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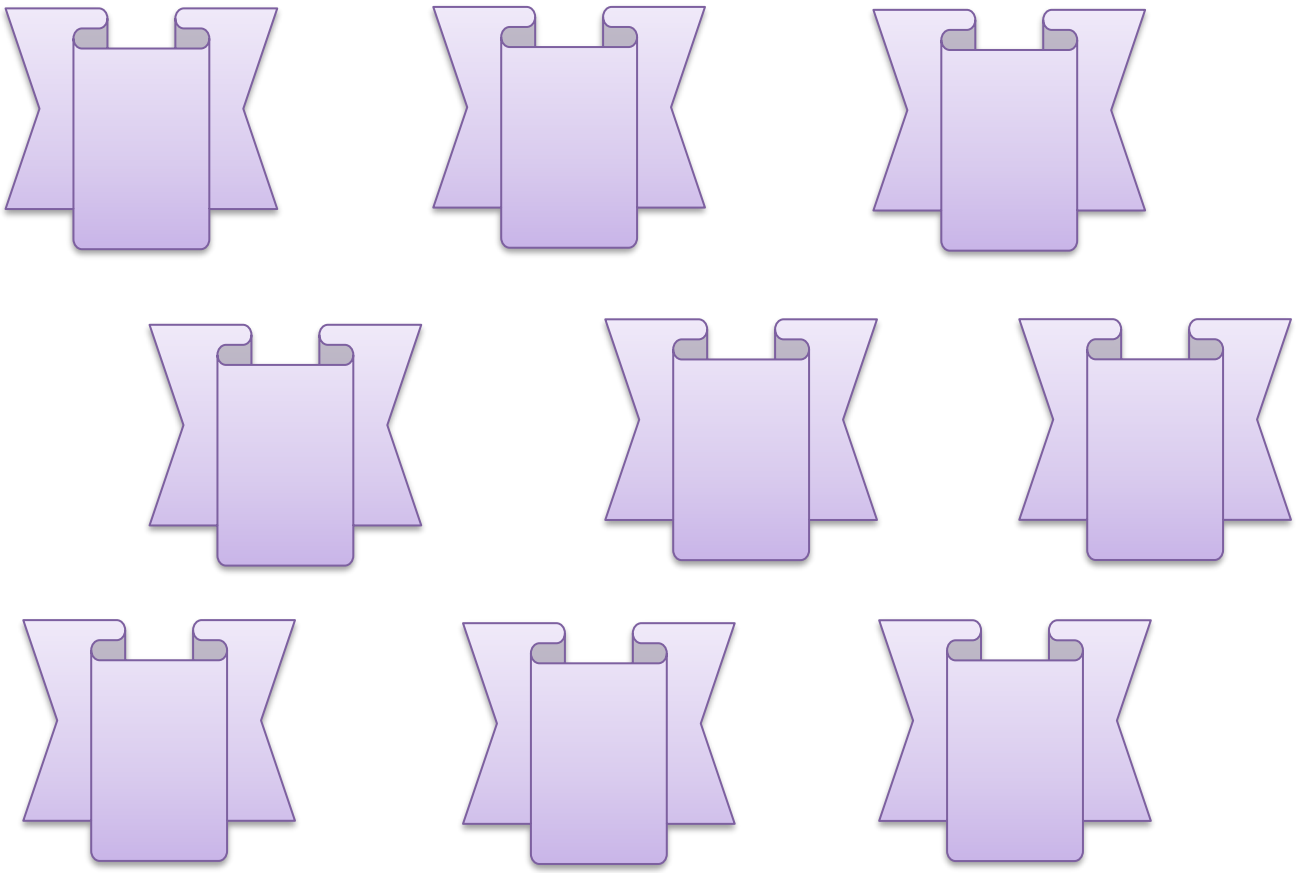

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Original Article

Procalcitonin Guided Antibiotic Therapy in Septic Critically Ill Patients Admitted to Critical Care Unit

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ABSTRACT

Background: An important contributor to mortality and morbidity in intensive care unit [ICU] is sepsis. Increased mortality has been linked to putting off diagnosis and beginning the right treatment.

Aim of the Study: In this investigation, the effectiveness of serum procalcitonin as a biomarker for septic critically unwell patients' antibiotic medication duration was be assessed.

Patients and Methods: In this research, 50 individuals who met the inclusion criteria and required antibiotic therapy due to confirmed or strongly suspected bacterial infections were randomly divided into two groups, each of which had 25 patients. The other 25 patients received antibiotics in accordance with our ICU protocol [Group C-control group], while 25 patients received antibiotics in accordance with serum procalcitonin [PCT] guidance [Group P-PCT guided group].

Results: PCT guidance enables a decrease in the dosage of antibiotics given to critically ill individuals with severe sepsis & septic shock. It was noticeable that the PCT group had much shorter periods of antibiotic therapy [mean of 4 days of less exposure to antibiotics and about 6 days shorter lengths of ICU stay]. The PCT group also had significantly fewer days spent in the hospital overall.

Conclusion: An algorithm utilizing serial procalcitonin [PCT] measurements has been found to enable a more prudent utilization of antibiotics in individuals diagnosed with severe sepsis and septic shock. This approach effectively and safely reduces the duration of antibiotic exposure, as well as the length of ICU and hospital stays.

Keywords: Procalcitonin; Antibiotic Therapy; Septic; Critically-ill.

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INTRODUCTION

The prompt of timely identification and suitable administration of antimicrobial therapy for infections continues to provide a significant obstacle within critical care environments. The absence of distinct clinical indicators during the initial phase of infection can result in a delay in diagnosis, perhaps leading to a postponement or withholding of antibiotic treatment. However, doctors in the intensive care unit [ICU] often resort to excessive usage of antimicrobials due to their apprehension regarding the failure to address potentially life-threatening infections and the subsequent danger of recurrence [1, 2].

Research findings have revealed that a significant proportion, approximately 50%, of antibiotics administered in hospital environments are deemed to be either unwarranted or unsuitable [3].

In contemporary times, it has become customary to administer extended antibiotic treatment protocols to patients in critical condition, with such regimens frequently relying on empirical guidelines. These potential consequences include heightened healthcare expenses, the rise of drug-resistant infections, extended hospital stays, and an increased chance of mortality [4].

The optimization of antibiotic therapy plays a significant role in the management of cases who were severely ill. The potential utility of procalcitonin [PCT] in the context of antibiotic stewardship has been acknowledged, while its effectiveness continues to be a subject of debate. Consequently, a meta-analysis was conducted to ascertain the effectiveness of PCT guided antibiotic therapy in the population of critically ill individuals [5].

In recent studies, PCT has demonstrated considerable potential as a biomarker for the detection of bacterial infections, exhibiting a significant correlation with the degree of infection severity [6].

Nevertheless, a recent comprehensive study yielded inconclusive evidence about the efficacy of daily PCT measurement in terms of expediting the administration of appropriate therapy or improving survival rates. However, it did reveal that this practice led to an extended duration of antibiotic treatment and prolonged stays in the ICU [6].

Due to the substantial variations in methodology and research objectives pertaining to diverse PCT guided strategies, prior investigations may not have provided a precise assessment of the impacts of algorithms based on PCT. In recent times, there have been two notable randomized controlled trials [RCTs] conducted to evaluate the efficacy of PCT-guided antimicrobial approach in patients admitted to the ICU. However, both trials have shown conflicting outcomes. The most extensive randomized controlled study [RCT] conducted thus far has revealed an unforeseen and substantial improvement in survival rates, alongside reduced utilization of antibiotics [7].

This research aims to evaluate the efficacy of serum PCT as a biomarker for reducing the duration of antibiotic treatment in septic critically ill individuals.

PATIENTS AND METHODS

Study settings and durations

This research performed at the ICUs of Emergency Medicine and Critical Care Departments [Bab Al-Shaeria University Hospital, Cairo, Egypt]. It was carried out between June 2022 and June 2023.

Study population

The study comprised a sample of 50 adult patients who required antibiotic therapy for proven or highly suspected bacterial infections. These patients were selected based on certain inclusion criteria and were randomly assigned to two groups, with each group consisting of 25 individuals.

Group P-PCT guided group: A total of 25 individuals received antibiotics based on their serum PCT levels, which was assessed at the beginning of the study and afterwards on a daily basis until the 7th day of follow-up, unless mortality or discharge transpires before to that time. Subsequently, the serum procalcitonin levels were assessed at intervals of five days afterwards until day 28 of the follow-up period, unless mortality or discharge transpires prior to that time. Predefined stopping rules of antibiotics in PCT group indicates that the patients were reassessed and antibiotics were discontinued if clinical signs and symptoms of infection improved and repeated levels of PCT dropped > 25-35 % of the initial value.

Group C-Control group: According to the protocol of our Critical Care Unit [CCU], a total of 25 patients were administered antibiotics. The levels of PCT were assessed at the beginning of the study and afterwards on a daily basis until the seventh day of follow-up, unless mortality or discharge takes place prior to that time. Thereafter, serum PCT were measured at 5-day interval until day 28 of follow up [unless mortality or discharge occurred earlier] but without interference with the duration of antibiotic therapy which was under control of the CCU protocol. This consisted of antibiotic administration with at least 10 days duration and follow up with traditional biomarkers [C-reactive protein [CRP] and total leucocytic count [TLC], besides clinical signs and symptoms.

Ethical Considerations: the ethical approval was acquired in accordance with the recommendations provided by the Ethics Unit of the Faculty of Medicine at Al-Azhar University in Cairo. In addition, the patients or their first-degree relatives were signed an informed written consent before the participation in the study.

Methods: A comprehensive medical history assessment was conducted. Daily monitoring of vital signs was performed. Furthermore, a comprehensive clinical examination was conducted to gather a thorough understanding of the patient's condition. The laboratory examinations conducted on a daily basis encompassed a range of assays, namely the Complete Blood Count [CBC], Liver Function tests [LFTs], Kidney Function Tests [KFTs], and Random Blood Sugar [RBS] assessment. The analysis of serum electrolytes, involving sodium [Na], magnesium [Mg], potassium [K] & calcium [Ca], as well as arterial blood gases, was of academic interest. The recommended imaging modality for monitoring the patient's condition was a daily plain chest X-ray [postero-anterior and lateral views]. Additionally, PCT levels were measured on a daily basis until day 7, and then at five-day intervals until day 28. The evaluation of organ dysfunction was conducted at the beginning and on a daily basis during the Critical Care Unit [CCU] stay, utilizing the Sequential Organ Failure Assessment [SOFA] score. Prior to the administration of the initial antibiotic dose, blood, sputum, and urine cultures were obtained upon admission. The determination of the patient's state upon admission was based on the Simplified Acute Physiology Score-II [SAPS II].

Statistical analysis: The data were examined utilizing the Statistical Program for Social Science [SPSS] version 22.0 [IBM Inc., Armonk, USA]. The quantitative data were presented as the mean ± standard deviation [SD]. The qualitative data were presented in terms of frequency and percentages. The t-test is employed for the purpose of comparing two means. The Chi-square [X^2] or Fisher exact test of significance was used to compare proportions among two qualitative factors. A p-value < 0.05 was deemed significant.

RESULTS

Both groups were comparable regarding patient demographics [age and gender] and pre-admission criteria [Table 1].

There was no significant variation amongst the groups concerning serial PCT levels. Furthermore, it was seen that both groups exhibited a similar declining trend in PCT levels [Table 2].

Primary outcomes: Table [3] demonstrates a very significant distinction between the two groups in terms of the time of antibiotic therapy. The PCT group exhibited a shorter mean duration of antibiotic treatment, with an average of 11.22 days, compared to the control group's mean of 15.1 days. In addition, a period of at least twenty-four hours in which an individual has not received any antibiotic treatment; this comprises the entirety of the follow-up time, which was a total of twenty-eight days; unless death or discharge has occurred earlier]. There was a significant disparity among the two groups regarding the days alive without antibiotic treatment with more days without antibiotic administration for individuals in the PCT than control group [17.52 days vs 14.11 days, respectively].

Secondary outcomes: Table [3] demonstrates a significant statistical distinction between groups in terms of the length of stay in the ICU. Notably, the PCT group exhibited a much shorter ICU stay, with a mean duration of 10.58 days, compared to the control group's mean duration of 16.38 days.

Table [1]: Patient characteristics and initial data among the study groups

Variable		PCT group	Control group	Test	P
Age [years]	Mean ±SD	57.5±9.6	58.2±8.3	0.117	0.907
	Min. – Max.	45-70	47-69		
Sex [n, %]	Male	19 [76%]	17 [68%]	0.009	0.752
	Female	6 [24%]	8 [32%]		
SPAS-II score	Mean ±SD	38.11±14.91	40.18±16.38	1.991	0.282
	Min. – Max.	21-55	22-58		
SOFA score	Mean ±SD	7.5 ± 1.1	8.3 ± 1.1	1.607	0.115
	Min. – Max.	5-10	6-10		
Blood culture [n, %]	Positive	10 [40%]	8 [32%]	0.087	0.768
	Negative	15 [60%]	17 [68%]		

Table [2]: Compare groups based on serial procalcitonin level

PCT measurements	PCT Group	Control Group	t-test	p-value
Day 1	2.92±0.44	2.77±0.42	0.617	0.296
Days 2	2.50±0.38	2.38±0.36	0.904	0.271
Days 3	2.20±0.33	2.09±0.31	0.662	0.292
Days 4	1.80±0.27	1.71±0.26	0.273	0.326
Days 5	1.60±0.24	1.52±0.23	0.691	0.290
Days 6	0.90±0.14	0.86±0.13	0.555	0.301
Days 7	0.85±0.13	0.81±0.12	1.061	0.257
Days 12	0.79±0.12	0.75±0.11	0.629	0.220
Days 17	0.50±0.08	0.48±0.07	0.259	0.791
Days 23	0.45±0.07	0.43±0.06	0.656	0.230
Days 28	0.44±0.07	0.42±0.06	0.527	0.185

Table [3]: Primary and secondary outcomes among study participants

Variable		PCT group	Control group	Test	P
Duration of antibiotic treatment [days]	Mean ±SD	11.22±1.61	15.1±2.17	7.180	**<0.001***
	Min. – Max.	5-17	8-20		
Days alive without antibiotic treatment	Mean ±SD	17.52±2.52	14.11±1.19	2.681	**0.011***
	Min. – Max.	15-20	12-16		
ICU length of stay	Mean ±SD	10.58±1.14	16.38±2.34	11.481	**<0.001***
	Min. – Max.	2-18	2-30		

DISCUSSION

The aim of our research was to estimate the effectiveness of serum PCT as a biomarker in decreasing the duration of antibiotic treatment in septic critically ill patients. Our aim was to provide evidence supporting the notion that utilizing PCT guidance can lead to a reduction in antibiotic usage among critically ill septic patients, without any negative impact on patient outcomes. The use of strategies aimed at minimizing the utilization of antibiotics in septic patients may yield numerous potential benefits. The current study involved a cohort of 50 adult patients who required antibiotic therapy for confirmed or highly suspected bacterial infections. These cases were separated into 2 groups, with 25 patients in each group. In both groups, PCT levels were measured. However, only the group receiving procalcitonin-guided therapy followed the PCT algorithm, while the control group adhered to our ICU protocol.

The findings of our study indicate that there was no significant disparity among the two groups regarding patient demographics, the pre-admission SAPS and SOFA scoring system. The results of the cultures are also comparable between groups.

In our study, the data analysis provides evidence in support of the notion that PCT guidance enables a reduction in antibiotic usage among critically ill septic cases. Furthermore, our findings indicate that this strategy does not result in worse outcomes, as demonstrated by our primary outcomes. Specifically, the duration of antibiotic treatment was notably shorter in the PCT group, with an average reduction of approximately 4 days compared to the control group. This variance was significant, with a

mean duration of 11.22 days in the PCT group and 15.1 days in the control group

Individuals in the PCT group had significantly longer times among antibiotic administrations, as measured by the research's primary outcome measure of "time to death" [defined as at least 24 hours without antibiotic administration] than those in the control group. A total of 28 days was spent following up. The PCT group had a significantly higher mean number of days alive [at 17.5] without antibiotics than the control group [at 14.11]. A p-value of 0.011 indicates that the distinction was significant.

These finding were in agreement with a study conducted by **Nobre *et al.*** [8] The study involved a sample of 68 adult individuals diagnosed with severe sepsis or septic shock. The aim of the research was to assess the influence of a specific intervention on the duration of antibiotic therapy in these cases. The consequences indicated that the intervention led to a decline in the median duration of antibiotic therapy from 10 to 6 days. Additionally, the intervention was related to an increase in the median number of days without antibiotic use, from 13.6 to 17.4 days.

These findings go hand in hand with a study done by **Bouadma *et al.*** [9] In a multicenter randomized study, approximately 600 critically ill adult people were examined. The study revealed a notable and significant variation amongst the PCT group and the control group. Specifically, the PCT group had a shorter duration of exposure to antibiotics in contrast to the control group. Furthermore, there was a significant disparity in the number of days patients remained alive without antibiotics. The PCT group had a longer average length of 14.3 days in comparison to the control group's 11.6 days.

The examination of the data in our study revealed a substantial and statistically significant disparity among the two groups in terms of the duration of stay in the ICU. The PCT group exhibited a mean length of stay of 10.58 days, which was notably lower than the mean length of stay of 16.38 days observed in the control group. These results corroborate those of a study by **Hochreiter *et al.*** [10] who included one hundred and ten adult individuals in the Surgical SICU who fit the criteria for Systemic Inflammatory Response Syndrome [SIRS] were investigated, and those who were treated via the PCT algorithm were shown to have significantly shorter ICU stays. People administered the PCT algorithm spent an average of 15.5 days in the intensive care unit, while those in the control group stayed there for an average of 17.7 days. However, our results disagree with **Schröder *et al.*** [11]. The study was conducted on a sample of 29 adult patients in the SICU. The investigation revealed that there was no significant distinction in the length of stay in the ICU between patients belonging to two distinct groups. Furthermore, the study also identified no significant disparity in the length of stay in the ICU among those who received PCT and those who did not [control group].

The data presented in our study provide evidence to support the notion that implementing procalcitonin guidance can effectively decrease the use of antibiotics in critically sick individuals suffering from severe sepsis and septic shock. Furthermore, our findings revealed that this approach does not result in adverse outcomes. Nevertheless, a potential limitation of our study is its single-center design and very modest sample size, which may restrict the generalizability of our results.

Additional research is required to ascertain the effects of reducing the duration of antibiotic treatment on significant consequences, such as the prevalence of hospital-acquired infections among critically sick individuals and the occurrence of colonization and infection with multidrug-resistant bacteria in the ICU.

Conclusion: The findings of this study indicate that implementing an algorithm utilizing serial PCT measurements can lead to a more prudent utilization of antibiotics in individuals diagnosed with severe sepsis and septic shock. This approach effectively reduces both antibiotic exposure and the duration of hospital and ICU stays. Importantly, the implementation of this strategy does not result in worse outcomes, as evidenced by the absence of significant differences in rates of death after twenty-eight days and clinical cure rates among patients treated in accordance with PCT guidance and those managed using standard practice.

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