ZKTB

ORIGINAL RESEARCH

Assessment of Procalcitonin as Diagnostic Marker in Children with Neutropenic Fever

Prokalsitonin'in Çocukluk Çağı Nötropenik Ateşinde Tanısal Değeri

Nilufer Eldes HACIFAZLIOGLU [1], Aynur OGUZ [2]
Ceyda KARADENIZ [2], Caglar Elvan CITAK [3]

1. Zeynep Kamil Maternity and Training Hospital, Pediatric Neurology, Istanbul, Turkey
2. Gazi University, Medicine Faculty, Pediatric Oncology Clinic, Ankara, Turkey
3. Mersin University, Medicine Faculty, Pediatric Oncology Clinic, Mersin, Turkey

ABSTRACT

Objective: *The aim of this study is to predict the usefulness of procalcitonin (PCT) for diagnosis of systemic and bacterial infections in children with neutropenic fever.*

Material and Method: *In this study 46 neutropenic fever attacks of the 32 cancer patients were evaluated. Newly diagnosed 35 cancer patients were selected as controls. Serum levels of PCT and CRP (C- reactive protein) were determined on the first and third days of fever and at the end of the antimicrobial therapy in study group. Neutropenic fever episodes were classified as fever of unknown origin (FUO), microbiologically and clinically documented infection (MDI, CDI). MDI were further subdivided into two groups as systemic and localized infection.*

Results: *Serum levels of PCT were highest on the first day of neutropenic fever in MDI group. The levels of PCT were higher in systemic infections than localized ones. There was no difference for the serum levels of CRP in FUO, CDI and MDI or systemic and localized infections. The PCT levels rapidly decreased to the normal range by resolution of fever with successful antimicrobial therapy.*

Conclusion: *We conclude that serial measurement of serum PCT levels is more sensitive and specific than that of CRP for diagnosis and sequential assessment of febrile neutropenic episodes.*

Keywords: *procalcitonin, neutropenic fever, children*

ÖZET

Amaç: *Bu çalışmanın amacı çocukluk çağı nötropenik ateşinde prokalsitonin (PCT)'in bakteriyel ve sistemik enfesiyonların tanısı ve izlenmesindeki yararlılığının tespit edilmesidir.*

Gereç ve Yöntem: *Bu çalışmada 32 kanser tanısı ile izlenen hastanın 46 nötropenik atağı değerlendirilmiştir. 35 yeni kanser tanısı alan olgu da kontrol grubu olarak seçilmiştir. Çalışma grubundaki olguların, ateşin 1. ve 3. günü ile antibiyotik tedavisinin sonunda; kontrol grubundaki olguların ise kanser tanısı aldıkları gün serum PCT ve CRP (C- reaktif protein) değerleri ölçülmüştür. Nötropenik ateş atakları; nedeni bilinmeyen ateş, mikrobiyolojik olarak kanıtlanmış enfeksiyon ve klinik olarak kanıtlanmış enfeksiyon olarak üç gruba ayrılmıştır. Mikrobiyolojik olarak kanıtlanmış infeksiyon grubu da; lokalize ve sistemik enfeksiyon olarak iki alt gruba ayrılmıştır.*

Bulgular: *Mikrobiyolojik olarak kanıtlanmış enfeksiyon grubunda en yüksek serum PCT düzeyi enfeksiyonun ilk gününde tespit edilmiştir. Serum PCT düzeyleri; sistemik enfeksiyonu olan olgularda, lokalize enfeksiyonu olan olgulara göre daha yüksek tespit edilmiştir. Nedeni bilinmeyen ateş, klinik ve mikrobiyolojik olarak kanıtlanmış enfeksiyon, lokalize enfeksiyon ve sistemik enfeksiyon gruplarında; serum CRP düzeyleri açısından farklılık saptanmamıştır.*

Sonuç: *Bu sonuçlar bize serum PCT düzeyinin bakteriyel ve sistemik infeksiyonun tanısı ve izleminde CRP'ye göre daha özgül ve duyarlı bir serum belirteci olduğunu düşündürmüştür.*

Anahtar Kelimeler: *prokalsitonin, nötropenik ateş, çocuk*

Contact:
Corresponding Author: Dr. Nilufer Eldes Hacifazlioglu
Address: Zeynep Kamil Maternity and Training Hospital, Pediatric Neurology, Istanbul, Turkey
Tel: +90 (216) 391 06 80
E-mail: niluferhacifazlioglu@gmail.com
Submitted: 01.12.2015
Accepted: 18.01.2016
DOI: http://dx.doi.org/10.16948/zktb.71019

INTRODUCTION

Severe infections are the major cause of mortality and morbidity in pediatric cancer patients because of immunsuppression due to the underlying primary malign disease and intensive chemotherapy related neutropenia. Approximately 60% of febrile neutropenic episodes were caused by bacterial infections with or without bacteriaemia. Timely and adequate treatment of invasive infections during neutropenia is critical because the development of septic shock may be rapid and outcome can be fatal [1].

Therefore early diagnosis of severe infections, prompt hospitalization and initiation of adequate broad spectrum anti-microbial therapy are essential for the successful treatment of febrile episodes. For that reason, new biochemical markers that are specific and sensitive for bacterial infections are needed. C-reactive protein (CRP) is one of the acute phase reactants used in the diagnosis of neutropenic fever. However its serum level correlates with the grade of tissue damage and primary malign disease and does not increase significantly until 24-48 h after onset of inflammation [2].

Another biochemical marker of inflammation is procalcitonin (PCT). It's composed of 116 amino acids with the same sequence of the prohormon of calcitonin synthesized in the C cells of the thyroid gland. Recent reports demonstrated that serum PCT level is significantly elevated in bacterial and systemic infections and does not change in viral and localized infections [3-11].

MATERIAL AND METHOD

Our study group consisted of 46 neutropenic fever attacks of 32 pediatric cancer patients (aged 0-16 years, 18 girls, 14 boys) undergoing intensive chemotherapy referred to our.

Pediatric Oncology Department of Gazi University, Ankara, Turkey between June 2002 and May 2003. Newly diagnosed, untreated 35 pediatric cancer patients (aged 0-16 years, 16 girls, 19 boys) without infection were selected as control group. Among the neutropenic patients 17 (36.9%) had central venous line and none of them were in antimicrobial prophylaxis.

The age, gender and the underlying diseases of patients were listed in Table I.

Table I: Patients' characteristics in the different diagnostic groups.

Diagnostic Group	Patients with neutropenic fever	Newly diagnosed cancer patients
Number	32	35
Age (median/range;years)	7.65±4.1(0-16)	7.9±4.6(1-17)
Gender (female/male)	18/14	16/19
Malignencies		
NHL	11 (34.4%)	7(20%)
HH	1 (3.1%)	2 (5.7%)
RMS	3 (9.4%)	
NBL	8(25%)	1(2.9%)
WILMS	2(6.3%)	5(14.3%)
CNS TUMOR	2(6.3%)	6(23.4%)
Germ cell tumors	1 (3.1%)	3(11.7%)
AML/ALL	3 (9.4%)/ 1 (3.1%)	1(2.9%)/6(23.4%)
Leiomyosarcoma		1(2.9%)
Tiroid carsinoma		1(2.9%)
Ewing sarcoma		1(2.9%)
Hepatoblastoma		1(2.9%)
Stage		
Stage I	1 (3.6%)	3 (2.6%)
Stage II	3(9.4%)	8(22.9%)
Stage III	12 (42.9%)	8(22.9%)
Stage IV	12(42.9%)	9(25.7%)

NHL: Non-Hodgkin Lymphoma, HL: Hodgkin Disease, RMS: Rhabdomyosarcoma, NBL: Neuroblastoma, AML: Acute myeloblastic leukemia, ALL: Acute lymphoblastic leukemia.

Depending on the kind of diagnosis of infection; neutropenic fever episodes were classified as fever of unknown origin (FUO), microbiologically and clinically documented infection (MDI, CDI). MDI were diagnosed by positive cultures of urine, blood, catheter and faeces; CDI were diagnosed by positive clinical symptoms of sinusitis and pneumonia supported by diagnostic methods. Then MDI were subdivided into two groups; localized infection and systemic infections on which blood cultures yielded positive results. The origins of infections and microorganisms obtained from the cultures are listed in Table II and Table III.

Table II: Origins of infections in microbiologically documented and clinically documented infections.

ORIGINE OF INFECTION	MDI (n=20)	CDI (n=6)
Urinary Tract Infection	8(7.3%)	
Catheter infection	3(6.5%)	
Sinusitis		3(6.5%)
Acute gastroenteritis	2(4.3%)	
Soft tissue infection	1(2.2%)	1(2.2%)
Wound infection	1(2.2%)	
Pneumonia	1(2.2%)	2(2.15%)
Septicemia	3(21.2 %)	

MDI: Microbiologically documented infection, CDI: Clinically documented infection.

Table III: Microorganisms documented by microbiologically methods.

ORIGINE OF INFECTION	MICROORGANISM
Urinary Tract Infection (n=8)	Escherichia Coli (n=4)
	Klebsiella (n=3)
	Proteus(n=1)
Catheter infection (n=4)	Staphylococcus aureus(n=2)
	Candida spp. (n=2)*
Pneumonia (n=1)	Candida spp(n=1) **
Wound Infection (n=1)	Staphylococcus aureus(n=1)
Septicemia (n=4)	Staphylococcus aureus(n=3)
	Candida spp(n=1)

**Candida spp. identified in blood cultures of patients with pneumonia, ** Both Candida spp. and S. Aureus identified in blood cultures of the same patient.*

During febrile episodes blood samples were obtained by venipuncture from all patients on the first and third day of neutropenic fever and at the end of the antimicrobial therapy. In control group, blood samples were obtained at admission in newly diagnosed cancer patient before the initiation of intensive chemotherapy. Serum samples were centrifuged at 5000/bpm for 3 minutes then stored at –40°C. All serum samples were analyzed on the same day. PCT was determined by an immunoluminometric assay (LUMItest-PCT, B.R.A.H.M.S Diagnostica) and CRP was determined by nephelometric method (Beckman Coulter specific protein analysater). Normal range for CRP is 0-6 mg/dl. The data of this study were evaluated using descriptive statistical methods (mean, standard deviation, ranges).

Mann Whitney U test and t- test were used for comparison of two groups; Kruskal Wallis variant analysis and one-way ANOVA were used for the comparison of more than two groups. A p-value less than 0.05 was considered significant. The diagnostic relevance was estimated as sensitivity (true positives/ total patients and specificity (true negatives/ total patients). Statistical calculations were done with the SPSS 10.0 software package for windows.

RESULTS

Serum levels of PCT and CRP on the first day of neutropenic fever were compared with those of control group. Mean PCT serum levels (1.32 ± 0.41 ng/ml) in the study group were higher than the control group (0.23 ± 0.04 ng/ml). In addition, mean CRP serum levels (58.5±9.5 mg/dl) in study group and in control group (13.73 ± 4.25 mg/dl) were different. The difference between two groups for both PCT and CRP were statistically significant ($p< 0.05$) (Figure 1).

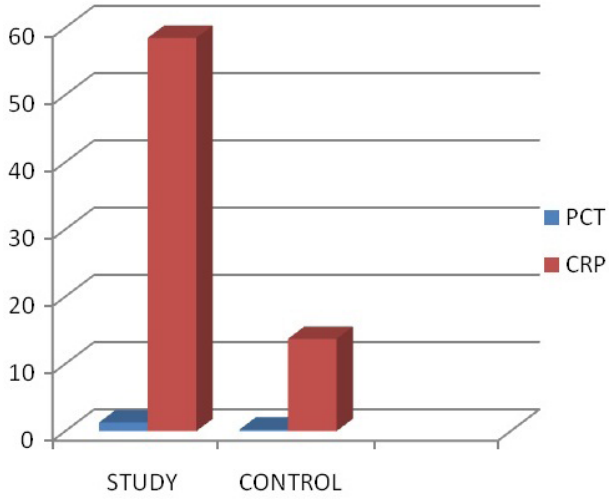

Figure 1: Serum levels of PCT and CRP on the first day of neutropenic fever.
PCT: ng/ml, CRP: mg/dl

Both on admission and during the course of neutropenic fever there were no difference between the serum levels of PCT and CRP of high risk (presence of mucositis, fever >10 days, duration of neutropenia >10 days, absolute neutrophil count (ANC) ≤ 0.1 x 10^3/L and low risk patients. The highest serum PCT levels in microbiologically documented infections on the third day of neutropenic fever and the lowest at the end of the antimicrobial therapy in FUO were predicted. Although there were no

differences between three groups for serum levels of CRP at admission and during the course of neutropenic fever; serum PCT levels in MDI, CDI and FUO are significantly different on the third day of fever and at the end of the antimicrobial therapy ($p< 0.05$) (Table IV). Both on admission and during the course of neutropenic fever there were no difference between the serum levels of PCT and CRP of high risk (presence of mucositis, fever >10 days, duration of neutropenia >10 days, absolute neutrophil count (ANC) $\leq 0.1 \times 10^3$/L and low risk patients. The highest serum PCT levels in microbiologically documented infections on the third day of neutropenic fever and the lowest at the end of the antimicrobial therapy in FUO were predicted. Although there were no differences between three groups for serum levels of CRP at admission and during the course of neutropenic fever; serum PCT levels in MDI, CDI and FUO are significantly different on the third day of fever and at the end of the antimicrobial therapy ($p< 0.05$) (Table IV).

For the group of patients who presented with localized infections with gram negative bacilli, the mean PCT levels on the first and third day of fever and at the end of the antimicrobial therapy were 1.22±0.47 ng/ml, 0.94±0.86 ng/ml, 0.42±0.04 ng/ml; for the patients with localized infections caused by gram positive cocci the mean PCT levels were 1.17±0.52 ng/ml, 0.38±0.07 ng/ml, 0.39±0.04 ng/ml respectively; the values were also similar ($p> 0.05$).

We established specificity, sensitivity, positive predictive value and negative predictive value for different values of PCT at the first day of fever in MDI, CDI, and FUO, systemic and localized infections (Table V, VI).

There was a positive correlation on the first day of fever between serum levels of CRP and PCT ($r=0,419$; $p=0.001$). There was no correlation between these markers on the third day of fever and at the end of the antimicrobial therapy.

Table IV: Serum levels of PCT and CRP on the first and third day of neutropenic fever and at the end of the antimicrobial therapy.

	MDI (n=20) (Mean ±SS)	CDI (n=6) (Mean ±SS)	FUO (n=20) (Mean ±SS)	p	Localized Infections (n=14) (mean ±SS)	Sysemic Infections (n=6) (mean ±SS)	p
PCT (ng/ml)							
1. measure	22.27±0.90	1.63±0.52	0.28±0.06	>0.05	1.11±0.26	5.51±2.62	<0.01
2. measure	0.97±0.28	0.79±0.33	0.22±0.05	<0.05	0.67±0.17	1.78±0.73	<0.01
3. measure	0.33±0.03	0.39±0.05	0.18±0.04	<0.05	0.36 ±0.03	0.30 ±0.06	<0.05
CRP (mg/dl)							
1. measure	70.12±18.49	56.55±13.57	47.62±11.22	>0.05	61.59±15.89	85.00±35.48	>0.05
2. measure	55.04±12.62	69.33±57.41	42.71±12.25	>0.05	48.24±18.13	92.00±29.72	>0.05
3. measure	36.34±12.89	16.65±8.24	16.65±8.24	>0.05	13.04±4.06	78.33±7.92	<0.05

1. measure: First day of fever, 2. measure: Third day of fever, 3. measure: At he end of the antimicrobial therapy .

Table V: Diagnostic relevance of different PCT cut-off values in predicting systemic infection.

PCT ng/ml	Spesificity (%)	Sensitivity (%)	PPV (%)	NPV(%)
≥0.5	66	55	66	45
≥1.0	83	35	83	65
≥1.5	100	20	100	80

PPV: Positive predictive value, NPV: Negtive predictive value.

Table VI: Diagnostic relevance of different PCT cut-off values in predicting microbiologically documentedinfection.

PCT ng/ml	Spesificity (%)	Sensitivity(%)	PPV (%)	NPV(%)
≥0.5	60	68	95	68
≥1.0	88	45	75	68
≥1.5	88	25	62	88

PPV: Positive predictive value, NPV: Negtive predictive value.

DISCUSSION

Although serum PCT levels are markedly elevated in immunocompromised children and adults with sepsis, meningitis, urinary tract infections and healthy volunteers after endotoxine injection; it is detected that serum PCT levels are in normal range or slightly elevated in localized and viral infections. PCT is a sensitive and specific early marker of bacterial infections in immunocompromised patients. Previous studies showed that, it could be used for the follow up of severe bacterial infections and sepsis [3-5, 7, 9-14]. Recent studies showed that serum PCT level is elevated especially in gram negative and systemic infections in neutropenic cancer patients and useful in the early diagnosis of septic and fungal infections in the detection of effectiveness of antimicrobial therapy and prediction of mortality risk [15-24]. In this study, in the first day of fever serum PCT levels of neutropenic cancer patients were significantly elevated more than the control group that includes the newly diagnosed cancer patients who have no fever and never treated with chemotherapy.

However, we determined that ANC <100/mm3, absolute monocyte count <100/mm3, absolute lymphocte count <100/mm3, duration of neutropenia >10 days, presence of mucositis had no effects on serum PCT levels. This result supports the recent studies that reveals the serum PCT level is elevated in serum independently from the underlying malign disease including during chemotherapy induced tissue damage (such as severe mucositis) and during the severe episodes of neutropenia, lymphopenia or monocytopenia [15,18,19]. In our study although the serum levels of CRP were above the normal range (0-6 mg/dl) in control group; there was a significant difference between control and study groups. Primary malign disease is the probable cause of fever in control group. In our study the ratios of MDI, CDI, FUO were (43.4%, 13%, 43.4%) were similar with the other studies [6,15,18]. The ratios of gram negative infections, gram positive infection, localized infections, systemic infections in MDI group were 40%, 35%, 70% and 30%. The highest serum PCT levels are detected especially on the third day of fever in microbiologically documented infections. This result supports the literature that serum PCT levels are more elevated in MDI than CDI and FUO [7,18,21]. Serum levels of PCT were higher in systemic infections group on the first, third day of neutropenic fever and at the end of antimicrobial therapy. This result was similar with the other authors' results [6, 15, 18, 21]. But we did not found any difference between serum PCT levels of gram positive and gram negative bacterial infections contrary to previous studies because all of the gram negative infections in our study are localized infections. Ideally, the applied diagnostic test should possess the maximum available sensitivity, specifity, positive and negative predictive value. Although there is no concentration of PCT that meets all three criteria and other authors as satisfactory have proposed considering a sensitivity of 73% for PCT [17]. PCT values of >1ng/ml seem adequate for the differentiation of MDI from CDI and FUO with 88% specificity, 45% sensitivity, and 75% positive predictive value.

In many studies PCT has been shown to be valuable in predicting bacteriaemia in neutropenic patients with sensitivity of 40-83%, and specificity 60-96% [19, 20, 23-25]. In this study we found that serum PCT concentrations above 0.5 ng/ml 66% specificity, 55% sensitivity, 66% positive predictive value; 1ng/ml seems 83% specifity, 35% sensitivity, 83% positive predictive value for systemic infections. The optimum PCT cut off value was 1ng/ml with high specifity, high positive predictive value and low sensitivity for systemic infections.
As the applied concentrations of PCT increase, sensitivity decrease but specificity and positive predictive value increase.

It has been proposed by other authors that serum PCT concentrations remain elevated for 3 days then started to decrease [6]. In this study serum PCT and CRP levels are correlated for three levels and we found that on the first day of fever there was a positive correlation between CRP and PCT, but there was no relationships between these two markers on the third day of fever and at the end of the antimicrobial therapy. This made us to think that on the first day of fever serum PCT and CRP levels elevate together but at the end of the antimicrobial therapy while serum PCT level is decreasing, serum CRP level remains elevated. In recent studies it was determined that while serum CRP levels reaches its maximum concentration at 36-50 hours; PCT reaches its maximum concentration at 6-8 hours and decreases to normal levels faster than CRP. Decreasing serum PCT levels shows success of antimicrobial therapy and defervescence of fever; increasing serum PCT levels shows systemic or fungal infections [6,15].

In our study, serum PCT levels decreased to normal ranges in FUO group at the third day of fever but in clinically or microbiologically documented infections at the end of the

antimicrobial therapy. This is the result of faster respond to antimicrobial therapy in FUO group.

According to these results, PCT might be a useful diagnostic marker for the early detection of systemic or bacterial infections and evaluation of antimicrobial therapy response.

REFERENCES

1. White L, Ybarra M. Neutropenic fever. Emerg Med Clin North Am. 2014 Aug; 32(3):549-61.

2. Gozzard DI, French EA, Blecher TE, Powell JR. C-reactive protein levels in neutropenic patients with pyrexia. Cancer.1985; 7(4): 307-15.

3. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet. 1993; 341(8844): 515-8.

4. Bossink AW, Groeneveld AB, Thijs LG. Prediction of microbial infection and mortality in medical patients with fever: plasma procalcitonin; neutrophilic elestase, alpha 1-antityripsin, and lactoferrin compared with clinical variables. Clin Infect Dis. 1999; 29 (2): 398-407.

5. Delèvaux I, André M, Colombier M, Albuisson E, Meylheuc F, Bègue RJ, et al. Can procalcitonin measurement help in differentiating between bacterial infection and other kinds of inflammatory processes? Ann Rheum Dis. 2003; 62(4); 337-40.

6. Fleischhack G, Cipic D, Juettner J, Hasan C, Bode U Procalcitonin-a sensitive inflammation marker of febrile episodes in neutropenic children with cancer. Intensive Care Medicine. 2000;26:202-11

7. .Dubos F, Korczowski B, Aygun DA, Martinot A, Prat C, Galetto-Lacour A, et al. Serum procalcitonin level and other biological markers to distinguish between bacterial and aseptic meningitis in children: a European multicenter case cohort study. Arch Pediatr Adolesc Med. 2008;162(12):1157-63.

8. Hatherill M, Tibby SM, Sykes K, McIntyre AG, Murdoch IA. Diagnostic markers of infection: comparison of procalcitonin with C reactive protein and leucocyte count. Arch Dis Child 1999; 81 (5): 417-21.

9. Meili M, Müller B, Kulkarni P, Schütz P. Management of patients with respiratory infections in primary care: procalcitonin, C-reactive protein or both? Expert Rev Respir Med. 2015; 9(5):587-601.

10. Reinhart K, Karzai W, Meisner M. Procalcitonin as a marker of the systemic inflammatory response to infection. Intensive Care Med 2000; 26(9)1193-200.

11. Milcent K, Faesch S, Gras-Le Guen C, Dubos F, Poulalhon C, Badier I, et al. Use of procalcitonin Assays to Predict Serious Bacterial Infection in Young Febrile Infants. JAMA Pediatr. 2015 23:1-8.

12. Gendrel D, Raymond J, Coste J, Moulin F, Lorrot M, Guérin S, et al. Comparison of procalcitonin with C-reactive protein, interleukin 6 and interferon-alpha for differentiation of bacterial vs. viral infections. Pediatr Infect Dis J. 1999; 18: 875-81.

13. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis. 2004 Jul 15; 39(2):206-17.

14. Sarmati L, Beltrame A, Dori L, Maffongelli G, Cudillo L, De Angelis G, et al. Procalcitonin is a reliable marker of severe systemic infection in neutropenic haematological patients with mucositis. Am J Hematol. 2010 May; 85(5):380-3.

15. Fleischhack G, Kambeck I, Cipic D, Hasan C, Bode U. Procalcitonin in paediatric cancer patients: its diagnostic relevance is superior to that of C-reactive protein, interleukin 6, interleukin 8, soluble interleukin 2 receptor and soluble tumour necrosis factor receptor II. Br J Haematol. 2000; 111 (4): 1093-102.

16. Hatzistilianou M, Rekliti A, Athanassiadou F, Catriu D. Procalcitonin as an early marker of bacterial infection in neutropenic febrile children with acute lymphoblastic leukemia. Inflamm Res. 2010 May; 59(5):339-47.

17. Gencer S, Salepci T, Ozer S. Evaluation of infectious etiology and prognostic risk factors of febrile episodes in neutropenic cancer patients. J Infect. 2003; 47(1):65-72.

18. Engel A, Steinbach G, Kern P, Kern WV. Diagnostic value of procalcitonin serum levels in neutropenic patients with fever: comparison with interleukin-8. Scand J Infect Dis. 1999;31(2): 185-9.

19. Gac AC, Parienti JJ, Chantepie S, Fradin S, Le Coutour X, Leclercq R, et al.. Dynamics of procalcitonin and bacteremia in neutropenic adults with acute myeloid leukemia. Leuk Res. 2011;35(10):1294-6.

20. Wu CW, Wu JY, Chen CK, Huang SL, Hsu SC, Lee MT, et al. Does procalcitonin, C-reactive protein, or interleukin-6 test have a role in the diagnosis of severe infection in patients with febrile neutropenia? A systematic review and meta-analysis. Support Care Cancer. 2015;23(10):2863-72.

21. Giamarellou H, Giamarellos-Bourboulis EJ, Repoussis P, Galani L, Anagnostopoulos N, Grecka P, et al. Potential use of procalcitonin as a diagnostic criterion in febrile neutropenia: experience from a multicentre study. Clin Microbiol Infect. 2004;10(7):628-33

22. Sakr Y, Burgett U, Nacul FE, Reinhart K,Brunkhorst F.The role of procalcitonin in febrile neutropenic patients: review of the literature. Infection. 2008;36(5):396-407.

23. Prat C, Sancho JM, Dominguez J, Xicoy B, Gimenez M, Ferra C, et al. Evaluation of procalcitonin, neopterin, C-reactive protein, IL-6 and IL-8 as a diagnostic marker of infection in patients with febrile neutropenia. Leuk Lymphoma. 2008;49(9):1752-61.

24. Koivula I, Hämäläinen S, Jantunen E, Pulkki K, Kuittinen T, Nousiainen T, et al. Elevated procalcitonin predicts Gram-negative sepsis in haematological patients with febrile neutropenia. Scand J Infect Dis. 2011;43(6-7):471-8.