Clinical Utility of Procalcitonin as a Marker of Sepsis: A Potential Predictor of Causative Pathogens

Atsuko Nakajima¹, Junko Yazawa¹, Daisuke Sugiki², Mari Mizuguchi³, Hironori Sagara³, Masahiro Fujisiro¹, Mitsuei Shibazaki¹, Akihiko Hitani¹, Masako To¹ and Kosuke Haruki¹

Abstract

Objective Sepsis is one of the leading causes of mortality in critically ill patients, and providing a timely diagnosis and early intervention is necessary for successful treatment. Procalcitonin (PCT) may be a better marker of sepsis than conventional inflammatory markers. The aim of this study was to evaluate the clinical utility of the PCT level as a marker of sepsis.

Methods Forty-five patients with sepsis, 24 patients with pneumonia who did not meet the SIRS criteria (PN) and 56 controls were enrolled in this study. The levels of PCT and other serum markers were measured, and their utility as markers of sepsis was assessed.

Results The serum PCT levels exhibited statistically significant differences between the three groups ($p < 0.0001$). The PCT levels in the sepsis group (29.3 ± 85.3 ng/mL) were significantly higher ($p < 0.001$) than those observed in the PN group (0.34 ± 8.6 ng/mL) and the control group (0.74 ± 2.1 ng/mL), according to a post hoc analysis. There were no differences in the white blood cell (WBC) counts or C-reactive protein (CRP) levels between the three groups. Fourteen of the 45 patients with sepsis had positive microbiological blood cultures (Gram-positive cocci [GPC] in seven patients, Gram-negative rods [GNR] in six patients, other types of bacteria in one patient). The 13 patients with GNR or GPC were categorized into the GNR group or GPC group according to the identified pathogens. The serum PCT levels were significantly higher in the GNR group (149.8 ± 199.7 ng/mL) than in the GPC group (19.1 ± 41.8 ng/mL) ($p < 0.05$), although there were no differences in the WBC counts or CRP levels between these groups. When the cut-off value for the PCT level was set at 16.9 ng/mL, the sensitivity and specificity for the detection of GNR infection were 85.7% and 83.3%, respectively.

Conclusion The PCT level is a potentially useful marker of the type of causative pathogen in patients with sepsis whose measurement may facilitate the selection of appropriate empiric antibiotic treatment.

Key words: procalcitonin, sepsis, bacterial blood culture

(Intern Med 53: 1497-1503, 2014)

(DOI: 10.2169/internalmedicine.53.1785)

Introduction

Sepsis is one of the leading causes of mortality in critically ill patients in the intensive care unit (1), and providing a timely diagnosis and early intervention for sepsis is important for preventing septic shock and death (2). While microbiological blood cultures are used to identify the causative pathogen of sepsis and help facilitate the selection of anti-

otics, the culture may require several days before the organism is isolated and identified; therefore, culture results may not be sufficiently timely to guide the choice of therapy for sepsis. In addition, microbiological culture exhibits a low sensitivity and specificity for the diagnosis of sepsis (3). Biomarkers of inflammation, such as the white blood cell (WBC) count and C-reactive protein (CRP) level, can also be used to diagnose sepsis, although their specificity is very low. In addition, the WBC count can decrease and the CRP

¹Department of Laboratory Medicine, Dokkyo Medical University Koshigaya Hospital, Japan, ²Shock Trauma Center, Dokkyo Medical University Koshigaya Hospital, Japan and ³Department of Respiratory Medicine, Dokkyo Medical University Koshigaya Hospital, Japan

Received for publication September 19, 2013; Accepted for publication January 21, 2014

Correspondence to Dr. Kosuke Haruki, kos-h@dokkyomed.ac.jp

Table 1. Infections in Patients with Sepsis

Infectious focuses	n
Pneumonia and/or pleural empyema	10
Meningitis	4
Microbial infection of burn wounds	3
Pyelonephritis	3
Cholangitis	3
Others	22

level can remain low in cases of severe sepsis. Therefore, identifying a biomarker with higher sensitivity and specificity for the diagnosis of sepsis would be of benefit.

Procalcitonin (PCT) is a 116-amino acid protein with a molecular mass of 13 kD. It is produced by thyroid C cells and converted to calcitonin before being released into the bloodstream. In healthy individuals, PCT is not usually present at a detectable level in the blood. In 1993, a study demonstrated that the serum PCT levels are elevated in patients with sepsis and decrease following successful treatment of sepsis with antibiotics (4). Furthermore, in the context of local bacterial or viral infection, the circulating PCT level remains at <1.6 ng/mL (4). Other studies have suggested that measuring the PCT level is useful for making an early diagnosis of sepsis (5), as well as assessing the severity (6) and prognosis (7, 8) of septic patients.

On the other hand, the serum PCT level can be affected by lipopolysaccharides, sepsis-related cytokines (9, 10) and possibly renal dysfunction (11). The goal of this study was therefore to characterize the clinical utility of the PCT level as a biomarker of sepsis.

Materials and Methods

Subjects

We used a prospective observational design for this study. The study population included patients with sepsis, pneumonia without sepsis and a high fever of non-infectious origin. The patients were recruited from the Shock Trauma Center and Department of Respiratory Medicine at Dokkyo Medical University Koshigaya Hospital between May 2010 and December 2010. The patients diagnosed with sepsis had a definitive focus of infection together with two or more systemic inflammatory response syndrome (SIRS) criteria, according to the American College of Chest Physicians/Society of Critical Care Medicine (12). Briefly, these criteria were: 1) a body temperature of >38°C or <36°C; 2) a pulse of >90 beats/min; 3) a respiratory rate of >20 breaths/min or a PaCO₂ of <32 mmHg; or 4) a WBC count of >12,000/μL or <4,000/μL. The infectious foci in the patients with sepsis are listed in Table 1. As a local bacterial infection group, patients with pneumonia (diagnosed according to the Japanese Respiratory Society (JRS) Guidelines for the Management of Community-Acquired Pneumonia in Adults) who did not meet the SIRS criteria (12) were recruited. Patients with a high fever (>38.0°C) of non-infectious origin were

Table 2. Comorbidities of Patients with Sepsis, of Patients with Pneumonia without Sepsis, and of Control Subjects

	n
Patients with sepsis	
Abdominal trauma	7
Cerebrovascular disease	6
Fracture	5
Diabetes mellitus	5
Heatstroke	4
Heart failure	4
Burn	3
Acute respiratory failure	2
Acute renal failure	1
Others	8
Patients with pneumonia without sepsis	
Lung cancer	6
Renal failure	1
Cardiovascular diseases	1
None	16
Control subjects	
Gastrointestinal diseases	9
Heart failure	8
Postoperative complication (fever)	8
Cerebrovascular disease	6
Renal failure	3
Leukemia	3
Others	19

enrolled in this study as controls. The comorbidities of the three groups of subjects are listed in Table 2.

Phlebotomy for the measurement of the levels of PCT and other serum markers was performed at the time of diagnosis of sepsis and pneumonia in the sepsis group and pneumonia group, respectively. Phlebotomy was performed in the controls at the time of a high fever.

This study was reviewed and approved by the Dokkyo Medical University Koshigaya Hospital Research Ethics Committee and conducted in accordance with the Helsinki Declaration.

PCT measurements

The PCT levels were measured via an electrochemiluminescent immunoassay using Elecsys reagent, Elecsys BRAHMS PCT and Cobas e411 (Roche Diagnostics, Tokyo, Japan), according to the manufacturer's instructions. The lower limit of detection was 0.02 ng/mL. The CRP levels were measured according to the latex agglutination method using Nanopia CRP reagent (Sekisui Medical Co., Ltd., Tokyo, Japan) and JCA-BM2250 (JEOL, Ltd., Tokyo, Japan). The WBC counts were measured using flow cytometry with XE5000 (Sysmex Corporation, Tokyo, Japan). The endotoxin levels were measured via a turbidimetric time assay, which was performed by a clinical laboratory testing company (SRL, Inc., Tokyo, Japan). Blood sampling for the microbiological blood culture was performed prior to the administration of antibiotics, and two sets of samples were obtained from each patient. Identical bacteria detected from both sets of samples were defined as causative pathogens.

Statistics

The results are presented as the mean±standard deviation

Figure 1. The serum PCT levels (A), WBC counts (B) and CRP levels (C) in the sepsis group, PN group and control group. A receiver operating analysis of the serum PCT levels, WBC counts and CRP levels in the patients with and without sepsis (control and PN groups) was performed (D). ***: $p < 0.001$; NS: not significant, PCT: procalcitonin, WBC: white blood cell, CRP: C-reactive protein, PN: pneumonia who did not meet the SIRS criteria

of the mean. Comparisons between two groups of data were made using the Mann-Whitney U test. Comparisons between three groups of data were made using the Kruskal-Wallis test, followed by a post hoc test. Correlations between two groups of data were analyzed using Spearman's rank correlation coefficient. A receiver operating characteristic (ROC) analysis was used to evaluate the results of diagnostic tests. A p value of less than 0.05 was considered to indicate statistical significance.

The statistical analyses were performed using the IBM SPSS Statistics version 20 (IBM, Armonk, USA) and Graph Pad Prism 5 (Graph Pad Prism, San Diego, USA) software programs.

Results

PCT as a diagnostic biomarker of sepsis

Forty-five patients with sepsis (29 men and 16 women; age, 57.2 ± 17.7 years), 24 patients with pneumonia who did not meet the SIRS criteria (PN) (15 men and nine women;

age, 70.5 ± 9.8 years) and 56 control patients (43 men and 13 women; age, 62 ± 18.3 years) were enrolled in this study. The serum PCT levels exhibited statistically significant differences between the three groups ($p < 0.0001$). Post hoc testing demonstrated that the PCT levels in the sepsis group (29.3 ± 85.3 ng/mL) were significantly higher ($p < 0.001$) than those observed in the PN group (0.34 ± 8.6 ng/mL) and the control group (0.74 ± 2.1 ng/mL) (Fig. 1A). There were no differences in the WBC counts or CRP levels between the three groups (WBC, $13,613 \pm 9,681/\mu\text{L}$ in the sepsis group, $11,146 \pm 5,088/\mu\text{L}$ in the PN group and $11,352 \pm 6,375/\mu\text{L}$ in the control group, $p = 0.49$; CRP, 12.3 ± 9.0 mg/dL in the sepsis group, 12.5 ± 7.6 mg/dL in the PN group and 8.54 ± 7.3 mg/dL in the control group, $p = 0.052$) (Fig. 1B, C). A ROC analysis was used to evaluate the utility of the markers for diagnosing sepsis (sepsis group vs. PN group plus control group). The ROC analysis showed an area under the curve (AUC) of 0.80 for the PCT level, 0.56 for the WBC count and 0.60 for the CRP level (Fig. 1D). The sensitivity and specificity of the PCT level for the diagnosis of sepsis were 57.6% and 87.5%, respectively, when the cut-off value was

set at 0.5 ng/mL. In contrast, the sensitivity and specificity of the WBC count for the diagnosis of sepsis were 97.8% and 8.9%, respectively, when the cut-off value was set at 3,500/ μ L. The sensitivity and specificity of the CRP level for the diagnosis of sepsis were 95.6% and 5.1%, respectively, when the cut-off value was set at 0.3 mg/dL.

Association between the PCT level and microbiological blood culture results

Fourteen of the 45 (31.1%) patients in the sepsis group had positive microbiological blood culture results, while 27 of the 45 (60.0%) patients had positive PCT results when the cut-off value was set at 0.5 ng/mL (Table 3). The rate of positive concordance between the results of the microbiological blood cultures and the PCT tests in the culture-positive patients was 85.7%, while that of negative concordance in the culture-negative patients was 51.6%.

The details of each patient with positive microbiological blood culture results are presented in Table 4. Gram-positive cocci (GPC) were identified in the blood samples of seven patients, Gram-negative rods (GNR) were identified in the blood samples of six patients, and Gram-positive rods were identified in the blood samples of one patient. The 13 patients with either GPC or GNR infection were divided into a GNR group and a GPC group according to the bacteria identified in the blood samples. The serum PCT levels in the GNR group (149.8 ± 199.7 ng/mL) were significantly higher

($p=0.035$) than those observed in the GPC group (19.1 ± 41.8 ng/mL) (Fig. 2A); however, there were no differences in the WBC counts or CRP levels between the two groups (WBC, $20,033 \pm 20,877$ / μ L in the GNR group and $12,086 \pm 4,317$ / μ L in the GPC group, $p=0.83$; CRP, 14.3 ± 7.6 mg/dL in the GNR group and 9.1 ± 7.9 mg/dL in the GPC group, $p=0.18$) (Fig. 2B, C). A ROC analysis showed an AUC value of 0.85 for the PCT level, 0.54 for the WBC count and 0.73 for the CRP level (Fig. 2D). When the cut-off value for the PCT level was set at 16.9 ng/mL, the sensitivity, specificity, positive predictive value and negative predictive value for GNR were 85.7%, 83.3%, 85% and 83%, respectively. Regarding the association between the endotoxin and PCT levels, the endotoxin-positive (0.8 pg/mL or higher) group had significantly higher PCT levels than the endotoxin-negative (less than 0.8 pg/mL) group (Fig. 2E).

Discussion

This study showed the PCT level, but not WBC count or CRP level, to be significantly higher in the sepsis group than in the control and PN groups. Furthermore, the ROC analysis showed an AUC for the PCT level of 0.80, suggesting that the PCT test had moderate accuracy (according to the classification of Akobeng (13)) for diagnosing sepsis. This finding is consistent with the observations of previous reports suggesting that the PCT level is superior to the endotoxin, interleukin (IL)-6 and CRP levels as a biomarker for the diagnosis of sepsis (5, 8, 14-19). In addition to the confirmation study, the present study provides novel evidence that: 1) the serum PTC level is a superior marker of sepsis, but not local infections, such as pneumonia, and 2) serum PCT elevation is more closely associated with GNR infection than GPC infection in patients with sepsis.

In this study, there were no significant differences in the PCT levels between the PN group and the control group.

Table 3. Association between the Results of Microbiological Blood Culture and the PCT Test

		PCT		Total
		Positive	Negative	
Culture results	Positive	12	2	14
	Negative	15	16	31
Total		27	18	45

PCT: procalcitonin

Table 4. Details of Each Patient with Sepsis with Positive Microbiological Blood Culture Results

Pt	Age (years)	Sex	Main Diseases	APACHE	PCT (ng/mL)	WBC (/ μ L)	CRP (mg/dL)	Endotoxin (pg/mL)	Bacteria	Outcome
1	61	M	Mud water aspiration, ARDS	20	285.0	1,800	4.8	513	<i>P. aeruginosa</i> , <i>E. coli</i>	Dead
2	62	M	Septic shock	23	496.1	26,500	18.9	185	<i>Klebsiella sp</i>	Dead
3	77	M	Pneumonia	26	0.7	8,800	8.3	< 0.8	<i>E. cloacae</i>	Dead
4	74	M	Pyelonephritis	23	17.3	9,300	25.5	< 0.8	<i>E. aerogenes</i>	Survived
5	59	M	Hematemesis	16	23.7	14,600	17.2	< 0.8	<i>E. coli</i>	Survived
6	79	M	Cholangitis	42	75.9	59,200	11.6	7.4	<i>E. coli</i>	Dead
7	58	F	Bacterial meningitis	18	16.5	8,100	16.3	< 0.8	<i>S. pneumoniae</i>	Dead
8	42	M	Ventricular fibrillation	31	0.5	11,400	4.7	< 0.8	<i>S. epidermidis</i>	Survived
9	61	M	Traffic injury	31	3.0	19,900	16.1	< 0.8	<i>S. epidermidis</i>	Survived
10	57	F	Diabetic acidosis	35	0.5	11,000	3.8	< 0.8	<i>Streptococcus sp.</i>	Survived
11	51	F	Aspiration pneumonia	12	113.0	15,900	19.7	< 0.8	<i>Peptostrep. micros</i>	Survived
12	50	M	Hyperammonemia, liver damage	13	0.1	10,000	0.5	< 0.8	<i>S. epidermidis</i>	Survived
13	73	M	Traffic injury, Cerebral hematoma	21	0.1	8,300	2.7	< 0.8	<i>S. epidermidis</i>	Survived
14	70	M	Cerebrovascular disease	32	0.7	16,400	13.8	< 0.8	<i>B. cereus</i>	Dead

APACHE: Acute Physiology and Chronic Health Evaluation, PCT: procalcitonin, WBC: white blood cell, CRP: C-reactive protein, *P. aeruginosa*: *Pseudomonas aeruginosa*, *E. coli*: *Escherichia coli*, *E. cloacae*: *Enterobacter cloacae*, *E. aerogenes*: *Enterobacter aerogenes*, *S. pneumoniae*: *Streptococcus pneumoniae*, *S. epidermidis*: *Staphylococcus epidermidis*, *Peptostrep. micros*: *Peptostreptococcus micros*, *B. cereus*: *Bacillus cereus*

Figure 2. Thirteen patients were categorized into one of two groups according to the pathogens identified in blood cultures (GNR or GPC), and their serum markers were compared. The PCT levels (A), WBC counts (B) and CRP levels (C). A receiver operating analysis of the serum PCT levels, WBC counts and CRP levels in the two groups of patients (D). The 13 patients were also categorized into two groups according to the endotoxin level (cut-off value: 0.8 pg/mL), and the PCT levels were compared between the two groups (E). *: $p < 0.05$; NS: not significant, GNR: Gram-negative rods, GPC: Gram-positive cocci, PCT: procalcitonin, WBC: white blood cell, CRP: C-reactive protein

This finding suggests that the PCT level may not be a good diagnostic marker of local infection, such as pneumonia. In fact, only 34.1% of the patients with pneumonia exhibited positive PCT levels (more than 0.5 ng/mL) (20), although it was not clear whether these patients had sepsis in addition to pneumonia. Furthermore, 93.3% of the patients with mild community-acquired pneumonia had a negative PCT level (20), suggesting that the sensitivity of this parameter is insufficient for diagnosing pneumonia. Therefore, the PCT level may be a marker of systemic inflammation, but not a diagnostic marker for local infection in patients without SIRS.

The rate of positive concordance between the results of the microbiological blood cultures and PCT tests was 85.7%, while that of negative concordance was 51.6%. This finding is likely related to the low sensitivity of blood cultures for the diagnosis of sepsis (31.1%) and is consistent

with the results of previous reports showing that the sensitivity of microbiological blood cultures is low, even in patients with severe sepsis (3). However, the rate of positive concordance between the results of the microbiological blood cultures and PCT tests in the culture-positive patients was fairly high; therefore, we compared the PCT levels between the patients with GNR infection and those with GPC infection. Interestingly, the PCT levels were significantly higher in the GNR group than in the GPC group, and the ROC analysis suggested that the PCT test had moderate accuracy (according to the classification of Akobeng (13)) for predicting the type of causative bacteria of sepsis (i.e., GPC vs. GNR). When the cut-off value for the PCT level was set at 16.9 ng/mL, good sensitivity and specificity for predicting the type of causative pathogen were observed. These findings suggest that the PCT level may be of use in predicting the type of causative bacteria in patients with sepsis, even

before definitive blood culture results become available.

In regards to the difference in the PCT levels observed between the GPC and GNR groups, the potential for contamination from the skin surface should be considered in the GPC group, as GPC is a major component of the normal skin flora. However, two sets of samples for microbiological blood culture were obtained from each patient, and identical bacteria detected in both sets were defined as causative pathogens in this study. Therefore, the possibility of contamination as a confounding factor is negligible. The mechanisms underlying the higher PCT levels noted in the GNR group relative to the GPC group remain unknown; however, the higher PCT levels observed in the GNR group may be associated with the elevated serum endotoxin levels measured in this group, as the endotoxin levels were not detectable in the GPC group, although a level of >0.8 pg/mL was observed in three of six patients with a high PCT level in the GNR group. A previous *in vitro* study also demonstrated that lipopolysaccharide, a major component of endotoxin, stimulates the PCT expression in isolated peripheral blood mononuclear cells (10). Therefore, the PCT level may also be a useful surrogate marker of the serum endotoxin concentration, which otherwise requires a very specialized assay to measure.

Another important clinical characteristic of PCT is the more dynamic change observed in the PCT level in response to changes in the patient's clinical state compared with the CRP level. In a previous study, there was a marked difference in kinetics between PCT and CRP under iatrogenic sepsis: the PCT level was detectable 2.5 hours after the injection of contaminated medicine, reaching a peak at 13.5 hours after injection, while the CRP level reached a peak 30 hours after injection (21). In addition, the half-life of serum PCT is shorter than that of serum CRP (22). This quality may enable the PCT level to be used to make an earlier diagnosis of sepsis and may also aid in decision-making regarding the timing of the initiation of empiric antibiotics and the discontinuation of antibiotic therapy (22-24). Furthermore, the present study showed that measuring the PCT level may help to raise the index of suspicion for Gram-positive vs. Gram-negative organisms as the causative pathogen, which further increases its utility in the selection of specific antibiotic regimens.

One limitation of this study is the small number of patients recruited, especially with respect to the analysis of the association between the results of the microbiological blood cultures (GPC vs. GNR) and the PCT tests. Further investigation using a larger scale study is needed to confirm our results and the diagnostic potential of the PCT level.

In conclusion, the present data demonstrate that the PCT level is a useful marker of the type of causative pathogen in patients with sepsis whose measurement may facilitate the selection of appropriate empiric antibiotic therapy.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors thank Dr. Keiichi Ikegami for his supervision of the recruitment of patients with sepsis for this study.

References

- Parrillo JE, Parker MM, Natanson C, et al. Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. *Ann Intern Med* **113**: 227-242, 1990.
- Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. *Crit Care Med* **31**: 2742-2751, 2003.
- 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* **7**: 210-217, 2007.
- Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet* **341**: 515-518, 1993.
- Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis* **13**: 426-435, 2013.
- Endo S, Kasai T, Inada K. Evaluation of procalcitonin levels in patients with systemic inflammatory response syndrome as the diagnosis of infection and the severity of illness. *Kansenshogaku Zasshi (The Journal of the Japanese Association for Infectious Diseases)* **73**: 197-204, 1999 (in Japanese, Abstract in English).
- 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* **34**: 2596-2602, 2006.
- Theodorou VP, Papaioannou VE, Tripsianis GA, et al. Procalcitonin and procalcitonin kinetics for diagnosis and prognosis of intravascular catheter-related bloodstream infections in selected critically ill patients: a prospective observational study. *BMC Infect Dis* **12**: 247, 2012.
- Becker KL, Snider R, Nylen ES. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. *Crit Care Med* **36**: 941-952, 2008.
- Oberhoffer M, Stonans I, Russwurm S, et al. Procalcitonin expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis-related cytokines *in vitro*. *J Lab Clin Med* **134**: 49-55, 1999.
- Kapoor S. Procalcitonin and its utility as a diagnostic and prognostic assay in patients with renal dysfunction and immunosuppressive conditions. *J Infect Chemother* **15**: 58, 2009.
- No authors listed. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* **20**: 864-874, 1992.
- Akobeng AK. Understanding diagnostic tests 3: receiver operating characteristic curves. *Acta Paediatr* **96**: 644-647, 2007.
- Aikawa N, Fujishima S, Endo S, et al. Multicenter prospective study of procalcitonin as an indicator of sepsis. *J Infect Chemother* **11**: 152-159, 2005.
- Buhaescu I, Yood RA, Izzedine H. Serum procalcitonin in systemic autoimmune diseases: where are we now? *Semin Arthritis Rheum* **40**: 176-183, 2010.
- Castelli GP, Pognani C, Meisner M, Stuardi A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. *Crit Care* **8**: R234-R242, 2004.
- Gibot S, Bene MC, Noel R, et al. Combination biomarkers to diagnose sepsis in the critically ill patient. *Am J Respir Crit Care*

- Med **186**: 65-71, 2012.
18. Jekarl DW, Lee SY, Lee J, et al. Procalcitonin as a diagnostic marker and IL-6 as a prognostic marker for sepsis. *Diagn Microbiol Infect Dis* **75**: 342-347, 2013.
 19. Tamaki K, Kogata Y, Sugiyama D, et al. Diagnostic accuracy of serum procalcitonin concentrations for detecting systemic bacterial infection in patients with systemic autoimmune diseases. *J Rheumatol* **35**: 114-119, 2008.
 20. Hirakata Y, Yanagihara K, Kurihara S, et al. Comparison of usefulness of plasma procalcitonin and C-reactive protein measurements for estimation of severity in adults with community-acquired pneumonia. *Diagn Microbiol Infect Dis* **61**: 170-174, 2008.
 21. Brunkhorst FM, Heinz U, Forycki ZF. Kinetics of procalcitonin in iatrogenic sepsis. *Intensive Care Med* **24**: 888-889, 1998.
 22. Kaur K, Mahajan R, Tanwar A. A novel marker procalcitonin may help stem the antibiotic overuse in emergency setting. *Int J Appl Basic Med Res* **3**: 77-83, 2013.
 23. Hohn A, Schroeder S, Gehrt A, et al. Procalcitonin-guided algorithm to reduce length of antibiotic therapy in patients with severe sepsis and septic shock. *BMC Infect Dis* **13**: 158, 2013.
 24. Schuetz P, Raad I, Amin DN. Using procalcitonin-guided algorithms to improve antimicrobial therapy in ICU patients with respiratory infections and sepsis. *Curr Opin Crit Care* **19**: 453-460, 2013.