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Procalcitonin for the early diagnosis of sepsis in burn patients: A retrospective study

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ABSTRACT

Background: The gold standard for sepsis diagnosis in burn patient still relies on microbiological cultures, which take 48–72 h to provide results, delaying the start of antimicrobial therapy. Thus, biomarkers allowing an earlier sepsis diagnosis in burn patients are needed.

Methods: This retrospective observational study included 150 burn patients with total burned surface area ≥15%. Clinical diagnosis of sepsis among these patients was done according to the American Burn Association criteria. Biomarker (procalcitonin, white blood cells and platelet countings, prothrombinemia, D-dimers, C-reactive protein, blood lactate and temperature) values were available for 48 patients without sepsis (2767 timepoints) and 102 patients with sepsis (652 timepoints). Quantitative variables were compared with Mann–Whitney tests and qualitative variables were compared with Pearson chi-square test. Effect size was measured by the probability of superiority. Receiver operating characteristic (ROC) curves evaluate capacity for sepsis diagnosis. Sensitivity, specificity, positive and negative predictive values were calculated for some cut-off values, including the best cut-off defined by the maximum of Youden index.

Results: Statistically significant differences between the groups of septic and non-septic patients, with medium to large effect size, were detected for all the biomarkers considered, except temperature. PCT was the biomarker with the largest AUC and effect size (AUC = 0.71). Analysis of the PCT ROC curve showed that 0.5 ng/mL cut-off presented highest sensitivity and lowest specificity, whereas 1.5 ng/mL cut-off was associated with lowest sensitivity and highest specificity.

Conclusion: Procalcitonin showed to be the best of the biomarkers studied for an early diagnosis of sepsis. Its use should be considered in antimicrobial stewardship programs in Burn Units.

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1. Introduction

Severe burns are considered a relevant public health issue as they affect patients' physical and mental health, having an important negative impact on their quality of life. The management of burns also represent significant costs for the healthcare sector, in particular due to prolonged hospitalization periods and care of disfiguring injuries [1]. Sepsis is a comorbidity commonly observed in severe burn patients and is the major cause of their death [2,3]. In fact, severe burns increase the susceptibility to sepsis, as they propitiate the development of infections, due to several factors including skin injury, necrosis, use of catheters and other invasive devices, and exposure to nosocomial flora [4,5]. According to a recent review the literature, the prevalence of sepsis in burn patients ranges from 8% to 42% and the associated mortality rate varies form 28% to 65%. [6], its values being naturally related to the severity of the process [7] and the promptitude of the diagnosis and the beginning of therapy, as in other causes of initial injury [8,9]. The arising of multidrug resistant microorganisms in the last years has contributed to an even worst scenario [10]. Thus, it is of critical importance to timely diagnose and treat septic episodes in these patients. However, the identification of sepsis causative microorganisms takes 2–4 days, which may delay the start of the specific antimicrobial treatment [11]. On the other hand, the clinical and laboratorial findings of sepsis are also present in other clinical conditions with a systemic inflammatory response (trauma, anaphylaxis, pancreatitis, hemorrhage, etc.) [12] which complicates the differential diagnosis [13]. In this context, the use of biomarkers has been advocated to improve clinicians' ability to detect sepsis early in order to start a timely and adequate antimicrobial therapy.

The ideal biomarker should be suitable for the early diagnosis of sepsis (either as a part of a routine screening exam or at the first sign of a suspect clinical sign); should follow the course of the infection and reflect the efficacy of the therapy, allowing for its monitoring and suspension; should be safe and easy to measure; should be cost effective to follow-up and consistent across gender and ethnic groups. Such a biomarker has not yet been discovered, but several ones are already in use and coupled with a sound clinical examination may in fact support clinicians on the decision to start, and stop, antimicrobial therapy.

Among over 170 biomarkers described in the literature in the last decades [14], procalcitonin (PCT) has emerged, not without some controversy [15], as one of the most useful and reliable [16–28]. PCT is the hormonally inactive 116-amino acid precursor of calcitonin, a hormone that is mainly secreted by the C-cells of thyroid gland that are involved in calcium metabolism [29]. PCT can also be synthesized in extrathyroid tissues in response to endotoxins and proinflammatory cytokines release during and infection, but also in non-infectious conditions with systemic inflammation (e.g. multiple trauma, drug adverse reactions, cardiogenic shock, etc.). PCT serum levels are very low in healthy individuals but these levels markedly increase up to 1000-fold within 2–4 h of sepsis onset [30], and then rapidly decline after successful antimicrobial therapy. Scientific evidence corroborated that this peptide has a good capacity to distinguish between systemic non-infectious inflammatory response and septic conditions caused by bacteria or fungi in patients with community-acquired pneumonia [16,17] and in septic patients in intensive care units [18,19,29]. Several reports also support the utility of PCT for the diagnosis of sepsis in burn patients [21–28], though other authors question this evidence [31,32]. The current study aims to contribute for the determination of the potential utility of PCT as a biomarker for the early diagnosis of sepsis in burn patients. For such a purpose, PCT levels were assessed in different periods during hospitalization of burn patients in a specialized burn care unit and its discriminatory power was compared against other commonly used biomarkers.

2. Material and methods

2.1. Patients

The sample under analysis was composed by burn patients with partial, deep partial and/or full thickness burns comprising 15% or more of total burn surface area (TBSA), admitted consecutively from January 2011 to December 2014 at Coimbra Burns Unit (CBU), a department of Coimbra Hospital and University Centre (CHUC), Portugal. Burn patient data were obtained retrospectively by consulting the hospital database.

The diagnosis of sepsis was based on the American Burn Society (ABA) criteria [33]: a clinical suspicion of infection coupled with the presence of the presence of three or more of the following parameters: temperature >39 °C or <36.5 °C; tachycardia >110 beats per min; tachypnea >25 breaths per minute or minute ventilation >12 L/min; thrombocytopenia <100,000/μL; hyperglycemia (untreated plasma glucose >200 mg/dL or intravenous glucose use >7 U/h over 24 h; enteral feeding intolerance: abdominal distension or gastric residuals more than two times feeding rate or diarrhea >2,500 mL/min.

A timepoint was defined as day of analysis results; each patient had several timepoints. The total timepoints were distributed in two groups, sepsis and non-sepsis, according to the ABA criteria above. In order to avoid bias, subjectivity and trying to give more strength to the analysis, only microbiological blood tests were considered, independently of the known or suspected primary focus of the septic episode. From all patients of the sample, at least 3 (three) blood samples per week, in different days, were collected for PCT assessment. When there was a clinical diagnosis of sepsis according to ABA criteria, PCT was evaluated daily. In the cases where for the same patient, by any reason, there were two assessments of PCT in the same day, the highest value was taken for study purpose.

2.2. Laboratory measurements

At each time point, the following data were collected from the database: PCT, white blood cell counting, platelet counting, prothrombinemia, D-dimers, C-reactive protein (CRP), blood lactate and temperature.