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# Procalcitonin-guided protocol use and impact on intensive care unit and antibiotic management: a pilot study

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## Abstract

**Objective:** To assess the procalcitonin protocol use and its impact on antibiotic therapy management of critically ill patients in the intensive care unit (ICU). **Method:** An observational descriptive and retrospective study conducted in an adult ICU with 28 beds from the Brazilian Unified Health System (SUS). **Results:** This present study observed a 78% (90/116) of PCT protocol adherence in the studied ICU. We observed a reduction in days of antibiotic treatment (DOT) going from 14 to 8,5 treatment-day duration (5.49 ± 2.2 days), impacting the overall antibiotic therapy cost for a decrease of 40.91%. **Conclusion:** The study revealed that PCT use was associated with substantial benefits, reducing hospital costs and days of exposure to antibiotic therapy applied to patients affected by infectious diseases in critical care settings.

**Keywords:** antimicrobial stewardship; respiratory infection; critical care; procalcitonin. pharmacological biomarker.

## Uso e impacto do protocolo guiado pela procalcitonina na unidade de terapia intensiva e gerenciamento de antibióticos: Um estudo piloto

## Resumo

**Objetivo:** Avaliar a utilização do protocolo de procalcitonina (PCT) e o seu impacto na gestão da terapia com antibiótica de pacientes críticos na unidade de terapia intensiva (UTI). **Método:** Um estudo descritivo e retrospectivo observacional realizado na UTI adulta com 28 leitos do Sistema Único de Saúde (SUS). **Resultados:** Este presente estudo observou uma adesão ao protocolo PCT de 78% (90/116) na UTI estudada. Observou-se uma redução dos dias de tratamento com antibióticos (DOT) de 14 para 8,5 dias de duração do tratamento (5,49 ± 2,2 dias), com um impacto no custo global da terapia antibiótica para uma diminuição de 40,91%. **Conclusão:** O estudo revelou que a utilização de PCT estava associada a benefícios substanciais, reduzindo os custos hospitalares e os dias de exposição à terapia antibiótica aplicada a doentes afetados por doenças infecciosas em ambientes de cuidados críticos.

**Palavras-chave**: gerenciamento de antimicrobianos; infecção respiratória; cuidados intensivos; procalcitonina; biomarcador farmacológico.

## Introduction

Antibiotic use has transformed clinical practice worldwide since infections once considered lethal are now treated with optimal clinical outcomes.[1] Despite advances in antibiotics, their use is related to serious bacterial resistance and therapeutic failure that affect approximately 20% of hospitalized patients.[2] Unnecessary exposure has contributed to toxicity, clostridioides difficile infection and bacterial resistance with a negative impact on patient health.[3] During decades, the world has observed an increase in bacterial infections resistant to common antibiotic therapies.[4,5] In this context, the WHO has published a list of multidrug-resistant bacteria (MDRs) classified as critical that include carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), carbapenem-resistant *Enterobacteriaceae* (CRE) and carbapenem-resistant producing β extended-spectrum lactamases (ESBLs) that represent a threat to hospital environments causing serious infections and new antibiotics targeting this list will help to reduce deaths.[6] According to the Centers for Disease Control and Prevention, 2 million people are affected by Multi-Drug Resistant Bacteria (MDR) infections every year in the United States of America and at least 23,000 people die.[7] The reasons for increasing bacterial resistance are complex, but studies have related prolonged antibiotic use as the indicative factor for incidence, selection of resistant bacteria, and long hospital staying.[8,9,10] Clinical markers use have contributed

to the monitoring of bacterial infection and have assisted critical patient treatment. Procalcitonin (PCT) has been a strategic tool to reduce exposure to antibiotics, mortality rate, adverse effects associated with antibiotics and reduce treatment risk failure.[11,12,13] A calcitonin precursor hormone, procalcitonin is a peptide composed of 116 amino acids present in thyroid by C cells and lung tissue. The marker remains at baseline levels in a normal state; however, it can be released into circulation by pro-inflammatory substances guided by bacteria, from where its clinical importance originates.[12] Traditionally, antibiotic treatment duration has followed empirical microbiological evaluations and procalcitonin has been used as an aid in antibiotic discontinuation during respiratory tract infections, precisely, because it differentiates the type of infection as bacterial or viral. Thus, this study evaluated the procalcitonin protocol implementation in an adult ICU from the Brazilian unified health system, exposure to antibiotics and projection of possible costs in antibiotic therapies.

## Methods

An observational descriptive and retrospective study was conducted from September 1st to December 31st of 2019 in a teaching hospital ICU, linked to the Unified Health System (Sistema Único de Saúde, SUS) network by the Pernambuco State Health Secretariat. The study locus is an acute care hospital, which has 833 beds and is a reference in neurosurgery and multisystem trauma, among other specialties, located in Recife, Brazil. The hospital uses electronic records under implementation phase for all multidisciplinary team registration.[14] This pilot study was launched in the ICU during daily rounds with the multi-disciplinary ICU team. This study was approved by ethical committee by the number: 23478919.5.0000.5198.

A sample group composed of 116 patients admitted to the intensive care unit was studied. Inclusion criteria were patients admitted to the adult ICU who began empirical antibiotic therapy focused on respiratory infection or ventilator-associated pneumonia and had length of stay in ICU longer than 48 hours during September 1st to December 31st of 2019. Excluded from the study were patients under antibiotic therapy used to treat other infectious focus or had antibiotic therapy outside the studied period.

The studied variables were medical protocol adherence rate, antibiotic exposure and possible antibiotic costs in the studied period.[4] In all patients, procalcitonin was dosed by electrochemiluminescence and test sensitivity of 0.02µg/L and immunoassay time less than 20 minutes.

The assays were performed at the institution laboratory and results were available within 24 hours. Patient serum levels were accessed on days 1, 3, 5, 7 of antibiotic therapy for respiratory infections. According to the institutional protocol, antibiotic therapy was strongly discouraged when serum levels were below 0.1µg/L and associated with clinical improvement, discouraged when serum levels were between 0.1 and 0.25µg/L and associated with clinical improvement. Initiation or continuation of antibiotic therapy was recommended when serum levels between 0.25 and 0.5µg/L, continuity of antibiotic therapy was strongly recommended when serum levels were higher than 0.5µg/L. (Table 1)

Patients who met the inclusion criteria were included in the study and followed-up daily by pharmacist according to the clinical protocol. Actions were predominantly focused on making available the institutional protocol and PCT serum levels to guide and complement mains antimicrobial treatments decision in critical care setting during the multi-disciplinary rounds in which the pharmacist is involved. Serie presentation of PCT serum levels to ICU physicians and based on patient clinical improvement, bacterial sensitivity profile and daily laboratory exams, antibiotic therapy was reviewed and then interrupted or maintained. After all, indicators were assessed and recorded on the institutional electronic records.

**Table 1**. Procalcitonin-guided protocol in the adult ICU.

| Procalcitonin Serum Levels | Recommendations |
|---|---|
| <0.1µg/L | Antibiotic therapy was strongly discouraged |
| 0.1 and 0.25µg/L | Antibiotic therapy was discouraged |
| 0.25 and 0.5µg/L | Initiation or continuation of antibiotic therapy |
| >0.5µg/L | Continuity of antibiotic therapy was strongly |

Legend: ICU: Intensive Care Unit

Protocol implementation was measured by adherence rate (total, partial and non-adherence). Total adherence were patients who reached PCT serum dosages below 0.25 µg/L associated to clinical improvement and there was antibiotic therapy discontinuation after pharmaceutical intervention. Partial adherence was PCT serum dosages below 0.25 µg/L associated to clinical improvement and non-antibiotic therapies discontinuation due to clinical reasons or changes in bacterial infectious focus apart from respiratory tract needing antibiotic. Non-adherence was all patients who reached PCT serum doses below 0.25 µg/L and improvement of patient clinical parameters, but there was no antibiotic treatment suspension due to non-medical acceptance. No restriction on prescription was included due to complexity of medical decision surrounding antibiotic prescription.

Regarding antibiotic exposure, DOT per patient-day was monitored for admitted patients in ICU and antibiotic-free days were assessed considering the protocol. Financial outcome was also assessed based on acquisition cost per day for antibiotic not used expressed in US dollars. The values were converted to US dollars and using purchasing power parity for the 2019Q4 and adjusted by the American Consumer Price Index for April of 2021.[15-16]

This study was submitted to statistical analysis using an arithmetic mean and standard deviation, a test of equality of means: paired t-test, chi-square test, with a confidence interval of 95%. A significance level of 5% ($p < 0.05$) was adopted.

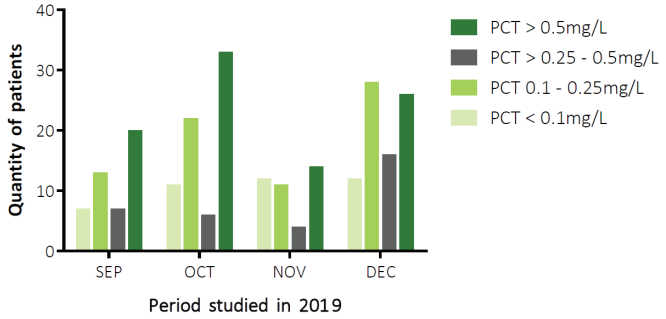
## Results

Between September 1st and December 31st of 2019, 116 patients with a confirmed or suspected diagnosis of respiratory infection were followed-up by PCT protocol in the ICU. The patient median age was 43 years and median length of ICU stay 35±25 days, most patients were men, 68.6% compared to women 31.4%.

During the study, it was observed a 78% for total and partial PCT-guided protocol adherence of which, 33% were total adhesion and 45% were partial adhesion. ($p = 0.2643$ and $n=116$).

Figure 1 shows a total of 242 procalcitonin measurements performed for studied patients, 48% was below 0.25µg/L and 52% was above 0.25µg/L and no statistically significant changes between PCT concentrations per month, ($p=0.2643$ and $n=116$).

**Figure 1**. Frequency distribution of procalcitonin serial measurement in an adult ICU in 2019.

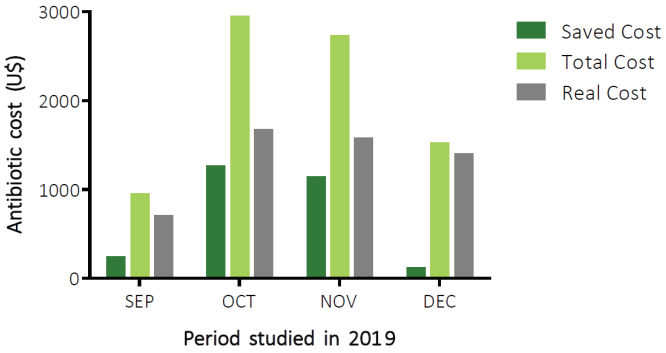



Data analyzed by Pearson's Chi-square test (contingency table). No significant difference was observed considering p=0.2643 and n=116. ICU: Intensive Care Unit

As for the days of antibiotic therapy, a reduction of 5.49 ± 2.2 days was observed, equivalent to a decrease of 14 to 8,5 treatment-day duration, impacting the overall antibiotic therapy costs of about 40.91%.

Also, analyzing antibiotic cost projection during the study, a total of U$ 5,379.74 would be added to the institution; but, only U$ 4.265,03 was the actual treatment costs, saving a total of U$ 2,200.87 as shown in Figure 2 and Table 2 (p=0.0557 and n=116).

**Figure2**. Analysis of antibiotic treatment cost for procalcitonin-guided protocol patient in the adult ICU in 2019.




Data analyzed by t-test, comparison was made between the cost with saved antibiotics and the actual cost. There was no statistical difference in the paired test (p=0.0557 and n=116). Saved cost are related to antibiotic discontinued, real cost are related to antibiotic therapy used in the ICU for patient treatment and total cost is a proposal treatment duration based on non-protocol intervention. ICU: Intensive Care Unit

**Table 2**. Monthly antibiotic treatment cost for procalcitonin-guided in the adult ICU

| Month | September | October | November | December |
|---|---|---|---|---|
| Saved Cost (U$) | 200.15 | 1,002.15 | 903.77 | 94.80 |
| Total Cost (U$) | 780.46 | 2,324.05 | 2,154.40 | 120.83 |
| Real Cost (U$) | 580.31 | 1,321.89 | 1,250.62 | 1,112.21 |

Legend: ICU: Intensive Care Unit

## Discussion

The PCT protocol became part of the routine in ICU in September through this pilot study. After implementation, it was possible to assess protocol impact to the institution, through adherence rate, related costs and antibiotic days of exposure. Clinical protocol initiated in ICU were made possible by pharmaceutical integration to multidisciplinary team and to ICU daily routine.

### PCT Protocol Implementation:

The PCT has proved its value as a complementary tool in critical patient's therapy due to its bacterial infection diagnosis, since PCT serum levels are increased in bacterial compared to viral infections.[4,13] Its value goes beyond bacterial to viral infection diagnosis, but also as a guide for antibiotic therapy.[9,18]

The protocol success was possible after intensive care professional's familiarization and has proved its benefits to hospitalized patients. The high PCT serum levels, 52% above 0.5µg/L, reveal the ICU profile, which are mostly composed by neurosurgical patients, with different comorbidities and in use of invasive devices that may lead to serious infectious or septic conditions.[19] This affirms that persistently high levels of PCT in critically ill patients have resulted in early detection of diagnostic failure or need for other infectious focus investigation.[18]

Evaluating protocol implementation in the ICU by its adherence, an average of 78.6% was obtained for total and partial adherence, which configures certain medical confidence in the negative predictive PCT value for antibiotic therapy discontinuation. A similar pilot study showed 78% of adherence after pharmaceutical interventions and protocol implementation.[21] Similarly Oliveira and collaborators obtained 86.2% acceptance of PCT as a therapeutic guide.[22] Haung obtained 72.9% of adherence by physicians who met the established clinical protocol recommendations.[18]

However, the non-adherence group, when questioned about maintaining the antibiotic even at safe PCT serum levels and good clinical improvement, clinicians still believed there was still a bacterial infection or an exacerbated chronic obstructive pulmonary disease requiring antibiotics.

Additionally, low adherence rate has been also reported in the literature exposing the challenge in predicting clinical protocol adherence outside of controlled trials, since in real life it is unlikely and, perhaps, unethical to eliminate medical subjectivity evolution when important therapeutic decisions need to be made,[23] which could explain the low saving cost found in December. Schuetz and collaborators evaluated adherence to the use of PCT as a challenging issue, which is due to the low prescriber's experience and, therefore, caution on serum dosage interpretation and antibiotic discontinuation.[13]

The study also unveiled that one of the barriers for clinical PCT use in routine have been the reference values considered safe for therapeutic discontinuation, since PCT serum levels are also high in some clinical conditions other than respiratory tract infections. However, when the serial measurements are associated with other clinical findings, it has proven to be effective in patient's therapy, cost-effective for hospitals and contributes to antimicrobial resistance reduction.[17,24]

### Analysis of antibiotic exposure

This study indicates a reduction in antibiotic duration in critically ill patients with respiratory tract infections for whom a decision could be made to discontinue antibiotic therapy based on serial PCT measurements. Evaluating antibiotic rate of exposure after protocol intervention showed a reduction of 5.49 ± 2.2 days of antibiotic therapy, equivalent for 14 to 8,5 days reduction.

This indicates that decreasing PCT serum levels associated with clinical improvements have optimized antibiotic treatments and reduced possible degrees of bacterial resistance. This also shows that antibiotic duration in critically ill patients can be safely guided by PCT protocols. Studies have confirmed that PCT implementation was responsible for 10 to 7 days reduction with no impact on clinical outcomes.[13] In a randomized, multicenter clinical trial analyzing 101 critically ill patients with respiratory tract infections, the treatment duration was reduced from 13 to 9.5 days, corroborating this study findings and its clinical value.[17]

A study conducted in France showed that patients followed up with procalcitonin had 2.7 (18.9%) antibiotic-free days compared with usual care group.[25] Schuetz and collaborators observed a reduction of 4 antibiotic-free days (33.3%) in patients admitted to ICU using antibiotics to treat respiratory infection.[12] Although the present pilot study had a short implementation period, different patients' profile and hospital settings, it was able to show an antibiotic exposure reduction allied to combat the emerging conditions of multidrug resistant infections in critically ill patients.

### Analysis of antibiotic-related costs

In respect to saved costs through antibiotic discontinuation compared to real costs of treatment in the study, no statistical significance changes were observed. Although, PCT-guided protocol antibiotic therapy decreased antibiotic costs by 40.91% during the pilot study, several limitations should be acknowledged.

First, the study evaluated only the antibiotics used in the treatments and not included healthcare products for the antibiotic administration, second, it is not possible to measure the intangible costs involving patient care which goes beyond antibiotic acquisition cost. Also, our study population were represented by severely ill patients with respiratory infections and many other comorbidities which have contributed to a non-antibiotic discontinuation and protocol adherence in some cases. Lately, physicians considered a potential harm of shortening the antibiotic therapy based on PCT serum measurement. Therefore, other studies in the Brazilian unified health system ICUs considering a larger patient group and antibiotic cost-effectiveness study should be considered.

Despite its limitation, antibiotic-free day increased, and major antibiotic cost savings were acquired, indicating a significant contribution to the patient's healthcare, risk minimization in drug adverse event, probable reduction in microbial resistance and also decrease in hospital costs by this pilot study.

Kip and collaborators evaluated PCT-guided therapy potential and estimated an economy of €289 per patient compared to the standard care group, €3503 per patient, mainly achieved by duration of antibiotic therapy.[26]

Harrison and Collins revealed cost-effectiveness considering variables such as protocol adherence, antibiotic days exposure, quantity and cost of tests. In this manner, PCT was not cost-effective when adherence was less than 42.3%, the antibiotic therapy duration was reduced to less than 1.6 days, if requests for tests were greater than nine per patient or if the cost of the test was greater than USD 46.37, corroborating these research findings and reaffirming that a clinical marker is crucial to patient care, therefore, its incorporation should be considered by the institutional leadership.

According to Kyeongman and collaborators in a clinical study, PCT-guided therapy led to a cost reduction by 20% of days in critically ill patients.[27] Stuenten and researches stated that test cost should be balanced by acquisition value and its benefits should focus not only on antibiotic discontinuation but also on the patient clinical improvement, ratifying this pilot study goal.[28] Protocol implementation success was achieved through effective medical team communication, a laboratory analyses responsibility and pharmacy team feedbacks and clinical engagement.

## Conclusion

The study revealed that PCT use was associated with substantial benefits, reducing hospital costs and days of exposure to antibiotic therapy applied to patients affected by infectious diseases in critical care settings.

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### Collaborators

All authors approve this final manuscript version and are responsible for all information on the work, ensuring the accuracy and integrity of any part of the work. DESO: 1. Conception, design, analysis and interpretation of data. DESO, DMSG, EGCC, VSB: 2. Writing of the article or relevant critical review of the intellectual content.

### Conflict of interests statement

The authors also declare that there are no conflicts of interests regarding this article.

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