI due to gram-positive and gram-negative bacteria. Most common isolate was *Staphylococcus aureus*, sensitive to most of the higher antibiotics like vancomycin, teicoplanin and linezolid, suggesting their use as empirical therapy in CLABSI-CKD patients.

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Author's Contribution:

MNS, SN, MS - Conceived the idea of the study, Developed the theory and performed the computations, Data analysis and manuscript preparation, all contributed equally towards the study; **MKM, KR** - Supervision of the study and data analysis, encouraged the investigators to plan and perform the study.

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