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# PROCALCITONIN-EARLY BIOCHEMICAL MARKER FOR DIAGNOSIS, PROGNOSIS, AND TREATMENT OF SEPSIS IN NEONATES AND ONCOLOGICAL PATIENTS WITH FEBRILE NEUTROPENIA

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**Abstract**

Pediatric sepsis is a life-threatening condition, in which the immune system, instead of controlling the infection,causes damage to tissues and organs. The aim of this study was to determine the role of procalcitonin (PCT)in the early diagnosis of sepsis in high-risk infants and Oncological patients with febrile neutropenia,its prognostic value,and the role of PCT in the choice of antibiotic.

The study is designed as retrospective-prospective, it is being worked at the PHI UC for Children Diseases Skopje. It includes 60 critical newborns and 40 Oncology patients.The examined group were divided into two subgroups:30 critical infants with bacterial sepsis in the intensive care unit and 20 Oncological patients with sepsis and febrile neutropenia.PCT was determined the first 24h,3-5 days and 6-14 days of hospitalization.The value of PCT during the first 24 hours of admission was increased in all 50 patients.Most of them had signs of severe sepsis and few od them had signs of septic shock. In all of them,double parenteral antibiotic therapy was started.Seven patients has died in the first five days.After 3-5 days of the start of antibiotic therapy, PCT values decreased.After the third measurement, PCT values continued to decrease and in majority of the patients the antibiotic therapy was discontinued.

By measuring the values of PCT, an early diagnosis of sepsis can be made. This is important to start with antibiotics to prevent sepsis and septic shock.The dynamic in the values of PCT determine the duration of antibiotic,its modification,the rational uses of antibiotics and the emergence of resistance to it.

***Keywords:*** sepsis, procalcitonin (PCT), antibiotic therapy

## Introduction

Sepsis is a leading cause of mortality in infants and hemato-oncology patients, characterized by severe systemic inflammation, tissue damage and impaired systemic inflammatory response [1]. It is a life-threatening condition, caused by microorganisms which consist a spectrum of disorders, in which the immune system instead of controlling the infection, causes damage to its own tissues and organs [2]. Early detection and initial treatment significantly improve the outcome in newborns and hemato-oncology patients with sepsis induced infections. Adequate and timely treatment should lead to stabilization and correction of metabolic, circulatory and respiratory disorders.

The use of appropriate antibiotic therapy and fluids should be started immediately after evaluation. Improper sepsis treatment can lead to development of severe sepsis and septic shock. Sepsis is characterized by microbial invasion into the blood, with early sings of circulatory disorders involving: tachycardia, tachypnea, peripheral vasodilation, and fever (or hypothermia), to circulatory collapse with multiple organic dysfunction syndrome and death [3].

The incidence of sepsis, severe sepsis and septic shock continues to increase. Although Gram-positive bacterial pathogens remain the most common cause of sepsis, fungal microorganisms are on the rise as well [3,4].

Over the past half-century, a significant progress in diagnosis and treatment of patients with sepsis is being made while, the mortality rate decrease. Diagnosis of infection caused by bacteria or other microbiological organisms is essential for effective treatment and prognostic evaluation [5,6]. Current clinical and laboratory methods for diagnosing bacterial infections are either nonspecific or require longer time to develop the agent. Procalcitonin (PCT) is a biomarker that exhibits greater

specificity than other proinflammatory markers in identifying pediatric patients with sepsis and can be used to diagnose bacterial infections[6].

Production is activated in all parenchymal tissues in response to bacterial infection mediated by cytokines interleukin-6 (IL-6), tumor necrosis factor-α (TNFα) and interleukin-1β (IL-β). On the other side, PCT production is attenuated by interferon-γ primarily secreted in response to viral infection.This feature makes PCT a more specific marker for bacterial infection [7].

In healthy pediatric patients the level of PCT is below 0.05 ng/ml. During the systemic inflammation, blood concentrations of PCT increase, mostly when it is caused by a bacterial infection [8]. When the PCT concentration exceeds 0.25ng / ml, the risk of local bacterial infection occurs. The risk of systemic bacterial infection occurs when the PCT level exceed 0,5 ng / ml [9]. It is shown that bacterial lipopolysaccharide (LPS) is a potent inducer of PCT release in systemic circulation. In the organism the PCT is detected 3 to 4 hours after the infection, reaches its peak after 6 hours and the plateau for up to 24 hours. The half-life of PCT in the blood is between 25 and 30 hours [10]. The dynamics of procalcitoninot (PCT) concentration determine the duration of antibiotic therapy or its modification [11].

**Objectives**

The aims of this study are:

1. To determine the role of procalcitonin as a marker in the early diagnosis of sepsis in high risk newborns.
2. To determine the role of procalcitonin in high risk newborns and hemato-oncology patients with febrile neutropenia in order to evaluate the prognostic values of this diagnostic method.
3. To determine the role of procalcitonin in the diagnosis of bacterial sepsis in pediatric hemato-oncology patients with febrile neutropenia.
4. To determine the role of procalcitonin in the choice and duration of antibiotic therapy in the managment of sepsis.

**Materials and Methods**

The study was designed to be retrospective and prospective and it was developed at JZU University Clinic for Pediatric Diseases – Skopje.

The study covers 60 high-risk newborns and 40 hemato-oncology patents with febrile neutropenia divided into two groups: Experimental and Control group.

Experimental group of 50 pediatric patients diagnosed with sepsis according to the standards protocols on disease diagnosis. The Experimental group is divided into two subgroups:

1. Subgroup of 30 high-risk newborns diagnosed with sepsis (PCT ≥2 ng/mL) at the Intensive Care and Therapy Department.
2. Subgroup of 20 hemato-oncology patients with febrile neutropenia diagnosed with sepsis (PCT ≥2 ng/mL) at the Hematology and Oncology Department.

Control group of 50 patients at the same age with an infection and sings of inflammation without proven sepsis according to the standards protocols on disease diagnosis.

The diagnosis of sepsis concerning the pediatric patients is diagnosed according to the standard protocols on disease diagnosis.

The PCT and the other markers of inflammation (WBC, Neu%, CRP) are produced at the Clinical Laboratory of JZU University Clinic for Pediatric Diseases – Skopje.

The PCT is determined through an immunological method: patented ELFA (Enzyme-linked fluorescent assay) technology, automated immunoanalyzer Vidas Biomerieux (ng/ml).

The PCT value of healthy persons is under 0.05 ng/ml. Sepsis occurs when the PCT value is over 0.5 ng/m; high PCT values of over 2 ng/ml appear in severe sepsis and septic shock. First PCT sample is obtained within 24 hours from hospitalization.Second PCT sample is obtained within 3-5 days and with commenced appropriate antibiotic treatment. Third sample of PCT is obtained within 6-

14 days. In case of enormous surges of PCT values, we start with double dose of antibiotic therapy that includes treatment with Meropenem and Vancomycin. The therapy starts immediately

upon the first hemoculture and, if applicable, we additionally include polyclonal intravenous immunoglobulin.

**Results**

During the first 24h from the admission at the hospital, the values of PCT were elevated in all 30 newborns and in all 20 hemato-oncology patients (PCT ≥2 ng/mL).

According to the gestational age of the experimental group, seven newborns were born spontaneously between 37-42 weeks of pregnancy. Eight were moderately to late preterm, born between 32-37 weeks of pregnancy, ten were very preterm, born between 27-32 weeks of pregnancy, and five of them were extremely preterm, born between 22-27 weeks of pregnancy. Fifteen of them were admitted due to asphyxia, and the other fifteen were admitted due to Respiratory Distress Syndrome. Twelve newborns had clinical signs of severe sepsis, and five had septic shock (PCT>10 ng/mL) [fig.1]. In 24 newborns, immunoglobulins and combined antibiotic therapy with Meropenem and Vancomycin were initiated according to the protocol of severe sepsis. The rest of them started with combined antibiotic therapy with Meropenem and Amikacin. Six newborns ended up with lethal outcome in the first five days. During the second measurement, 3-5 days after starting the antibiotic therapy, the PCT values started to decrease regardless of whether the results of the hemoculture showed positive or negative findings. After the third measurement (6-14 days) the levels of PCT decreased. In seven newborns the antibiotic therapy was excluded and in the rest seventeen newborns, the antibiotic therapy was excluded on the twenty first day [fig. 2].

The hemato-oncology patients had clinical signs of sepsis and febrile neutropenia and fever (>38C) over two hours, and also neutrophils < 0,5 x 10^9. The patients who had receiving more aggressive hematological therapy, have had severe clinical signs.

They were divided into two subgroups: fifteen hemato-oncology patients with white blood cells proliferation, and five hemato-oncology patients with solid tumors. Nineteen hemato-oncology patients had clinical signs of severe sepsis a one had septic shock (fig. 1). In thirteen hemato-oncology patients combined antibiotic therapy was initiated according to the protocol for severe sepsis, with Meropenem and Amikacin and in the other seven patients, combined antibiotic therapy with Vancomycin and Amikacin was initiated. One patient has had a fatal outcome in the first five days. During the second measurement, 3-5 days after the start of appropriate antibiotic therapy, the PCT values decreased, regardless of whether the results of the hemoculture showed positive or negative findings. After the third measurement (6-14 days) the levels of PCT decreased. In 15 hemato-oncology patients the antibiotic therapy was excluded and in the rest four patients, the antibiotic therapy was excluded on the twenty first day [fig. 2].

Newborns with proven bacterial infection and children with febrile neutropenia have high levels of PCT. The level of PCT is associated with changes in other inflammatory markers. In case of clinical sepsis, the PCT can be an early diagnostic and prognostic biomarker. Successful treatment with combination of two antibiotics and immunotherapy results with normalization of PCT levels.

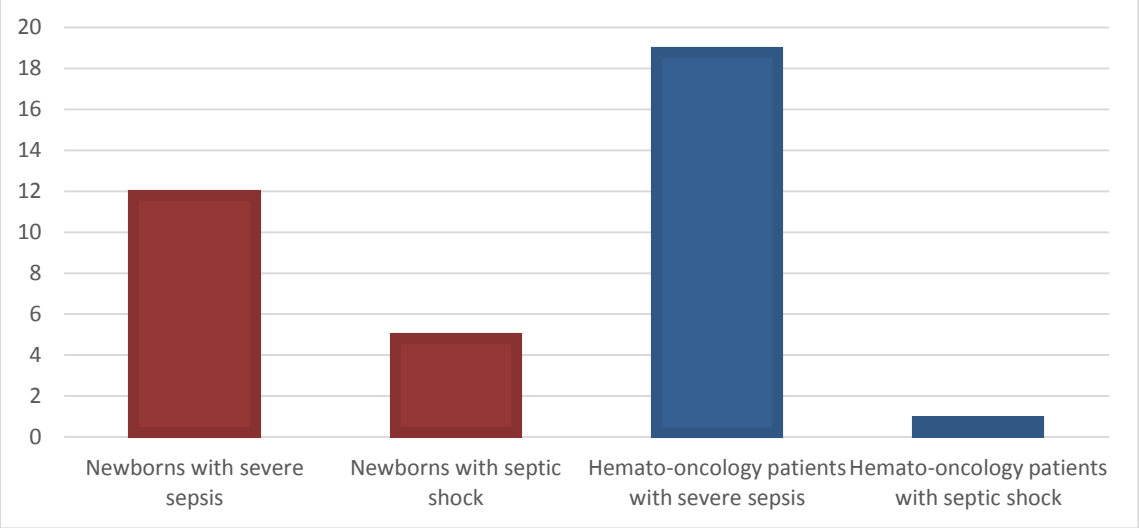


**Figure 1**. The ratio of Newborns and Hemato-oncology patients with severe sepsis and septic shock

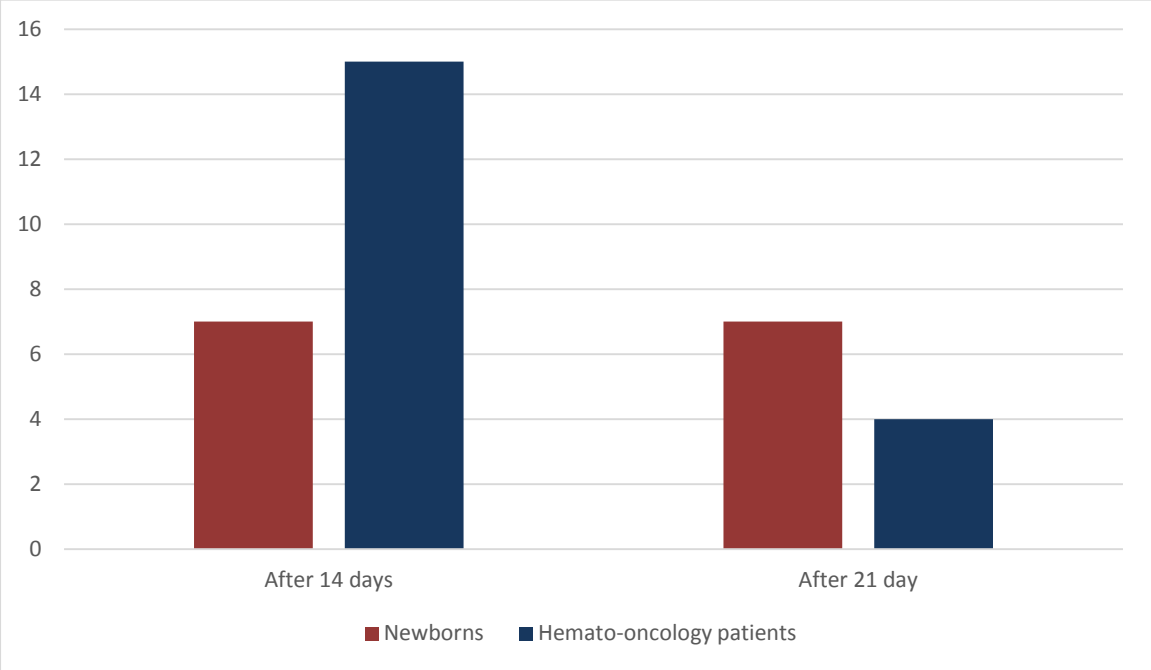


**Figure 2**. The ratio of Newborns and Hemato-oncology patients, 14 and 21 day after excluding antibiotic therapy.

**Discussion**

New findings from the latest research about the levels of PCT and its sensitivity and specificity in early diagnosis of sepsis in pediatric patients have been described in a large number of studies [12]. PCT can be detected in the body only 3-4 hours after the infection has started, and it reaches its maximum in 6 hours, and a plateau up to 24h. On the contrary, the levels of CRP (C-reactive protein) increases between 12 and 36 hours from the beginning of the infection [13]. In the blood, the PCT has a half-life of 25-30 hours. The levels of PCT increase during a systematic inflammation, especially those with bacterial etiology [14]. The risk of local bacterial infection becomes significant when the levels of PCT exceed 0.25 ng/ml. The risk of a systematic bacterial infection becomes significant when the levels of procalcitonin exceed 0.5 ng/ml, whilst the levels of

procalcitonin are very high in cases of severe sepsis and septic shock. Patients with enormously high levels of PCT usually have a lethal outcome, which gives it an important role in the prognosis of sepsis [14,15]. Studies show that the early diagnosis and the positive response from the given therapy lead to better outcome in pediatric patients with infections that lead to sepsis. This opens up a whole new perspective in the use of PCT as a marker of choice in the early diagnosis and determining the duration of the antibiotic treatment in pediatric patients with sepsis [16,17]. There are many studies from the Cochrane medical database which claim that intravenous polyclonal immunoglobulins reduce the death rate in sepsis, whilst monoclonal antibodies aren't that efficient, although there is still not enough proof [18]. Also, studies have shown that low doses of corticosteroids over 5 days are effective in increasing the possibility of surviving septic shock without causing damage [19].

The addition of aminoglycosides to beta-lactam cones in sepsis manure does not demonstrate clinical efficacy relative to self-administration of beta lactams. Combined treatment carries the risk of nephrotoxicity [20,21].

Other studies have shown that in febrile patients with granulocytopenia (neutropenia), the therapy, including beta-lactam with a broad spectrum, such as third-generation cephalosporin 3 (ceftazidime or ceftriaxone) plus single ammonoglycoglycosidic must be initiated after checking the haemoculture [22]. Patients with neutropenia may develop sepsis if they remain unresponsive to antibiotic therapy for several hours after fever [23,24]. Changing the antibiotic therapy, based on changing the course of the infection and the response to the therapy prevents the onset of severe sepsis and septic shock [25].

From the studies above, we can see the importance of PCT as an early biochemical marker for the diagnosis and prognosis of sepsis in pediatric patients, which shows greater specificity and sensitivity than other proinflammatory markers.

The dynamics of procalcitoninot (PCT) concentration determine the duration of antibiotic therapy or its modification

**Conclusion**

Sepsis in newborns is a life-threatening condition, caused by microorganisms which consist a spectrum of disease, in which the immune system instead of controlling the infection, leads to damaging the own tissues and organs.Early detection and treatment significantly improve the outcome in newborns and hemato-oncology patients with febrile neutropenia with sepsis-induced infections.The PCTisan early marker for the diagnosis and prognosis of sepsis in newborns and hemato-oncology patients with febrile neutropenia.We examined a group of 50 pediatric patients diagnosed with sepsis according to standard diagnostic protocols.

The PCT values were increased at the time of patients' admission with sepsis, while the values of other inflammatory marker (C-reactive protein, leukocytes, neutrophils) gradually increased.

It is very important in initiating appropriate antibiotic therapy as well as immunotherapy according to the standard therapy protocol in order to prevent worsening of the condition to the development of severe sepsis and septic shock.The dynamics in the values of procalcitonin also determine the duration of antibiotic therapy or its modification, thus contributes in the non-rational use of antibiotics, the emergence of their resistance and a great financial benefit.

**References**

1. Angela W.S. Fung, Daniel Beriault, and Eleftherios P. The Role of Procalcitonin in Diagnosis of Sepsis and Antibiotic Stewardship: Opportunities and Challenges.Clinical Chemistry 63:9 1436–1441 (2017).
2. Becker KL, Snider R, Nylen ES. Procalcitonin in sepsis and systemic inflammation: a harmful biomarker and a therapeutic target. Br J Pharmacol 2010;159:253– 64.
3. Sager R, Kutz A, Mueller B, and Schuetz P. Procalcitoninguided diagnosis and antibiotic stewardship revisited. BMC Medicine 2017;15:15.
4. Meisner M. Update on procalcitonin measurements. Ann Lab Med. 2014 Jul;34 (4):263-73.

5. Broyles MR. Impact of procalcitonin-guided antibiotic management on antibiotic exposure and outcomes: realworld evidence. Open Forum Infect Dis 2017;4:4.
6. Huang DT, Yealy DM, Filbin MR, Brown AM, Chang CH, Doi Y, et al. Procalcitonin-guided use of antibiotics for lower respiratory tract infection. N Engl J Med 2018;379: 236 – 49.
7. Linscheid P, Seboek D, Nylen ES, Langer I, Schlatter M, Becker KL, et al. In vitro and in vivo calcitonin I gene expression in parenchymal cells: a novel product of human adipose tissue. Endocrinology. 2003;144:5578–84.
8. Dellinger RP, Carlet JM, Masur H, et all; Surviving Sepsis Campaign Management
   a. Guidelines Committee. Surviving Sepsis Campaign guidelines for management of
   b. severe sepsis and septic shock. Crit Care Med. 2004 ;32(3):858-73. Review.
9. Llewelyn M, Cohen J; International Sepsis Forum. Diagnosis of infection in sepsis.
   c. Intensive Care Med. 2001;27 Suppl 1:S10-32. Review.
10. Giunti M, Peli A, Battilani M, Zacchini S, Militerno G, Otto CM. Evaluation of CALC-I gene (CALCA) expression in tissues of dogs with signs of the systemic inflammatory response syndrome. J Vet Emerg Crit Care (San Ant. 2010 Oct;20 (5):523-7.
11. Lee H. Procalcitonin as a biomarker of infectious diseases. Korean J Intern Med. 2013 May;28 (3):285-91
12. Schneider HG, Lam QT. Procalcitonin for the clinical laboratory: a review. Pathology. 2007 Aug;39 (4):383-90.
13. Kim H, Kim Y, Lee HK, Kim KH, Yeo CD.Comparison of the delta neutrophil index with procalcitonin and C-reactive protein in sepsis.Clin Lab. 2014;60(12):2015-21.
14. Fioretto J. R. et al.. Comparison between procalcitonin and C-reactive protein for early diagnosis of children with sepsis or septic shock. Inflamm. Res. 59, 581–586 (2010).
15. Jensen JU, Heslet L, Jensen TH, Espersen K, Steffensen P, Tvede M.Procalcitonin increase in early identification of critically ill patients at high risk of mortality.Crit Care Med. 2006 Oct; 34(10):2596-602.
16. Kim H, Kim Y, Lee HK, Kim KH, Yeo CD.Comparison of the delta neutrophil index with procalcitonin and C-reactive protein in sepsis.Clin Lab. 2014;60(12):2015-21.
17. Groselj-Grenc M, Ihan A, Pavcnik-Arnol M, Kopitar AN, Gmeiner-Stopar T, Derganc M.Neutrophil and monocyte CD64 indexes, lipopolysaccharide-binding protein, procalcitonin and C-reactive protein in sepsis of critically ill newborns and children.Intensive Care Med. 2009 Nov;35(11):1950-8. doi: 10.1007/s00134-009-1637-7.
18. Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. BMC Med. 2011;9:107.
19. Ugarte H, Silva E, Mercan D, De Mendonça A, Vincent JL. Procalcitonin used as a marker of infection in the intensive care unit. Crit Care Med. 1999;27:498–504.
20. Hansson LO, Lindquist L. C-reactive protein: its role in the diagnosis and follow-up of infectious diseases. Curr Opin Infect Dis. 1997;10:196–201.
21. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Calandra T, Feld R, Pizzo PA, Rolston KVI, Shenep JL, Young LS. Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis. 2002;34:730–51. doi: 10.1086/339215.
22. Caterino J. M., Scheatzle M. D., Forbes M. L. & D'Antonio J. A. Bacteremic elder emergency department patients: procalcitonin and white count. Acad. Emerg. Med. 11, 393–396 (2004).
23. Katz JA, Mustafa MM, Bash RO, Cash JV, Buchanan GR. Value of C-reactive protein determination in the initial diagnostic evaluation of the febrile, neutropenic child with cancer. Pediatr Infect Dis J. 1992;11:708–712.
24. Giamarellos-Bourboulis EJ, Grecka P, Poulakou G, Anargyrou K, Katsilambros N, Giamarellou H. Assessment of procalcitonin as a diagnostic marker of underlying infection in patients with febrile neutropenia. Clin Infect Dis. 2001;32:1718–1728.

25. Castelli GP, Pognani C, Meisner M, Stuani A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. Crit Care. 2004;8:R234–R242.