DIAGNOSTIC AND TREATMENT STRATEGIES IN CUTANEOUS SEPSIS

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Summary

The increased incidence of organ dysfunction and the high mortality rate due to sepsis, make it necessary and beneficial to detect early cutaneous sepsis, for the early initiation of appropriate treatment, from the first hours, from the diagnosis. Cutaneous sepsis is a life-threatening clinical dysfunction, due to the alteration of the body's response to infection and involves in its management, a multidisciplinary collaboration, in which skin manifestations are the trigger for imbalances of internal organs. Any skin infection, bacterial, viral, fungal or parasitic, can trigger sepsis, but the most common in dermatological practice are bacterial, such as cellulitis, erysipelas, trophic ulcers from the advanced stages of chronic venous insufficiency, bullous dermatoses with cutaneous denudations (pemphigus, pemphigoid, Steavens Johnson syndrome), erythroderma, vasculopathy, etc. The germs frequently involved are: methicillin-resistant Staphylococcus aureus (MRSA), Escherichia coli, Pseudomonas aeruginosa, species of the genus Streptococcus and Enterococcus. For assessing the severity, evolution and prognosis, certain serological markers are used, but there are no standard markers, unanimously accepted in the early diagnosis of sepsis. Routine diagnostic methods from the medical practice are useful, but they do not have high sensitivity and specificity. In recent years, C-reactive protein (CRP), procalcitonin (PCT), presepsin (sCD14-ST), proadrenomodulin (Pro-ADM) and proinflammatory cytokines have been extensively studied. The management of cutaneous sepsis, as a medical emergency, involves a multidisciplinary approach, following the evolution and possible complications, depending on the severity of organ dysfunction, throughout the entire patient's hospitalization. The possibility of dosing the new inflammatory biomarkers urges the establishment of antimicrobial therapy, significantly contributing to the improvement of the prognosis and reduces mortality.

Key words: *sepsis, inflammatory biomarkers, prognosis, proinflammatory cytokines.*

Received: 16.08.2021 *Accepted: 17.09.2021*

Introduction

Dermatological diseases, due to the diversity of signs and symptoms they present, sometimes require prompt intervention to ensure basic life support, which shows that dermatological emergencies are a continuous challenge of diagnosis, treatment and prognosis in current practice. Skin sepsis is a topical issue in international research because it is a dynamic, life-threatening clinical dysfunction which threatens live by altering the body's response to the infection [1]. It trains in its management a multidisciplinary approach, in which the cutaneous manifestations represent the trigger factor of the imbalances of the internal organs.

Most of the sepsis cases occurs outside hospitals, and the affected patients come to the Emergency Department with various signs and symptoms, which sometimes causes difficulties in diagnosing this disease. The new criteria for sepsis and early antibiotic therapy have been the focus of research and debate in recent years [2].

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Material and Method

Any type of skin bacterial infection, viral or fungal, can cause sepsis, but the most common are bacterial infections. In the skin and subcutaneous cellular tissue, bacterial infections can generate sepsis by triggering a complex cascade of disorders of several organs and systems, with their functional insufficiency [3]. The most common in dermatological practice are cellulite, erysipelas, trophic ulcers in the advanced stages of chronic venous insufficiency, bullous dermatoses (pemphigus, pemphigoid) with extensive skin denudation, and the germs involved are often represented by Staphylococcus aureus, very resistant (MRSA), Escherichia coli, Pseudomonas aeruginosa, species of the genus Streptococcus and Enterococcus [4].

According to statistics, the mortality rate from sepsis in 2012 was 41% in Europe and 28.3% in the United States [5]. The high incidence of organ dysfunction and the high mortality rate make it necessary and beneficial to detect early sepsis, for the rapid initiation of an aggressive systemic treatment, from the first hours after diagnosis [6, 7].

Advances in the last decades in understanding the pathophysiology of sepsis have shown that its manifestations can no longer be attributed only to the infectious agent and the immune response that it generates, but also to changes in the parameters of coagulation, immunosuppression and organ dysfunction [8]. At the same time, knowledge and monitoring of evolutionary and prognostic markers are key elements in the current management of sepsis. Early recognition of the signs and symptoms of sepsis and septic shock, but also the corroboration of biochemical and microbiological investigations aims a rapid and effective intervention, with a significant decrease in morbidity and mortality [9].

For assessing the severity, evolution and prognosis, certain serological markers are used, but there are no standard markers, unanimously accepted in the early diagnosis of sepsis. An ideal biomarker, which can be used in an emergency, must have good accuracy, reproducibility, predictive value (diagnosis), to allow the detection of patients at risk for complications (prognosis), to have a high specificity and sensitivity, to appreciate the effectiveness of therapy and to be affordable (low price) [10]. The development of scores, such as APACHE-II and the sequential assessment of organic insufficiency (SOFA), provided simple but useful clinical tools in the assessment and prognosis of sepsis [5, 11].

Routine diagnostic methods in medical practice are useful, but do not have high sensitivity and specificity. In recent years, C-reactive protein (CRP), procalcitonin (PCT), presepsin (sCD14-ST), proadrenomodulin (Pro-ADM) and proinflammatory cytokines have been intensively studied [12].

C-reactive protein (CRP), named after the ability to precipitate polysaccharide C from the structure of Streptococcus pneumoniae, is a marker for systemic inflammation and tissue destruction. It is synthesized by hepatocytes, but also by smooth muscle cells, macrophages, endothelial cells, lymphocytes and adipocytes. Hepatic synthesis is controlled by interleukin-6 (IL-6). CRP has elevated serum levels in infections, but also in non-infectious diseases, such as autoimmune diseases, rheumatism, acute coronary syndromes, malignant tumors, after trauma or surgeries. The CRP sensitivity in the diagnosis of acute infections has values ??between 30% and 97.2%, and the specificity is between 75% and 100%. The main disadvantages of CRP are: lack of specificity in the diagnosis of bacterial infections, low sensitivity, and the fact that it does not allow the differentiation between sepsis and systemic inflammatory response (SIRS) of non-infectious etiology. With high specificity but low sensitivity, CRP is used for its negative predictive value [13].

Procalcitonin (PCT) is used as a biomarker of sepsis, both for diagnosis and for assessing the evolution and prognosis, because it increases rapidly in the first hours after infectious stimulation and decreases significantly under appropriate antibiotic therapy [14]. It is a precursor of calcitonin (regulatory hormone in calcium homeostasis), produced by hepatocytes and macrophages, in response to factors such as: infections, trauma, surgeries. Studies suggest that procalcitonin level is a practical indicator for early diagnosis of sepsis, but should be correlated with other clinical parameters [15, 16]. It also

correlates with the extent and severity of bacterial infections. Elevated serum levels were associated with an increased mortality rate and correlated with various clinical severity scores: SOFA (Sequential Organ Failure Assessment), APACHE (Acute Physiology and Chronic Health Evaluation) and SAPS (Simplified Acute Physiology Score). [17]. As a marker of infection, sensitivity and specificity are 75-100% [13].

Presepsin (sCD14-ST) is another early indicator of infections in the body [18].

Presepsin secretion is considered a stimulus of monocyte phagocytosis. Therefore, presepsin is also detectable in people without infection. The concept for presepsin requires that its levels be measurable in non-infectious individuals, to increase in the initial stages of bacterial infections, being considered an indicator of innate immune effector cells, activated in response to the action of invasive pathogens [19]. According to current studies, the level of presepsin is an adequate indicator for monitoring the effectiveness of antibiotic therapy, so there were decreases in the level of presepsin, starting with the 7th day of treatment with appropriate antibiotics, in patients with positive blood cultures [20, 21] .

Other new biomarkers analyzed were: proadrenomedulin (Pro-ADM) differentiates sepsis from non-infectious systemic inflammatory reaction and together PCT increases the probability of diagnosis, in comparison with the individual determination of each marker [22].

The soluble urokinase-like plasminogen receptor (suPAR) shows elevated plasma levels in critically ill patients, being a good indicator in assessing the severity and risk of mortality. The secretion of multiple proinflammatory cytokines also correlates with the severity and mortality of sepsis and indicates that the process of uncontrolled inflammation has begun. The most involved cytokines associated with the early phase of inflammation are the interleukins IL-1β, IL-6 and tumor necrosis factor (TNF-α) [13].

Hemopexin (HPX), a biochemical parameter, included by some authors in the category of acute phase reactants, has high values in the systemic inflammatory response syndrome [23]. If the HPX value is higher the severity of the disease is decreased, a high concentration of it at hospitalization, being associated with a favorable prognosis of patients with sepsis [24].

Recent studies have concluded that sentinel biomarkers, represented by the association between IL-6, PCT and soluble trigger receptor expressed on myeloid-1 cells (sTREM-1), remain early predictors of sepsis, before that symptoms set in. The three factors are specific to different aspects of the inflammatory process. Thus PCT is a general marker of inflammation, sTREM-1 is released by myeloid cells, being specific to the chemotactic process, involved in antibacterial control, and IL-6 is part of the cascade of proinflammatory cytokines [25]. None of the mentioned markers, dosed individually, has 100% specificity and sensitivity for the early diagnosis of sepsis, but the combined dosing of at least two indicators, especially among sentinel markers, significantly increases the accuracy of the diagnosis [26].

The development and application of nanotechnology offers opportunities in the management of patients with critical illness with sepsis, being useful in microbial infections treatment, including resistant pathogens. [27].

In the urgent approach to sepsis with cutaneous starting point, in addition to the above-mentioned serological indicators, the risk factors that negatively influence the prognosis must also be taken into consideration:

- age: patients over 65 years of age and infants ≤ 1 year are vulnerable groups, due to the depressed or incomplete developed immune system to act adequately to bacterial invasion;
- comorbidities: cardiac, oncological, renal or any other medical condition, which compromises immunity and decreases the body's ability to defend itself (diabetes, AIDS, transplantation, immunosuppressive drugs, hypoalbuminemia);
- invasive devices: peripheral or central venous catheters, urinary catheters, mechanical ventilation;
- antibiotic resistance: may promote sepsis (e.g. MRSA infections, E coli, enterococci) [28].

The SOFA severity score, based on six different scores, one for each of the respiratory, cardiovascular, hepatic, renal, cerebral and

coagulation systems, marked from 0 to 4 reflects the aggravation of organ dysfunction [29]. The APACHE II assessment system presents 3 areas: acute physiology, chronic health assessment and age. The first field refers to the acute changes, from the first 24 hours after hospitalization, of some physiological parameters such as: oxygenation (SaO2), rectal temperature, average blood pressure, blood pH, heart rate, respiratory rate, electrolytes (Na, K), creatinine, hematocrit, leukocytes and Glasgow score (GSC). The second field concerns the assessment of comorbidities, which contribute with 7% to mortality [30].

Diagnosis of early-stage sepsis is essential for improving quality of life and reducing mortality [31, 32].

The treatment of sepsis is complex and includes early resuscitation, adequate ventilatory support, vasopressors agents, steroids, anticoagulants, anti-inflammatory drugs and glycemic control [33, 34]. In choosing the treatment schema, the gateway to the infection and the potentially involved germs, the age and comorbidities of the patient are taken into consideration. Most of the times, an empirical antibiotic is administered, with a wide spectrum, with good tissue penetrability, with the possibility of subsequent transition to a restricted antibiotic therapy, according to the antibiogram [35].

There are over 170 biomarkers, but none of them has sufficient sensitivity and specificity to be commonly used in clinical practice. Therefore, the combined use of two or more biomarkers is more efficient than a single biochemical parameter [36].

Conclusions

Knowing the role of inflammatory biomarkers in sepsis, it can significantly improve the patient's quality of life, only with early intervention with broad-spectrum antimicrobial agents. The correlation of these factors with the severity of clinical signs emphasizes the importance of diagnosing sepsis in the early stages. The possibility of dosing of new inflammatory biomarkers accelerates the establishment of antimicrobial therapy, contributing to improved the prognosis and reducing mortality.

The management of cutaneous sepsis, as a medical emergency, involves a multidisciplinary approach, following the evolution and possible complications, depending on the severity of organ dysfunction, throughout the entire patient's hospitalization. The possibility of dosing the new inflammatory biomarkers urges the establishment of antimicrobial therapy, significantly contributing to the improvement of the prognosis and reduces mortality.

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Conflict of interest
NONE DECLARED

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