# OPTIMIZATION OF THE DIAGNOSIS AND TREATMENT OF SEPSIS BY PRESEPSIN AND PROCALCITONIN IN YOUNG CHILDREN IN THE REPUBLIC OF UZBEKISTAN (REVIEW)

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## ABSTRACT

Early diagnosis of sepsis allows you to make a diagnosis on time, correctly assess the condition of young children, and start timely treatment. The article analyzes the diagnostic potential of new presepsin. When monitoring sepsis, presepsin unlike other markers, it reliably reflects the real dynamics of its severity, quickly and adequately changes depending on the effectiveness of therapy, predicts relapses of sepsis after remission, when the clinical signs of sepsis and procalcitonin levels normalize. With surgical pathology, injuries and burns in the absence of an infection, presepsin does not increase. A review of the results of international and domestic studies suggests that presepsin is an effective method for the early diagnosis and monitoring of systemic infections of young children.

**Keywords**: Young children, presepsin, procalcitonin, intrauterine infection, early sepsis, C systemic infection, sepsis, diagnostics.

## INTRODUCTION

Nowadays, the health systems of many countries of the world have achieved considerable success in combating infectious diseases. However, despite this, over the past decade, infectious pathology has come in second place in the general structure of human diseases. Among the causes of mortality, the proportion of infections is 23–25%, and in intensive care units (ICUs) it is about 40–60%.

Sepsis (Systemic Inflammatory Response Syndrome) is one of the most common causes of inpatient death. Diagnosis of CVD is an urgent and important problem for the health care of all countries. In the USA, sepsis and septic shock are diagnosed 10 times more often than myocardial ischemia or pulmonary embolism, its level is in the same range as myocardial infarction [1]. The number of hospitalizations for sepsis per 100,000 people increased from 143 in 2000 to 343 in 2007 [2]. In absolute figures, the number of cases of sepsis in 2000 was 414280, in 2003 - 711763 (an increase of 71%). The total cost of treating sepsis in 2003 was $ 15.4 billion; in 2007, $ 24.3 billion (an increase of 57%) [3]. Forecast until 2020 – annual an increase of 1.5% [4].

An epidemiological multicenter cohort study covering Europe, Israel and Canada found that patients with CVD accounted for 17.4% of cases of intensive care [4, 5]. Epidemiological studies conducted in Europe (EPISEPSIS) and Australia (ANZICS) showed that the frequency of this syndrome in developed industrial countries is 50–100 cases per 100,000 populations [4].

The frequency of severe SARS in intensive care units and intensive care units is about 18% everywhere, and septic shock 3-4% [4].

The incidence rate is currently not tending to decrease and incidence hospital infections increase annually by 3–9%. In this case, mortality reaches 19–40% with severe sepsis, and 70% with septic shock [5, 6]. Surgical sepsis accounts for 30% of all cases [7] and is the leading cause of death in surgical wards intensive care (ICU) [8, 9]. The development of septic shock during planned surgical interventions, mortality reaches 30%, and in emergency - from 39% [9].

Analysis of statistics of pediatric and neonatal sepsis (children aged 0 to 19 years) in seven US states over 5 years, the number of cases of severe pediatric sepsis increased from 45 to 81%, and the number of cases of severe sepsis in newborns increased from 4.5 to 9, 7 cases per 1000 births [10].

**Materials and methods**

The traditionally widely used biomarkers of sepsis are cytokines, C-reactive protein (CRP), and procalcitonin (PCT). Numerous studies have shown that the earliest increase in the development of both systemic infections and in “sterile” inflammations is demonstrated by such pro-inflammatory cytokines as TNF-alpha, IL-10 and IL-6, whose levels peak in 2–4 hours [13–15]. After this, the level of PCT begins to increase, which reaches a maximum after 8-12 hours and then, if the inflammation is “sterile”, decreases, and if a systemic infection develops, it rises, and then, depending on the dynamics of sepsis, it rises or decreases [16].

After this, the main early marker of the acute phase of inflammation, both “sterile” and infectious - CRP, begins to rise, which reaches a peak after 12-24 hours [17, 18]. Until recently, PCT was considered the most specific marker of sepsis. However, problems associated with the use of PCT include:

1) a large "gray zone" of uncertainty in which the levels of PCT are (ng / ml):

a) with CVD without infection - below 1.0;

b) with local bacterial infections without systemic manifestations - 0.3–1.5;

c) in severe viral infections - 0.5–2.0 (in all these cases, the diagnosis of sepsis cannot be made with confidence, it is recommended to repeat the measurements after 6-24 hours);

2) an increase that is nonspecific with respect to infection within 24–48 hours in conditions associated with massive tissue damage: surgery, burns, injuries;

3) an increase that is nonspecific with respect to infection in newborns in the first 48 hours of life;

4) the long half-life of PCT (25-30 hours) complicates the operational monitoring of sepsis.

A list of conditions associated with a “non-infectious” increase in PCT is given in reviews [18–23]. This review analyzes the results of studies published in 1996–2011. and on the effectiveness of PCT for diagnosis and monitoring and sepsis. The authors draw the following conclusions:

must be established

diagnostic levels of PCT for differentiation between CVD, sepsis and severe sepsis [24]. Despite the fact that high levels of PCT indicate a systemic bacterial infection (unlike the viral, fungal, or inflammatory etiology of sepsis), serum levels of PCT do not correlate with the severity of sepsis or mortality [20, 24].

Thus, at present, the serum levels of PCT used to assess the effectiveness of antibiotic therapy and formulate a decision on the feasibility of increasing (decreasing) its intensity have only research applications [20, 21, 24].

Nevertheless, serum concentrations of PCT are important: a) for monitoring the clinical consequences of medical and surgical therapy for sepsis; b) to observe the development of CVD in burn patients and ICU patients; c) may play a role in reducing the intensity of antibiotic therapy [20, 21, 23, 24].

In general, it is noted that the main problem associated with the use of PCT is its diagnostic uncertainty in the first few days, when its "non-infectious" increase can occur. Therefore, PCT has a lower diagnostic value precisely when this value has the highest price [24].
Presepsin (PSP) is a circulating protein whose concentration in the blood increases rapidly with the development of systemic infections, sepsis, severe sepsis and septic shock. It was first described in 2005 by a group of researchers from Iwate University of Medicine, Japan [25]. Further international multicenter studies have shown that:

1) the mechanism for increasing PSP levels is fundamentally different from the mechanism for increasing such pro-inflammatory markers as TNF-α, IL-6, IL-10, PCT, CRP;

2) with the induction of systemic inflammation, an increase in PSP occurs earlier and faster than an increase in other markers of sepsis.

Thus, the SRP levels a) reflect the real dynamics of sepsis; b) predicts outcomes and c) even with a decrease in the severity of clinical symptoms of sepsis (remission), nevertheless, unlike other markers, it predicts its relapse [26–32].

The key role in the formation of PSP is played by the activation of macrophages / monocytes, on the surface of which the membrane receptor protein mCD14 is located - membrane glycoprotein with m.m. 55 Kda. Normally, mCD14 is expressed on the surface of monocytes / macrophages, neutrophils, chondrocytes, B cells, dendritic cells and other mature myeloid cells, being a receptor that responds to a signal about the presence of infectious bacteria and includes a system of nonspecific immunity and associated with it inflammatory process [33, 34].
In bacterial inflammation, mCD14 binds to various bacterial ligands, including: a) components of gram-negative bacteria, the main of which is lipopolysaccharide (LPS, endotoxin, one of the main components of the cell wall); b) components of gram-positive bacteria; c) components of fungi [34–37]. The mCD14 receptor can independently bind to LPS and include a macrophage activation signal, but a special lipopolysaccharide binding protein (LBP - lipopolysaccharide binding protein) increases the efficiency of such binding by 100–1000 times. In vivo at low LPS level (a small number of bacteria that can rapidly increase) LBP “amplifies” the signal in advance to activate the inflammatory response [38]. In addition to endotoxin of gram-negative bacteria, LBP specifically binds to the components of the cell wall: a) gram-positive bacteria - lipotechoeic acids, peptidoglycans [36, 39]; b) mycobacteria - lipoproteins, lipomannans [34]; c) mycoplasmas

- lipopeptides [40]; d) spirochetes - glycolipids and lipoproteins [35] and e) - fungi [37].
Induction of education PSP. The mCD14 receptor, which binds to the LBP-LPS complex, is activated and transmits a signal to the TLR4 coreceptor, which is located next to the membrane and belongs to the so-called toll-like receptors, which activate non-specific immunity [37]. After macrophage activation, mCD14 is disconnected from the membrane, goes into circulation and becomes soluble sCD14. Functionally, sCD14 induces inflammation in endothelial and other cells that do not have mCD14 and do not respond to endotoxins [37]. It is believed that circulating sCD14 is a marker of the response of monocytes to the action of LPS; an increase in blood sCD14 level is associated with the severity of inflammation and the development of septic shock [41].
The next stage of the inflammatory process is the activation of phagocytosis using lysosomal proteinases (cathepsin D, etc.), which cleave the circulating sCD14 with the formation of its specific fragment (subtype) sCD14-ST, which was later called presepsin [25 , 32, 42].

Thus, the formation of PSP and its circulating concentrations reflect the fact of phagocytosis activation and its intensity. Although the activation of mCD14 in vivo requires the presence of LPS (and, obviously, ligands of other microorganisms), the injection of sterile LPS preparations into laboratory animals does not lead to the synthesis of PSP. And infection induced by ligation and puncture of the cecum dramatically raises PSP levels. This indicates that leukocyte activation by endotoxin for the formation of PSP is insufficient, and phagocytosis of viable bacteria is necessary for the formation of PSP [42].

Special studies have shown that PSP increases with gram-positive, gram-negative and fungal infections, but practically does not increase with viral [43].

Thus, in a multicenter study of patients (n = 207) with suspected sepsis, it was found that the AUC ROC values for the diagnosis of sepsis were: for PSP - 0.908, for PCT - 0.905 and for IL-6 - 0.825. The optimal borderline level for the detection of sepsis for PSP was 600 pg / ml, clinical specificity - 87.8%.

However, PSP did not discriminate between gram-positive and gram-negative sepsis. The sensitivity of hemocultures was 35.4%, and the sensitivity of PSP was 91.4%. The authors concluded that presepsin is applicable for the diagnosis of sepsis, and its diagnostic characteristics are superior to those for conventional markers of sepsis and blood cultures [44].

Similar results were obtained in another study when observing patients (n = 43), among which 19 had gram-negative infections, 20 were gram-positive and 4 were fungal [45]. As follows, PSP levels increased with bacterial and fungal sepsis. Moreover, the coincidence of elevated PSP levels with blood culture data was significantly higher than that for PCT. Moreover, an increase in SRP to a greater extent than elevated levels of PCT reflected the severity of sepsis.

In a special study, it was found that the average level of PSP (pg / ml) in healthy indie species (n = 128) was 190 pg / ml. When observing patients (n = 41) who were admitted with at least two criteria for CVD, the following PSP levels (pg / ml) were established:

Norm: 294.2 ± 121.4; SSVO: 333.5 ± 130.6; local infection: 721.0 ± 611.3; sepsis: 817.9 ± 572.7; severe sepsis: 1992.9 ± 1509.2 [46].

Patients with local infections had a PSP level significantly increased compared to patients who did not have infections. When comparing with other markers, it turned out that the AUC ROC values for PSP were 0.845, for PCT - 0.652, for CRP - 0.815 and for IL-6 - 0.672 [46].

At the border level of the PSP, which amounted to 0.17; severe sepsis - 787 and 1.09; septic shock 600 pg / ml sensitivity for the detection of sepsis - 1084 and 6.99.

From the above results it follows that an increase in PSP levels to a greater extent than an increase in PCT levels is associated with an increase in the severity of systemic infection. An increase in PCT occurred mainly in severe sepsis and septic shock.

For the diagnosis of sepsis:

• At a borderline level of PSP 317 pg / ml, the sensitivity was 70.8%, specificity - 85.8%, positive predictive value - 92.3%, negative - 51.5%.

• At a borderline level of PCT 0.25 ng / ml, the sensitivity was 60.0%, specificity - 77.7%, positive predictive value - 92.8%, negative - 28.4%. The values of AUC ROC for the diagnosis of sepsis were: for PSP - 0.820, for PCT - 0.724.

For the diagnosis of severe sepsis

• At a borderline level of PSP 449 pg / ml, the sensitivity was 82.4%, specificity - 72.4%, positive predictive value - 71.3%, negative - 83.2%.

• At a borderline level of PCT of 1.435 ng / ml, the sensitivity was 52.0%, specificity - 79.8%, positive predictive value - 69.6%, negative - 65.1%. The AUC ROC values for SRP were 0.840, for PCT - 0.741.

For the diagnosis of septic shock

• At a borderline level of PSP of 550 pg / ml, sensitivity is 85.7%, specificity is 63.6%, positive predictive value is 28.5%, and negative is 96.3%.

• At the borderline level of PCT 4.415 ng / ml, sensitivity - 54.1%, specificity - 81.1%, positive predictive value - 34.2%, negative - 90.7%.

The AUC ROC values for PSP were 0.790, for PCT - 0.768, but the differences between these indicators were statistically unreliable.

Thus, "in the early stages of the development of systemic infection, PSP is the most sensitive and specific marker of sepsis, reflecting its dynamics, severity of the patient's condition, and predicting outcomes" [47].

In a preliminary study (n = 146), it was shown that for detection of sepsis on the day of admission to ONT with signs of CVD, the values of AUC ROC were: for PSP - 0.878, for PCT - 0.668 and for APACHE II - 0.815 [50].

For stratification of patients entering ONT, the following boundary values of the initial levels of PSP (pg / ml) were proposed:

• <200 - very low risk of developing sepsis;

• 200–300 - low risk of developing sepsis;

• 300–500 - moderate risk of developing sepsis;

• 500–1000 - sepsis;

• ≥ 1000 - severe sepsis, septic shock [50]. In a multicenter study [51], it was shown that upon admission to ONT (n = 93), the boundary levels of PSP (pg / ml, median) and PCT (ng / ml, median) were:

• with acute symptoms of CVD: PSP - 517;

FCT - 1.0;

• with sepsis: PSP - 875, PKT - 9.0;

• in severe sepsis and septic shock: PSP - 1460; FCT - 19.0.

It is very significant that in patients with an established diagnosis of infection, the PSP level was maximum at admission (T0) compared with that after 24 hours (T1) and 72 hours (T2), while the maximum level of PCT was observed after 24 h (T1).

At the same time, the boundary value of PSP for the detection of sepsis was 600 pg / ml; sensitivity - 78.95%, specificity - 61.9%; for FCT - 0.18 ng / ml, sensitivity - 89.47%, specificity - 75.90% [51].

In another study [52], patients (n = 226) who were admitted to ONT with signs of CVD were also observed. Measurements were taken immediately upon post-exposure. In 37 patients, blood cultures were subsequently positive.

The diagnostic characteristics of the PSP and PCT were:

• PSP, borderline level - 729 pg / ml, sensitivity - 81.1%, specificity - 63.0%: positive predictive value - 30.0% negative - 94.4%, AUC ROC - 0.750;

• PCT, borderline level - 0.45 ng / ml, sensitivity - 75.7%, specificity - 64.0%, positive predictive value - 29.2%, negative - 93.1%, AUC ROC - 0.785 [52].

When observing patients (n = 68) who were admitted to the ICU with clinical signs of sepsis, for the detection of sepsis, the AUC ROC values were 0.775 for PSP and 0.712 for PCT [53].

Patients entering ONT, as a rule, represent a very clinically heterogeneous group of patients with various acute pathologies and complications of both an infectious and non-infectious nature.

In a study of patients (n = 144) who entered 117 different ONTs and did not have acute infectious pathologies, it was found that the PSP levels were: for men (pg / ml, median) - 443 (343–563) and for women 430 (337–561) [54]. Patients older than 70 years had elevated PSP

levels compared to younger patients and amounted to (pg / ml, median) 470 (380–602 versus 300 (201–457). Also, PSP levels were slightly increased in patients with reduced GFR [54].

When observing 69 patients, it was found that 41 patients had sepsis, and 3 patients (7.3%) died; 18 - severe sepsis, 8 patients died (44.4%); 10 - septic shock, 8 patients died (80%). The total 30-day mortality rate was 27.5%. PSP levels with high reliability discriminated patients with both favorable and unfavorable outcomes, and outcomes of varying severity (placement in ICU, mechanical ventilation, dialysis).

The AUC ROC values were:

• to predict mortality: for APACHE II - 0.835; for PSP - 0.833; for PCT - 0.568;

• to predict the severity of outcomes among survivors: for APACHE II - 0.923; for PSP - 0.796; for PCT - 0.624 [49].

In a multicenter study, which included monitoring patients (n = 106) who received ONT with signs of CVD, it was shown that elevated PSP levels on admission predicted 60-day survival, while PCT levels did not have such predictive ability [51]. So, upon admission, the initial mean PSP level of 4232.4 pg / ml was associated with mortality, and 3451.2 pg / ml with survival. The PCT levels measured on the first and second day did not have predictive value [51].

In another multicenter study of patients admitted to ICU with sepsis and septic shock (n = 100), it was shown [55]:

• the PSP level (pg / ml, median), which was 2269 (1171–4300) on the first day, was associated with 28-day mortality, and the level of 1184 (875–2113) was associated with survival.

• the level of PCT (ng / ml, median), which amounted to 18.5 (3.4–45.2) on the first day, did not have prognostic characteristics.

Predictive efficacy (AUC ROC) for PSP was: on the first day, 0.69; in the second - 0.70; on the seventh day - 0.74, for PCT - 0.56; 0.55 and 0.64, respectively. The predictive efficacy of the SOFA scale on these days was 0.69; 0.65 and 0.75, respectively [55].

In the already mentioned multicenter study of patients (n = 858) admitted to ONT with the signs of SIRS, data were obtained regarding the prognostic characteristics of the SRP [47].

To predict the development of severe sepsis, the AUC ROC values were:

• for PSP - 0.840, for PCT - 0.741;

• for indicators MEDS + SRP versus MEDS - 0.875 versus 0.818;

• for indicators APACHE II + SRP against

APACHE II - 0.858 vs 0.744.

To predict the development of septic shock, the values of AUC ROC were:

• for PSP - 0.790, for PCT - 0.768;

• for MEDS indicators - 0.924;

• for APACHE II indicators - 0.868.

The combination of MEDS + SRP and APACHE II + SRP prognostic values for severe sepsis did not improve.

To predict 28-day mortality in septic patients, AUC ROC values were: for PSP, 0.658; for PCT - 0.679; for MEDS indicators - 0.719; for APACHE II - 0.722; for MEDS + PSP - 0.731; for APACHE II + PSP, 0.734 [47].

An editorial in the May 2014 issue of Clinical Biochemistry noted that “in patients with sepsis, baseline presepsin levels predict outcomes; for other biomarkers, including procalcitonin, such a characteristic has not yet been shown ”[29].

SRP in monitoring sepsis therapy. The marker half-life is crucial for the speed of sepsis monitoring. If this time is large, the concentration of the marker will not reflect the current sepsis severity, but that which was in the past. During intravenous injection of the PSP

preparation to laboratory animals and recording of its appearance in urine, it was found that its half-life in circulation is from 30 minutes to 1 hour [56]. Recall that the half-life of PCT is 25–30 hours.

However, in the group with an unfavorable prognosis, there was also a decrease in the levels of PCT, IL-6 and CRP, but not PSP. At the same time, the duration of antibiotic therapy in the group with an unfavorable prognosis was higher, and the 28-day mortality rate was higher.

According to SOFA, the median values of the levels of PSP, PCT, IL-6 and CRP during monitoring of sepsis with a favorable prognosis (7.0 points) and with an unfavorable (9.0 points) were:

• PCT (ng / ml, median), favorable prognosis - 27.3, unfavorable - 16.2 (decrease by 40%);

• IL-6 (pg / ml), favorable prognosis - 1972, non-favorable - 1555 (decrease by 8%);

• CRP (mg / l), favorable prognosis - 137.0, non-favorable - 121.0 (decrease by 12%);

• PSP (pg / ml, median), favorable prognosis - 1512, unfavorable - 1539 (increase by 2%).

As indicated, since PSP is induced during phagocytosis of bacteria independently of LPS and cytokines, the mechanism of production of PSP is different from that of those for IL-6, PKT and SRB. The authors suggest that "PSP can reflect the severity of infection to a greater extent than the severity of the inflammatory response" [44].

The results of a multicenter retrospective study of 50 surviving and 50 non-surviving ICU patients with sepsis and septic shock are very indicative [55]. Measurements were taken on the 1st, 2nd, and 7th day after admission to the ICU. Outcomes were recorded after 28 and 90 days.

On the day of receipt

• PSP levels (pg / ml, median) were 1184 (875–2113) among survivors, 2269 (1171–4300) among non-survivors, and significantly differed,

• PCT levels (ng / ml, median) were 10.8 (2.7–41.9) for survivors, 18.5 (3.4–45.2) for non-survivors, and did not differ significantly.

The kinetics of PSP and PCT in surviving and non-surviving patients is also indicative. For survivors, PSP decreased, for non-survivors it did not decrease. PCT decreased both in those and others. 28-day mortality was predicted only by SRP levels, but not by PCT.

Legend: black circles for non-surviving patients, gray circles for surviving [55]

The results of monitoring PSP and PCT in 9 patients who underwent therapy for nosocomial infections, and in whom remission was observed with a subsequent relapse, turned out to be very important.

In 7 (77.8%) patients who were diagnosed with severe sepsis upon admission, at the initial stage of infection, the PSP level was

> 1000 pg / ml and remained high all the time, despite antibiotic therapy, the disappearance of symptoms of sepsis and the normalization of PCT levels.

We emphasize once again that in patients who had a relapse of sepsis, PSP levels remained high (> 1000 pg / ml), and PCT levels decreased during remission and then increased again with sepsis. It is significant that in 9 patients with recurrence of sepsis and high PSP during clinical remission in samples of rectal contents in large quantities was found to be thyresistant Klebsiella pneumonia.

In general, the authors believe that "this study confirms the importance of monitoring sepsis using a combination of different markers in order to get a reliable diagnosis. Maximum presepsin levels can give the clinician an alarm so that he does not cancel antibiotic therapy

and carefully monitors the health status of the septic patient even after the clinical symptoms disappear and the PCT levels return to normal"[57].

Patients with ONT and ICU are very often on mechanical ventilation.

Patients (n = 120) who were admitted to ICU with acute pathologies and needed mechanical ventilation were observed [58]. During the observation, 38 (31.7%) patients died, 16 (13.3%) developed sepsis, 9 patients with sepsis died. PSP measurements were carried out immediately after intubation, before turning on the ventilator, after extubation, and before discharge from the ONT. The kinetics of PSP in surviving and non-surviving patients is shown in Fig. 11. The median values of PSP (pg / ml) for differentiation between septic patients and aseptic patients were 1098 (886–1263) and 3185 (1734–3904), respectively. The optimal borderline level for detecting the development of sepsis with mechanical ventilation is 1965 pg / ml, sensitivity - 85.7%, specificity - 84.0%. In the absence of sepsis, PSP remained below 1600 pg / ml [58].

Preoperative PSP levels. 60 patients were admitted to the ONT with signs of CVD and with indications for emergency abdominal surgery.

When observing pediatric oncological patients (n = 37) with febrile neutropenia (absolute neutrophil count <0.5 * 109 / L), it was found that patients with sepsis (positive blood cultures) compared with patients with fever of unclear origin (negative blood cultures) the levels of PCT (ng / ml, median) were increased (0.83 versus 0.27), but the levels of PSP (pg / ml, median) were not significantly different (401 versus 356) [71].

Fundamentally different data were obtained at the Hematological Scientific Center (Moscow) when observing adult oncohematological patients (n = 27) with leukopenia (leukocytes <0.5 * 109 / l) [72]. Of these, 15 patients were with septic shock and 12 without infectious complications. It was shown that in patients with septic shock (compared with those without infections), the levels of PSP, PCT, IL-6 and CRP were increased.

Of particular interest was the kinetics of these markers in the development of septic shock. On the first day of the development of septic shock, PSP levels (pg / ml) did not differ between surviving and non-surviving patients. However, on the 2nd, 3rd, and 7th day, surviving patients had significantly lower PSP levels than non-surviving patients and amounted to (pg / ml, median) on the 2nd day - 2208 against 4790, on the 3rd - 2085 against 4920 and on the 7th day - 993 against 7972. Moreover, the PSP levels were correlated with the levels of IL-6, CRP , plasma antithrombin III activity, XIIa-dependent fibrinolysis duration, and SOFA and APACHE II scores, but did not correlate with PCT levels and white blood cell counts.

The authors suggest that "despite leukopenia, plasma levels of PSP can be used to assess the severity of septic shock and organ dysfunction" [72].

The results of studies on the diagnostic role of PSP in the development of severe infectious complications associated with diseases of various etiologies are very indicative.

The study included patients (n = 25) with rheumatoid arthritis (RA) complicated by bacterial infection, 34 patients with severe RA and 34 healthy individuals. Patients with RA in whom the pathogen was identified were identified as iRA (infection); patients with severe RA, but without infection, like fRA (flare - burn with a bright flame).

The levels of PSP (PG / ml) were at iRA - 2088.4 ± 4243.7; at fRA - 319.3 ± 321.8 pg / ml; in the control, 136.0 ± 57.0. At iPA, PSP correlated with CRP levels; at fPA, it did not correlate. Significantly, with iRA therapy, PSP and CRP levels decreased, and with fRA therapy, CRP decreased, but not PSP levels.

The diagnostic effectiveness of PSP for the diagnosis of infectious RA according to AUC ROC values was 0.817, which indicated "the effectiveness of measuring PSP levels for the diagnosis of infectious rheumatoid arthritis" [73].

Patients (n = 25) with cirrhosis were observed, measurements were performed to detect bacterial infection upon admission and to monitor therapy after 48, 96 and 144 hours and after

15 days. In 16 patients, PSP levels (pg / ml, average) were 1854 ± 1744. After 72 ± 4.8 hours, microbiological tests confirmed the presence of infections in all 16 patients. When monitoring in 5 (31%) patients after 24 and 48 hours, the PSP remained unchanged, these patients did not respond to empirical antibiotic therapy, after receiving the results of the antibiogram, the therapy was changed. The authors suggest that "measuring PSP levels is 100% specific to blood cultures and can be used to identify infectious complications of liver cirrhosis and monitor its therapy" [74].

Spontaneous bacterial peritonitis (SBP) is the most frequent and dangerous complication in patients with cirrhosis associated with viral hepatitis C. Patients (n = 30) with chronic hepatitis with ascites were observed, 10 of them (group 1) had sterile ascites , 20 (group II) - SBP. Concentrations of PSP (pg / ml, average values) were 148.6 ± 34.9 with sterile ascites; with SBP - 3473.0 ± 1911.6; median - 4621.5. In patients with SBP, PSP was also measured 10 days after the start of antibiotic therapy, while PSP levels were reduced and amounted to an average of 673.4 ± 245.0, median - 3473 ± 1911.6. Mortality in the group with SBP was 20% (4 cases out of 20), in non-survivors, the PSP levels were average - 4631, median - 3915.

According to the authors, "PSP can be a useful marker for the early diagnosis of spontaneous peritonitis in patients with cirrhosis, since PSP has 100% specificity for the detection of spontaneous peritonitis and in such patients reliably correlates with outcomes" [75].

A preliminary study included patients (n = 18) with pancreatic necrosis. From the moment of the disease, the levels of PSP and PCT were measured in all patients. In 14 patients, PCT increased from the 2nd – 5th day of the disease. Eight of these patients had an increase in PSP; it was these patients who were subsequently diagnosed with purulent-septic complications - pancreatic abscess (n = 2), pancreatic phlegmon (n = 2), retroperitoneal phlegmon (n = 1 ), pneumonia (n = 4). Clinical signs of these complications appeared 1.8 ± 0.3 days later than an increase in PSP. 6 patients with elevated PCT and normal PSP showed signs of CVD and intoxication (APACHE II> 24), but without purulent-septic complications. It is believed that "PSP is a more sensitive marker of purulent-septic complications of pancreatic necrosis than PCT, PSP rises before the clinical manifestations of purulent-septic complications" [76].

Sepsis is the most common cause of AKI. Moreover, data is heating up that patients who are in ICU for an initially aseptic AKI develop sepsis with a high frequency. It is extremely significant that there is a direct correlation between the severity of initial sepsis and the severity of subsequent AKI and, conversely, between the severity of initial AKI and the severity of subsequent sepsis. The heavier the initial sepsis, the higher the risk of developing severe AKI and vice versa [77–79].

When observing patients (n = 144) who received ONT, it was noted that a decrease in GFR <60 ml / min / 1.73 m2 was associated with a slightly increased PSP (pg / ml) to 470, with GFR ≥ 60 mm / 1 73 m2, the level of PSP was 386 pg / ml [80].

In another study, septic patients (n = 20) who underwent cardiovascular surgery and were on hemodialysis, control (n = 10, healthy individuals) were observed for 1 year. PSP levels (pg / ml) in patients with sepsis were 4368 ± 3088 versus 694.1 ± 239.1 in the control.

At the same time, the levels of PSP and PCT (ng / ml) did not change after hemodialysis. No difference in the PSP and PCT levels between survivors and non-survivors was observed PSP - 4184.1 ± 3039.5 versus 4593.5 ± 3316.2; PCT - 9.66 ± 17.55 versus 14.93 ± 20.54 [81] .

The results of observation of patients (n = 254) who were admitted to ONT with suspected sepsis and other diseases, in particular, with acute kidney damage (AKI), turned out

to be interesting. It turned out that upon admission, PSP levels (pg / ml, median) and AUC ROC values were:

• without sepsis and without AKI (n = 78) PSP - 406 (6–4374);
• sepsis without AKI (n = 37) - 1065 (86–9960). AUC ROC - 0.789;
• AKI without sepsis (n = 14) - 1607 (454–8516);
• sepsis and AKI (n = 27) - 1523 (293–16764), AUC ROC - 0.593.

It was concluded that severe renal dysfunction reduces the diagnostic accuracy of PSP for the diagnosis of sepsis [82].

Then, in the continuation of the previous study, patients (n = 629) were admitted to ONT with suspected sepsis. Patients were divided into two groups - with AKI and without AKI. The AUC ROC values for the diagnosis of sepsis for PSP and PCT were without AKI - 0.883 and 0.870, respectively;

with OPP - 0.669 and 0.804. However, after normalizing (dividing) the AUC ROC values of the AKI + sepsis group by creatinine levels, the AUC ROC values began to be 0.828 and 0.852, respectively. The authors suggest that "the optimal borderline levels of PSP and PCT for the diagnosis of sepsis in patients with acute renal failure are 409 pg / ml / creatinine for PSP, sensitivity - 66.0%, specificity - 91.7%, and for PCT - 1.5 ng / ml / creatinine (sensitivity - 63.5% and specificity - 95.8%), respectively [83].

It is significant that problems with the diagnosis of sepsis in AKI also exist in PCT. A recent meta-analysis (201 studies, n = 803, 255 episodes of bacterial infection) showed that the total sensitivity of PCT for the detection of sepsis in severe renal dysfunction is 73% (54–86%), and for CRP - 78% (52–83%), and the total specificity for PCT is 88 % (79– 83%) and for CRP - 84% (52–86%). It is believed that "for the diagnosis of systemic infection in patients with kidney damage, PCT and CRP have low sensitivity, but acceptable specificity. Given the low negative predictive value of these markers, their suitability for eliminating sepsis in AKI remains open to question "[84].

Moreover, for the diagnosis of sepsis with renal dysfunction, higher border levels are also needed, as in surgery. So, when observing patients (n = 276) who underwent elective cardiac surgery, 67 were infected, and 75 (27%) had renal dysfunction. In patients with infection, PCT was increased, but it was even higher with infection and renal dysfunction at the same time. For patients with infection only, the borderline level of PCT (ng / ml) was 0.80; with infection and renal dysfunction, 2.57 [85].

In a recent meta-analysis of the registers (n = 1331), it was found that borderline PCT levels for sepsis increase with decreasing GFR. So, the average PCT values (ng / ml) for the detection of sepsis (positive blood cultures) were:

• with GFR ≥ 60 ml / min (n = 836) - 1.7 ± 6.8,
boundary level - 0.37;
• with GFR 30 - <60 (n = 481) - 6.6 ± 17.5, limited
personal level - 1.06;
• with GFR <30 (n = 497) - 12.6 ± 25.9, border-
the lowest level is 2.50 [86].

Thus, taking into account that in patients with ONT and ICU very often there are impaired renal function, in the diagnosis of sepsis it is necessary to take into account the quantitative indicators of these disorders. Unfortunately, there are no clear and agreed recommendations on how to do this yet. Studies of the diagnostic utility of PSP to assess the risk of developing sepsis with renal dysfunction have practical and scientific significance that can hardly be overestimated.

PSP: information content for the appointment and monitoring of hemofiltration

The development of renal dysfunction is one of the reasons for the need for extracorporeal purification methods for hemocorrection in septic patients.

The effectiveness of prolonged veno-venous hemofiltration (PVVHF) is highly dependent on the on-time diagnosis of sepsis and, in particular, on the timeliness of indications to its onset. Some sepsis markers have a theoretical potential.

Removal from the vascular bed through the hemofilter membrane. In this regard, at the very early stages of intensive care, difficulties may arise in interpreting the result of monitoring sepsis. LPS plays a crucial role in the pathogenesis of sepsis and multiple organ failure, which requires the development of specific and nonspecific methods for its removal from the vascular bed, reduction of its endogenous production and translocation of endotoxin. Indications for the use of LPS sorption are based on high values of lipopolysaccharidemia with the effectiveness of surgical debridement of the focus or foci of infection.

In a study conducted in a clinical hospital (Tashkent), 11 patients with abdominal sepsis during LPS sorption measured PSP levels [87]. It was found that in all patients, high levels of PSP correlated with high LPS values of gram-negative bacteria and with CRP levels; in two patients, PCT levels were less than 2 ng / ml. After LPS sorption, PSP levels decreased from 2149 to 970 pg / ml, LPS from 318 pg / ml to 117 pg / ml. However, the levels of PCT and CRP during LPS sorption did not change. In 2 patients, due to the persistent activity of the foci of infection, the repeated growth of LPS was accompanied by an increase in PSP, which determined the indications for the continuation of selective detoxification therapy. It is significant that a decrease in the PSP and LPS levels was accompanied by the correction of hemodynamic, respiratory and renal dysfunctions with a decrease in the need for inotropic stimulation, infusion therapy, an increase in the respiratory coefficient and urine output. The authors believe that “the control of presepsin during selective LPS sorption additionally justifies the detoxifying tactics and allows controlling its effectiveness” [87].

In a prospective randomized study conducted by the same group of authors, in the first postoperative day, 21 patients with abdominal sepsis of various etiologies obtained similar results [88]. Initially, all patients showed high levels of PSP, which determined the high probability of death. During the first 12 hours of intensive care during PVVHF, the average levels of PSP significantly decreased. At the same time, the PSP level in the filtrate was approximately 10% of its concentration in the blood flowing to the hemofilter. The authors suggest that “one of the pathophysiological mechanisms of regression of presepsinemia in early PVVHF is the restoration of transcapillary metabolism and, accordingly, a decrease in the activity of translocation processes” [88].

**RESEARCH RESULTS AND DISCUSSION**

High scores on the CURB65 scale were an independent predictor of acute respiratory distress syndrome (ARDS), and a high PSP was an independent predictor of DIC. The combination of CURB65 + PSP was a stronger predictor of 28-day mortality, TBPD, and ICE development than CURB65 and PSP levels individually. Moreover, PSP was a stronger predictor of DIC than CURB65 and white blood cell count. The authors suggest that “PSP is a more valuable marker for predicting the severity and outcome of patients with ONT with PFS, and the combination of PSP and CURB65 significantly increases these predictive characteristics” [89].

Of particular note is the clinical case of observing a patient with cystic fibrosis at the stage of exacerbation of chronic obstructive mucopurulent bronchitis [90].

Patient V., 8 years old. The diagnosis is cystic fibrosis, a mixed form (with damage to the lungs, gastrointestinal tract, pancreas).

The diagnosis is confirmed genetically. He was on a permanent enzyme, anti-inflammatory, inhalation therapy. On admission: chronic obstructive mucopurulent bronchitis, stage of exacerbation, continuously recurring course. Chronic staph infection.

Intermittent colonization. Septic condition. Hemocultures are negative. In sputum, conditionally pathogenic multiresistant microflora.

Initial therapy: aminocaproic acid, amoxiclav, ventolin through a nebulizer, vitamin K, clacid, lazolvan through a nebulizer, pulmozyme, Ringer's solution, ursosan. Given the pronounced infectious and inflammatory picture, measurements were made in the blood of PSP and CRP.

Given the significantly increased levels of PSP, an amoxiclav is replaced by thienam immediately.

The results of monitoring the effectiveness of therapy with using PSP presented [90].

## CONCLUSIONS

1. PSP is a fundamentally new marker of bacterial and fungal systemic infections.
2. The mechanism of production of PSP during the induction of sepsis and its course differs from that characteristic of traditional sepsis markers, such as TNF-alpha, IL-6, IL-10, PCT and CRP.
3. The mechanism of production of PSP is mainly associated with the activation of phagocytosis, the details of this mechanism and the role of PSP in the pathogenesis of systemic infections are poorly understood.
4. With the development of systemic infections, PSP rises earlier than other markers of sepsis and regardless of their increase or decrease.
5. PSP with 100% reliability, subsequently
confirmed by blood cultures:
a) diagnoses sepsis before the manifestation of its clinical symptoms, which allows timely initiation of therapy
b) predicts favorable and unfavorable outcomes.
6. When monitoring sepsis, PSP, unlike other markers:
a) reliably reflects the real dynamics of its severity;
b) quickly and adequately changes depending on the effectiveness of therapy;
c) predicts the recurrence of sepsis after remission, when the clinical characteristics of sepsis and PCT levels are temporarily normalized.
7. During surgery, injuries and burns in the absence of infection, PSP does not increase.
8. PSP also increases with infectious complications of pathologies such as pneumonia, obstructive purulent-mucous bronchitis, with purulent-septic complications of acute pancreatitis, with septic shock with leukopenia, with rheumatoid arthritis, cirrhosis, in particular caused by hepatitis C virus and probably with some other diseases associated with severe infectious complications.
9. The results of international and domestic studies suggest that PSP is a very effective marker for the early diagnosis and monitoring of systemic infections.
10. Preliminary results suggest that PSP is a very promising marker of extensive infectious complications in diseases of various etiologies.

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