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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.

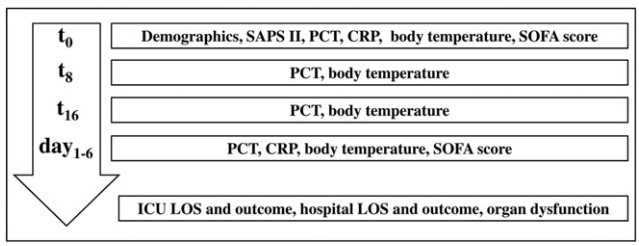

Fig. 1. Flowchart. $t_{0\text{-}24}$ indicates sampling within the first 24 hours after commencement of empirical antimicrobials; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; LOS, length of stay.