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A Prospective, Randomized Controlled Trial Design To Evaluate The Effective Role Of Procalcitonin In Adopting Antibiotic Therapy In Sepsis Patients In A Tertiary Care Center

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ABSTRACT

Background: Sepsis is a critical health challenge associated with high morbidity and mortality. Judicious use of antibiotics is highly essential to combat sepsis effectively while mitigating the rise of antimicrobial resistance. Procalcitonin (PCT), a biomarker that elevates during bacterial infections, offers the potential for adopting antibiotic therapy due to its dynamic response to treatment. This study enables to evaluate the efficacy of PCT-guided therapy in optimizing antibiotic use among sepsis patients.

Methods: This prospective, randomized controlled trial enrolled 150 patients diagnosed with sepsis based on Sepsis-3 criteria. Participants were randomized into two groups: 1)PCT-Guided Therapy Group: Antibiotic initiation and cessation guided by PCT levels.2)Standard Care Group: Antibiotic management based on clinical assessment . The primary outcome was the duration of antibiotic therapy. Secondary outcomes included clinical cure rate, length of ICU stay, 28-day mortality, and development of antibiotic resistance. Data were analyzed using appropriate statistical tests, with a p-value < 0.05 considered significant.

Results: The PCT-guided group showed a significant reduction in the duration of antibiotic therapy(7.2 vs. 10.5 days, $p < 0.001$) and ICU stay (10.1 ± 3.4 vs. 12.7 ± 4.1 days, $p < 0.01$). Clinical cure rates (88% vs. 85%, $p = 0.52$) and 28-day mortality (18.7% vs. 20%, $p = 0.79$) were comparable between groups. The incidence of antibiotic-resistant infections was lower in the PCT group (7% vs. 15%, $p = 0.04$). No significant adverse events were reported.

Conclusion: PCT-guided therapy effectively reduced antibiotic duration, ICU stay, and antibiotic resistance without compromising clinical outcomes, demonstrating its potential to enhance antimicrobial stewardship in sepsis management. Future studies should refine PCT algorithms and assess long-term effectiveness in diverse settings.

Keywords: *Sepsis, organ dysfunction, PCT, antibiotics, CRP*

1. INTRODUCTION

Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, remains a significant global health challenge due to its high morbidity and mortality rates. Early and appropriate management, including prompt initiation and judicious use of antibiotics, is pivotal in improving patient outcomes. However, the inappropriate or prolonged use of antibiotics has been linked to the emergence of antimicrobial resistance, a pressing public health issue (1,2). In this context, biomarkers such as procalcitonin (PCT) have emerged as promising tools for guiding antibiotic therapy and optimizing treatment strategies in sepsis patients.

Procalcitonin is a peptide precursor of the hormone calcitonin, and its serum levels rise significantly during bacterial infections. Unlike other biomarkers, such as C-reactive protein (CRP), PCT exhibits a more rapid response to bacterial infection and a quicker normalization following effective therapy, making it an attractive candidate for clinical applications

(3). Research has demonstrated that PCT-guided antibiotic therapy can help reduce the duration of antibiotic treatment in septic patients without adversely affecting clinical outcomes (4,5). This aligns with antimicrobial stewardship goals, aiming to limit unnecessary antibiotic exposure while ensuring effective management of infections.

The rationale for investigating PCT as a guide for antibiotic therapy lies in its potential to address critical challenges in sepsis care: minimizing antibiotic overuse, and curbing the development of drug-resistant pathogens. Moreover, studies indicate that PCT levels correlate with the severity of bacterial infections, offering prognostic value in the management of septic patients (6). Given these benefits, understanding the role of PCT in antibiotic decision-making can significantly impact clinical practice and patient safety.

2. AIM

To evaluate the role of procalcitonin (PCT) as a biomarker in guiding antibiotic therapy among sepsis patients

3. MATERIALS AND METHODS

Study Design: This study employed a prospective, randomized controlled trial (RCT) design to evaluate the role of procalcitonin (PCT) in guiding antibiotic therapy in patients diagnosed with sepsis. The study was conducted in the Intensive Care Units (ICUs) of a tertiary care hospital.

Study Population

Inclusion Criteria:

- Adults aged ≥18 years.
- Patients diagnosed with sepsis based on the Sepsis-3 criteria (suspected or confirmed infection and an increase in Sequential Organ Failure Assessment [SOFA] score of ≥2 points).
- Patients in need of antibiotic therapy as part of critical care for better recovery.
- Written informed consent obtained from patients.

Exclusion Criteria:

- Patients with non-infectious systemic inflammatory conditions.
- Severe immunosuppression (e.g., post-transplant patients, advanced HIV/AIDS, or chemotherapy-induced neutropenia).
- Pregnant or lactating women.
- Patients with known hypersensitivity to PCT measurement reagents.

Sample Size: The sample size was calculated based on prior study (4) evaluating PCT-guided antibiotic therapy. Assuming a 15% reduction in antibiotic duration with PCT guidance, with a power of 80% and a significance level of 0.05, a total of 150 patients (75 in each group) were enrolled.

Randomization

Participants were randomized into two groups:

1. Intervention Group (PCT-guided therapy): Antibiotic initiation and cessation were guided by serum PCT levels. Antibiotics were stopped if PCT levels decreased by >80% from peak values or fell below a threshold of 0.5 ng/mL, provided clinical stability was achieved.
2. Control Group (Standard care): Antibiotic therapy was managed according to current clinical guidelines and physician discretion without reference to PCT levels.

Randomization was achieved using a computer-generated randomization sequence, stratified by age and baseline SOFA score.

Intervention

1. PCT Measurement: Blood samples were collected at baseline (day 0) and every 48 hours during antibiotic treatment. Serum PCT levels were measured using a commercially available, FDA-approved immunoassay.
2. Antibiotic Therapy: All patients initially received empirical broad-spectrum antibiotics as per local sepsis management guidelines. De-escalation and cessation of antibiotics in the PCT group followed a predefined algorithm based on PCT levels and clinical judgment.

Data Collection

- Baseline Data:
  - Demographic details (age, sex, comorbidities) were recorded.
  - Severity scores (SOFA, APACHE II) were calculated.
  - Source of infection and initial antibiotic regimen were documented.
- Outcome Measures:

1. Primary Outcome: Duration of antibiotic therapy (in days).

2. Secondary Outcomes: Clinical cure rate at day 28. Length of ICU stay. 28-day mortality. Development of antibiotic resistance.

Monitoring and Follow-Up: Patients were monitored for clinical and biochemical parameters daily during their ICU stay. Follow-up was conducted up to 28 days post-randomization to assess outcomes and complications.

Statistical Analysis: Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range), and categorical variables as frequencies and percentages. Between-group comparisons were performed using: Student's t-test or Mann-Whitney U test for continuous variables. Chi-square or Fisher's exact test for categorical variables. Kaplan-Meier survival analysis was used to compare 28-day mortality between groups. Multivariable regression models adjusted for potential confounders, such as age, baseline SOFA score, and comorbidities. A p-value < 0.05 was considered statistically significant.

4. RESULTS

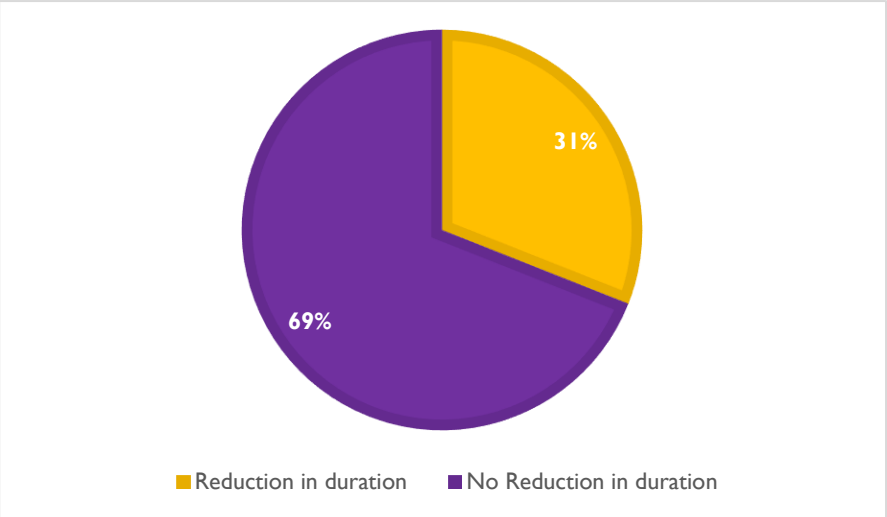
A total of 150 patients were enrolled in the study, with 75 randomized to the PCT-guided therapy group and 75 to the standard care group. Both groups were comparable in terms of baseline characteristics: Mean age: 58.2 ± 12.3 years in the PCT group and 59.1 ± 11.7 years in the standard care group. Gender distribution: 47% male in the PCT group and 49% male in the standard care group. Baseline SOFA score: Median of 8 (IQR 6–10) in both groups. Source of infection: Similar distributions in both groups, with pneumonia (40%), urinary tract infections (25%), and intra-abdominal infections (20%) being the most common sources.

Table 1: Baseline Characteristics

Characteristic	PCT-Guided Therapy Group n=75 (%)	Standard Care Group n=75 (%)
Mean Age (years)	58.2 ± 12.3	59.1 ± 11.7
Gender		
Male	47%	49%
Female	53%	51%
Baseline SOFA Score (Median [IQR])	8 [6-10]	8 [6-10]
Source of Infection		
Pneumonia (%)	40%	40%
Urinary Tract Infection (%)	25%	25%
Intra-abdominal Infection (%)	20%	20%

The median duration of antibiotic therapy was significantly reduced in the PCT-guided group compared to the standard care group: PCT group: 7.2 days (IQR 6.0–9.5). Standard care group: 10.5 days (IQR 8.0–13.0), p-value: < 0.001. This represents a 31% reduction in the duration of antibiotic therapy in the PCT-guided group.

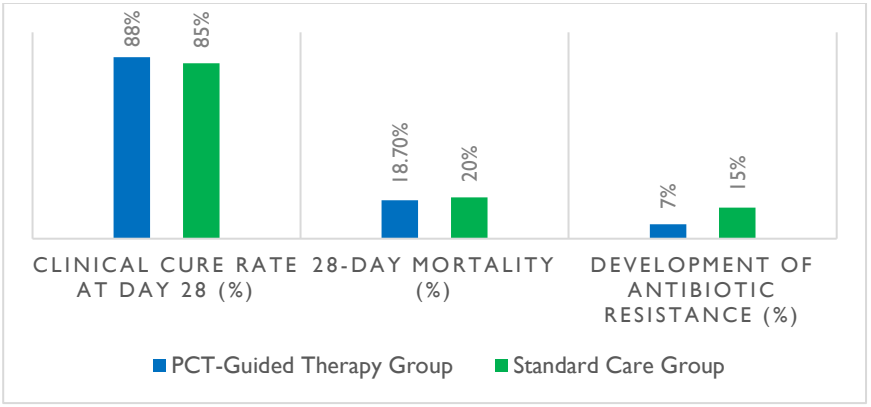
Figure 1: Percentage of Reduction Duration of Antibiotic Therapy



The clinical cure rate at day 28 was comparable between the two groups, with 88% in the PCT-guided therapy group and 85% in the standard care group (p = 0.52). Similarly, 28-day mortality rates showed no significant difference, recorded at 18.7% in the PCT group and 20% in the standard care group (p = 0.79). However, patients in the PCT group experienced a significantly shorter length of ICU stay, averaging 10.1 ± 3.4 days compared to 12.7 ± 4.1 days in the standard care group (p < 0.01). Additionally, the incidence of antibiotic-resistant infections was notably lower in the PCT group (7%) compared to the standard care group (15%), a statistically significant difference (p = 0.04). These findings suggest that while clinical outcomes like cure rate and mortality were similar, PCT-guided therapy was associated with reduced ICU stay and a lower rate of antibiotic resistance.

Table 2: Outcomes of PCT-Guided Therapy vs Standard Care

Outcome	PCT-Guided Therapy Group n=75 (%)	Standard Care Group n=75 (%)	p-value
Clinical Cure Rate at Day 28 (%)	88%	85%	0.52
28-Day Mortality (%)	18.70%	20%	0.79
Length of ICU Stay (days)	10.1 ± 3.4	12.7 ± 4.1	**< 0.01**
Development of Antibiotic Resistance (%)	7%	15%	**0.04**



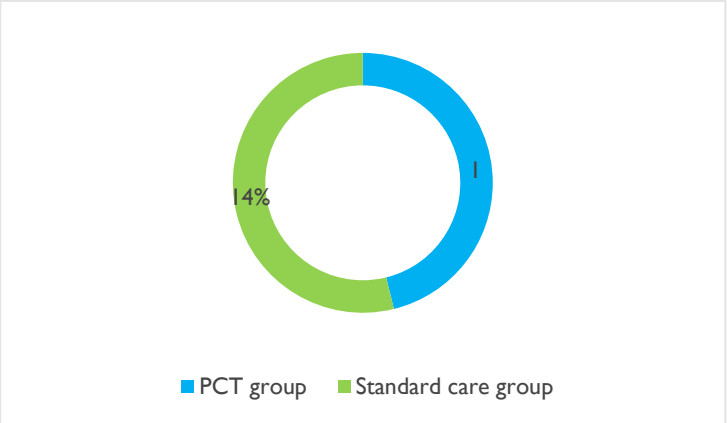
Baseline PCT Levels: Median of 3.5 ng/mL (IQR 2.8–5.0) in both groups. PCT levels showed a significant reduction by day 4 in the PCT-guided group compared to the standard care group (p < 0.01). In the PCT group, 80% of patients achieved an 80% reduction in PCT levels by day 6, which was a key determinant for antibiotic cessation.

Table 3: PCT Kinetics

Parameter	PCT-Guided Therapy Group n=75 (%)	Standard Care Group n=75 (%)	p-value
Baseline PCT Levels (ng/mL)	3.5 (IQR 2.8-5.0)	3.3 (IQR 2.4-5.0)	0.65
PCT Levels on Day 4 (ng/mL)	1.2 (IQR 0.8-1.8)	2.5 (IQR 2.0-3.0)	**0.04**
Reduction in PCT Levels by Day 4 (%)	65%	29%	**<0.01**
Patients Achieving 80% Reduction by Day 6 (%)	80%	60%	**<0.01**

No significant adverse events related to early cessation of antibiotics were reported in the PCT group. The rates of secondary infections were comparable between the groups: PCT group: 12%. Standard care group: 14%, p-value: 0.67.

Figure 2: Safety Outcomes



5. DISCUSSION

The results of this study provide robust evidence supporting the utility of procalcitonin (PCT)-guided therapy in managing sepsis patients, particularly in optimizing antibiotic use without compromising patient safety or clinical outcomes. Both the PCT-guided therapy group and the standard care group were comparable at baseline, ensuring that observed differences in outcomes were attributable to the intervention rather than confounding factors.

One of the most noticeable outcomes was the significant reduction in the duration of antibiotic therapy in the PCT-guided group, which achieved a median duration of 7.2 days compared to 10.5 days in the standard care group, representing a 31% reduction. This aligns with previous research that highlights PCT as a reliable biomarker for guiding antibiotic de-escalation. The shorter duration of therapy supports antimicrobial stewardship by reducing unnecessary antibiotic exposure, potentially mitigating the risk of adverse drug reactions and the emergence of resistance. The **PRORATA trial** by Bouadma et al. demonstrated a 23% reduction in antibiotic exposure in the PCT-guided therapy group without compromising patient safety or mortality rates (4). Our study showed a slightly greater reduction of 31%, highlighting the utility of PCT in optimizing antibiotic use. Similarly, a meta-analysis of randomized controlled trials found that PCT-guided strategies reduced the duration of antibiotic therapy by 2-4 days compared to standard care (7).

Despite the reduced antibiotic exposure in the PCT-guided group, clinical cure rates were comparable between the two groups (88% vs. 85%, p = 0.52), and 28-day mortality rates were similarly non-significant (18.7% vs. 20%, p = 0.79). These findings show the safety and effectiveness of PCT guidance, ensuring that clinical outcomes are not compromised while reducing antibiotic use. Consistent with our findings of comparable clinical cure rates (88% vs. 85%, p = 0.52) and 28-day mortality (18.7% vs. 20%, p = 0.79), a study by de Jong et al. confirmed that PCT-based decisions did not negatively impact clinical outcomes (8). This reinforces the safety of early antibiotic cessation when guided by biomarker kinetics.

Patients in the PCT-guided therapy group experienced a significantly shorter length of ICU stay (10.1 ± 3.4 days vs. 12.7 ± 4.1 days, p < 0.01). This reduction is clinically meaningful, as prolonged ICU stays are associated with increased risks of nosocomial infections. The ability of PCT-guided therapy to facilitate early discharge from the ICU is an important benefit, improving resource allocation and patient throughput. Our study demonstrated a significant reduction in ICU length of stay

(10.1 ± 3.4 days vs. 12.7 ± 4.1 days, $p < 0.01$) and lower rates of antibiotic resistance (7% vs. 15%, $p = 0.04$). Similarly, the Surviving Sepsis Campaign 2021 emphasized the importance of biomarkers like PCT in reducing unnecessary antibiotic use, which can mitigate resistance and improve resource allocation in critical care settings (9).

A critical finding of this study was the lower incidence of antibiotic-resistant infections in the PCT group (7% vs. 15%, $p = 0.04$). This result highlights the potential of PCT-guided therapy to contribute to antimicrobial resistance containment efforts, a global healthcare priority. Reduced antibiotic exposure likely limits the selective pressure for resistant strains, demonstrating the broader public health benefits of PCT-guided strategies. The kinetics of PCT levels further validated its utility as a biomarker. By day 4, the PCT-guided group exhibited a 65% reduction in PCT levels compared to 29% in the standard care group ($p < 0.01$). Additionally, 80% of patients in the PCT group achieved an 80% reduction by day 6, a key determinant for antibiotic cessation. These findings emphasize the responsiveness of PCT to bacterial infection resolution, making it a valuable tool for individualized therapy decisions. In our study, a significant reduction in PCT levels by day 4 (65% vs. 29%, $p < 0.01$) and an 80% reduction by day 6 in the majority of patients were key determinants for antibiotic cessation. These results align with prior studies emphasizing the importance of dynamic PCT monitoring for individualized therapy (7).

Importantly, no significant adverse events or increase in secondary infections were observed in the PCT-guided group (12% vs. 14%, $p = 0.67$). This confirms the safety of early antibiotic cessation guided by PCT, addressing a common concern regarding the potential under-treatment of infections.

The findings of this study strongly support the integration of PCT-guided therapy into routine sepsis management protocols. The reduction in antibiotic duration and ICU stay can lead to substantial resource optimization in healthcare settings while maintaining high cure rates and safety. Moreover, the association between PCT guidance and lower rates of antibiotic resistance demonstrates its role in advancing antimicrobial stewardship efforts. While this study demonstrated the efficacy of PCT-guided therapy, some limitations should be acknowledged. The study was conducted in tertiary care ICUs, and results may not be directly generalizable to resource-limited settings. Additionally, long-term outcomes beyond 28 days were not assessed, and further research is needed to evaluate the impact of PCT-guided therapy on chronic complications and healthcare utilization.

Procalcitonin (PCT) has several limitations that impact its clinical utility as a biomarker for guiding antibiotic therapy. While it is generally sensitive for detecting bacterial infections, its specificity can be confounded by conditions such as trauma, surgery, or autoimmune diseases, which can also elevate PCT levels (10). Furthermore, its effectiveness in distinguishing bacterial from viral infections, particularly in complex cases like pneumonia, is limited, as demonstrated by a meta-analysis showing sensitivity and specificity values of 55% and 76%, respectively (11). The lack of universally accepted thresholds for PCT levels across different settings also complicates its application, potentially leading to inconsistent decision-making (12). PCT's response is attenuated in immunosuppressed patients, reducing its reliability in such populations (13). Cost is another challenge, as PCT testing is more expensive than traditional biomarkers, potentially limiting its use in resource-constrained settings (14). Despite these limitations, PCT remains a valuable marker when used alongside clinical judgment and validated algorithms.

PCT-guided therapy represents a safe and effective approach to optimizing antibiotic use in sepsis patients. By reducing antibiotic duration, ICU stay, and the risk of resistance, PCT-guided strategies align with clinical and public health priorities. Future studies should focus on broader implementation strategies of PCT guidance across diverse healthcare settings.

6. CONCLUSION

This study reveals the significant role of procalcitonin (PCT) in optimizing antibiotic therapy among sepsis patients. By integrating PCT-guided strategies, we demonstrated a substantial reduction in antibiotic duration, length of ICU stay, and the incidence of antibiotic resistance, without compromising clinical cure rates or mortality. These findings emphasize the potential of PCT to enhance antimicrobial stewardship, improve resource utilization, and address the growing challenge of antibiotic resistance. However, the study also emphasizes the limitations of PCT, such as its variable specificity and reduced sensitivity in non-bacterial or immunosuppressed conditions. While PCT is a valuable adjunct, its effectiveness is maximized when combined with clinical judgment and standardized protocols. Future research should focus on refining PCT-guided algorithms, exploring in diverse healthcare settings, and addressing its limitations to further strengthen its role in managing sepsis and infectious diseases.

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