



Paper Accepted*

ISSN Online 2406-0895

Original Article / Оригинални рад

Zhigang Qu, Bingmu Fang[†], Guangli Ma, Jinhong Jiang, Xiaoli Wang,
Junnv Wang, Shuping Liu, Xiaoqiu Wang, Yonghua Liu, Qiaolei Zhang

Significance of procalcitonin in bacterial infections among acute leukemia patients with post-chemotherapy agranulocytosis

Прокалцитонин као показатељ бактеријске инфекције у
постхемиотерапијској агранулоцитози код акутне леукемије

Department of Hematology, People's Hospital of Lishui City and the Sixth Affiliated Hospital of Wenzhou Medical University, Lishui 323000, Zhejiang, China

Received: August 11, 2016

Accepted: November 22, 2016

Online First: March 14, 2017

DOI: 10.2298/SARH160811066Q

* **Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.

When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

[†] **Correspondence to:**

Bingmu FANG

Department of Hematology

People's Hospital of Lishui City and the Sixth Affiliated Hospital of Wenzhou Medical University,

No. 15 Dazong Street Liandu District, Lishui 323000, Zhejiang, China

E-mail: bingmufang@126.com

Significance of procalcitonin in bacterial infections among acute leukemia patients with post-chemotherapy agranulocytosis

Прокалцитонин као показатељ бактеријске инфекције у постхемиотерапијској агранулоцитози код акутне леукемије

SUMMARY

Introduction/Objective Bacterial infection caused by the lack of granulocyte that results from the chemotherapy of acute leukemia is the leading cause of death. At present, there are few sensitive markers to reflect the bacterial infection, and there is no obvious specificity for the diagnosis of infection. Procalcitonin (PCT) is a precursor of calcitonin, and it has been found that PCT is a rapid and accurate marker of infectious diseases in more studies. In this study, the clinical value of serum PCT in patients with acute leukemia after chemotherapy were detected, aiming to understand its clinical value.

This study aims to explore the clinical significance of procalcitonin (PCT) levels in patients with acute leukemia who have acquired bacterial infections during the agranulocytosis period post-chemotherapy.

Methods Serum samples were collected from 92 patients with acute leukemia, who had acquired bacterial infections during the agranulocytosis period post-chemotherapy, and serum PCT levels were analyzed.

Results Serum PCT levels in patients with blood cultures positive were significantly higher than those in patients with negative blood cultures ($p < 0.05$), Gram-negative bacterial infection group were significantly higher than those in the Gram-positive group ($p < 0.05$). Furthermore, for patients with positive blood cultures, serum PCT levels were significantly higher of those that subsequently died than that those who survived ($p < 0.05$).

Conclusion In the period of agranulocytosis combined with bacterial infection that occurred after the chemotherapy of acute leukemia, the PCT can show the situations of bacterial infection, infected bacterial types and severities.

Keywords: procalcitonin; acute leukemia; bacterial infections; agranulocytosis

САЖЕТАК

Увод/Циљ Бактеријска инфекција због мањка гранулоцита је последица хемиотерапије акутне леукемије и водећи је узрок смрти. Више показатеља указије на бактеријску инфекцију али ни један није довољно специфичан. У више студија прокалцитонин (ПКТ), прекурсор калцитонина, показао се као брз и сигуран показатељ инфекције, али је његов клинички значај нејасан.

Циљ овог рада је био да се одреде клинички значај нивоа ПКТ код болесника са акутном леукемијом и инфекцијом услед постхемиотерапијске агранулоцитозе.

Метод Ниво ПКТ у серуму је анализиран код 92 болесника са акутном леукемијом и инфекцијом услед постхемиотерапијске агранулоцитозе.

Резултати Ниво ПКТ у серуму болесника са позитивном хемокултуром је значајно виши него код болесника са негативном хемокултуром ($p < 0.05$). Грам-негативне бактерије су биле значајно чешћи узрочник инфекције од Грам-позитивних ($p < 0.05$). Болесници са позитивном хемокултуром и повишеним ПКТ су значајно чешће умирали него преживљавали ($p < 0.05$).

Закључак. У периоду агранулоцитозе са бактеријском инфекцијом услед хемиотерапије акутне леукемије ПКТ може указати на бактеријску инфекцију, врсту и тежину инфекције

Кључне речи: прокалцитонин; акутна леукемија; бактеријска инфекција; агранулоцитоза

INTRODUCTION

Acute leukemia is a malignant, life-threatening, clonal disease of the hematopoietic tissues. The preferred treatment for acute leukemia is chemotherapy [1]. Due to the characteristics of the disease, and the side effects of chemotherapy drugs, chemotherapy can often result in severe bone marrow suppression, leading to agranulocytosis, thrombocytopenia, and anemia. This can consequently result in increased risk of infection, bleeding, or in some severe cases, death. With developments in medical technology, administration of hemostatics and transfusion of red blood cells and platelets, the incidence of anemia and death has been greatly reduced.

However, chemotherapy-induced agranulocytosis is still very serious, and can cause sepsis, leading to fever, chills, necrosis, organ failure, or even death [2]. Bacterial infections still contribute

to the high mortality rate seen in patients with acute leukemia, in spite of the application of broad-spectrum antibiotics. During the agranulocytosis period, patients with acute leukemia are susceptible to infection with both gram-positive bacteria and gram-negative bacteria [3].

Culture of pathogens is still the gold standard for their identification in a variety of specimen types. However, there are inevitable limitations to this method, such as the delay in obtaining results [4]. For patients with acute leukemia in the agranulocytosis period post-chemotherapy, time waiting for pathogen culture results is limited, as the onset of infection is acute and severe. To date, there are no specific and sensitive evaluation indexes to monitor the onset of infection and its severity. Thus, the development of methods that enable early diagnosis of bacterial infections, and evaluation of the prognosis of disease, has become a popular research focus.

Many researchers are focused on identifying accurate and quickly measured markers for monitoring of infectious diseases. A recently identified infection-related biomarker, procalcitonin (PCT) has been measured in a clinical setting, and this strategy has been effective in diagnosing infection at an early stage, in grading severity of infection, and in enabling prognostic assessment [5-8]. Some researchers believe that PCT can be used as an early indicator of infection in patients with acute leukemia during the agranulocytosis period [9], while the others have argued that the significance of PCT remains unclear at this stage [10]. Therefore, we believe it is necessary to further investigate the clinical significance of PCT in providing a basis for subsequent anti-infective therapy and in assessing the patient's clinical condition, in patients with acute leukemia who acquire bacterial infections during the agranulocytosis period post-chemotherapy. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of People's Hospital of Lishui City and the Sixth Affiliated Hospital of Wenzhou Medical University. Written informed consent was obtained from all participants.

To investigate the clinical value of PCT in granulocyte deficiency with bacterial infection of patients with acute leukemia after chemotherapy, which provides evidence for clinical anti-infection treatment and disease assessment.

METHODS

Subjects

92 patients with acute leukemia (48 males and 44 females; 12 to 65 years old, with median age of 38.5 years) who were admitted to the Department of Hematology of People's Hospital of Lishui City and the Sixth Affiliated Hospital of Wenzhou Medical University from July 2009 to December 2013 were enrolled in this study. The inclusion criteria were as follows: The age of patient was 12-65 years. The fever occurred in pro-chemotherapy agranulocytosis period. The first blood culture was bacteria positive or negative, but the clinical symptom indicated infection. The cytomegalovirus, EB virus, herpes simplex virus, varicella zoster virus and glucan negative tests were negative. The exclusion criteria were as follows: fungal infection indicated by the pathogen culture and chest CT;

virus infection indicated by the serological examination; transfusion associated fever; persistent fever without infection due to use of high-dose cytarabine. According to the hematopoietic and lymphoid tissue tumor classification standard from WHO, there were 68 patients with acute myeloid leukemia (AML) and 24 patients with acute lymphoblastic leukemia (ALL). 68 AML patients consisted of 8 t(8;21) cases, 12 inv(16) cases, 7 t(16;16) cases, 8 t(15;17) cases and 33 cases without specific classification (M1, 3; M2, 12; M4, 13; M5, 5). The 24 ALL patients included 19 cases of B-ALL and 5 cases of T-ALL. All patients were the cases with complete bone marrow remission after chemotherapy. The intensive treatment scheme for AML patients included HD Ara-C, IDA, ID-Ara-C+Mit, ID-Ara-C+VP16, etc., and that for ALL patients included HD Ara-C+HD-MTX, HD-MTX+VP, CDOLP, etc.

All patients were at the agranulocytosis period post-chemotherapy and had acquired bacterial infections. The diagnosis of neutropenic fever, infection and severe sepsis was as follows: (1) Neutropenic fever [11]. Neutropenia was defined as neutrophil count of $<0.5 \times 10^9 /L$, or count of $<1 \times 10^9 /L$ with a predicted decrease to $<0.5 \times 10^9 /L$. Fever was defined as a single oral temperature of $\geq 38.5^\circ C$ or a temperature of $\geq 38.0^\circ C$ for $\geq 1h$. (2) Bacterial infection. The single oral temperature was $\geq 38.5^\circ C$ or the body temperature was $\geq 38.0^\circ C$ for $\geq 1h$. The blood culture suggested bacterial infection, with or without clinical infection sign. This was defined as bacteremia. For blood culture negative patients, there were clinical infection signs such as cough, diarrhea, abdominal pain, urine or anal pain. Patients had unexplained drop in blood pressure or blood oxygen saturation. CT, X-ray and abdominal B ultrasound indicated new infection focus. The antibiotic treatment was effective. The fungus and virus infection were excluded. (3) Severe sepsis. The sepsis was associated with the organ dysfunction, hypoperfusion or hypotension. The perfusion abnormalities included, but not limited to, lactic acidosis, oliguria or acute alteration in mental status [12].

Based on blood culture results, specimens were divided into a positive group ($n = 30$), and a negative group ($n = 62$). Blood culture-positive referred to patients with at least one positive blood culture result; and blood culture-negative referred to patients who had negative blood culture results, but had the signs and symptoms of bacterial infection, as well as positive imaging findings for bacterial infection, and were sensitive to antibiotics. Bacteriological examination was performed using the VITEKAMS60 automatic bacterial analyzer (BioMerieux, Lyon, France). Among the blood culture-positive group, specimens were further divided into a Gram-positive bacteria subgroup (G+, $n=14$), and a Gram-negative bacteria subgroup (G-, $n=16$).

Before chemotherapy, all patients were given tests in routine blood, routine urine, liver and kidney function, C reactive protein, procalcitonin, cardiac ultrasound, hepatobiliary and urinary B ultrasound, chest CT, hepatitis B virus, cytomegalovirus, EB virus, herpes simplex virus and varicella zoster virus. If there is no abnormality, the intensive therapy was performed. After emergence of agranulocytosis, the respiration, pulse, blood pressure and peripheral oxygen saturation were daily detected for revealing the potential infection focus. For occurrence of fever, the blood culture was

conducted, with other cultures such as urine culture and throat swab culture. The routine tests were performed again. Finally the broad-spectrum antibiotic treatment was performed. The evaluation standard of curative effect was as follows: After using antibiotics for 3-5 days, the patient body temperature gradually returned to normal, and the vital signs were gradually stable. The disappearance of clinical symptoms suggested that the patient was sensitive to antibiotics. After the white blood cells recovered to normal, the CT, X-ray and abdominal B ultrasound were performed to re-examine the new infection focus. The obvious remission or disappearance of infection focus presented the cure.

PCT measurement

Venous blood (2 ml) from patients with neutrophil counts $\leq 0.5 \times 10^9 / L$ and a single oral temperature of $\geq 38.5^\circ C$ or axillary temperature of $\geq 38.0^\circ C$ for $\geq 1h$ were collected before using antibiotics (D0) for serum isolation. Serum PCT levels were determined within 4 hours by using colloidal gold technology and detection with the LIAISON automated fluorescence immunoassay analyzer (Mirandola Sorin, Italy). Values ≥ 0.5 ng/ml were regarded as cut off.

Blood culture

Venous blood (16-20 ml) from patients with neutrophil counts $\leq 0.5 \times 10^9 / L$ and single oral temperature of $\geq 38.5^\circ C$ or axillary temperature of $\geq 38.0^\circ C$ for $\geq 1h$ were collected at D0 for 2 sets of blood culture (the interval between them was within 5 min). Each set of blood culture included 1 bottle of anaerobic bacteria and 1 bottle of aerobic bacteria.

Statistical analysis

Statistical analysis was performed using SPSS12.0 statistical software. Comparisons of serum PCT between groups were carried out using the Chi-square test.

RESULTS

Treatment results

All patients were given conventional treatment with broad-spectrum antibiotics. For some patients the antibiotics were adjusted according to drug sensitive test results. 5 patients died due to severe sepsis during treatment. Other patients were cured according to the efficacy evaluation standard.

Relationship between blood culture results and serum PCT

The median blood neutrophil absolute value of 92 patients was $0.03 \pm 0.16 \times 10^9 / L$. In 92 specimens tested by blood culture, 30 specimens obtained from 30 patients were bacteria-positive (32.6%, 30/92), and 62 specimens obtained from 62 patients were bacteria-negative (67.4%, 62/92). The bacteria of blood culture were shown in Table 1. On D0, 68 cases exhibited $PCT \geq 0.5$ ng/ml, accounting for 73.9% of total patients. $PCT \geq 0.5$ ng/ml in 87% of the bacteria-positive specimens, with 67.7% of bacteria-negative specimens ($p < 0.05$). The D0 serum PCT was negative in 13% of

Table 1. Bacterial species in 30 patients with positive blood culture.

Bacterial species	Number of strain
Gram+ bacteria	14
Staphylococcus epidermidis	3
Staphylococcus aureus	4
Streptococcus viridans	2
Hemolytic streptococcus	2
Enterococcus faecalis	1
Stick slip bacteria Ross	1
Enterococcus faecium	1
Gram- bacteria	16
Escherichia coli	3
Enterobacter cloacae	2
Pseudomonas maltophilia	2
Pseudomonas aeruginosa	2
Klebsiella pneumoniae	4
Fusobacterium	2
Mohs bacteria Morgan	1

Table 2. Serum PCT levels in the 92 specimens grouped by the blood culture results.

Groups	Cases (n)	PCT subgroup, no. and mean (ng/ml)	
		<0.5	≥0.5
Bacteria-positive	30	4 (13%) 0.1	26 (87%) 12.4
Bacteria-negative	62	20 (32.3%) 0.11	42 (67.7%) 5.6
Total	92	24	68

Table 3. Serum PCT levels in the G+ and G- infection groups.

Groups	Cases (n)	PCT, no. and mean (ng/ml)	
		<0.5	≥0.5
G-	16(53.3%)	1 0.11	15 14
G+	14(46.7%)	3 0.09	11 7.5
Total	30	4	26

and 1 case was G+ bacteria. The comparison of rest 25 patients with bacteria-positive specimens. In 5 death cases, the average PCT value was 28.2 ng/ml. The survived cases were with the average PCT value as 12 ng/ml. The serum PCT levels in the patients that died significantly higher than those in the patients that survived ($p < 0.05$).

DISCUSSION

PCT constitutes 116 amino acids and has a molecular weight of 13KDa [13]. PCT is cleaved in vivo into procalcitonin and binding calcitonin, with binding calcitonin being further converted enzymatically into calcitonin, which plays a physiological role in vivo. In the event of infection, PCT

bacteria-positive specimens, with 32.3% of bacteria-negative specimens ($p < 0.05$). The expression intensity for serum PCT ≥ 0.5 ng/ml in the bacteria-positive group was 12.4 ng/ml, while it was 5.6 ng/ml in the bacteria-negative group. PCT in the bacteria-positive group was significantly higher than that in the bacteria-negative group ($p < 0.05$, Table 2).

Serum PCT levels in patients with different bacterial infections

Of the 30 specimens obtained from 30 patients that were bacteria-positive, 14 specimens showed Gram-positive bacterial infection (46.7%, 14/30), and 16 specimens showed Gram-negative bacterial infection (53.3%, 16/30). In serum PCT positive patients, the average serum PCT levels in the G- group was 14 ng/ml, G+ group was 7.5 ng/ml, the serum PCT levels in the G- group were significantly higher than those in the G+ group ($p < 0.05$, Table 3).

The prognostic significance of serum PCT

To explore the prognostic significance of serum PCT level for the patients with acute leukemia during the agranulocytosis period post-chemotherapy who had acquired bacterial infections. We further analyzed data on serum PCT levels from patient specimens that were bacteria-positive. In this study, 5 patients died of infections, the blood culture of 4 patients was G-bacteria,

levels increase hundred-folds. Thus, serum PCT measurement has been increasingly applied to the monitoring of infectious disease in a clinical setting [14, 15].

During the agranulocytosis period, post-chemotherapy patients with acute leukemia are at increased risk of bacterial infections, the leading cause of death in these circumstances. Thus, early diagnosis and prompt treatment of infection is very important in patients' prognosis. Studies have shown that, with the cut-off value for PCT level set to 0.5 ng/ml, diagnostic sensitivity to bacterial infection was 65%, and specificity 96%. Additionally, at serum PCT levels higher than 1.2 ng/ml, sensitivity reaches 100% [16]. In many studies [17], 0.5 ng/ml is often used as the cut-off value of PCT. We conducted this study according to above reported methods and found that, patients with etiologically confirmed bacterial infections had significantly higher serum PCT, as did patients that were diagnosed clinically, but had negative blood culture results, especially for PCT positive cases. This is consistent with other studies mentioned above. Our study found that, on the exact day of fever, 73.9% patients had PCT over the threshold, the PCT-positive-rate of the positive blood culture group (≥ 0.5 ng/ml) was higher than the negative blood culture group (87% vs 67.7%, $P < 0.05$), indicating that the PCT value of the positive blood culture group was higher than the negative blood culture group. Our study also shows that patients infected with Gram-negative bacteria had significantly higher serum PCT levels than those patients infected with Gram-positive bacteria ($P < 0.05$). In serum PCT positive patients, the average serum PCT levels in the G- group was 14 ng/ml, G+ group was 7.5 ng/ml. Furthermore, serum PCT levels in patients that died were also significantly higher than those that survived; this indicates that measurement of serum PCT can be applied to the early diagnosis of infection and to the classification of disease severity. These results are consistent with the findings of Jeddi et al. [18], Neofytos et al. [19] and Hatzistilianou et al. [20] Our study has confirmed this conclusion. However, this is a single center study. Due to less sample size, it needs to be further verified.

For patients with agranulocytosis who do not show obvious symptoms of infection, measurement of serum PCT at the early stages of infection will not only help to assess the infection severity and increase the efficacy of anti-infective therapy [21] but also help to distinguish between Gram-negative and Gram-positive bacterial infection to provide a reasonable basis for the clinical administration of antibiotics [22, 23]. For patients with acute leukemia acquiring bacterial infection during the agranulocytosis period post-chemotherapy, our findings are consistent with most other studies [24, 25]. We found that the PCT level of G-infected patients was higher than the G+infected patients. In 5 cases of death, the average PCT reached 28.2 ng/ml. and the average PCT level of these patients was higher than other positive blood culture patients. Therefore, we initially thought that the increasing level of PCT could reflect the severities of bacterial infections, especially the severely infected patients, PCT was obviously increased. Our results initially considered that in the period of agranulocytosis combined with bacterial infection that occurred after the chemotherapy of acute leukemia, the procalcitonin had the clinical significance in predicting the situations of bacterial

infection, infected bacterial types and severities. Combined with the previous studies, it could be used as a confirmed clinical examination index to guide the clinical judgment.

CONCLUSION

Our results showed that the PCT of bacterial infection confirmed by etiology was significantly increased, while the positive results of patients who were considered as bacterial infection in clinic with blood-free culture also increased. It indicates that PCT can not only be used in early diagnosis of diseases, but also can be used in the classification of the severity of the disease. For patients with granulocyte deficiency, who had no obvious symptoms and fast condition changes, the detection of serum PCT levels in early infection can not only make a judgment on the severity of infection and anti-infection effect, but can distinguish G- bacteria from G+ bacteria, providing the basis for the reasonable application of antibiotics. For patients in granulocyte deficiency with bacterial infection with acute leukemia after chemotherapy, the serum PCT levels have an important value for reflecting the extent of bacterial infection and the anti-infection treatment, which is a reliable index for monitoring and has important clinical value.

REFERENCES

1. Fey M, Dreyling M, On behalf of the ESMO Guidelines Working Group. Acute myeloblastic leukemia in adult patients: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol.* 2008; 19 Suppl 2: ii58–9.
2. Buck BH, Liebeskind DS, Saver JL, Bang OY, Yun SW, Starkman S, et al. Early neutrophilia is associated with volume of ischemic tissue in acute stroke. *Stroke.* 2008; 39(2): 355–60.
3. Lerenbecher T, Varwig D, Kaiser J, Reinhardt D, Klingebiel T, Creutzig U. Infectious complications in pediatric acute myeloid leukemia: Analysis of the prospective multi-institutional clinical trial AML-BFM 93. *Leukemia.* 2004; 18(1): 72–7.
4. Schaub N, Frei R, Muller C. Addressing unmet clinical needs in the early diagnosis of sepsis. *Swiss Med Wkly.* 2011; 141: w13244.
5. Chung YG, Won YS, Kwon YJ, Shin HC, Choi CS, Yeom JS. Comparison of serum CRP and procalcitonin in patients after spine surgery. *J Korean Neurosurg Soc.* 2011; 49(1): 43–48.
6. Limper M, de Kruif MD, Duits AJ, Brandjes DP, van Gorp EC. The diagnosis role of procalcitonin and other biomarkers in discriminating infectious from non-infectious fever. *J Infect.* 2010; 60(6):409–16.
7. Kibe S, Adams K, Barlow G. Diagnostic and prognostic biomarkers of sepsis in critical care. *J Antimicrob Chemother.* 2011; 66 Suppl 2: ii33–40.
8. Hatzistilianou M. Diagnostic and prognostic role of procalcitonin in infections. *Scientific World Journal.* 2010; 10: 1941–6.
9. 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.
10. Buyukberber N, Buyukberber S, Sevinc A, Camci C. Cytokine concentrations are not predictive of bacteremia in febrile neutropenic patients. *Med Oncol.* 2009; 26(1): 55–61.
11. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis.* 2002; 34: 730–51.
12. Balk RA. Severe sepsis and septic shock: definitions, epidemiology, and clinical manifestations. *Crit Care Clin.* 2000; 16(2): 179–92.
13. Maruna P, Nedelniková K, Gürlich R. Physiology and genetics of procalcitonin. *Physiol Res.* 2000; 49Suppl 1: S57–61.
14. Liaudat S, Dayer E, Praz G, Bille J, Troillet N. Usefulness of procalcitonin serum level for the diagnosis of bacteremia. *Eur J Clin Microbiol Infect Dis.* 2001; 20(8): 524–7.
15. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infect Dis.* 2007; 7(3): 210–7.

16. 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.
17. Juutilainen A, Hämäläinen S, Pulkki K, Kuittinen T, Nousiainen T, Jantunen E, et al. Biomarkers for bacteremia and severe sepsis in hematological patients with neutropenic fever: multivariate logistic regression analysis and factor analysis. *Leuk Lymphoma*. 2011; 52(12): 2349–55.
18. Jeddi R, Ghédira H, Ben Amor R, Turki A, Kacem K, Ben Abdennebi Y, et al. Risk factors of septic shock in patients with hematologic malignancies and *Pseudomonas* infections. *Hematology*. 2011; 16(3): 160–5.
19. Neofytos D, Lu K, Hatfield-Seung A, Blackford A, Marr KA, Treadway S, et al. Epidemiology, outcomes, and risk factors of invasive fungal infections in adult patients with acute myelogenous leukemia after induction chemotherapy. *Diagn Microbiol Infect Dis*. 2013; 75(2): 144–9.
20. 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; 59(5): 339–47.
21. Koivula I, Juutilainen A. Procalcitonin is a useful marker of infection in neutropenia. *Leuk Res*. 2011; 35(10): 1288–9.
22. Fu Y, Chen J, Cai B, Zhang J, Li L, Liu C, et al. The use of PCT, CRP, IL-6 and SAA in critically ill patients for an early distinction between candidemia and Grampositive/negative bacteremia. *J Infect*. 2012; 64(4): 438–40.
23. 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.
24. Carnino L, Betteto S, Loiacono M, Chiappella A, Giacobino A, Ciuffreda L, et al. Procalcitonin as a predictive marker of infections in chemoinduced neutropenia. *J Cancer Res Clin Oncol*. 2010; 136(4): 611–5.
25. 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.