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Sepsis/Infection

Early procalcitonin kinetics and appropriateness of empirical antimicrobial therapy in critically ill patients☆
A prospective observational study

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ABSTRACT

Purpose: The purpose was to investigate the value of procalcitonin (PCT) kinetics in predicting the appropriateness of empirical antimicrobial treatment in critically ill patients.
Materials and methods: This prospective observational study recruited patients in whom empirical antimicrobial therapy was started for suspected infection. Biochemical and physiological parameters were measured before initiating antimicrobials (t_0), 8 hourly (t_8, t_{16}, t_{24}), and then daily ($day_{2\text{-}6}$). Patients were grouped post hoc into appropriate (A) and inappropriate (IA) groups.
Results: Of 209 patients, infection was confirmed in 67%. Procalcitonin kinetics were different between the IA (n = 33) and A groups (n = 108). In the IA group, PCT levels (median [interquartile range]) increased: t_0= 2.8 (1.2-7.4), t_{16}= 8.6 (4.8-22.1), t_{24}= 14.5 (4.9-36.1), P< .05. In the A group, PCT peaked at t_{16} and started to decrease by t_{24}: t_0= 4.2 (1.9-12.8), t_{16}= 6.99 (3.4-29.1), t_{24}= 5.2 (2.0-16.7), P< .05. Receiver operating characteristic analysis revealed that a PCT elevation greater than or equal to 69% from t_0 to t_{16} had an area under the curve for predicting inappropriate antimicrobial treatment of 0.73 (95% confidence interval, 0.63-0.83), P< .001; from t_0 to t_{24}, a greater than or equal to 74% increase had an area under the curve of 0.86 (0.77-0.94), P< .001. Hospital mortality was 37% in the A group and 61% in the IA group (P= .017).
Conclusions: Early response of PCT in the first 24 hours of commencing empirical antimicrobials in critically ill patients may help the clinician to evaluate the appropriateness of therapy.

1. Introduction

Sepsis remains the leading cause of death among critically ill patients worldwide [1,2]. It is well documented that delaying appropriate antimicrobial treatment increases mortality [3,4], but empirical antimicrobials have been proven to be inadequate in almost 30% of cases [5]. Diagnosing infection and assessing the progress of the patients' condition have been supported by biomarkers for decades. Procalcitonin (PCT) and C-reactive protein (CRP) are the most commonly used biomarkers in the clinical setting, of which PCT seems to have a better sensitivity and specificity for differentiating bacterial infection from nonbacterial systemic inflammatory response [6–9]. There is considerable evidence that PCT-guided antimicrobial management considerably reduces antimicrobial use in lower respiratory tract infections, and it may also shorten the duration of antimicrobial treatment in the intensive care unit (ICU) [10,11].

However, during the initial phase of treatment, physicians often have no way of confirming the adequacy of the commenced antimicrobials. As PCT is a fast-reacting biomarker with a half-life of 24 hours, theoretically, it is possible that the early kinetics of PCT, within this first 24 hours after commencing empirical antimicrobial therapy, may reflect the efficacy of the treatment. Therefore, our aim was to perform a prospective observational study to investigate the value of PCT kinetics

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measured 8 hourly during the first 24 hours for predicting the appropriateness of empirical antimicrobial treatment in critically ill patients.

2. Methods

2.1. Patient selection

This prospective observational study was undertaken between October 2012 and October 2013 and was approved by the Regional and Institutional Human Medical Biological Research Ethics Committee, University of Szeged, Hungary (WHO-3005; 19.04.2012, Chairperson Prof T Wittmann). The investigation was performed at the University of Szeged (Szeged, Hungary) Albert Szent-Györgyi Health Center in a 27-bed multidisciplinary tertiary ICU. The study was registered at ClinicalTrials.gov with registration number NCT02294695. Written informed consent was obtained from all subjects or from their relatives.

2.1.1. Inclusion criteria

All patients older than 18 years with suspected infection on admission or during their stay on the ICU were screened for eligibility. Patients were enrolled when the attending physician suspected infection and empirical antimicrobial therapy was started.

2.1.2. Exclusion criteria

The exclusion criteria were as follows: age less than 18 years, antimicrobial therapy within 48 hours, conditions that have been shown to interfere with the inflammatory response such as acute renal replacement therapy in the first 24 hours [12] and cardiopulmonary resuscitation [13], patients with end-stage diseases, and immunocompromised patients.

2.2. Subgroups and definitions

Diagnosis of infection and appropriateness of the empirical antimicrobials were established based on recommendations [14], clinical parameters, and biochemical and microbiological results evaluated by 2 experts blinded for the PCT data apart from the first PCT result: an infectologist (EH) and an intensivist (JF). Patients were then grouped into infectious and noninfectious groups. Patients with suspected infection but negative microbiology were also excluded from the final analysis.

Antimicrobial therapy was evaluated by 2 independent experts (EH and JF), and it was considered appropriate if (*a*) the isolated pathogens were susceptible to at least 1 of the commenced antimicrobials [15] and (*b*) the appropriate dosage, as recommended by our local protocols, was administered. Based on these results, patients were grouped post hoc into appropriate (A group) and inappropriate (IA group) antimicrobial treatment groups.

Patients were further divided into "medical" and "surgical" groups. The medical group represented patients without surgical intervention. In the surgical group, infection either was related to surgery or required surgery for source control [16]. These groups were also further divided into appropriate, $A_{m(edical)}$ and $A_{s(urgical)}$, and inappropriate, IA_m and IA_s, groups.

2.3. Protocol and data collection

When infection was suspected (based on temperature, white blood cell count, clinical picture, PCT levels) by the attending physician, specimens were sent for microbiology, and antimicrobial therapy was commenced. The choice of antimicrobials was determined by local protocols based on international guidelines [17–19].

2.3.1. Data collection

After enrollment, demographic data, parameters of vital organ functions, and laboratory data were collected for 6 days. Length of ICU and hospital stay and mortality were also documented.

2.3.2. PCT measurement

Procalcitonin levels were determined immediately before the initiation of antimicrobials (t_0), 8 hourly (t_8, t_{16}, t_{24}) during the first 24 hours, and then daily (day_2-day_6). The flowchart of the data collection is summarized in Fig. 1.

Serum PCT levels were measured with Cobas 6000 analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan). Analyzer reagents (Elecsys B·R·A·H·M·S PCT assay) were developed in collaboration with B·R·A·H·M·S Corporation (Hennigsdorf, Germany) and Roche Diagnostics (Mannheim, Germany). Procalcitonin was determined by electrochemiluminescence immunoassay serum on the automated Roche Elecsys and Cobas immunoassay analyzers.

2.3.3. Microbiological staining and antibiograms

Microbiological tests were performed and sent at t_0 (before the first antimicrobial dose was administered) and, if necessary, repeated on the following days to identify microorganisms and their resistance. The type of antimicrobials, the dosage, the bacterial strains, and their antibiogram profile were recorded.

2.4. Statistical analysis

The primary end point of the study was the difference in PCT kinetics after 24 hours of starting the antimicrobial treatment. According to our former pilot study [20], a PCT increase of less than 70% within the first 24 hours compared with the baseline value (t_0) had an 84% positive predictive value with 80% sensitivity and 41% specificity ($P = .059$), indicating appropriate antimicrobial treatment. Therefore, for the study to have 80% power to show the smallest clinically relevant difference of 15%, an increase of PCT between the A and IA groups (ie, 70% increase in the IA group and 55% increase of PCT in the A group from t_0 to t_{24}) with a $P < .05$, the required sample size was at least 161 patients. Based on this calculation, we decided to enroll patients for at least 12 months.

Data were analyzed using IBM SPSS Statistics Version 20 (Armonk, NY) and Systat Software Inc SigmaPlot 12.5 (London, UK) software. For continuous data, the Shapiro-Wilk tests were performed to assess normal distribution. Demographic data were analyzed between groups with the Student *t* test or nonparametric data with the Mann-Whitney *U* test as appropriate. Biomarkers were analyzed by using 2-way repeated-measures analysis of variances (all pairwise multiple comparison procedures: Holm-Sidak method). Categorical data were compared using χ^2 tests. Receiver operating characteristic (ROC) curve and the respective areas under the curves (AUCs) were calculated for PCT and CRP levels. The best cutoff values were determined to maximize the Youden index ($J = \max[\text{Sens} + \text{Spec} - 1]$). The test parameters (sensitivity, specificity, and positive and negative predictive values) were compared by their 95% confidence intervals (CIs). A level of $P < .05$ was defined as statistically significant. Data are given as mean ± standard deviation or median (25%-75% interquartile range) as appropriate.

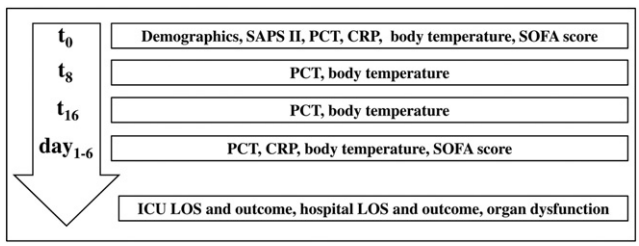


Fig. 1. Flowchart. $t_{0\text{-}24}$ indicates sampling within the first 24 hours after commencement of empirical antimicrobials; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; LOS, length of stay.

Table 1
Demographics and infection sources in the entire cohort

		Total (N = 209)	Appropriate AB (n = 108)	Inappropriate AB (n = 33)	*P* value
Age (y)		68 (19)	68 (19)	69 (20)	.842
Male, n (%)		117 (56)	60 (55)	16 (48)	.476
Body height (cm)		170 (12)	169 (14)	165 (19)	.422
Body weight (kg)		76 (25)	70 (18)	80 (27)	.218
SAPS II points		67 ± 19	68 ± 19	72 ± 16	.333
SAPS II PM		78 (47)	81 (32)	88 (27)	.298
SOFA score points at t_0		14 (5)	14 (4)	15 (6)	.298
delta SOFA score points (t_0-t_{24})		0 (2)	0 (2)	0 (2)	.568
ICU days before enrollment		1(2)	0 (2)	1 (2)	.798
ICU LOS (d)		8 (9)	8 (10)	9 (11)	.263
ICU survival, n (%)		151 (72)	84 (78)	14 (42)	<.001
Hospital LOS (d)		15 (17)	16 (22)	17 (16)	.444
Hospital survival (%)		126 (60)	68 (63)	13 (39)	.017
Mechanical ventilation (d)		4 (8)	4 (9)	7 (8)	.011
Vasopressor therapy (d)		3 (4)	3 (3)	5 (4)	.004
Renal replacement therapy, n (%)		65 (31)	33 (31)	19 (57)	.005
Nosocomial infection, n (%)			53 (49)	16 (48)	.953
Source of infection, n (%)	Respiratory		54 (50)	25 (76)	.007
	Abdominal		19 (18)	5 (15)	.744
	Soft tissue		15 (14)	2 (6)	.227
	UTI		10 (9)	2 (6)	.564
	BSI		7 (6)	0	.134
	Meningitis		5 (5)	0	.208
	Other		1 (1)	1 (3)	.371

Data are given as median (interquartile range) or mean ± standard deviation as appropriate. Total = infection (appropriate and inappropriate) + no infection group. Regarding the source, a patient may have more than 1 infection at the same time. AB indicates antimicrobial therapy; n, number of patients; SAPS, Simplified Acute Physiology Score; PM, predicted mortality; LOS, length of stay; UTI, urinary tract infection; BSI, bloodstream infection.

3. Results

Over the study period, 209 patients were enrolled. Demographics are summarized in Table 1. From the 209 patients, 141 (67%) had proven infection, with infection unproven in 44 (21%). In 24 patients, although infection was highly likely, microbiology did not reveal pathogens; hence, these subjects were excluded from the final analysis. Procalcitonin at t_0 was significantly higher in the infectious group compared with noninfectious group: 4.53 (1.76-16.30) vs 1.0 (0.13-2.98) ng/mL, P= .024, respectively. In the infectious group (n = 141), 108 (77%) patients received appropriate antimicrobial therapy (A group), and in 33 (23%), antimicrobials proved to be inappropriate (IA group). Detailed descriptions of the source and pathogens are summarized in Tables S4 and S5.

Regarding demographics, there were no differences between the A and IA groups, but ICU and hospital survival was significantly higher in the A group (Table 1). These patients also required less vasopressors and renal replacement therapy compared with the IA group. From the 33 patients in the IA group, antimicrobials were changed in 20 patients on day 2 or 3, without any significant effect on PCT kinetics, compared with the other 18 patients (data not shown).

3.1. PCT kinetics

In both groups, the increase in PCT levels continued after the initiation of empirical antimicrobial treatment (t_0) until 16 hours (t_{16}) (Fig. 2A). In the IA group, there was a significant increase from t_{16} to t_{24}, whereas in the A group, there was a significant decrease from t_{16} to t_{24}. By t_{24}, the PCT reached significantly higher levels in the IA group and remained higher the following day compared with the A group. In the A group, PCT levels peaked at t_{16}, whereas in the IA group, the peak was at t_{24}. From t_{24} until the fifth day, PCT levels decreased in both groups (Fig. 2A).

There was a nonsignificant increase in CRP from t_0 to t_{24} in both groups. In the A group, CRP peaked at t_{24}. In the IA group, CRP remained high on day_2, with levels remaining higher compared with the A group on $days_{3\text{-}5}$. After day_2, CRP levels decreased in both groups (Fig. S4A). Body temperature showed no significant change over time (Fig. S4B).

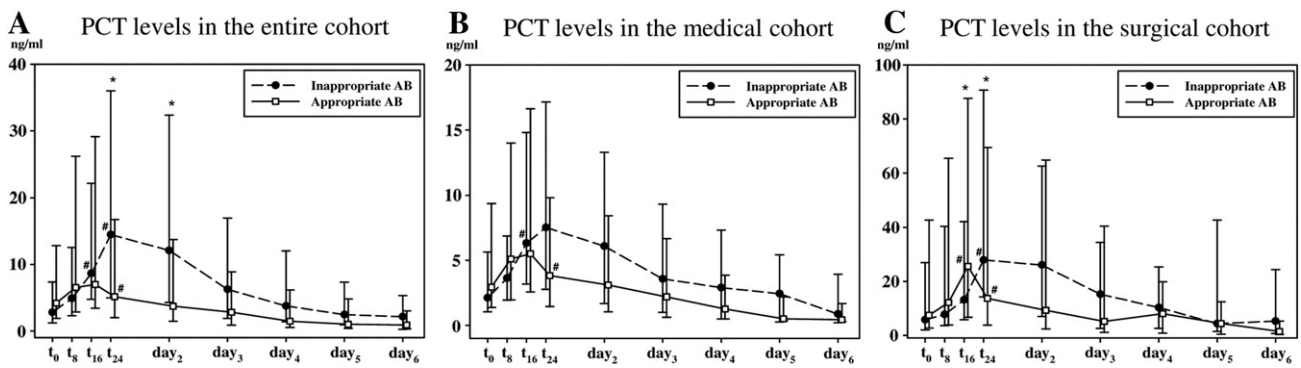
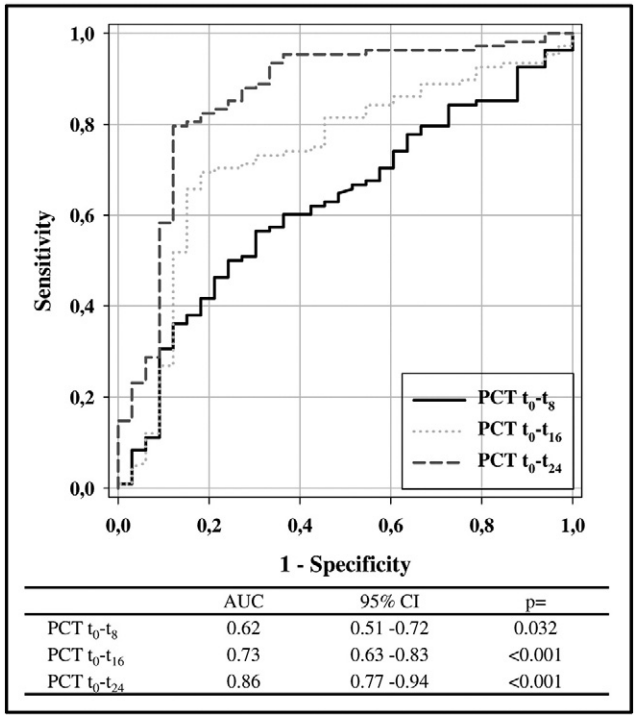


Fig. 2. PCT absolute values in the entire cohort and in the medical and surgical cohort. Data are presented as median and interquartile range. AB indicates antimicrobial therapy. #P< .05 within groups; * P< .05 between groups.



	AUC	95% CI	p=
PCT t_0-t_8	0.62	0.51 -0.72	0.032
PCT t_0-t_{16}	0.73	0.63 -0.83	<0.001
PCT t_0-t_{24}	0.86	0.77 -0.94	<0.001

Fig. 3. Receiver operating characteristic curve.

3.2. PCT kinetics in medical and surgical patients

In patients with infection, PCT followed similar kinetics in medical (n = 91) and surgical (n = 50) patients, with substantial differences in the absolute values at t_0 (median: 2.74 [25%-75% interquartile range: 1.30-7.72] vs 6.46 [2.61-40.07], P= .002) and at t_{24} (4.41 [1.52-13.55] vs 17.02 [6.74-69.45] ng/mL, P< .001, respectively). Medical and surgical patients were further divided into appropriate—A_m (n = 70) and A_s (n = 38)—and inappropriate—IA_m (n = 21) and IA_s (n = 12)—subgroups. Kinetics in all subgroups followed the same pattern as described for the whole sample (Fig. 2B and C).

Kinetics of CRP were similar in both groups, with no significant differences within and between groups during the study period (Fig. S5A and B). The same holds true for body temperature, with the only difference being that, in the medical cohort at t_{24}, temperature was higher for the next 3 days (Fig. S5C and D) (Table S3).

3.3. Predictive value of PCT for indicating appropriate antimicrobial treatment

The ROC analysis revealed that a PCT elevation from t_0 to t_{16} had an AUC of 0.73 (95% CI, 0.63-0.83; P< .001) and that from t_0 to t_{24} had an AUC of 0.86 (95% CI, 0.77-0.94; P< .001) (Fig. 3). According to the Youden index, the best cutoff for PCT increase from t_0 to t_{16} was 69.2%, and from t_0 to t_{24}, it was 73.5% (Table 2).

4. Discussion

The main findings of this study were that PCT kinetics during the first 24 hours after commencing empirical antimicrobial therapy show significant differences in patients on appropriate antimicrobial therapy compared with those on inappropriate antimicrobial therapy and that there were significantly higher absolute PCT values but similar kinetics in surgical compared with medical patients with infections.

4.1. Diagnosing infection

Although the classical definitions of *sepsis syndromes*[21] and *consensus criteria* of sepsis [22] have been implemented worldwide for decades, differentiating systemic inflammatory response from bacterial infection remains a challenge [23,24], and mortality from sepsis and septic shock is still very high. This uncertainty in the diagnosis may lead to unnecessary overuse of antimicrobials resulting in increased bacterial resistance, adverse effects from the antimicrobials, and increased costs [25].

In this diagnostic dilemma, there has been considerable interest in the use of infection/sepsis biomarkers. Among these biomarkers, the two most commonly used are PCT and CRP. Several studies have shown that PCT has a better sensitivity and specificity for indicating bacterial infections than CRP [26]. This was confirmed by the results from this study, where only PCT was able to differentiate patients with proven infection from patients with no infection. These results are similar to those reported by recent large randomized trials [10,11].

4.2. Appropriate antimicrobial therapy

Inappropriate empirical antimicrobials have a strong adverse effect on survival [27], although such therapy is a common feature in the ICU, reportedly as high as 25% to 30% [5,15]. Once inappropriate antimicrobials are initiated, it often takes days (until organism isolation and sensitivities are produced) to correct them. In our study, 23% of patients received inappropriate antimicrobials. This high incidence may be due to the lack of fast and reliable diagnostic tests for bacterial infections and to the subsequent delay in microbiological results. Earlier recognition of potential inappropriate microbial therapy may allow an opportunity to substantially improve outcome.

To our knowledge, this is the first study to show that the early kinetics of PCT measured within the first 24 hours may help clinicians to evaluate the appropriateness of empirical antimicrobial therapy in critically ill patients. The rationale for measuring successive PCT levels within this time frame came from the assumption that, by giving appropriate antibiotics, this may slow the inflammatory response within hours and that this could be detected by serial measurements of PCT.

In a study by Charles et al [15], they observed a signal of lower PCT levels on day 2 in the appropriate group, but the difference was not significant. This may be due to the fact that, in their study, PCT was measured retrospectively; therefore, the time elapsed between the PCT measurements and the antibiotic therapy was uncontrolled, unlike this study where investigating PCT kinetics as precisely as possible during the first 24 hours was a particular aim. In this study, although PCT continued to increase after the initiation of empirical antimicrobial

Table 2
Cutoff values for appropriate and inappropriate antimicrobial treatment in the entire cohort

	Cutoff value	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	*P*
PCT t_0-t_8	≥45.6%	56.5% (0.46-0.66)	69.7% (0.51-0.84)	31.7% (0.28-0.54)	85.4% (0.78-0.92)	.090
PCT t_0-t_{16}	≥69.2%	65.7% (0.56-0.74)	84.8% (0.68-0.94)	42.1% (0.33-0.60)	92.8% (0.82-0.95)	.048
PCT t_0-t_{24}	≥73.5%	79.6% (0.70-0.86)	87.8% (0.71-0.96)	53.5% (0.41-0.70)	95.2% (0.84-0.98)	<.001

The best cutoff value was determined using the Youden index. PPV indicates positive predictive value; NPV, negative predictive value.

treatment during the first 16 hours in both the A and IA groups, in the A group, there was a significant PCT decrease during the next 8 hours (t_{24}), whereas in the IA group, PCT continued to increase, reached a significantly higher level by t_{24}, and remained higher the next day compared with the A group. A PCT increase of at least 69.2% during the first 16 hours or a PCT increase of at least 73.5% during the first 24 hours was the best cutoff value to indicate inappropriate antimicrobial treatment. It is known that PCT increases within hours after an infectious insult and levels halve daily once the infection is under control [28]. This feature explains the significant difference found in the PCT kinetics between the A and IA groups during the first 24 hours. It is also important to note that, after day 1, PCT decreased in both groups, although PCT levels remained significantly higher in the IA group. This is in line with the results from Charles et al [15], who measured PCT during the first 4 days of treatment and found a decrease from day 2 to day 3 in both the appropriate and inappropriate groups, but the decrease was more pronounced in the appropriate group. This can be explained by the finding that adequate supportive therapy on its own may attenuate the inflammatory response [29]. Furthermore, monocytes become exhausted after a certain period of time, also affecting PCT production [30,31]. It may be of significance that the grouping was based on the initial antibiotic therapy; hence, no patients were "crossed over" from the inappropriate to the appropriate group. However, from the 33 patients in the IA group, antibiotics were changed on day 2 or day 3 in 18 cases. We analyzed and compared PCT kinetics in patients in whom we changed (n = 18) as compared with patients in whom we did not change (n = 15) antibiotics over the study period but found no significant differences (data not shown).

Translating the results of the current study into clinical practice means that, when measuring PCT on commencement of antimicrobials (t_0) and then at 16 and 24 hours, a "large" increase within the first 16 to 24 hours (≥69.2%-73.5%) may indicate inappropriate antimicrobial therapy, whereas a lower-grade increase or a decreasing tendency after 16 hours would support appropriate antimicrobial therapy. The clinical importance of our findings is emphasized by the significant difference in hospital mortality between the A group and the IA group (37% vs 61%).

Another important finding of the current study is that CRP did not differentiate between the appropriate and inappropriate groups within the first 48 hours. This is in accordance with previously published data indicating that CRP is a "slow" marker and not as reliable as PCT in the critically ill [32,33]. The same holds true for body temperature, which, as with other studies, highlights that its use for guiding antimicrobial therapy is questionable [23].

4.3. PCT kinetics in surgical as compared with medical patients

Our results also support that PCT is several times higher in surgical compared with medical patients, but we also found that early kinetics were similar to those found in the whole sample. Our data also suggest that percentage changes of PCT may be a better, universally applicable approach for monitoring treatment progress rather than absolute values.

There is strong evidence that, because of direct cellular damage as in severe trauma, major surgery, and after ischemia-reperfusion, also known as *damage-associated molecular patterns*, there is an inflammatory mediator release very similar to that following an infectious insult, called *pathogen-associated molecular patterns* (PAMPs) [34]. Therefore, unspecific elevations in PCT levels can typically be seen in the absence of a bacterial infection [33,35]. Theoretically, in surgical patients with sepsis, damage-associated molecular pattern and PAMP take place at the same time, leading to a pronounced inflammatory response, whereas in medical patients, PAMP may occur on its own, resulting in a less extensive inflammatory response [16]. This feature is the reason why the same absolute values of PCT may mean completely different information in a medical compared with a surgical patient but, as shown in our results, kinetics follow a uniform pattern.

4.4. Limitations of the study

The most important limitation for us during the analysis of the results was the lack of criterion standard for diagnosing infection. Although we attempted to reduce the potential error in judgment by allocating patients into each group by 2 independent experts blinded for PCT kinetics in a post hoc fashion taking all clinical and microbiology data into account, one cannot exclude that mistakes may have still appeared in the process. Furthermore, the power analysis sample size could have been larger to detect a stronger signal, so a multicenter design would have been better. In addition, because of the exclusions, the sample size eventually included in the final analysis (141 patients) was substantially less than that calculated in the power analysis. It may also be important to note the uneven proportion of patients in the appropriate and inappropriate groups (75% vs 25%), a general limitation of every study in this field, which may also have affected our results. Finally, the clinical impact of our findings will have to be tested in a prospective randomized trial to see whether tailoring empirical antimicrobial therapy to PCT kinetics has any effect on outcome.

5. Conclusion

In this study, PCT kinetics within the first 24 hours after commencing empirical antimicrobial therapy showed a significant increase in patients in whom therapy proved to be inappropriate, whereas in the appropriate group, after a brief increase at 16 hours, there was a significant decrease by 24 hours. Applying this approach may be helpful in quickly tailoring antimicrobial therapy for the patient's specific needs. However, the clinical relevance of this "PCT kinetics–guided approach" should be confirmed in a prospective randomized fashion.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2016.04.007.

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None.

Conflicts of interest

JF and ZM have received lecture fees from ThermoFisher Scientific and BRAHMS GmbH. The other authors declare no conflicts of interest.

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