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ABSTRACT

Introduction. Early diagnosis of sepsis allows 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 early marker like procalcitonin. **Material and methods.** The research involved 82 children with the diagnosis of sepsis, severe sepsis, or septic shock, who were under observation in the Tashkent Medical Academy. The study population constituted all children from newborns to 3 years old patients. All patients were divided into documented bacterial (n=22) versus abacterial inflammation (n=60) infections in order to assess serum PCT

concentrations with a cutoff value of >0.5 ng/mL. The traditionally widely used biomarkers of sepsis are cytokines, CRP and PCT. **Results and discussion**. In the process of sepsis monitoring, procalcitonin unlike other markers, 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, procalcitonin does not increase. Early diagnosis of sepsis is difficult issue in pediatric practice, whilst it can be vital for positive patient outcomes in sepsis management. Any delay in diagnosis and treatment may bring on multiple organ failure and can be hazardous with elevated mortality consequences. Early diagnosis and effective management of sepsis not only gives an opportunity for prompt antibiotic therapy and a potential decrease in mortality, it can also belittle the unnecessary use of antibiotics. **Conclusion.** A review of the results of international and domestic studies suggest that procalcitonin is an effective method for the early diagnosis and monitoring of systemic infections of young children.

KEY WORDS: sepsis, severe sepsis, septic shock, procalcitonin, presepsin, calcitonin, biomarker**.**

THE LIST OF ABBREVIATIONS

SIRS - Systemic Inflammatory Response Syndrome
SARS- Severe Acute Respiratory Syndrome
ICU- intensive care unit
PCT- procalcitonin
WHO- World Health Organization
CRP-C-reactive protein
WBC-white blood cells
C-GRP-calcitonin gene related peptide
CALC-1-calcitonin gene-related peptide and katacalcin
mRNA- Messenger RNA
SCCM-Society of Critical Care Medicine
ESICM- European Society of Intensive Care Medicine
TNF-alpha-Tumour Necrosis Factor alpha
IL-10-Interleukin 10
IL-6-Interleukin 6
CVD-Cardiovascular disease
PSP-Presepsin
AUC-*Area under the Curve*
ROC-Receiver operating characteristic
NTO-National Transplant Organization

APACHE II-Acute Physiology and Chronic Health Evaluation II
MEDS-Medical Emergency Distribution System
SOFA score-The sequential organ failure assessment score
iRA-infectious RA
fRA-flare RA-without infection
SBP-Spontaneous bacterial peritonitis
AKI-acute kidney injury
GFR-glomerular filtration rate
PVVHF-prolonged veno-venous hemofiltration
LPS-Lipopolysaccharides

INTRODUCTION

Sepsis (Systemic Inflammatory Response Syndrome) is considered to be one of the most common reasons of inpatient death. The number of hospitalizations for sepsis per 100,000 people increased from 143 in 2000 to 343 in 2007 [1]. Epidemiological studies conducted in Europe (EPISEPSIS) and Australia (ANZICS) showed that the frequency of Systemic Inflammatory Response Syndrome (SIRS) in developed industrial countries is 50–100 cases per 100,000 populations. The frequency of Severe Acute Respiratory Syndrome (SARS) in intensive care units is about 18%, as well as, septic shock is about 3-4% [2]. 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 [3,4]. Surgical sepsis accounts for 30% of all cases [5] and is the leading cause of death in surgical wards intensive care unit (ICU). The development of septic shock during planned surgical interventions, mortality reaches 30%, and in emergency - from 39% [6,7]. Prompt diagnosis and treatment of neonatal early-onset sepsis are crucial to prevent severe morbidity and mortality [8]. However, the initial, clinical presentation is often subtle and nonspecific, and commonly used biomarkers have low predictive values for early sepsis, which presents a daily challenge to clinicians involved in neonatal care [9]. Over the years, there has been an urgent need to find a sufficiently sensible and specific laboratory biomarker, which could allow distinguishing between a non-infectious SIRS and sepsis. One of these biomarkers is undoubtedly procalcitonin (PCT). PCT has the highest negative predictive value (87–100%) of all established biomarkers for severe, invasive bacterial infections in neonates. PCT seems to be the best intervention to reduce duration of antibiotic treatment in neonates suspected of early-onset sepsis, because PCT has the highest negative predictive value of all established biomarkers for infection [10,11]. The interpretation of PCT values in neonates is complicated by a physiological increase up to 48 h postpartum, and other perinatal factors—such as chorioamnionitis, hypoxaemia,

perinatal asphyxia, and maternal pre-eclampsia—can also cause it to increase [12]. Reference values of PCT in neonates with and without early-onset sepsis have been established [13,14]. PCT-guided decision making has been used to safely reduce antibiotic treatment in critically ill adults and children with suspected or proven invasive bacterial infections [15,16]. Compliance with antimicrobial stewardship is difficult to obtain and rarely reported in neonatology. In this era of globally increasing antibiotic resistance rates, World Health Organization (WHO) have highlighted the urgent need for enhanced antimicrobial stewardship to address this issue [17-21]. Increasing evidence suggests, however, that every dose of antimicrobial therapy counts in the emergence of antimicrobial resistance and in changing the human microbiome, and other evidence suggests that changes in the microbiome in early life are particularly important in shaping the individual's immune system and future health [22-25]. It is also one of the leading causes of death among critically ill patient [26]. Out of 60 clinical trials that have studied the utility of serum PCT levels for establishing an infectious cause of sepsis, 58 resulted in positive results, and 2 was negative [27]. It is important to identify prognostic factors early as this may necessitate modification of further management. PCT is a precursor of the hormone calcitonin, and is increased early in sepsis and falls rapidly with therapy [28]. PCT has been used in the pediatric population to differentiate sepsis from other non-septic causes of fever/SIRS [29-33]. The past century has witnessed a rising trend in the incidence of infections, sepsis, and septic shock regardless of overwhelming development in treatment modalities [34]. Diagnosis is optimized by using biochemical tests for sepsis, such as C - reactive protein (CRP) or white blood cells (WBC) which have reportedly low diagnostic accuracy and are at times ambiguous [35]. PCT has been used as marker of sepsis with sensitivity and specificity of 83% and 62% respectively with significantly high levels in the patients having sepsis and positive blood culture results than with culture negative results [36,37]. PCT is a glycoprotein present in C cells of thyroid gland. It belongs to the group of related peptide (C-GRP) encoded by the CALC-1 gene and is formed from the common precursor pre-calcitonin [38]. In healthy subjects, CALC-1 genes synthesize Calcitonin, but presence of microbial infection through endotoxin or pro-inflammatory cytokines increases calcitonin gene expression and PCT mRNA is mostly synthesized. This leads to release of PCT from all parenchymal tissue, exclusively in response to bacterial infection only and not viral or inflammatory disease. PCT has a disintegration of ~22–29 h and, during bacterial infections, its levels start to rise 4 h after onset and reach the peak between 12 and 24 h, earlier than C-reactive protein (CRP), which peaks after 2–3 days [39,40]. This makes PCT to be a

specific diagnostic marker to detect bacterial sepsis. On the other hand, serum levels of PCT increase briskly within 2–6 h after the stimulus making it a rapid diagnostic marker compared to culture [41,42].

Both sepsis and septic shock are major health care problems, affecting 20 to 30 million people every year worldwide, with mortality ranging from 10% to 60% with increasing disease severity [43]. The effect of sepsis treatment is extremely time dependent. Survival chance of patients is maximized if antibiotics are administered within 1 h from clinical presentation and each hour of delay in antibiotic administration results in a significant increase of mortality for septic shock [44]. In 2016, Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) jointly proposed a new definition of sepsis as a “life-threatening organ dysfunction caused by a dysregulated host response to infection”. It is important to be able to formulate and recognize the clinical presentation of sepsis, although consideration of serum biomarkers is also a key component of formulating a definitive diagnosis. Therefore, the purpose of this research is to analyze the clinical use of PCT as a biomarker of sepsis.

Materials and methods.

This research is an experimental study which was performed for the period from 2017 to 2019. 82 children were observed with the diagnosis of sepsis, severe sepsis, or septic shock in the Tashkent Medical Academy. The study population constituted all children from newborns to 3 years old patients. All patients were divided into documented bacterial (n=22) versus abacterial inflammation (n=60) infections in order to assess serum PCT concentrations with a cutoff value of >0.5 ng/mL. The traditionally widely used biomarkers of sepsis are cytokines, CRP and 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. 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. 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. 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 (cardiovascular disease) 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 disintegration 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 [45-50]. 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; there must be established diagnostic levels of PCT for differentiation between CVD, sepsis and severe sepsis.

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

• At the 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 the 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".

Research results and discussion.

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. 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. 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.

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. Presepsin (PSP) is a circulating protein which concentration in the blood increases rapidly with the development of systemic infections, sepsis, severe sepsis and septic shock. 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.

In a preliminary study (n=146), it was shown that for detection of sepsis on the day of admission to NTO with signs of CVD, the values of AUC ROC were: for PSP - 0.878, for PCT - 0.668 and for APACHE II - 0.815 [51].

For stratification of patients entering ONT, the following boundary values of the initial levels of PSP (ng / 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. In a multicenter study, it was shown that upon admission to ONT (n = 93), the boundary levels of PSP (ng / 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%.

In another study, 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 ng / 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.

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 [52].

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=114) who entered 117 different NTOs 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) [53]. 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.

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%) [54]. 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.

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 [55]. 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.

In another multicenter study of patients admitted to ICU with sepsis and septic shock (n = 100), it was shown [56]:

• 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.

SRP in monitoring sepsis therapy. The marker of disintegration 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 its determination in urine, it was found that disintegration in circulation is from 30 minutes to 1 hour. 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 average 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".

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.

It should be emphasized 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 amounts was found to be 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 NTO 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 average values of PSP (ng / 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 ng / ml, sensitivity - 85.7%, specificity - 84.0%. In the absence of sepsis, PSP remained below 1600 ng / ml.

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.

Cases associated with rheumatoid arthritis. 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.

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".

Cases associated with cirrhosis. 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”.

Cases associated with 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; average - 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.

Cases associated with pancreatic necrosis. 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".

Cases associated with acute kidney damage. 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.

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.

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.

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.

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.

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".

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.

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.

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.

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.

PCT has developed as an ideal biomarker for sepsis and early detection of bacteremia. Early diagnosis of sepsis is difficult issue in pediatric practice, whilst it can be vital for positive patient outcomes in sepsis management. Any delay in diagnosis and treatment may bring on multiple organ failure and can be hazardous with elevated mortality consequences. Early diagnosis and effective management of sepsis not only gives an opportunity for prompt antibiotic therapy and a potential decrease in mortality, it can also belittle the unnecessary use of antibiotics. The study concluded that only 19 (86,3%) of the patients with bacterial infections met their cutoff value (>0.5 ng/mL). PCT can differentiate between bacterial infections without etiologic organism and other severe inflammatory processes that are also illustrating with an increase of classic inflammatory biomarkers, such as CRP, IL-1 and IL-6.

Consequently, this data supports the utility of PCT as an effective management to establish an adequate diagnosis of sepsis. The study displayed a positive correlation between serum PCT concentrations and SOFA scores (p =<0.001), illustrating that when the serum PCT concentrations increase, end-multiorgan failure worsened by APACHE II and the Multiple Organ Dysfunction Score. Serum PCT concentrations have been noted in patients that do not have sepsis, although concentrations are usually not very high (< 2 ng/mL).

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. PCT and 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. The results of international and domestic studies suggest that PCT and PSP is a very effective marker for the early diagnosis and monitoring of systemic infections.

8. Preliminary results suggest that PCT and PSP is a very promising marker of extensive infectious complications in diseases of various etiologies.

9. To have a specific and sensitive biomarker like PCT and PSP would be valuable for early diagnosis and management of patients with sepsis in order to reduce mortality.

10. PCT and PSP can be early marker for physicians for reducing the duration of antibiotic treatment, minimizing sepsis-associated complications, morbidities and deaths as well.

11. Interpretation of PCT and PSP levels is a navigator for appropriate antibiotic therapy.

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