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Review

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Burns, Sepsis and Procalcitonin

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ABSTRACT The basis of the pathogenesis of burn disease is a systemic inflammatory response syndrome with episodes of bacteremia and the development of sepsis. An analysis of the literature showed that the existing clinical diagnostic scales for sepsis do not allow a confident diagnosis. The interest in changes in the concentration of procalcitonin in the blood serum is justified by the fact that this prohormone is one of the proinflammatory mediators, the concentration of which quickly increases during local and systemic bacterial and fungal infections. It seems important to consider the possibilities of various scales for determining the criteria for sepsis, analyze the values of procalcitonin and its monitoring for more effective diagnosis and procalcitonin-controlled antibiotic therapy in patients with burns.

CONCLUSION The problem of clinical diagnosis of sepsis in patients with burns has not yet been solved. Procalcitonin is an effective biomarker of bacterial infection, and its monitoring reflects the dynamics of the burn disease, predicts the outcome, indicates the effectiveness of antibiotic therapy and allows for its correction.

Keywords: burns, sepsis, procalcitonin, diagnosis, outcome prediction, antibiotic therapy control

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ARF – acute respiratory failure
AUC — Area under Curve
b.s. — body surface area
CMA — Chinese Medical Association
CNS — central nervous system
CRP — C-reactive protein
ICU — intensive care unit
II — inhalation injury
IL — interleukin
MOD/F — multiple organ dysfunction/failure
NPV — negative predictive value
OR — odds ratio
PCT — procalcitonin
PPV — positive predictive value
PSP — presepsin
ROC curve — Receiver operating characteristic curve
SIRS — systemic inflammatory response syndrome
SOFA — Sequential Organ Failure Assessment
TNF-α — tumor necrosis factor-alpha

RELEVANCE

The diagnostic efficiency of procalcitonin (PCT) as one of the biomarkers of the acute phase of inflammation has been considered in multiple studies. The use of PCT for diagnosis, prediction of infectious-septic complications and mortality, management and control of antibacterial therapy in various pathologies seems to be a promising and relevant direction, since high mortality in purulent-septic diseases persists, microbial polyresistance to antibiotics is expanding, and treatment costs are increasing [1, 2].

Over the past decades, the survival rates of burn victims have improved, but the mortality rate remains very high. The main causes of death have also changed. If previously burn victims often died from burn shock, now they die mainly from purulent-septic complications. The incidence of sepsis in patients with burns covering a total area of more than 15–20% of the body surface (b.s.), according to various authors, is 3–68.5% [3–5], and the mortality rate for extensive and deep burns is 16.5–20.3% [4–6].

Diagnosis and treatment of purulent-septic complications in patients with burn injury are relevant [7, 8], therefore the search for "ideal" biomarkers that can help solve the clinical problem continues.

The aim of the review is to summarize information on the diagnosis of sepsis and the results of PCT studies in patients with burn injury.

The search for sources was conducted in open electronic databases of scientific literature – PubMed, Scopus and eLibrary. For the search, we used the keywords: burn trauma, burns, infection, sepsis, SIRS, procalcitonin, biomarkers, and the corresponding terms in Russian. The search depth was 25 years. The criterion for inclusion of sources in the study was the availability of the full text or abstract of the article. Exclusion criteria: clinical cases, abstracts of reports.

PROCALCITONIN AS A PROTEIN OF ACUTE PHASE OF INFLAMMATION

Calcitonin is a hormone synthesized by parafollicular cells, or C-cells, within the thyroid gland. Its precursors are preprocalcitonin and PCT, the latter from the end of the last century to the present day has been considered as a rapidly reacting protein of the acute phase of inflammation, a biomarker of severe bacterial, fungal infections and sepsis [9, 10].

The PCT glycoprotein may not be detected in the serum of healthy adults, or its level is less than 0.05 μg/L (μg/L = ng/ml). In severe infections, it is detected in high concentrations in the blood serum. The PCT molecule is very stable. The half-life of PCT is 25–30 hours [11, 12].

Stimulation of PCT production is associated with bacterial endotoxins and proinflammatory cytokines (tumor necrosis factor-alpha (TNF-α), interleukin-IL-2, IL-6 and others). In severe bacterial infections, its content in the blood serum increases mainly due to extrathyroidal production by neuroendocrine cells of various tissues, including the liver, lungs, kidneys, adrenal glands, prostate gland, small intestine, testicles, mononuclear cells and granulocytes of peripheral blood [11, 12].

In viral infections, serum PCT levels in patients do not change significantly, since its regulation is suppressed by interferon-γ, which is released in response to viral infections. It has been shown that in case of combined administration of interferon-γ and proinflammatory IL-1β, PCT secretion is inhibited by 78% [13].

Neutralizing antibodies to PCT improve survival, which allows this molecule to be classified as a proinflammatory mediator. Sepsis experiments on animals have shown that PCT administration is toxic, and immunoneutralization with immunoglobulin G significantly improves survival. Immunoneutralization of PCT may prove to be a novel therapeutic approach for the treatment of human sepsis [14, 15].

PCT concentration increases in the first days after major surgeries, trauma, heat stroke, some malignant tumors and hematological diseases without severe infection or sepsis [16]. Recently, it was shown that PCT is a predictor of the development of acute respiratory failure (ARF) in patients with isolated inhalation injury (II) in the first day after injury [17].

A PCT level of less than 0.5 ng/ml is considered low; 0.5–2.0 ng/ml is considered average and is associated with localized infections; more than 2–5 ng/ml is considered high and is associated with severe systemic (bacterial, parasitic or fungal) infections; more than 10 ng/ml is considered very high and indicates the development of severe sepsis or septic shock [16, 18].

PCT is currently widely used for early and differential diagnosis, prognosis of disease outcomes and complications; and PCT monitoring is used to decide on the prescription and withdrawal of antibacterial drugs, and to assess the effectiveness of antibiotic therapy. PCT levels correlate with the severity of systemic inflammatory response syndrome (SIRS), with TNF-α and IL-6 levels [19, 20].

The PCT test may give false negative results in patients on steroid therapy, immunosuppression or neutropenia, its level increases in renal failure and decreases with renal replacement therapy [21].

STAGES OF DEVELOPMENT OF DIAGNOSTIC CRITERIA FOR SEPSIS

In 1991, an American Consensus Conference formulated the concept of Systemic Inflammatory Response Syndrome (SIRS), which included 4 clinical indicators: tachycardia over 90 beats per minute; tachypnea over 20 breaths per minute or hyperventilation (PaCO2 ⩽ 32 mm Hg); body temperature above 38°C or below 36°C; leukocyte count above 12.0*109/l, below 4.0*109/l, or the number of their immature forms above 10%. Each sign was proposed to be assessed at 1 point, and the presence of 2 points or more was considered evidence of the development of SIRS and sepsis. The Consensus Conference unified the concepts of “sepsis,” “severe sepsis,” “septic shock,” and “multiple organ dysfunction syndrome” [22].

In 1996, the SOFA (Sepsis-related Organ Failure Assessments, subsequently Sequential Organ Failure Assessment) scale developed by Vincent J.L. et al. was published to determine the degree of organ dysfunction in sepsis. The scale allows for the assessment of 4 degrees of multiple organ dysfunction/failure (MOD/F) for six systems or organs: the central nervous system (CNS), respiratory, cardiovascular systems, kidneys, liver, and platelet count [23].

In 2001, the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, the American College of Chest Physicians, the American Thoracic Society, and the Surgical Infection Society held a second consensus meeting (Sepsis-2), where additional parameters were introduced that combined the diagnosis of sepsis and organ dysfunction: arterial hypotension and hypoxemia, hyperglycemia, thrombocytopenia, hyperbilirubinemia, oliguria, hyperlactatemia, C-reactive protein (CRP) and PCT levels exceeding reference values by 2 times [24].

In 2016, a sepsis task force of 19 experts proposed a third definition (Sepsis-3). Sepsis was recommended to be defined as a life-threatening organ dysfunction caused by an unregulated host response to infection, and septic shock – as a type of sepsis with profound circulatory, cellular and metabolic disorders and a higher risk of death. The term "severe sepsis" was rightly considered redundant by the specialists. It was recommended to evaluate sepsis criteria dynamically using the SOFA scale, with an increase of 2 points or more considered as confirmation of the diagnosis. A new clinical scale for assessing the patient's condition in cases of suspected infection was proposed - the quick SOFA (qSOFA) score which is based on respiratory rate (22/min or higher), systolic blood pressure (100 mmHg or lower), and altered consciousness [25].

Acute phase reactants, as in other critical conditions [26, 27], are important additional criteria for the diagnosis of sepsis in burn injury. Currently, up to 200 biomarkers associated with burn injury which indicate systemic and local disorders are known. Important biomarkers of systemic inflammation initiated by infection are PCT and presepsin (PSP) [28].

The diagnosis of sepsis in burns differs from other sections of intensive care. This is due to the fact that a skin burn over an area of over 10–12% of the b. s. immediately after injury initiates the development of SIRS with all its inherent clinical signs, pathophysiological and morphological disorders leading to POD/F and death even in the absence of generalized infection. In burn injuries, the development of sepsis is often masked by the similarity of manifestations with SIRS. This is why the search and use of highly effective inflammation markers for the early diagnosis of sepsis in burn patients is of such great importance [29, 30].

One of the first scales used in burn patients was the Baltimore Sepsis Scale. In patients with extensive burns, the scale correlated well with mortality and the development of septicemia, but poorly with the level of endotoxin in plasma and the type of bacteremia (gram-positive or gram-negative) [31].

In 2007, an American Burn Association (ABA) conference defined standards for the diagnosis of sepsis and infection-related diagnoses in burn patients. The ABA consensus committee developed specific guidelines that included thresholds for body

temperature (above 39°C or below 36.5°C), progressive tachycardia (more than 110 beats/min) and tachypnea (more than 25 breaths per 1 min without ventilation or ventilation of more than 12 l/min), thrombocytopenia (less than 100,000 cells/μl; not used for up to 3 days of burn shock), as well as hyperglycemia over 200 mg/ml or intestinal paresis. In addition, along with clinical indicators, it is necessary to document infection or clinical response to antimicrobial drugs. The presence of more than 3 criteria is a suspicion of infection [32].

Almost simultaneously, the Chinese Medical Association (CMA) proposed diagnostic criteria for sepsis and treatment recommendations for burn infection. It was indicated that suspicion of systemic infection (sepsis) should arise even with a negative blood culture result, as well as with a positive patient response to antimicrobial therapy. The list of diagnostic criteria for systemic infection in burn patients was expanded [33].

In 2013, Mann-Salinas E.A. et al. assessed the ABA criteria in burn sepsis in 59 patients and developed the BURN-6 model for its prediction, which includes 6 variables: heart rate greater than 130 beats per minute, mean arterial pressure less than 60 mmHg, base deficit less than -6 mEq/L, temperature below 36°C, glucose level greater than 150 mg/dL, use of vasoactive drugs [34].

In the same year, the editorial board of the CMA for the treatment of burn infection proposed diagnostic criteria for sepsis in adult patients: agitation, hallucinations, disorientation or depression; abdominal distension, decreased bowel sounds; rapid negative dynamics of burn wounds; temperature above 39.0°C or below 36.5°C; tachycardia greater than 130 bpm; tachypnea greater than 28 breaths/min (without mechanical ventilation); thrombocytopenia less than 50×109/L; peripheral blood leukocyte count more than 15×109/L or more than 5×109/L, neutrophils more than 80% or immature granulocytes more than 10%; serum PCT greater than 0.5 μg/L; blood sodium greater than 155 mmol/L; blood glucose greater than 14 mmol/L (without history of diabetes). A preliminary diagnosis of sepsis is established if 6 of the listed criteria are present. The diagnosis is confirmed by a positive bacterial blood culture or a positive response to antibacterial therapy. Recommendations for the treatment of sepsis include: source control, rational use of antibiotics, extracorporeal detoxification methods, use of glucocorticoids, immunomodulation, symptomatic and supportive treatment, and prevention of nosocomial infection [35].

In 2018, the BURN-6 criteria for burn sepsis were revised. A multivariable analysis of 6 parameters in positive blood cultures in burn patients found that the best evaluation criteria were fever (above 39°C or below 36°C), hypotension (decrease in systolic blood pressure by at least 10%), tachycardia (more than 130 beats/min) and gastrointestinal dysfunction [36].

In 2021, German authors developed and proposed using a new SOFA scale for assessing the POD/F in burns and the 3H (Hypoxia, Hypovolemia, Hyperthermia) scale for diagnosing burn sepsis in the burn intensive care unit (ICU). The Burn-SOFA scale includes a 4-point assessment of respiratory function, cardiovascular system, platelets, kidneys (creatinine/diuresis), metabolism (glucose level), CNS (in patients without sedation and with sedation). An increase in the POD/F score by 2 or more indicates deterioration of the patient's condition. If 2 or more criteria are present, the 3H burn sepsis scale indicates sepsis with a recommendation for urgent determination of lactate, PCT, and IL-6. If lactate increases above 2 mmol/L, antimicrobial therapy should be started immediately. The authors indicate that the proposed Burn-SOFA and 3H burn sepsis scales are based on current literature and are consistent with the ABA criteria and recommendations for burn sepsis [7].

EVALUATION OF THE VALIDITY OF SEPTIC MODELS IN BURN INJURY

In 2012, a retrospective multivariate analysis (196 patients) revealed that of the 6 clinical criteria for ABA sepsis (temperature, tachycardia, tachypnea, thrombocytopenia, hyperglycemia, intestinal paresis), only heart rate and temperature significantly correlated with bacteremia [37].

Comparative studies by a number of authors showed that the Sepsis-1, Sepsis-2 and Sepsis-3 guidelines are not suitable for diagnosing sepsis in patients with severe burns. Moreover, Sepsis-3 eliminated the SIRS criteria in the diagnosis of sepsis, which is questionable since the new definition diagnoses only organ dysfunction. Sepsis-3 criteria also did not show high prognostic accuracy for mortality in patients with severe burns [5, 38].

When evaluating the Sepsis-1, Sepsis-3, and ABA criteria in 1,185 adult burn patients, it was found that the number of sepsis cases varied: Sepsis-1 - 812,

Sepsis-3 - 809, and ABA — 565. Overall mortality was 20.3%. The sensitivity and specificity in assessing sepsis on ABA were 84.6% and 61.8%, respectively; and on Sepsis-3 — 63.1% and 96.5%, respectively. In all sepsis groups, the highest values were the area under the Receiver Operating Characteristic (ROC) curves when assessing the POD/F scores. The Sepsis-3 criteria did not demonstrate high prognostic accuracy for mortality in patients with severe burns. The authors consider the best diagnostic criterion for sepsis in patients with burns to be a SOFA score greater than or equal to 6 points [5].

When comparing the diagnostic capabilities of the ABA, BURN-6, and Sepsis-3 criteria in patients with sepsis, a positive result was obtained in 59%, 28%, and 85% of cases, respectively. The most reliable criteria were: increased oxygen requirement, altered mental status, hypothermia/hyperthermia, tachycardia, and arterial hypotension. None of the models proved to be a diagnostic standard, but Sepsis-3 proved to be the best. The authors believe that predictive models of sepsis in burn patients require further testing in larger populations and prospective studies [4].

The obtained results on the effectiveness of sepsis diagnosis based on Sepsis-3 signs for patients with burns are consistent with the data of Meza-Escobar L.E. et al. At the same time, the authors consider the validity of PCT and CRP as biomarkers of sepsis in burns to be questionable [39].

Studies of the diagnostic efficacy of the Burn-SOFA and 3H scales compared to others have not been published to date.

PROCALCITONIN IN THE DIAGNOSIS OF SEPSIS IN BURN PATIENTS

As a biomarker of bacterial infection and septic complications, PCT was first identified at the end of the last century during the treatment of 79 children (0 to 12 years old) with infectious diseases. In children with severe bacterial infection, the serum PCT level was 6–53 ng/ml, and less than 0.1 ng/ml in those without signs of infection. In patients with severe complicated burns, the PCT level reached 120 ng/ml. The authors noted that during antibacterial therapy, the PCT content decreased rapidly. In case of noninvasive and viral infections, the PCT level increased slightly (0.1–1.5 ng/ml). While the calcitonin level was within the reference range and did not depend on the PCT level. It was concluded that the concentration of PCT increased in purulent-septic conditions and, apparently, correlated with the severity of microbial invasion [9].

In adult patients with thermal injury without proven infection and a total burn area of more than 30% of the b.s. (in some of them in combination with inhalation injury (IT)), PCT and IL-6 levels were elevated during the first week, correlated with burn severity, and were not associated with IT, according to the authors. The study concluded that at the time of hospitalization, PCT and IL-6 were prognostic factors for mortality [40].

In 51.8% of patients with extensive burns in burn shock, Liu Z. et al. revealed elevated PCT levels which positively correlated with the burn area, its depth, the degree of inhalation damage, the delay in starting an infusion therapy, the APACHE II and SOFA scales. In addition, it was found that PCT levels were significantly higher in the deceased than in the survivors: in shock - 11.16 ng / ml versus 1.48 ng / ml, and in infection - 22.29 ng / ml versus 1.59 ng / ml, respectively. The areas under the ROC curves of PCT levels for predicting death in shock and infection were 0.788 and 0.926, respectively. Kaplan-Meier survival analysis showed that the 120-day survival rates for PCT less than 5.4 ng/mL and PCT at least 5.4 ng/mL were 92.9% and 51.2%, respectively. A predictor of death in patients with severe burns was a PCT level in shock exceeding 5.4 ng/ml (odds ratio (OR) = 5.33), and in infection exceeding 8.5 ng/ml (OR = 14.49). When these two indicators were combined, the risk of death increased by 55 times [41].

In severe burn shock, intestinal wall permeability increases, and bacteria and endotoxins translocate into the mesenteric lymph nodes. The interaction of inflammatory mediators, accompanied by intestinal hyperpermeability, is involved in the formation of SIRS, determines the high risk of developing sepsis, POD/F, and lethal outcome [42].

In a series of experiments on rats with deep burns of 30% of the b.s., it was found that intestinal microbes labeled with fluorescein (*Pseudomonas aeruginosa*, *Bacteroid fragilis*, and *Candida albicans*) moved through the intestinal wall and were found in internal organs. The concentration of 125I-labeled endotoxin increased in the portal vein 15 minutes after the burn. Labeled endotoxin granules were detected on liver sections radiographs. With the formation of mesenteric lymphatic fistulas, the clearance of endotoxin and TNF-alpha in the lymphatic fluid leaving the intestine increased

significantly. The intestine is a potential source of endogenous infection, which explains the development of sepsis in the early stages of burn injury without a confirmed infectious focus [43].

Daily monitoring of PCT levels in ICU burn patients showed that in "infectious" SIRS, PCT levels were statistically significantly different from "non-infectious" SIRS (11.8±15.8 ng/ml versus 0.63±0.043 ng/ml, respectively, $p<0.001$), unlike other markers of systemic inflammation. The area under the ROC curve for PCT was 0.975 and demonstrated good discriminatory ability in predicting sepsis. The authors also concluded that in patients with severe burn injury, PCT monitoring should be used as an early marker of septic complications, which will allow timely changes in the antimicrobial therapy regimen [44].

A systematic review of the literature confirmed the usefulness of the PCT test in diagnosing sepsis in critically ill patients. The area under the ROC curve for the pooled studies was 0.78 with an OR of 7.79 [45].

In a prospective study, serum PCT was measured in burn victims on the first day after the burn and then daily. The PCT concentration on admission was 0.69 (0.3–1.4) ng/ml. A PCT level of 7.8 ng/ml was considered a predictor of death. The authors determined the following thresholds of PCT level which had sufficient sensitivity and specificity: for diagnosing sepsis – 1.5 ng/ml, respiratory tract infections – 0.52 ng/ml, and wound infections – 0.56 ng/ml. A decrease in PCT levels on the 3rd day of antibiotic therapy confirmed the effectiveness of sepsis treatment. The authors consider daily monitoring of PCT levels to be an important indicator of the progression of burn disease and a criterion for the effectiveness of antibacterial therapy [6].

Based on a meta-analysis including 9 studies (566 patients), Ren H. et al. assessed PCT as a diagnostically valuable biomarker for the early diagnosis of sepsis in burn patients. The sensitivity and specificity of PCT were 0.74 and 0.88, respectively, and the area under the ROC curve was 0.92. However, the PCT threshold for sepsis was not determined in the studies analyzed [46].

A meta-analysis including 14 studies (830 patients) showed that PCT can be considered as a biomarker with a strong diagnostic capacity to distinguish burn patients with and without sepsis. The prognostically significant PCT level for sepsis was 1.47 ng/ml. The authors characterize PCT as the best of the studied biomarkers for the early diagnosis of sepsis in burn patients, and believe that this test should be included in programs for the rational use of antibiotics in burn units, and a PCT level of 1.5 ng/l or more should be used as an indicator of sepsis and an absolute indication for the initiation of massive antibacterial therapy [47].

Although many researchers claim that PCT is an effective biomarker for the early diagnosis of sepsis, not all the findings are unambiguous. Thus, data obtained on a limited number of patients with suspected generalized infection did not reveal statistically significant differences between PCT levels in patients with and without sepsis. PCT levels did not differentiate patients with SIRS from patients with sepsis (area under the ROC curve - 0.546). No correlation was found between SOFA and PCT. A correlation was revealed between PCT levels and tissue hypoperfusion. The authors believe that PCT is not an accurate indicator of sepsis [48].

A meta-analysis (10 studies, 704 adult patients) showed that the combined sensitivity of PCT was 0.67, specificity 0.87, positive predictive value (PPV) 0.52, negative predictive value (NPV) 0.38, OR=13.70, and area under the ROC curve 0.85. The diagnostic threshold for sepsis was heterogeneous. The authors concluded that serum PCT can be used as a biomarker for the early diagnosis of burn sepsis in adults, and to increase sensitivity and specificity, the PCT test should be combined with other diagnostic markers [49].

PREDICTION OF BURN INJURY OUTCOME

To predict the outcome of injury in extensive burns and sepsis, a retrospective study divided patients into survivors and deceased. Serum PCT levels immediately after sepsis diagnosis were significantly higher in the deceased than in the survivors (38.5±41.3 and 6.1±2.3 ng/ml, respectively); on days 1–4: 26.8±38.5 and 5.4±2.9 ng/ml, respectively; and on days 5–8: 19.3±16.3 and 4.9±3.6 ng/ml, respectively. The total area under the ROC curve of serum PCT level for predicting mortality in patients with burn sepsis was 0.990, and the threshold value of PCT was 10.9 ng/ml with a sensitivity of 91% [50].

Mokline A. et al. examined patients, dividing them into groups depending on the outcome: without sepsis and with sepsis, according to the ABA criteria. The cutoff value of PCT of 0.69 ng/ml for

predicting sepsis was characterized by the optimal combination of sensitivity (89%), specificity (85%), PPV (82%) and NPV (88%). On the 5th day after the burn, the authors found a statistically significant difference in the serum PCT level between septic patients and those without sepsis (5.44±6.23 ng/ml and 0.41±0.64 ng/ml, respectively). The area under the ROC curve on the day of sepsis diagnosis was 0.929. In patients with sepsis, a significant increase in PCT levels was observed when gram-negative microorganisms were detected (5.91±6.48 ng/ml) in contrast to gram-positive ones (2.21±2 ng/ml). PCT levels in surviving sepsis patients on the day of sepsis diagnosis were significantly lower than in nonsurvivors (1.6 ng/mL vs. 21.43 ng/mL, respectively). PCT levels predicted injury outcome, and monitoring was more valuable than single values [51].

To assess the prognostic significance of changes in serum PCT in patients with extremely severe burns and sepsis, serum PCT levels were determined at weeks 1, 2, 3, and 4 of burn disease. At weeks 1 and 2, no difference was found between the deceased and the survivors. At weeks 3 and 4, PCT levels were statistically significantly higher in deceased patients (amounting to 15.8±14.9 and 13.6±5.6 ng/ml), than in the group of survivors (2.4±1.8 and 4.9±6.1 ng/ml). The total areas under the ROC curves for predicting mortality in patients with severe burns and sepsis at weeks 3 and 4 were 0.938 and 0.906, respectively; and the cutoff values of PCT were 7.45 ng/mL and 8.77 ng/mL, respectively, with a sensitivity of 75% and 100%. The authors concluded that the PCT level at weeks 3 and 4 of burn injury may serve as an important indicator of its outcome prognosis [52].

Sinha A. et al. believe that serum PCT levels on the first day of burn injury greater than 1.772 ng/ml and CRP greater than 71 mg/ml, or subsequently PCT levels greater than 2.163 ng/ml and CRP greater than 90 mg/l indicate an unfavorable prognosis. The indicated serum PCT and CRP levels are independent predictors of mortality with an increase in probability of 4.5 and 23.6 times, respectively [53].

DIAGNOSTIC VALUE OF PCT COMPARED TO OTHER INFLAMMATION MARKERS

A group of authors studied the diagnostic efficiency of PCT, CRP and leukocytes in a small number of patients with extensive burns and pneumonia who were on mechanical ventilation. In burns with lung damage, PCT did not prove to be a more valuable diagnostic marker of sepsis than CRP and leukocyte count (smaller area under the ROC curve, low sensitivity) [54]. Nosocomial pneumonia develops in approximately 50% of patients with skin burns, isolated inhalation injury (II), combined skin and respiratory tract lesions, which is significantly more common than in other critical conditions [55]; however, we came across data on the study of PCT in burn victims with respiratory tract infections only in one other work [6].

Barati M. et al., when comparing the levels of PCT, CRP, erythrocyte sedimentation rate, and leukocyte count in burn patients, showed that only the PCT level was statistically significantly higher in the group of patients with sepsis than in those without sepsis (8.45±7.8 ng/ml versus 0.5±1.0 ng/ml). The area under the ROC curve for sepsis diagnosis was 0.97 for PCT with a sensitivity of 100% and specificity of 89.3%. In deceased individuals, the average PCT level was significantly higher than in survivors [26].

Zhilinsky E.V. et al. showed that in patients with burn sepsis (CMA criteria), the sensitivity and specificity for sepsis at a diagnostic PSP level of 600 pg/ml was significantly higher than PCT at a level of 0.5 ng/ml. Comparison of the dynamics of mediator levels showed that PSP began to increase 2 days before the onset of clinical manifestations, while PCT - only on the first day of sepsis diagnosis (the presence of a positive blood culture or 6 CMA criteria). In contrast to PCT, PSP was elevated throughout the septic episode and could be used to assess the effectiveness of antibacterial and antifungal therapy [56].

Comparison of CRP and PCT levels in patients with and without sepsis revealed that a dynamic increase in PCT differentiates these diagnoses, while a dynamic increase in CRP does not. ROC curve analysis showed that an increase in PCT level by 0.25 ng/mL could predict sepsis (area under the curve 0.75). Preliminary findings showed that PCT has better discriminatory power than CRP, but a larger sample size is required for confirmation [57].

Retrospective analysis showed that the PCT level in the first week after injury was statistically significantly higher than the reference values, and correlated with the CRP level in bacterial infection. In the deceased patients, the average PCT level was statistically significantly higher than in the survivors [58]. Combined monitoring of PCT and CRP levels is an effective indicator of the severity of the systemic

inflammatory response and the development of infectious complications [59].

In patients with severe burn injury, SIRS, or sepsis (at least three ABA features), in the presence of a bacterial culture of the burn wound (*Staphylococcus aureus* or *Staphylococcus epidermidis*), PCT and CRP levels increased. However, PCT and CRP results were not statistically different in patients with sepsis and SIRS [60].

Based on a meta-analysis including 28 studies (1517 burn patients), the diagnostic performance of 57 different biomarkers for the early diagnosis of sepsis was assessed. The authors assessed the PCT test as moderately sensitive (73%) and specific (75%), CRP as highly sensitive (86%) but of low specificity (54%). The white blood cell count had low sensitivity (47%) and moderate specificity (65%). Promising results were shown by brain natriuretic peptide, stroke volume index, TNF-alpha and cell-free DNA (deoxyribonucleic acid) at 14 days after injury [27].

PROCALCITONIN AND SURGICAL TREATMENT

The kinetics of PCT levels were studied during the first 5 days after injury, before surgery, and during the 5 days after surgery in patients with burns of more than 15% b.s. In the first five days, PCT levels were statistically significantly higher in patients who developed at least one "sepsis episode" compared with patients who did not develop sepsis. PCT values greater than 1.00 ng/mL were associated with sepsis. On the 2nd day after surgery, the PCT level in all cases reached a maximum and decreased to the preoperative level on the 3rd day or later. PCT kinetics in combination with clinical assessment of the patient's condition are useful for diagnosing sepsis in the first days after burn injury and surgery [61].

In patients with burns covering the area of 40% of the b.s. or more, PCT kinetics was retrospectively studied during the first week after burn, in the perioperative period, and in cases of clinical suspicion of sepsis. The PCT level in the first week was higher in case of a larger total burn area and lower in pediatric patients (14 years and younger). The PCT level statistically significantly increased 48 hours before clinical diagnosis of sepsis. The areas under the ROC curves of PCT concentration and its kinetic levels were 0.788 (at 48 hours) and 0.826 (on the day of clinical diagnosis), respectively. The diagnostic threshold for the PCT level was 1.41 ng/ml, which was 1.34 times higher than the baseline level. PCT kinetics in the early stages after burn serves as a prognostic factor for sepsis and mortality in patients with extensive burns [62].

PROCALCITONIN AND BACTEREMIA FEATURES

When studying episodes of bacteremia and PCT levels, Charles P.E. et al. found that in patients with gram-negative bacteremia, PCT was significantly higher than in patients with gram-positive bacteremia. While the number of points on the SOFA scale was the same in both groups. A PCT level of 16.0 ng/ml demonstrated PPV of 83.0% and NPV of 74.0% in the group with gram-negative bacteremia (area under the ROC curve - 0.79) [63].

Mironov P.I. et al. believe that in patients with severe burn injury (Frank index over 60 points) with negative blood cultures on days 2–5, the combination of bacterial colonization of the wound of at least 105 CFU/g and a PCT level in the blood serum of 2 ng/ml or higher is a diagnostic marker of burn sepsis [64]. The highest PCT levels were associated with non-fermenting gram-negative bacteria, as well as *Klebsiella pneumoniae* and other *Enterobacteriaceae*. According to the authors, determination of PCT levels can help choose empirical antimicrobial therapy, since blood culture takes from 48 to 72 hours [65].

Similar data were obtained by other authors. The mean value of PCT levels in gram-negative bloodstream infections was 2.67 ng/ml, which is significantly higher than in gram-positive infections - 1.04 ng/ml or bloodstream infection caused by *Candida albicans* - 1.09 ng/ml. The area under the ROC curve for PCT, distinguishing gram-negative infections from all others, was 0.761. In gram-negative infections, high PCT levels may be associated with multidrug-resistant gram-negative microorganisms (*Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) [66].

PROCALCITONIN AND ANTIBIOTIC THERAPY

To date, a significant number of studies and meta-analyses have been conducted worldwide in patients with critical conditions, sepsis, lung infections, and surgical infections, which report the effectiveness of PCT-controlled antibiotic therapy [67, 68].

As for combustiology, such studies are rare.

Among burn patients with sepsis (ABA criteria), PCT levels were statistically significantly higher in those who died during the first and last weeks.

During antibacterial therapy, the PCT level was also higher in those deceased in the first 7 days. Over the next week, the PCT level in the deceased increased rapidly and significantly, indicating the ineffectiveness of antimicrobial therapy. The authors believe that although PCT is not an ideal marker, it is prognostically effective [69].

Lavrentieva A. et al. daily determined serum PCT in the ICU patients with and without PCT-controlled antibiotic therapy. Patients in both groups were comparable in demographic and clinical data (47.7±19 years, 74% men, burn area 35.5±16% of b.s., APACHE II score: 10.5±4, SAPS II score: 23±10, SOFA score: 3.9±2). PCT concentrations were 0.69 ng/ml upon admission, and maximal in infectious complications — 7.8 ng/ml. The duration of antibiotic treatment was statistically significantly shorter in the PCT-controlled group (10.1+4 days) than in the comparison group (15.3±8 days). The number of days without antibiotic therapy in the first 28 days was statistically significantly higher in the PCT-controlled group (13.7±6 days) than in the comparison group (7.5±-6 days). Overall mortality, mortality in sepsis, incidence of superinfection, duration of stay in the ICU and on mechanical ventilation did not differ statistically significantly. The data obtained by the authors are consistent with the results of antibiotic therapy under the control of PCT in critically ill patients [70].

CONCLUSION

Burn injury is a damage in which the body loses a significant part of one of the important organs - the skin, which is accompanied by the launch of a systemic inflammatory response. To date, the search for the most effective clinical and laboratory criteria for sepsis in burn victims is ongoing.

The discussions and comparison of Sepsis-1, Sepsis-2, Sepsis-3, American Burn Association, Mann-Salinas and Chinese Medical Association diagnostic models continue, but their value for patients with burns and sepsis needs to be studied in more depth. This is confirmed by the incidence of sepsis reaching 68.5%. One of the reasons for such hyperdiagnosis is that the authors mistake episodes of bacteremia in burns for sepsis, which is a feature of the pathogenesis of burn disease.

Comparative assessment of the validity of clinical models for sepsis diagnosis to date shows that Sepsis-3 and a SOFA score of 6 or more points have proven to be the best in burn injury. The Burn-SOFA and 3H scale developed and published by the Chinese Medical Association have not been well studied and require further research on large populations in prospective studies.

One of the proinflammatory mediators is PCT which quickly responds to infection, inflammation and sepsis. As has been shown, its level is elevated in patients with extensive burns already in shock upon admission to hospital (0.69–2.1 ng/ml), and correlates with the severity of thermal injury. It is possible that increased PCT levels in burn shock is due to bacterial translocation from the intestine, or stimulation of its production by proinflammatory cytokines. After shock, the entire acute period of burn disease is accompanied by clinical signs of the presence of systemic inflammatory response syndrome and an increased level of acute phase inflammatory reactants.

Most authors assess PCT in burn injury as a "useful, highly effective, and even ideal" biomarker, superior to C-reactive protein and other markers of the systemic inflammatory process. It is very rarely characterized as an inaccurate indicator of sepsis and less specific than presepsin and C-reactive protein. Most authors consider monitoring of PCT levels to be the most valuable for diagnosing sepsis and predicting the outcome of burn injury. In sepsis survivors, its levels are significantly lower than in deceased patients, and the maximum values are noted before the patient's death. The threshold levels of PCT for sepsis diagnosis range from 1.0–1.5 to 10 ng/ml and more. The authors note that an increase in the level to 1.5 ng/ml should be regarded as the onset of sepsis, and the patient should be treated as septic. The threshold level of PCT in sepsis (1.5 ng/ml) is significantly higher than in respiratory tract infections (0.52 ng/ml) and wound infections (0.56 ng/ml).

A number of studies have shown that PCT levels are significantly higher in burn patients with gram-negative sepsis than with gram-positive sepsis or in the comparison group. This is associated with the presence of multidrug-resistant gram-negative bacteria (*Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*). The opinion that determining the PCT level can help in choosing empirical antimicrobial therapy is premature, since threshold levels for a particular microbial flora have not been established.

In single studies, PCT values in the perioperative period were determined. It was noted that in all cases

they reached a maximum on the 2nd day after surgery and decreased to preoperative levels on the 3rd day or later.

Even in the first works of the last century it was noted that with antimicrobial therapy the PCT content quickly decreased. However, by now there are isolated studies on the use of PCT-controlled antibiotic therapy in burn patients, the results of which are consistent with those obtained in patients in critical condition. PCT testing is recommended to be included in programs for the rational use of antibiotics in burn units, and that a level of 1.5 ng/ml or higher be used as an indicator of sepsis and an absolute indication for the initiation of massive antibacterial therapy.

Today, it is obvious that PCT is the most effective diagnostic test among known biomarkers, allowing us to assess the course of burn disease, differentiate systemic inflammatory response syndrome and sepsis, predict the development and outcome of burn injury. Multicenter randomized controlled trials are needed to standardize its levels for the accurate diagnosis of sepsis, prognosis and outcome of burn injury, determination of the etiology of bacteremia and sepsis, evaluation of PCT-controlled antibiotic therapy, and development of an algorithm for the use of this test in patients with burn injury.

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