Original Article

Procalcitonin-guided antimicrobial stewardship in critically ill patients with sepsis: A pre– post interventional study

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Abstract

Aim: Injudicious usage of antibiotics has led to the emergence of antibiotic resistance which is a major health-care problem in developing countries such as India. Our aim was to show how antibiotic therapy based on serial procalcitonin (PCT) assay can help in antibiotic de-escalation in septic patients.

Materials and Methods: A pre–post interventional study was conducted among 300 septic patients admitted to an intensive care unit (ICU). All septic patients admitted 2 months before and 2 months after the introduction of monitoring of PCT were included and they were divided into Group P (with PCT monitoring) and Group C (without PCT monitoring). The proportion of patients for whom antimicrobials were de-escalated, the average time taken to de-escalate antimicrobials, and the average duration of ICU stay were compared. Proportions and averages with standard deviations were calculated to describe the data. A test of proportions was done to compare the proportion de-escalated and a Student's *t*-test was done to compare the average duration of antibiotic therapy.

Results: The proportion of patients in whom de-escalation of antimicrobials was done was 125 (83.33%) in Group P as compared to 92 (61.33%) in Group C. The time taken to de-escalate was 3.04 ± 0.83 days (95% confidence interval [CI] 2.89–3.18) in Group P compared to 4.7 ± 1.4 days (CI 4.41–4.98) in Group C. The duration of ICU stay was also less in Group P - 3.08 ± 0.91 days (CI 3.08–3.38) as compared to Group C - 5.16 ± 2.17 days (4.80–5.51).

Conclusion: Serial PCT assay-based antimicrobial therapy helped to wean patients with sepsis off antimicrobials earlier thus reducing the duration of ICU stay.

Keywords: Antibiotic resistance, antibiotic stewardship, biomarker assay, procalcitonin, sepsis

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INTRODUCTION

Sepsis accounts for more than half of admissions in intensive care units (ICUs) worldwide with a mortality rate ranging from 30% to 50%.[1] Early recognition of bacterial infection and initiation of antimicrobial therapy is extremely crucial for the treatment of sepsis.[1,2] However, this task can be very challenging to the clinician resulting in unwarranted and prolonged antimicrobial therapy. Injudicious use of

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antibiotics can lead to the emergence of opportunistic infections, antibiotic resistance, prolonged ICU stay, and healthcare costs.[1,2] This can cause a huge economic burden, especially in developing countries such as India.[3-5] High infectious burden, poor living conditions, and easy availability of antibiotics are some of the other contributing factors to the rising antimicrobial resistance in India.[3-5] Antibiotic stewardship is the only logical way to curtail this menace.[3-5]

Biomarkers can serve as a helpful tool in the judicious use of antimicrobials in sepsis.[1] Procalcitonin (PCT), an amino acid precursor to calcitonin is released as a component of the inflammatory cascade in response to endotoxins released during bacterial infections. PCT levels are selectively elevated in patients with bacterial infections and can be used as a biomarker to differentiate bacterial sepsis from other causes of sepsis.[1,6-8] In comparison to other diagnostic tools, such as C-reactive protein and white blood cell count, PCT has the advantage of showing an early and highly specific increase in response to bacterial infections.[9] In addition, a low serum PCT level accurately rules out the diagnosis of bacteremia and thus can be used to discontinue antibiotic therapy.[9] PCT elevation occurs within 2–4 h of active bacterial infection and peaks between 8 h and 24 h.[10] Moreover, PCT is stable in serum samples and the results are available within 2–4 h which makes it very useful in daily practices.[10] PCT monitoring along with detailed clinical workup can be used to guide antibiotic initiation and de-escalation for bacteremia, thus reducing unnecessary antimicrobial exposure.[10]

Several studies show the efficacy of PCT assay in the diagnosis of bacterial sepsis, timely prescription, and de-escalation of antibiotic therapy thus limiting ICU stay.[1,2,6,7,11,12] On the contrary, some studies also exist that show there was no difference in duration and in average time to de-escalation of antibiotic therapy, average ICU and hospital stay, and mortality rate.[13,14] Only a few studies have been conducted on the Indian population to corroborate these findings.[11] In this background, we set out to find out how efficiently serial PCT assay will help in antibiotic de-escalation and in reducing ICU stays at a tertiary hospital in South India. A study was done to compare the proportion of patients with sepsis for whom de-escalation of antimicrobial therapy was done, the average time taken to de-escalate, and the average duration of ICU stay among patients with sepsis on antimicrobial therapy while in the ICU, with and without serial PCT assay.

MATERIALS AND METHODS

This study was conducted in a multidisciplinary critical care unit (MDCCU) of a tertiary care hospital in South India. Approval was obtained from the institutional ethics committee and research committee. All patients admitted to the MDCCU with sepsis on antimicrobials in 2 months (May–June 2020) before the introduction of regular monitoring of PCT and 2 months (July–August 2020) after the introduction of regular monitoring of PCT were included in the study after getting informed written consent. For comparison purposes, two groups of patients were formed - Group P (with PCT monitoring) and Group C (control group without PCT monitoring). Sample size calculations were derived from the findings of Shehabi *et al*. in which the overall median (interquartile range [IQR]) number of antibiotic treatment days was 9 (6–21) versus 11 (6–22) in the intervention and control groups, respectively.[13] Assuming a median baseline exposure level of 9 days and a standard deviation (SD) of 6 days, a sample size of 141 was calculated with an alpha error of 0.05 and 80% power.

All patients older than 18 years of age admitted to MDCCU with suspected sepsis or septic shock and on antimicrobial therapy were included in the study. Patients who refused to give consent, postoperative and trauma patients, severely immunocompromised patients, such as patients infected with human immunodeficiency virus and with a cluster differentiation 4 T-cell count of <200 cells/mm^3, neutropenic patients (<500 neutrophils/mm^3), pregnant patients, and patients in whom antibiotic therapy was started 48 h or more before enrolment were excluded from the study.[1,11] Outcomes measured were (1) the proportion of patients in each group in whom antibiotic therapy was de-escalated during ICU stay, (2) the average time taken to de-escalate antimicrobial agents, and (3) the duration of ICU stay. PCT assay was done daily in patients belonging to Group P. The access PCT assay used in our study is a paramagnetic, chemiluminescent immunoassay for *in vitro* quantitative determination of PCT levels in human serum and plasma. It can accurately measure the samples within the analytical range of the lower limit of detection and the highest calibrator value (approximately 0.01–100 ng/mL). De-escalation of therapy was defined as a switch to a narrower spectrum agent, reduction in the number of antibiotics, or cessation of antibiotic treatment.[1,11] For patients in Group P, antibiotic therapy was stopped if the PCT level was <0.5 ng/mL or if there was a decline in PCT level more than 80% from baseline.[1,11]

Statistical analysis

Continuous data are presented as medians with IQRs while categorical variables are presented as numbers and percentages. Data were compared using the Mann–Whitney *U*-test for the continuous variables and Pearson's

Chi-squared test or Fisher's exact test for the categorical variables. The Kaplan–Meier method was used to estimate the cumulative rates of antibiotic cessation. Proportions and averages with SD were calculated to describe the data. Test of proportions was done to compare the proportion de-escalated and Student's *t*-test was done to compare the average duration of antibiotic therapy in the two groups.

RESULTS

The baseline characteristics of patients in both groups were similar [Table 1]. There were 100 males in Group C, whereas Group P had 96 males. The majority of patients were in the age group of 60–90 years. Associated comorbidities were diabetes, chronic obstructive lung disease, end stage renal disease, cancer, and congestive cardiac failure. Diabetic mellitus was the most common comorbidity found in both groups. In both groups, lung infection was the major source of sepsis followed by urinary tract infection. The most commonly used antibiotic was vancomycin followed by meropenem. The sequential organ failure assessment score was 8.5 ± 1.3 in both groups. The average PCT values ranged from 7.9 ng/mL on day 1 of assessment to 0.5 ng/mL on day 7 [Figure 1]. The duration of ICU stay was 2 days longer in Group C (5.16 vs. 3.08 days, $P < 0.0001$) [Figure 2]. The proportion of patients in whom antibiotic therapy was de-escalated during ICU stay was higher in Group P (125 vs. 92, $P < 0.00001$). The time taken to de-escalate antibiotic therapy was around 2 days more in Group C (4.7 vs. 3.04 days, $P < 0.0001$) [Figure 3].

DISCUSSION

A pre–post interventional study was done to examine the role of PCT in the de-escalation of antibiotic therapy in sepsis patients. Our study supports the fact that PCT based antibiotic therapy can help the clinician to reduce the time taken to de-escalate antibiotics and also the total ICU stay in a greater proportion of patients. We were able to reduce the time taken for de-escalation and ICU stay by about 2 days.

Similar findings have been observed by de Jong *et al*. in 2016,[15] Nobre *et al*. in 2008[16], and by Hochreiter *et al*. in 2009[17] in their respective studies. PRORATA trial[12] and SAPS study[15] also showed that PCT can help to reduce antibiotic exposure by shortening treatment duration. A meta-analysis done in 2017 which included 11 studies and 4482 sepsis patients in ICU showed a significant reduction in mean treatment duration (from 10.4 days to 9.3 days, $P = 0.001$). It was also shown that the mortality rate was lower in the PCT-guided group.[2] Similarly, Shafiq *et al*. in their meta-analysis concluded that while hard endpoints of mortality and need for ICU admissions remained unaffected, there was a significant reduction in the use of antibiotics in the emergency, ICU setting, and the ward setting due to the use of PCT-guided dosing.[18]

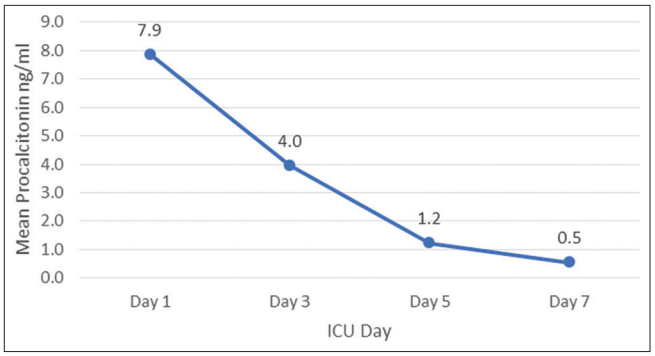

Figure 1: Average procalcitonin values in Group P. ICU: Intensive care unit

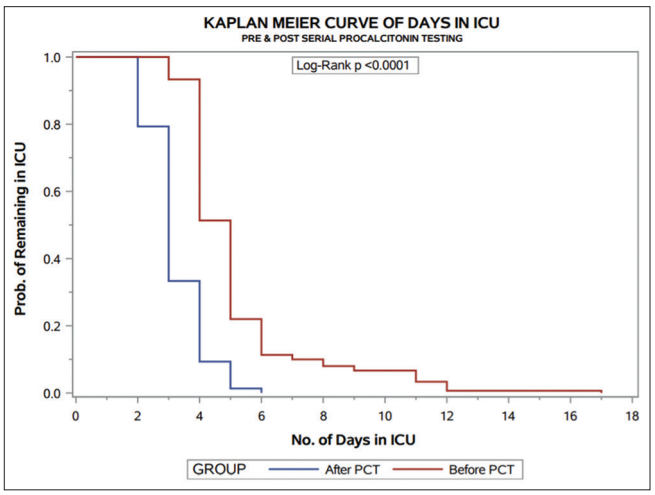

Figure 2: Kaplan-Meier curve depicting the duration of intensive care unit stay in Groups P and C. ICU: Intensive care unit, PCT: Procalcitonin

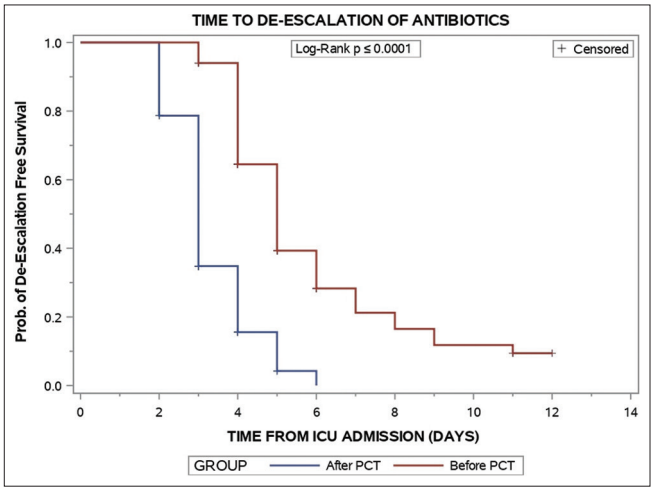

Figure 3: Kaplan–Meier curve depicting the rate of de-escalation of antibiotics in Groups P and C

Table 1: Baseline characteristics of patients enrolled in the study

Characteristics	Preimplementation of PCT (Group C) (*n*=150), *n* (%)	Postimplementation OF PCT (Group P) (*n*=150), *n* (%)	*P*
Male	100 (66.67)	96 (64)	0.718
Age group (years)			0.051
<30	14 (9.3)	4 (2.6)	
30–60	45 (30)	47 (31.3)	
60–90	91 (60.7)	99 (66.1)	
Comorbidities			0.508
Diabetes mellitus	36 (24)	41 (27.3)	
Chronic obstructive lung disease	16 (10.6)	13 (8.6)	
Congestive cardiac failure	3 (2)	6 (4)	
End stage renal disease	12 (8)	14 (9.3)	
Cancer	4 (2.6)	2 (1.3)	
SOFA score	8.5±1.3	8.5±1.3	1
Total leukocyte count (cells/mm^3)	15,900±3102.8	16,400±3700.8	0.205
Temperature (degree Fahrenheit)	98.82±1.69	99.25±2.12	0.053

PCT=Procalcitonin, SOFA=Sequential organ failure assessment

On the contrary, Covington *et al*. analyzed the effect of PCT monitoring on inpatient antibiotic duration for sepsis at a community hospital in the USA in 2018 and results showed that there was no difference in the mean duration of inpatient antibiotics (6.1 ± 3.9 vs. 5.4 ± 2.9 days, $P = 0.50$). In addition, there was no difference in the average time to antibiotic de-escalation, average hospital length of stay, or ICU length of stay. However, PCT monitoring did result in a significant reduction in discharge antibiotics and the duration of overall inpatient and postdischarge antibiotics.[14] Shehabi *et al*. showed in a study that a PCT algorithm with a low cutoff value of 0.1 ng/mL did not reduce the duration of antibiotic treatment days by more than 25%.[13] A commonly accepted algorithm for the utilization of PCT has been long lacking. The current body of evidence proposes that a PCT cutoff value of <0.5 μg/L or a decrease of 80%–90% from the peak level indicates recovery from bacterial infections and in such cases, discontinuation of antibiotic treatment is favorable and we have followed this protocol in our study.[1,10,11,19]

Reduced ICU stay and duration of antibiotic therapy can help to bring down health-care costs. This can go a long way in reducing the overall economic burden, especially in developing countries like India. A study conducted in North India in 2018 by Kaur *et al*. pointed out some common but serious lapses in antibiotic prescription patterns in India. Out of 517 screened patients, 300 were prescribed antimicrobials although no evidence of infectious etiology was found in 129 out of the 300 patients.[3] Antibiotic stewardship is the only way to curtail the rising menace of antibiotic resistance in such settings. Jeon *et al*. performed a cost minimization analysis of PCT-guided antibiotic discontinuation in their study and found that PCT-guided therapy decreased antibiotic costs by United States Dollar 30.[11]

Our study was a single-centre study with a limited sample size. Multicentric studies with a larger sample size may be required to confirm our findings. PCT is not routinely used in clinical practice, especially in low resource and middle-income countries like India. Many barriers such as clinicians knowledge about biomarkers, cost-effectiveness, and availability could make the routine implementation of PCT-based algorithm difficult and need to be evaluated further.

CONCLUSION

Our study concludes that PCT based antibiotic therapy can help the clinician to de-escalate antibiotic therapy earlier in a greater proportion of patients with sepsis and thus shorten ICU stay. PCT algorithm-based antibiotic stewardship can help bring down the rising menace of antibiotic resistance in developing countries like India.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Vishalashi SG, Gupta P, Verma PK. Serum procalcitonin as a biomarker to determine the duration of antibiotic therapy in adult patients with sepsis and septic shock in intensive care units: A prospective study. Indian J Crit Care Med 2021;25:507-11.
2. Gregoriano C, Heilmann E, Molitor A, Schuetz P. Role of procalcitonin use in the management of sepsis. J Thorac Dis 2020;12:S5-15.
3. Kaur A, Bhagat R, Kaur N, Shafiq N, Gautam V, Malhotra S, *et al*. A study of antibiotic prescription pattern in patients referred to tertiary care center in Northern India. Ther Adv Infect Dis 2018;5:63-8.
4. Laxminarayan R, Chaudhury RR. Antibiotic resistance in India: Drivers and opportunities for action. PLoS Med 2016;13:e1001974.
5. Ganguly NK, Arora NK, Chandy SJ, Fairoze MN, Gill JP, Gupta U, *et al*. Rationalizing antibiotic use to limit antibiotic resistance in India. Indian J Med Res 2011;134:281-94.

6. Chomba RN, Moeng MS, Lowman W. Procalcitonin-guided antibiotic therapy for suspected and confirmed sepsis of patients in a surgical trauma ICU: A prospective, two period cross-over, interventional study. S Afr J Surg 2020;5:143-9.
7. Gupta S, Jaswani P, Sharma RK, Agrawal S, Prasad N, Sahu C, *et al*. Procalcitonin as a diagnostic biomarker of sepsis: A tertiary care centre experience. J Infect Public Health 2019;12:323-9.
8. Nakajima A, Yazawa J, Sugiki D, Mizuguchi M, Sagara H, Fujisiro M, *et al*. Clinical utility of procalcitonin as a marker of sepsis: A potential predictor of causative pathogens. Intern Med 2014;53:1497-503.
9. Arai T, Ohta S, Tsurukiri J, Kumasaka K, Nagata K, Okita T, *et al*. Procalcitonin levels predict to identify bacterial strains in blood cultures of septic patients. Am J Emerg Med 2016;34:2150-3.
10. Khilnani GC, Tiwari P, Zirpe KG, Chaudhry D, Govil D, Dixit S, *et al*. Guidelines for the use of procalcitonin for rational use of antibiotics. Indian J Crit Care Med 2022;26:S77-94.
11. Jeon K, Suh JK, Jang EJ, Cho S, Ryu HG, Na S, *et al*. Procalcitonin-guided treatment on duration of antibiotic therapy and cost in septic patients (PRODA): A multi-center randomized controlled trial. J Korean Med Sci 2019;34:e110.
12. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, *et al*. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): A multicentre randomised controlled trial. Lancet 2010;375:463-74.
13. Shehabi Y, Sterba M, Garrett PM, Rachakonda KS, Stephens D, Harrigan P, *et al*. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. Am J Respir Crit Care Med 2014;190:1102-10.
14. Covington EW, Eure S, Carroll D, Freeman C. Impact of procalcitonin monitoring on duration of antibiotics in patients with sepsis and/or pneumonia in a community hospital setting. J Pharm Technol 2018;34:109-16.
15. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, *et al*. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: A randomised, controlled, open-label trial. Lancet Infect Dis 2016;16:819-27.
16. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: A randomized trial. Am J Respir Crit Care Med 2008;177:498-505.
17. Hochreiter M, Köhler T, Schweiger AM, Keck FS, Bein B, von Spiegel T, *et al*. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: A randomized prospective controlled trial. Crit Care 2009;13:R83.
18. Shafiq N, Gautam V, Pandey AK, Kaur N, Garg S, Negi H, *et al*. A meta-analysis to assess usefulness of procalcitonin-guided antibiotic usage for decision making. Indian J Med Res 2017;146:576-84.
19. Carr JA. Procalcitonin-guided antibiotic therapy for septic patients in the surgical intensive care unit. J Intensive Care 2015;3:36.