Procalcitonin Versus C-Reactive Protein for Guiding Antibiotic Therapy in Sepsis: A Randomized Trial*

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Objective: We sought to evaluate whether procalcitonin was superior to C-reactive protein in guiding antibiotic therapy in intensive care patients with sepsis.

Design: Randomized open clinical trial.

Setting: Two university hospitals in Brazil.

Patients: Patients with severe sepsis or septic shock.

Interventions: Patients were randomized in two groups: the procalcitonin group and the C-reactive protein group. Antibiotic therapy was discontinued following a protocol based on serum levels of these markers, according to the allocation group. The procalcitonin group was considered superior if the duration of antibiotic therapy was at least 25% shorter than in the C-reactive protein group. For both groups, at least seven full-days of antibiotic therapy were ensured in patients with Sequential Organ Failure Assessment greater than 10 and/or bacteremia at inclusion, and patients with evident resolution of the infectious process had antibiotics stopped after 7 days, despite biomarkers levels.

Measurements and Main Results: Ninety-four patients were randomized: 49 patients to the procalcitonin group and 45 patients to the C-reactive protein group. The mean age was 59.8 (SD, 16.8) years. The median duration of antibiotic therapy for the first episode of infection was 7.0 (Q1–Q3, 6.0–8.5) days in the procalcitonin group and 6.0 (Q1–Q3, 5.0–7.0) days in the C-reactive protein group ($p = 0.13$), with a hazard ratio of 1.206 (95% CI, 0.774–1.3; $p = 0.13$). Overall, protocol overruling occurred in only 13 (13.8%) patients. Twenty-one patients died in each group ($p = 0.836$).

Conclusions: C-reactive protein was as useful as procalcitonin in reducing antibiotic use in a predominantly medical population of septic patients, causing no apparent harm. (*Crit Care Med* 2013; 41:2336–2343)

Key Words: antibiotic therapy; C-reactive protein; intensive care; procalcitonin; sepsis

***See also p. 2447.**

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Dr. Nobre conceived the study idea. Dr. C. F. Oliveira, Dr. C. R. A. Oliveira, Ms. Silva, and Ms. Pereira acquired the data. Drs. C. F. Oliveira and Nobre analyzed and interpreted the collected data. Drs. C. F. Oliveira, Botoni, C. R. A. Oliveira, and Nobre wrote the manuscript. Drs. C. F. Oliveira, C. R. A. Oliveira, Botoni, Serufo, and Nobre delineated the hypothesis. All the authors reviewed the manuscript prior to submission.

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Uncertainty in diagnosis often leads to excessive use of antibiotics (1). The early and empirical initiation of antibiotic treatment is recommended for patients with suspected severe bacterial infection and is associated with lower mortality (2, 3). ICUs are a common setting for this practice; however, antibiotic treatment is often maintained for longer than necessary (4). Reducing the duration of antibiotic treatment, even in cases of confirmed infection, is one of the most efficient ways to reduce the pressure for selecting bacteria resistant to these drugs (5).

Several authors have suggested the use of inflammatory biomarkers to guide the interruption of antibiotic treatment. Procalcitonin (PCT) has been proved to be useful in guiding duration of antibiotic therapy, promoting the reduction of antibiotic use in several settings, including the ICU (6–10). This finding has been confirmed in four recent meta-analyses

(11–14). Regarding C-reactive protein (CRP), various observational studies have demonstrated the correlation between the rapid consistent reduction of its circulating levels in the first days of treatment and a better prognosis in patients presenting with severe infections (15–21). Despite being used routinely in several intensive care services as an auxiliary criterion for decisions regarding antibiotic therapy, no CRP-based protocol has been tested in clinical trials to guide the reduction of antibiotic use in patients with sepsis.

We sought to test the hypothesis that a protocol based on serum PCT levels would be superior to a protocol based on serum CRP levels for reducing the duration of antibiotic treatment in critically ill patients presenting with severe sepsis or septic shock. In addition, we tested the feasibility and safety of using a superior limit of 7 days for antibiotic therapy in patients presenting clinical and laboratory resolution of sepsis.

MATERIALS AND METHODS

Study Design and Subjects

This was a controlled open randomized clinical trial conducted at two teaching ICUs in Brazil. All adult patients older than or equal to 18 years with suspected severe sepsis or septic shock (22, 23) were assessed for potential inclusion between September 2009 and May 2012. The exclusion criteria, for both groups, were as follows: 1) confirmed microbiological infection by *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Listeria* species, *Mycobacterium tuberculosis*, or fungi; 2) *Staphylococcus aureus* bacteremia; 3) suspected or confirmed severe infections caused by viruses or parasites; 4) infections that required long-term treatment, regardless of the etiologic agent (e.g., bacterial endocarditis); 5) localized chronic infections (e.g., chronic osteomyelitis); 6) more than 48 hours of antibiotic treatment; 7) immunosuppressed patients (such as those diagnosed with HIV), patients with neutropenia (less than 500 neutrophils/mm^3), patients post solid-organ transplant, patients under immunosuppressive therapy, and patients who received more than 1 mg/kg of prednisone or equivalent; 8) patients under palliative care; 9) patients who suffered multiple trauma, burns, or major surgery in the previous 5 days; 10) patients diagnosed with pulmonary neoplasias, carcinoid tumors, or medullary tumors of the thyroid; and 11) patients who remained in the ICU for 24 hours or less.

Patients who were eligible for the study were preincluded and monitored for 72 hours before randomization. Patients who did not meet any of the exclusion criteria were randomized to have the duration of antibiotic therapy guided by PCT or by CRP levels.

The local ethics in research board approved the study. All the patients or their guardians signed an informed consent form. This article was written in accordance with the recommendation of the CONSORT statement for Clinical Trials (24).

Interventions

The procedures followed to include patients in the study are detailed in **Figure 1**. Randomization was performed using a table of random computer-generated numbers. Sealed opaque envelopes were used for the randomization.

Serum levels of CRP or PCT were used to encourage discontinuation of antibiotics according to randomization group (Fig. 1). For both groups, the decision to stop antibiotics took into account the clinical response and the behavior of Sequential Organ Failure Assessment (SOFA) score. For patients presenting clinical resolution of infection, a superior limit of 7 days of antibiotic therapy was set, regardless of the CRP and PCT serum levels. Furthermore, patients with positive blood cultures or who had an initial SOFA score > 10 received at least 7 days of antibiotic treatment, even when the remaining discontinuation criteria had been fulfilled (**supplemental data**, Supplemental Digital Content 1, http://links.lww.com/CCM/A671).

The composition of the antibiotic therapy was based on internationally accepted recommendations (25–28), and the treating physicians took the final decision regarding when to discontinue treatment.

Measuring PCT and CRP Markers

The reactive test VITROS (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY) was used for quantitatively measuring the concentration of serum or plasma CRP. This test has a functional sensitivity of 5 mg/L and linearity between 5 and 90 mg/L. The Vidas BRAHMS PCT (bioMérieux, Lyon, France) was used to measure serum PCT. This test has a functional sensitivity of 0.05 ng/mL and linearity between 0.05 and 200 ng/mL.

Outcomes

The primary outcome was the duration of antibiotic therapy for the first episode of infection. The secondary outcomes were as follows: 1) total number of days on antibiotic therapy; 2) days off antibiotic therapy; 3) death from any cause during the 28 days of follow-up in the hospital; 4) length of stay (LOS) in the ICU and LOS in the hospital; and 5) clinical cure, recurrent infection, and nosocomial infection. Deaths were classified as either related or unrelated to sepsis (see **supplemental data**, Supplemental Digital Content 2, http://links.lww.com/CCM/A672, for definitions of the secondary outcomes).

Regarding the occurrence of nosocomial infections in the studied patients, courses of antimicrobial therapy administered with an interval of more than 48 hours were considered being directed to distinct infection episodes (29).

Statistical Analysis

Sample size calculation was based on data from a previous study (6), in which the mean duration of antibiotic therapy for the index infection was 8.6 ± 5.0 days among patients treated according to a PCT-guided protocol as compared with 10.7 (± 4.0) days in the control group (V. Nobre, unpublished observation, 2008). Thus, we hypothesized that the duration of the antibiotic therapy in patients treated with a PCT-guided protocol would be at least 25% shorter than the duration observed in patients treated according to a protocol based on the serum CRP levels. We found that

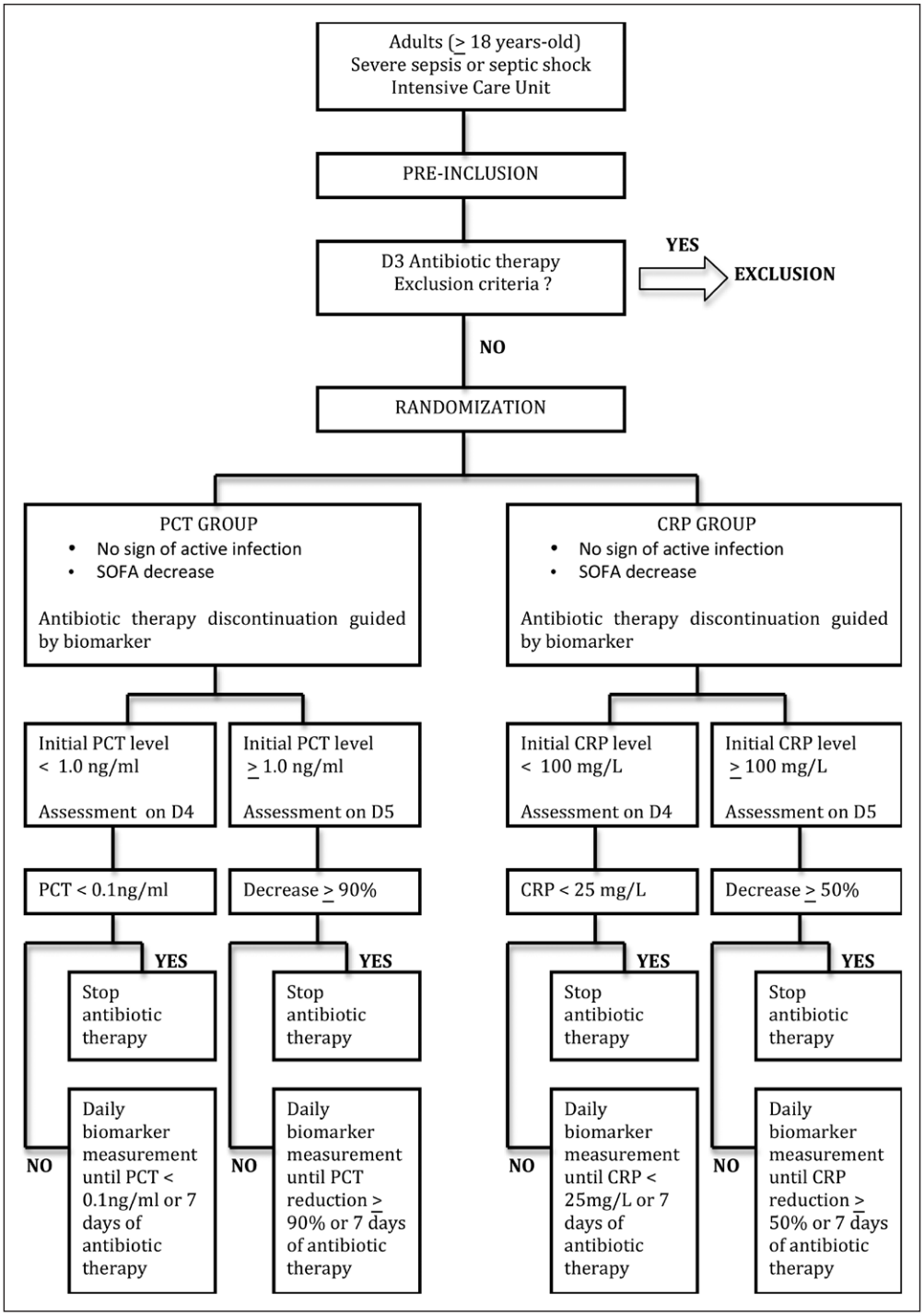

Figure 1. Flowchart for the decision to discontinue antibiotic treatment. PCT = procalcitonin, SOFA = Sequential Organ Failure Assessment, CRP = C-reactive protein.

58 patients per group—totalizing 116 individuals—would be necessary to demonstrate this difference, with a power of 80% and an alpha error of 5%.

The categorical variables are presented according to their absolute and relative frequency. Regarding the continuous data, the median and the 25–75% interquartile interval (Q1–Q3) were used for the nonnormally distributed variables, whereas the mean and SD were used for the normally distributed variables.

The patients were followed-up for 28 days or until their death or hospital discharge. The occurrence of primary and secondary outcomes was determined by intention-to-treat. Both groups were compared using the chi-square test or Fisher exact test and Student *t* test or Mann-Whitney *U* test, as appropriate.

To further investigate the primary outcome, a cumulative antibiotic-discontinuation curve that compared both groups (survival analysis) was created using the log-rank test. Subsequently, Cox proportional hazard model was used to compare the risk of antibiotic discontinuation for the first episode of infection. A severity-adjusted analysis was then performed (Simplified Acute Physiology Score [SAPS] III, Acute Physiology and Chronic Health Evaluation [APACHE] II, and SOFA). The results were displayed using a bivariate analysis with hazard ratios (HRs) and their respective 95% CIs.

A two-tailed test at a significance p value of less than 0.05 was set for all of the analyses. All data were analyzed using the SPSS statistical package, version 15.1 (SPSS, Chicago, IL).

RESULTS

Patients

Three hundred fifty-five patients were assessed for inclusion; of these, 102 were preincluded. Five patients were excluded before randomization, and 97 patients were randomized (**Fig. 2**). Three patients were excluded after randomization: two patients from the PCT group and one patient from the CRP group. The reasons for exclusion were withdrawal of the consent form (two patients) and technical problems with measuring the markers (one patient). Therefore, 94 patients were included in the final analysis (Fig. 2).

The average age for the entire studied population was 59.8 ± 16.8 years, and 60.6% of the patients were men. Overall,

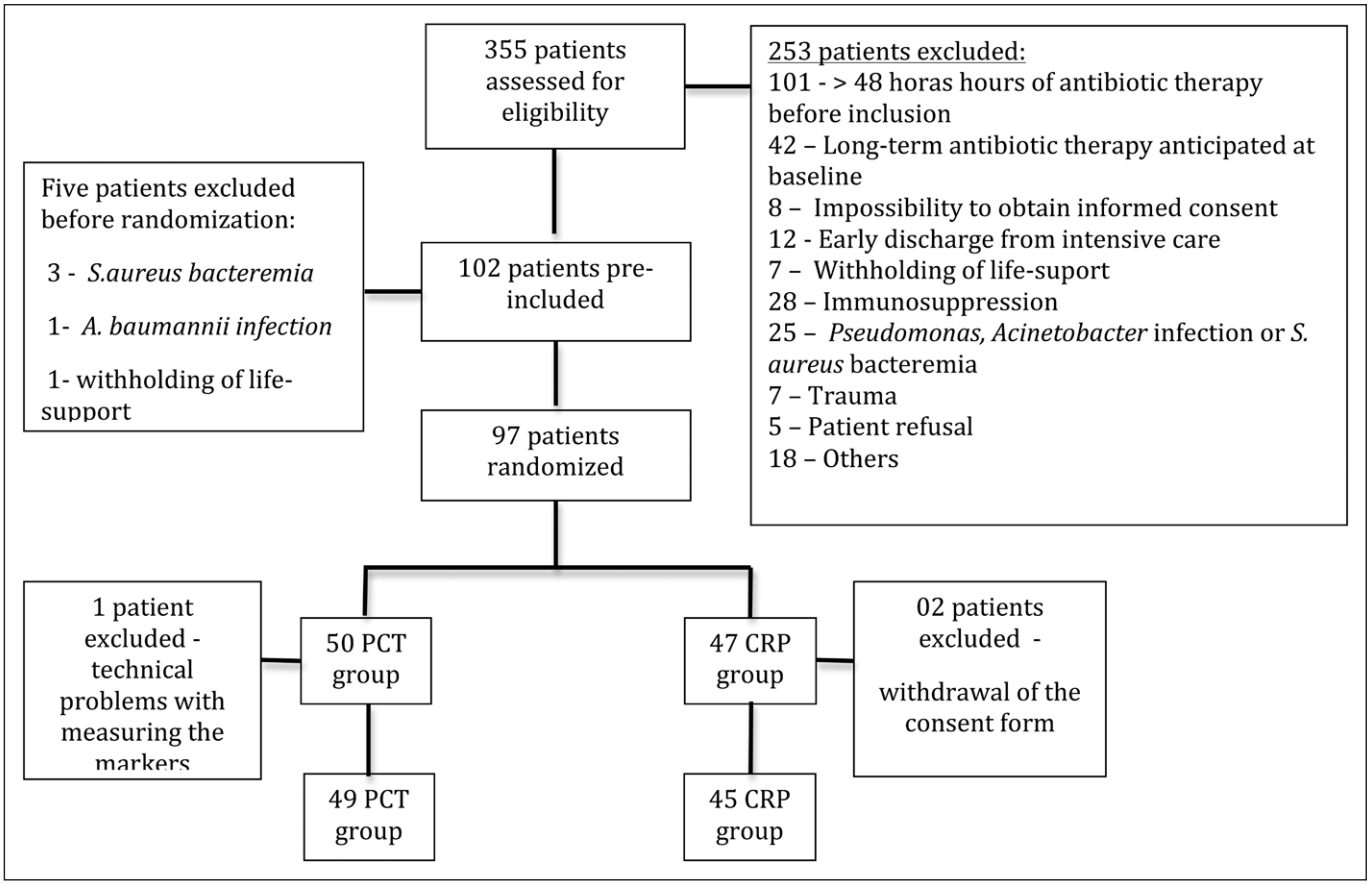

Figure 2. Flowchart of inclusion of patients in the study. PCT = procalcitonin, CRP = C-reactive protein.

clinical patients and patients with nosocomial infections were predominant in both groups. No difference in severity scores and in frequency of septic shock was found between the two groups. The main characteristics of the patients included in the study are detailed in **Table 1**.

Sites of Infection and Microbiology

As shown in **Table 1**, pulmonary sepsis was the most common infection site in both groups. The proportion of sepsis confirmed through microbiological analysis did not differ significantly between the groups (48.9% for the CRP group vs 42.9% for the PCT group; $p = 0.679$). The most commonly isolated microorganisms in both groups were *S. aureus, Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae,* and *Haemophilus influenzae.*

Primary Outcome

The duration of antibiotic therapy for the first episode of infection was similar in both groups (**Table 2**), with a median of 7.0 (Q1–Q3, 6.0–8.5) days in the PCT group and 6.0 (Q1–Q3, 5.0–7.0) days in the CRP group ($p = 0.06$). The Cox analysis comparing the risk of having the first course of antibiotic therapy interrupted during the follow-up corroborated these findings, with a HR of 1.206 (95% CI, 0.774–1.3; $p = 0.13$) (**Fig. 3**). These results were similar even after adjusting for severity using the APACHE II (HR, 1.172 [95% CI, 0.747–1.838]), SAPS III (HR, 1.204 [95% CI, 0.771–1.879]), and SOFA (HR, 1.183 [95% CI, 0.756–1.851]) scores.

Secondary Outcomes

The number of days on antibiotic therapy during follow-up period was greater in the PCT group than in the CRP group; however, this difference was not significant (13 d vs 8 d, respectively; $p = 0.183$). The number of antibiotic-free days per 1,000 live days during follow-up was similar for both groups (357.10 vs 357.14; $p = 0.998$).

The remaining secondary outcomes are presented in **Table 3**. No significant difference was observed between the two studied groups regarding the rate of clinical cure and recurrence of the first episode of infection, prevalence of nosocomial infection during follow-up, ICU LOS, and hospital LOS. Death by any cause during the 28 days of follow-up was also similar for both groups (32.7% of the patients in the PCT group and 33.3% of the patients in the CRP group; $p = 1.0$; Table 3).

Protocol overruling occurred in only 13 patients: six (12.2%) patients in the PCT group and seven (15.5%) patients in the CRP group. In 17 (34.7%) patients of the PCT group and eight (17.8%) patients of the CRP group, the antibiotics were maintained for 7 days because of bacteremia and/or a SOFA score above 10 at inclusion ($p = 0.037$). However, with the exclusion of these 25 patients from the primary outcome

TABLE 1. Characteristics of the Patients Included in This Study

Characteristics	Procalcitonin Group (*n* = 49)	CRP Group (*n* = 45)	*p*
Age (yr), mean ± SD	59.6 ± 13.3	59.6 ± 18.5	0.992
Females, *n* (%)	18 (48.8)	19 (42.2)	0.674
Medical patient	42 (85.7)	40 (88.9)	0.761
Acute Physiology and Chronic Health Evaluation II, median (Q1–Q3)	20 (14–28.5)	22 (14–24)	0.828
Simplified Acute Physiology Score III, median (Q1–Q3)	61(49.5–81.5)	68 (52.5–79)	0.318
SOFA, median (Q1–Q3)	7.5 (5–10)	7 (4–10)	0.400
Initial SOFA > 10, *n* (%)	10 (20.4)	8 (17.7)	0.746
Initial SOFA > 10 and/or positive blood culture (%)	17 (37.8)	17 (34.6)	0.449
Organ dysfunction, *n* (%)			
Acidosis	12 (24.5)	9 (20)	0.630
Coma	10 (20.4)	10 (22.2)	1.000
Heart failure	8 (16.3)	9 (20.0)	0.790
Kidney failure	15 (30.6)	10 (22.2)	0.356
Respiratory failure	40 (81.6)	40 (88.9)	0.393
Comorbidities, *n* (%)			
Cardiomyopathy	25 (51.0)	24 (53.3)	0.839
Chronic obstructive pulmonary disease	8 (16.3)	5 (11.1)	0.557
Peripheral vascular disease	1 (2.0)	1 (2.2)	1.000
Cerebrovascular disease	11 (22.4)	12 (26.7)	0.811
Chronic kidney disease	9 (18.4)	10 (22.2)	0.798
Liver failure	3 (3.0)	2 (4.4)	1.000
Insulin-dependent diabetes	9 (9.57)	3 (3.19)	0.124
Neoplasias	1 (2.2)	1 (2.2)	1.000
Sepsis characterization, *n* (%)			
Lungs	32 (65.3)	25 (55.6)	
Abdomen	1 (2.2)	1 (2.2)	
Urine	4 (8.2)	5 (11.1)	0.522
Catheter	3 (6.1)	1 (2.2)	
Others	10 (20.4)	13 (28.9)	
Septic shock	31 (63.3)	25 (55.6)	0.530
Community-acquired infection	19 (38.8)	17 (37.8)	1.000
Laboratory			
Positive blood culture, *n* (%)	8 (16.3)	12 (26.7)	0.313
Positive microbiology, *n* (%)	21 (42.9)	22 (48.9)	0.679
Procalcitonin at inclusion (ng/mL), median (Q1–Q3)	3.87 (1.56–19.96)	3.81(1.37–18.6)	0.691
CRP at inclusion (mg/L), median (Q1–Q3)	242 (133.7–313.2)	186.1 (74.4–299)	0.403
Organ/system support, *n* (%)			
Ventilatory support (invasive ventilation + noninvasive ventilation)	46 (93.9)	42 (93.3)	1.000
Hemodialysis	17 (34.7)	13 (28.9)	0.659

CRP = C-reactive protein, Q1–Q3 = quartile 1 to quartile 3, SOFA = Sequential Organ Failure Assessment.

TABLE 2. Primary Outcome Analysis Assessed According to the Intention-to-Treat

Outcome	Procalcitonin Group ($n = 49$)	C-Reactive Protein Group ($n = 45$)	p
Duration of antibiotic therapy, mean days (SD)	8.1 (3.7)	7.2 (3.5)	0.25
Duration of antibiotic therapy, median days (quartile 1 to quartile 3)	7 (6.0–8.5)	6 (5.0–7.0)	0.06

TABLE 3. Secondary Outcomes Assessed According to Intention-to-Treat

Outcomes	Procalcitonin Group ($n = 49$)	C-Reactive Protein Group ($n = 45$)	p
Total exposure to antibiotic (d), median (Q1–Q3)	13 (7–18)	8 (6–18)	0.183
Antibiotic-free period (d), median/1,000 live days (Q1–Q3)	357.1 (0–541)	357.14 (33.3–509.2)	0.998
Clinical cure, *n* (%)	40 (81.6)	36 (80)	1.000
Mortality in 28 d, *n* (%)	16 (32.7)	15 (33.3)	1.000
Hospital mortality, *n* (%)	21 (42.9)	21 (46.7)	0.836
Sepsis-related death (deaths %)	6 (37.5)	6 (40)	0.731
Recurrence of the first episode of infection, *n* (%)	3 (6.1)	1 (2.2)	0.618
ICU length of stay, median days (Q1–Q3)	14 (9–24)	12 (7–18)	0.164
Hospital length of stay, median days (Q1–Q3)	36 (20–59)	25 (13–52)	0.175
Nosocomial infection (%)	29 (59.2)	23 (51.1)	0.534

Q1–Q3 = quartile 1 to quartile 3.

analysis, no difference in the median duration of antibiotic therapy between the CRP and PCT groups was observed ($p = 0.339$).

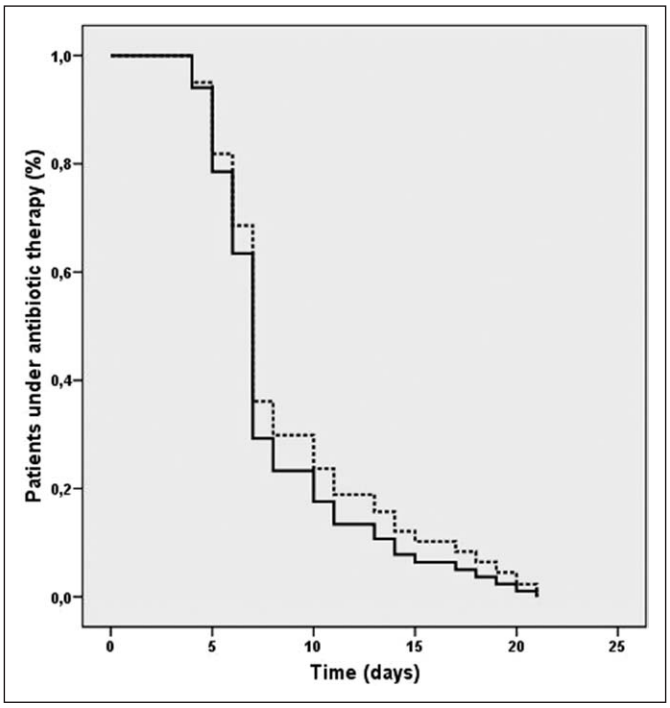

Figure 3. Cox analysis showing the risk of antibiotic therapy discontinuation in the first episode of infection for the procalcitonin group (*dotted line*) and C-reactive protein group (*continuous line*) (hazard ratio, 1.206 [95% CI, 0.774–1.3]; $p = 0.13$).

DISCUSSION

In this study of patients with sepsis in the ICU, we found that a PCT-based protocol was not superior to a protocol based on the serum levels of CRP for guiding the duration of antibiotic treatment. Furthermore, our findings suggest that "seven full-days" represent a feasible and safe superior limit of antibiotic therapy in medical patients with severe sepsis and septic shock.

Antimicrobial therapy is usually based on nonstandardized clinical and laboratory criteria, which often lead to antibiotic abuse, especially in critically ill patients (1). The rational use of antibiotics has several benefits, including the reduction of multiresistant bacteria (5, 30), treatment costs (31), and the frequency of adverse effects related to these drugs (32). Recently, several investigations have aimed to define objective criteria for initiating and suspending antibiotic treatment (33, 34). The usefulness of serial measurements of serum PCT levels has been widely studied for the aforementioned purpose in different settings, including the ICU (6, 7, 10–14, 35). Protocols for antibiotic use guided by serum PCT levels seem to pose no major risks for patients (12) and allow a safe reduction of exposure to these drugs. A French multicenter study that included 630 critically ill patients with sepsis has demonstrated that the antibiotic-free period is significantly higher for the group with treatment guided by PCT (14.2 ± 9.1 d) when compared with routinely used criteria (11.6 ± 8.2 d) (10). Although the benefit of PCT guidance in reducing the use of antibiotics has been well established (11, 13, 14), it has some limitations, particularly in facilities with fewer financial resources. Furthermore, the duration of antibiotic therapy observed in

the control groups of most trials was longer than what could be considered the best practice of antibiotic use (36).

CRP is an inflammatory marker that has been used in clinical practice for decades (37). Differently from PCT, CRP is widely available at low costs (the cost per test in our service is U.S. $1 for CRP vs U.S. $39 for PCT). Various investigations involving different populations with serious infectious conditions have demonstrated that a rapid and consistent reduction in the CRP levels during the first days of antibiotic treatment is related to a better prognosis (17, 20, 38). Besides the nonsuperiority of PCT as compared with CRP in guiding antibiotic therapy for the first episode of infection, we found that the duration of therapy in patients with severe sepsis or septic shock was brief in both groups (a median of 6–7 d). This can partially be explained by the predefined time limit of 7 days used in our protocol. Remarkably, the mean duration of antibiotic therapy observed in our patients was shorter than those observed in the control group of previous trials comparing PCT-guided protocols versus standard care (6, 10). In a recent systematic review and meta-analysis of individual data from patients with respiratory infections, including three trials testing PCT-guided protocols, the median duration of antibiotic treatment was 12 (Q1–Q3, 8–18) days in studies conducted with ICU populations. It is worth mentioning that despite lower exposure to antibiotics, the observed mortality was not higher than expected given the severity of the patients' conditions (12).

In this study, we tested a protocol aimed at defining objective criteria for using serum CRP levels as additional support to the decision of discontinuing antibiotic treatment in critically ill patients with sepsis. To this end, CRP was compared with PCT, whose usefulness has already been exhaustively tested in controlled and randomized trials. The main idea behind the study proposal is to customize the duration of antimicrobial treatment, establishing a superior limit of 7 days. The tested biomarkers were used to encourage treating physicians to follow this proposal, avoiding unnecessarily long courses of antibiotic therapy. Furthermore, we used the SOFA score, as well as other data commonly used in clinical practice, to help in the decision-making process. The inclusion of the SOFA score sought to increase patient safety (39).

Certain limitations of this study should be considered. First, the sample size was small—indeed, smaller than the sample initially proposed—and we only included patients from two similar centers, with predominantly medical patients. Despite this important limitation, our findings are sufficiently representative to suggest that PCT is neither the only nor the best inflammatory biomarker to guide antibiotic therapy in sepsis. Second, the study did not include a third group composed of patients whose antimicrobial treatments were guided by routine practices alone, using only the PCT group as a reference for comparison. Third, most of the patients who were assessed for inclusion were excluded before the randomization, which might indicate a limitation to the practical usefulness of the tested protocol. Regarding this point, most exclusions occurred in patients who had "more than 48 hours of antibiotic therapy before the first assessment" as the sole exclusion criteria. Furthermore, based on our findings, we believe that some exclusion criteria used in the present protocol (e.g., *P. aeruginosa* and *A. baumannii* infection) can be disregarded in future studies.

CONCLUSIONS

In conclusion, this comparative trial of two biomarkers to guide the antibiotic therapy in patients with sepsis demonstrated that a PCT-based protocol is not superior to a protocol based on serum CRP level for reducing the use of antibiotics. Remarkably, the length of antibiotic therapy was shorter in the CRP group, less than the maximum duration of therapy proposed in our protocol (7 d). Finally, no difference in morbidity or mortality was observed between the two groups. The present findings must be confirmed in larger studies, but they markedly suggest that a protocol based on a best care practice of antibiotic use allied to a cheaper and more readily available biomarker can safely reduce the exposure to antibiotics in patients with sepsis.

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