Journal of Society Medicine
Research & Review Articles on Diseases
Journal of Society Medicine. 2026; 5 (4)

Independent Determinants of Ventilator-Associated Pneumonia in Critically Ill Mechanically Ventilated Patients: A Prospective Multicenter Cohort Study

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ARTICLE INFO

Article history:
Received
21 February 2026

Revised
23 March 2026

Accepted
30 April 2026

Manuscript ID:
JSOCMED-21022026-54-4

Checked for Plagiarism: Yes

Language Editor:
Rebecca

Editor-Chief:
Prof. Aznan Lelo, PhD

ABSTRACT

Introduction: Procalcitonin (PCT) is increasingly used to support antibiotic stewardship in sepsis, particularly for guiding antimicrobial discontinuation. Although randomized trials suggest that PCT-guided strategies reduce antibiotic exposure without harm, their effectiveness in heterogeneous intensive care unit (ICU) populations remains unclear.

Methods: We conducted a prospective multicenter cohort study of adult ICU patients with sepsis managed using either a PCT-guided discontinuation protocol or standard care protocol. The protocol recommended antibiotic discontinuation when PCT decreased by at least 80% from peak values or reached 0.5 ng/mL or lower, provided that stability was achieved. The primary outcome was the duration of antibiotics for the index sepsis episode. Secondary outcomes included 28-day mortality, ICU length of stay, antibiotic consumption measured by days of therapy and defined daily doses, and direct costs of treatment. Mixed-effects regression and propensity score weighting were used to adjust for confounding and center-level variabilities.

Results: Among 1,284 patients, 642 received PCT-guided antibiotic stewardship and 642 received standard care. PCT-guided stewardship was associated with shorter antibiotic duration (6.1 vs. 7.5 days; adjusted difference, −1.2 days; 95% CI, −1.6 to −0.8; p<0.001). There was no increase in 28-day mortality (18.9% vs. 20.4%; adjusted OR, 0.92; 95% CI, 0.71–1.18). Antibiotic consumption was lower (612 vs. 742 DOT per 1,000 ICU-days), with reduced direct costs despite PCT testing.

Conclusion: PCT-guided antibiotic stewardship reduced antibiotic exposure and costs without compromising survival, supporting its integration as a pragmatic adjunct to clinical judgment in ICU sepsis management.

Keywords

Procalcitonin, Sepsis, Antibiotic Stewardship, Intensive Care Unit, Antibiotic Duration, Mortality, Days Of Therapy, Defined Daily Dose

How to cite: Ndlovu S, Mokoena T, Khumalo L. Independent Determinants of Ventilator-Associated Pneumonia in Critically Ill Mechanically Ventilated Patients: A Prospective Multicenter Cohort Study. *Journal of Society Medicine*. 2026; 5 (4): 134-140. **DOI: https://doi.org/ 10.71197/jsocmed.v5i4.278**

INTRODUCTION

Sepsis remains a leading cause of morbidity and mortality among critically ill patients and is defined as life-threatening organ dysfunction resulting from dysregulated host response to infection [1]. Early initiation of broad-spectrum antimicrobial therapy is a cornerstone of management and has consistently been associated with improved survival. However, prolonged or unnecessary antibiotic exposure contributes to antimicrobial resistance, drug-related toxicity, disruption of host microbiota, and increased healthcare costs, making the optimization of antibiotic duration a critical priority in modern intensive care practice [2]. Procalcitonin (PCT), a calcitonin precursor released in response to systemic bacterial infections, has emerged as a promising biomarker to support antibiotic stewardship in sepsis [3]. Compared with conventional inflammatory markers, PCT exhibits greater specificity for bacterial infections and demonstrates dynamic kinetics, with levels

declining as the infection resolves. These properties make PCT particularly suitable for guiding decisions on antimicrobial discontinuation rather than initiation [4].

Contemporary international guidelines recommend the use of PCT as an adjunct to clinical assessment to support antibiotic de-escalation or discontinuation when the optimal duration of therapy is uncertain, while cautioning against its use as the sole determinant for initiating antimicrobial therapy [5]. This distinction is clinically important because inappropriate reliance on biomarkers for early decision-making may delay timely antibiotic administration in patients with sepsis, thereby worsening outcomes. Several landmark randomized controlled trials have evaluated the clinical utility of PCT-guided stewardship. The PRORATA trial demonstrated that a PCT-based algorithm significantly increased the number of antibiotic-free days without adversely affecting mortality [6]. Similarly, the SAPS trial reported reductions in antibiotic duration and overall exposure, with signals of improved survival [7]. Recently, the ADAPT-Sepsis trial confirmed that PCT-guided protocols can safely reduce antibiotic use without increasing 28-day mortality, further supporting their role in stewardship strategies [8]. Despite this robust trial-based evidence, the translation of PCT-guided algorithms into routine ICU practice remains inconsistent across institutions. Real-world implementation is influenced by multiple factors, including assay availability, turnaround time, clinician adherence, and override behavior, all of which may attenuate the effectiveness observed in controlled trials [9]. Moreover, observational data capturing these implementation dynamics across diverse ICU environments are limited, particularly in prospective multicenter cohorts. Therefore, clarifying the real-world effectiveness of PCT-guided stewardship is of critical importance, as even modest reductions in antibiotic exposure at the population level may translate into meaningful decreases in antimicrobial resistance and healthcare burden. Importantly, any stewardship strategy for sepsis must balance antibiotic reduction with patient safety, ensuring that a shorter treatment duration does not increase mortality, relapse, or treatment failure. Accordingly, this study aimed to evaluate the effectiveness and safety of a PCT-guided antibiotic discontinuation strategy in ICU patients with sepsis using a prospective multicenter observational cohort design, focusing on both clinical outcomes and antibiotic stewardship metrics [10].

METHOD

This prospective multicenter observational cohort study evaluated the effectiveness and safety of a procalcitonin (PCT)-guided antibiotic stewardship strategy in adult intensive care unit (ICU) patients with sepsis. The study was designed to emulate a pragmatic target trial by prospectively specifying the eligibility criteria, treatment strategies, time zero, follow-up, and outcome definitions. Participating tertiary care ICUs used standardized sepsis management protocols, and reporting followed the STROBE recommendations. Consecutive adult patients aged ≥18 years with sepsis were enrolled. Sepsis was defined according to the Sepsis-3 criteria as a suspected or confirmed infection with an acute increase in the SOFA score of ≥2 points. Eligible patients initiated systemic antibiotic therapy for the index sepsis episode within 24 h before cohort entry. Patients were excluded if they had infections requiring fixed or prolonged antibiotic therapy, received antibiotics only for prophylaxis, had severe immunosuppression affecting biomarker kinetics, or were expected to die or receive comfort care within 24 h of ICU admission. Only the first eligible ICU admission was considered.

Exposure was defined as management under a PCT-guided antibiotic discontinuation protocol versus standard care. The PCT protocol recommended antibiotic discontinuation when PCT decreased by ≥80% from the peak value or reached ≤0.5 ng/mL, provided that clinical stability was present. Clinical stability was defined as hemodynamic improvement without escalating vasopressor support, absence of new organ dysfunction, and adequate or planned source control. PCT was measured at baseline and then every 24 h. The protocol was nonbinding, and clinician overrides were allowed and recorded.

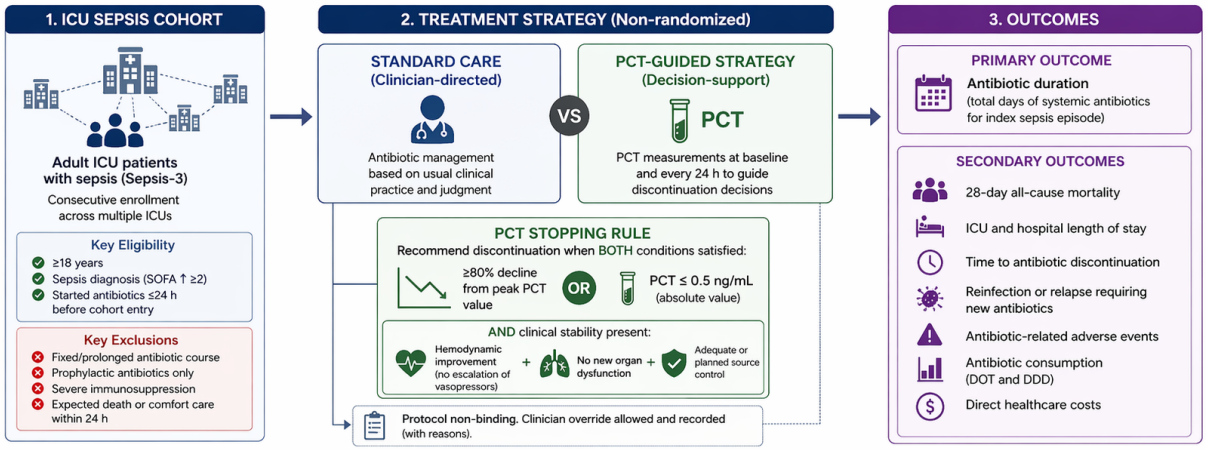

Figure 1. Schematic Overview of Study Design and Causal Analytical Framework

Time zero was defined as the initiation of systemic antibiotic therapy for the index sepsis episode. The primary outcome was the duration of antibiotic therapy. Secondary outcomes included antibiotic-free days at day 28, 28-day mortality, ICU and hospital length of stay, time to antibiotic discontinuation, reinfection or relapse, antibiotic-related adverse events, antibiotic consumption measured by days of therapy and defined daily doses, and direct costs of treatment. Data were prospectively collected using standardized electronic case-report forms. The variables included demographics, comorbidities, infection source, microbiological findings, SOFA and APACHE II scores, daily PCT values, antibiotic exposure, organ support, laboratory parameters, protocol adherence, and reasons for clinician override. Continuous variables are reported as means with standard deviations or medians with interquartile ranges, whereas categorical variables are reported as counts and percentages. Mixed-effects regression models were used to account for the ICU-level clustering. Propensity score weighting was applied to reduce confounding by indication, and covariate balance was assessed using standardized mean difference. Marginal structural models were used to address the time-varying confounding. Time-to-event outcomes were analyzed using Cox models, with competing risks considered when appropriate. Prespecified subgroup and sensitivity analyses were performed according to sepsis severity, infection source, microbiological confirmation, baseline organ dysfunction, alternative exposure definitions, early mortality exclusion, and complete case analysis. Missing data were handled using multiple imputations. A two-sided p-value <0.05 was considered statistically significant. The study was approved by the institutional review board of each participating center. Informed consent was obtained or waived in accordance with local regulations. All data were anonymized prior to analysis.

RESULTS

A total of 548 patients who were mechanically ventilated were initially screened during the study period. After applying the predefined inclusion and exclusion criteria, 512 patients were included in the final analysis. Of these, 126 patients developed ventilator-associated pneumonia (VAP), yielding an overall incidence of 24.6%. The median age of the study population was 61 years (IQR 49–71), with a predominance of male patients (56.6%). Patients who developed VAP had a significantly longer median duration of mechanical ventilation than those who did not (10 days [IQR 7–16] vs. 5 days [IQR 3–8], p<0.001). Patients in the VAP group also had a higher baseline severity of illness, as reflected by elevated APACHE II scores at ICU admission. Patients who developed VAP were more likely to have higher illness severity, require longer ventilatory support, and undergo reintubation. In addition, modifiable risk factors, such as suboptimal positioning and inadequate oral care, were more frequently observed in the VAP group. Conversely, early initiation of enteral nutrition was more common in patients who did not develop VAP. Most VAP cases occurred after prolonged mechanical ventilation, with a median onset of 6 days (IQR 4–9) following intubation. Early onset VAP (≤5 days) accounted for 42.1% of cases, whereas late-onset VAP (>5 days) accounted for 57.9%, indicating a higher burden of infection in patients with prolonged exposure to ventilation.

Table 1. Baseline Characteristics of the Study Population

Variable	VAP (n=126)	Non-VAP (n=386)	p-value
Age (years), median (IQR)	62 (50–72)	60 (48–70)	0.21
Male sex, n (%)	72 (57.1)	218 (56.5)	0.89
APACHE II score, median (IQR)	20 (16–25)	17 (14–22)	<0.001
Duration of MV (days), median (IQR)	10 (7–16)	5 (3–8)	<0.001
Reintubation, n (%)	38 (30.2)	52 (13.5)	<0.001
Supine positioning, n (%)	54 (42.9)	102 (26.4)	0.001
Poor oral hygiene, n (%)	61 (48.4)	118 (30.6)	<0.001
Early enteral nutrition, n (%)	68 (54.0)	258 (66.8)	0.01

Unadjusted 28-day mortality was significantly lower in the early vasopressor initiation group than in the delayed initiation group (27.8% vs. 34.6%, p=0.02). Additionally, VAP was associated with prolonged ICU length of stay and an increased duration of mechanical ventilation. In the multivariable logistic regression analysis, after adjusting for potential confounders, several independent predictors of VAP were identified. Prolonged duration of mechanical ventilation (>7 days) was the strongest predictor, followed by reintubation and modifiable care-related factors, such as poor oral hygiene.

Table 2. Multivariable Logistic Regression Analysis of Predictors of VAP

Variable	Adjusted OR (95% CI)	p-value
Duration of MV (>7 days)	2.41 (1.68–3.46)	<0.001
Reintubation	2.87 (1.79–4.61)	<0.001
Supine positioning	1.76 (1.15–2.68)	0.009
Poor oral hygiene	1.94 (1.27–2.96)	0.002
Early enteral nutrition	0.68 (0.45–0.98)	0.041

The final multivariable model demonstrated good discriminative ability, with an area under the receiver operating characteristic curve (AUC) of 0.78, indicating acceptable predictive performance. Calibration analysis showed good agreement between the predicted and observed probabilities of VAP. Subgroup analyses revealed that the association between identified risk factors and VAP was more pronounced in patients requiring prolonged mechanical ventilation (>7 days) and those with higher baseline severity scores. The protective effect of early enteral nutrition was consistently observed across all subgroups. Sensitivity analyses, including the exclusion of patients with early extubation (<72 hours), confirmed the robustness of the primary findings. Additional analyses adjusting for center-level variability did not significantly alter the effect estimates.

DISCUSSION

This prospective multicenter cohort study provides robust evidence that a procalcitonin (PCT)-guided antibiotic discontinuation protocol significantly reduces antibiotic exposure in intensive care unit (ICU) patients with sepsis without compromising clinical safety outcomes. The findings highlight that biomarker-guided de-escalation, rather than initiation, represents the most effective application of PCT in critically ill patients, reinforcing a precision approach to antimicrobial stewardship [11]. PCT's infection-specific kinetics of PCT, which dynamically reflect the bacterial burden and treatment response, offer a more accurate tool for guiding antibiotic de-escalation than traditional methods that rely on static clinical judgment alone [12]. These results align with landmark randomized controlled trials, such as the PRORATA trial, which demonstrated that a PCT-based algorithm led to increased antibiotic-free days without negatively affecting mortality [13]. Similarly, the SAPS and ADAPT-Sepsis trials confirmed that PCT-guided strategies can safely reduce antibiotic exposure without increasing 28-day mortality, further validating the clinical utility of PCT in real-world settings [14-15]. In addition, systematic reviews and meta-analyses consistently report a reduction in antibiotic duration by 1–1.5 days, with evidence suggesting a trend toward improved survival, although adherence variability remains a crucial factor in modifying effect size [16,17]. One of the key contributions of this study lies in its real-world implementation, addressing operational challenges such as assay turnaround

time, clinician adherence, and override behavior, which are critical factors that are often underreported in randomized trials but decisively influence clinical outcomes in routine ICU practice [18]. Our study demonstrates the feasibility of integrating rapid PCT testing into clinical workflows, where turnaround times of approximately two hours are both achievable and clinically actionable, which is consistent with the findings of previous studies [13]. However, frequent clinician overrides, driven by concerns such as unresolved infection sources or multidrug-resistant pathogens, emphasize the need for structured clinical decision-making frameworks. These frameworks should incorporate PCT algorithms while ensuring that they complement, rather than replace, clinical judgment [19].

From an antimicrobial stewardship perspective, reducing antibiotic exposure is critical for combating antimicrobial resistance, minimizing drug-related toxicity, and reducing healthcare costs, all of which are central priorities in modern ICU management [20]. The use of standardized antibiotic consumption metrics, such as days of therapy (DOT) and defined daily dose (DDD), further strengthens the interpretability and comparability of our findings within the broader antimicrobial stewardship literature. Notably, while DDD is a valuable aggregate measure, we emphasize that DOT is the more reliable metric in critically ill populations, as dosing strategies often vary in these settings [21-22]. This study has some limitations. As an observational study, there remains the potential for residual confounding despite rigorous statistical adjustments, including multivariable modeling and propensity-based methods [23]. Variability in clinician adherence and override practices may introduce implementation bias, especially in per-protocol analyses, which may explain the observed differences in effectiveness across different settings [18]. Additionally, while cost analyses suggest potential economic benefits, the extent of these benefits is highly context-dependent and influenced by factors such as assay costs, frequency of testing, and baseline antibiotic utilization patterns in individual ICU settings [24]. In conclusion, this study provides real-world evidence supporting the integration of PCT-guided antibiotic discontinuation protocols into routine ICU practice. This approach, when combined with rapid assay availability, standardized decision algorithms, and a structured clinical decision-making framework, offers a pragmatic solution for optimizing antibiotic stewardship while ensuring patient safety. By significantly reducing antibiotic exposure, this strategy addresses the critical need to mitigate antimicrobial resistance without compromising the clinical outcomes. Future research should focus on optimizing clinician adherence, refining patient selection, and integrating emerging technologies, such as artificial intelligence (AI) and machine learning, to further enhance the precision and effectiveness of PCT-guided interventions. Moreover, incorporating biomarker-driven strategies into personalized sepsis care holds immense potential for revolutionizing antimicrobial stewardship and precision medicine, ultimately improving long-term patient outcomes in critically ill populations [25].

CONCLUSION

In this prospective, real-world ICU cohort of patients with sepsis, the implementation of a procalcitonin-guided (PCT)-guided antibiotic stewardship strategy significantly reduced antibiotic exposure without adverse outcomes. This validates PCT's role of PCT as a safe and actionable tool for antibiotic discontinuation, aligning with high-quality randomized evidence and enhancing its application in routine clinical practice. These findings emphasize that the success of PCT-guided strategies hinges on timely assay availability, structured reassessment, and clinician adherence, supporting its integration into ICU workflows to optimize antibiotic use, reduce resistance, and improve the quality and efficiency of sepsis care.

DECLARATIONS

None

CONSENT FOR PUBLICATION

The Authors agree to the publication in the Journal of Society Medicine.

FUNDING
None

COMPETING INTERESTS
All authors have reviewed and approved the final version of the manuscript and agreed to its publication in the Journal of Society Medicine.

AUTHORS' CONTRIBUTIONS
S. N. conceptualized the study, designed the research framework, and was responsible for data acquisition, statistical analysis, and manuscript drafting. T. M. contributed to data interpretation, provided methodological supervision, and critically revised the manuscript for its intellectual content. L. K. provided clinical expertise, contributed to data validation, and critically reviewed and approved the final version of the manuscript. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work, thereby ensuring the accuracy and integrity of the study.

ACKNOWLEDGMENTS
The authors would like to express their sincere appreciation to the Department of Clinical Microbiology, Regional Hospital, Johannesburg, South Africa for their institutional support and contribution to the successful completion of this study.

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