

Validity of the D4/D0 plasma procalcitonin level ratio as a predictor for mortality in ventilation-associated pneumonia patients

Ehab El-Shahat and Mohamed A. Alrabiey

Department of Anesthesia and Intensive Care, Faculty of Medicine, Benha University, Benha, Egypt

Correspondence to Mohamed A. Alrabiey, MD, Department of Anesthesia and Intensive Care, Faculty of Medicine, Benha University, 13511 Benha, Egypt
Tel: + 002 010 2050 3009;
e-mail: ashrafrabiey@yahoo.com

Received 2 December 2012

Accepted 24 January 2012

Ain-Shams Journal of Anesthesiology
2012, 5:218–222

Objectives

To evaluate the plasma procalcitonin (PCT) levels estimated at the time of (D0) and 4 days (D4) after the diagnosis of ventilator-associated pneumonia (VAP) as a predictor for mortality.

Patients and methods

VAP was diagnosed when pneumonia developed after 48 h of mechanical ventilation. Patients were evaluated clinically using the APACHE II score and septic status was graded according to Bone's criteria. Blood samples were obtained D0 and D4 for the estimation of plasma PCT levels. Patients were categorized into two groups: survivors, that is, patients discharged through or at the end of 28 days (day 28), and nonsurvivors. Clinical data, plasma PCT levels and the D4/D0 ratio were analyzed as predictors for mortality.

Results

The study included 40 patients, but 15 patients died, yielding a mortality rate of 37.5%. The mean duration of mechanical ventilation before D0 (day of VAP diagnosis) was 5 ± 1.5 days; 29 patients developed early VAP, whereas 11 patients developed late VAP. The mean D0 and D4 plasma PCT levels were significantly higher in all the patients compared with the control levels. The mean D4 plasma PCT levels were significantly higher in all the patients studied and in the patients categorized according to outcome compared with D0 levels and in nonsurvivors compared with survivors. The mean D0/D4 ratio of PCT plasma levels was significantly higher in nonsurvivors compared with survivors. Receiver operating characteristic curve analysis defined the D4/D0 plasma PCT ratio and severity of sepsis as significant predictors for mortality, but the difference was more significant for the D4/D0 ratio.

Conclusion

VAP is associated with a high mortality rate and estimated levels of plasma PCT were significantly higher in nonsurvivors despite treatment compared with survivors. A high D4/D0 ratio of plasma PCT levels was found to be a highly specific predictor of mortality among VAP patients.

Keywords:

mortality, plasma procalcitonin, ventilator-associated pneumonia

Ain-Shams J Anesthesiol 5:218–222

© 2012 Department of Anesthesiology, Intensive Care and Pain Management,
Faculty of Medicine, Ain-Shams University, Cairo, Egypt
1687-7934

Introduction

Plasma procalcitonin (PCT), the precursor molecule of calcitonin, is a 116-amino acid, 13 kDa peptide that has no known hormonal activity. PCT is produced in the C cells of the thyroid gland and normally all PCT is cleaved intracellularly into calcitonin, katacalcine, and an N-terminal residue and none is released into the blood stream. In humans, the serum levels of PCT are very low in healthy individuals; however, the serum levels increase during bacterial infections, but not during viral infections or inflammatory reactions of noninfectious origins. Current PCT assays are rapid, specific, and have sufficient sensitivity to detect increases in PCT serum levels within 4–6 h of the initiation of infection. Clinically, PCT levels may aid decisions on the need for

empirical antibiotic therapy, 'source control' of infection, and the duration of antibiotic therapy [1–3].

Ventilator-associated pneumonia (VAP) is defined as pneumonia that develops more than 48 h after endotracheal intubation and the initiation of mechanical ventilation. When a clinical diagnosis of VAP is suggested by a new or a progressive pulmonary infiltrate associated with fever, an increased white blood cell count, and purulent tracheobronchial secretion, efforts directed toward the establishment of a microbial diagnosis of VAP by invasive or noninvasive techniques are justified [4].

The diagnosis of VAP remains controversial; different approaches have been advocated, but none has been shown to be superior. Moreover, it remains unclear and

debated whether the type of culture (quantitative or nonquantitative) or the sampling method (invasive or noninvasive) influences the etiological diagnosis or outcomes in VAP. It is unlikely that any single approach is the optimal diagnostic assessment whenever VAP is suspected [5,6].

Several previous studies have defined the estimation of plasma PCT levels as an early prognostic marker for patients with septic complications after major surgical procedures, major burns, multiple trauma, and at medical or surgical ICU. Moreover, PCT has been found to be useful compared with various other clinical and laboratory parameters for the estimation of sepsis-related mortality [7–11].

However, despite the proved prognostic validity of PCT, the timing of estimation is a matter of debate; Luyt *et al.* [12] assessed the utility of the daily monitoring of PCT in addition to a clinical evaluation during the early management of sepsis and found the PCT kinetics between D2 and D3 to be significantly different. Thus, the present study was designed to evaluate the prognostic yield of the estimation of plasma PCT at day 0 and on the fourth day after the diagnosis of VAP.

Patients and methods

All patients admitted to the ICU at Benha University hospital and suspected to have VAP were included in the study after obtaining a written fully informed consent signed by the patients' closest relative. The diagnosis of pneumonia was suspected when a patient developed a new and persistent radiographic infiltrate in association with either body temperature above 38°C or less than 36°C; white blood cells of at least $11 \times 10^9/l$ or up to $4 \times 10^9/l$; and/or a macroscopically purulent tracheal aspirate [13]. VAP was diagnosed if pneumonic infiltrates appeared 48 h after the initiation of mechanical ventilation in a patient whose chest radiography was free before the initiation of mechanical ventilation and was considered early onset when it occurred during the first 4 days of mechanical ventilation [14].

Patients were evaluated clinically using the APACHE II score [15] and their septic status was assessed according to Bone's criteria [16] for the presence of systemic inflammatory response syndrome, sepsis, severe sepsis, or septic shock. A chest X-ray scan and routine laboratory investigations including arterial blood gases, complete blood count, and renal and liver function tests were performed. Sterile endotracheal aspirate was obtained on the day of diagnosis (D0) and on the third day after the diagnosis, and then obtained weekly. Venous blood samples were collected before the initiation of antimicrobial therapy for blood culture.

Two venous blood samples were collected in EDTA-containing tubes under complete aseptic conditions, the first on D0 (day of VAP diagnosis) and the second on D4 (4 days after the preliminary diagnosis of VAP), for the

estimation of PCT using a competitive radioimmunoassay method [17].

All the patients enrolled received empirical antimicrobial therapy on D0 to be modified according to the results of the aspirate and blood cultures. Mechanical ventilation, physiotherapy, and airway management were performed according to feasibility. Patients were categorized according to progress into two groups: survivors, that is patients who were discharged within or at the end of 28 days after developing VAP, and nonsurvivors, that is patients who died within 28 days after developing VAP.

Statistical analysis

The data obtained were presented as mean \pm SD, ranges, numbers, and ratios. The results were analyzed using the χ^2 -test, a paired *t*-test for intergroup comparisons, and the Wilcoxon signed ranks test for between-group comparisons. The receiver operating characteristic (ROC) curve analysis on the basis of the area under the curve (AUC) was used to evaluate various parameters, namely, age, sex, severity of sepsis, the APACHE II score at admission, ICU stay before the development of VAP, time until the development of VAP, plasma PCT at D0 and D4, and D4/D0 PCT plasma levels ratio, as predictors for mortality throughout 28 days of ICU stay after the diagnosis of VAP. All reported AUC were compared versus the null hypothesis (true area = 0.5) that the evaluated parameter was diagnostic and specific if the AUC was significantly different compared with the actual area. Statistical analysis was carried out using the SPSS (version 10, 2002, Apache Software Foundation, USA) for Windows statistical package. A *P* value less than 0.05 was considered statistically significant.

Results

Throughout the study period, 40 patients, 27 men, and 13 women, fulfilled the inclusion criteria and were enrolled in the study. Twenty-one patients (52.5%) were admitted to ICU for medical causes, 12 patients (30%) required postoperative admission to ICU, and the other seven patients (17.5%) had multiple trauma that necessitated immediate transfer to ICU for resuscitation and required mechanical ventilation. Associated medical comorbidities were reported in 17 patients (42.5%). Twelve patients (30%) had systemic inflammatory response syndrome, 23 patients (57.5%) had sepsis, which was severe in eight patients (20%), and five patients (12.5%) had septic shock. At the end of the follow-up period (28 days after the diagnosis of VAP), 15 patients died, yielding a mortality rate of 37.5%, whereas 18 patients were discharged from the ICU within the observation period and seven patients were still alive at the end of the observation period, yielding a survival rate of 62.5%. There was a nonsignificant difference between survivors and nonsurvivors in terms of the above-mentioned data (Table 1).

The mean APACHE II score at admission was 15.1 ± 2.2 (12–19) and was significantly higher in nonsurvivors (16.3 ± 2.3) compared with survivors (14.4 ± 1.8). All

Table 1 Estimated plasma levels of PCT (ng/ml) at D0 and D4 after the start of treatment of VAP categorized according to the outcome and compared with the control levels

	D0 plasma level	D4 plasma level	D4/D0 ratio
Control	0.451 ± 0.155		
Patients			
Total			
Mean ± SD	1.16 ± 0.42	2.94 ± 2.16	2.8 ± 2.57
Statistical analysis			
Z	5.443	5.511	
P ₁	<0.001	<0.001	
t		5.313	
P ₂		<0.001	
Survivors			
Mean ± SD	1.18 ± 0.39	1.8 ± 0.97	1.54 ± 0.72
Statistical analysis			
Z	4.157	4.373	
P ₁	<0.001	<0.001	
T		3.594	
P ₂		=0.001	
Nonsurvivors			
Mean ± SD	1.13 ± 0.48	4.83 ± 2.29	4.84 ± 3.18
Statistical analysis			
Z	2.982	3.408	
P ₁	=0.003	=0.001	
t		6.539	
P ₂		<0.001	
Z	1.363	3.124	3.408
P ₃	>0.05	=0.002	=0.001

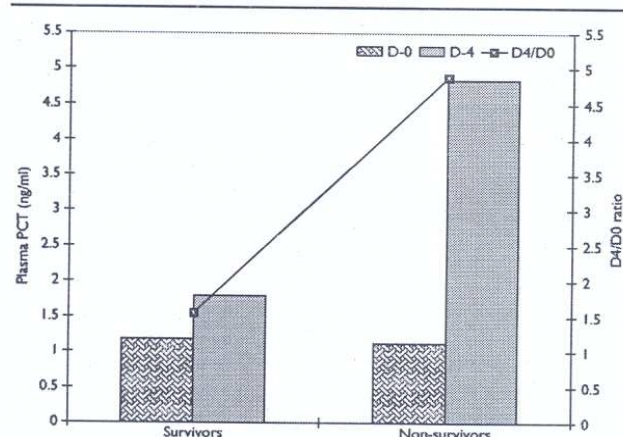
P₁, significance versus control levels; P₂, significance versus D0 levels; P₃, significance versus survivors' levels.

PCT, plasma procalcitonin; VAP, ventilator-associated pneumonia.

patients, except those who had renal failure, were urinary catheterized and 17 patients received central venous catheterization. The mean duration of mechanical ventilation before the development of VAP was 5 ± 1.5 , range 3–8 days. Four patients underwent tracheostomy; in two patients, a nasotracheal tube was used and in 34 patients an orotracheal tube was used. There was a nonsignificant difference between survivors and nonsurvivors in terms of these data.

Twenty-nine patients (72.5%) developed early VAP after a mean duration of mechanical ventilation of 3 ± 0.8 , range 2–4 days; the other 11 patients (27.5%) developed late VAP after a mean duration of mechanical ventilation of 6.9 ± 1 , range 5–8 days. Eighteen survivors had early and seven had late VAP, whereas 11 nonsurvivors had early and four had late VAP. There was a nonsignificant difference between survivors and nonsurvivors in terms of the type of VAP.

The mean PCT plasma levels estimated at both D0 and D4 were significantly higher in all the studied patients compared with the control level and in patients categorized according to outcome, with a nonsignificant difference between survivors and nonsurvivors. Compared with the D0 PCT plasma levels, the mean plasma PCT levels estimated at D4 were significantly higher in all the studied patients and in patients categorized according to outcome. Furthermore, the mean PCT plasma levels estimated at D4 were significantly ($P_3 < 0.001$) higher in nonsurvivors compared with the levels estimated in survivors. The mean D0/D4 ratio of the PCT plasma levels of the studied patients was significantly higher in nonsurvivors compared with survivors (Table 1, Fig. 1).

Figure 1

Mean plasma PCT levels estimated at D0 and D4 in VAP patients categorized according to outcome with respect to the D4/D0 ratio. PCT, plasma procalcitonin; VAP, ventilator-associated pneumonia.

The receiver operating characteristic curve analysis defined the D4/D0 plasma PCT ratio and severity of sepsis as the significant predictors for mortality, whereas the other parameters showed a nonsignificant difference versus the null hypothesis. Moreover, the D4/D0 ratio showed a more significant difference versus the null hypothesis compared with the severity of sepsis, and can thus be considered as the most specific independent predictor for mortality of the patients who developed VAP (Table 2, Fig. 2).

Discussion

Forty mechanically ventilated patients who developed VAP during their stay in the ICU, 28 patients had early VAP and 12 patients had late VAP, and during the 28-day follow-up, 15 patients died, yielding a mortality rate of 37.5%, irrespective of the cause or the duration of ICU stay before they developed VAP. These data are in agreement with those of Chastre and Fagon [18], who reported that the mortality rate for VAP ranges from 24 to 50% and can reach 76% in specific settings or when lung infection is caused by high-risk pathogens, and those of Nseir *et al.* [19] and Uno *et al.* [20], who reported that VAP was associated with a longer duration of mechanical ventilation and ICU stay and an increased ICU mortality rate of COPD and hemodialysis patients, respectively. Recently, Zilberberg *et al.* [21] reported, in a base case analysis, a VAP-attributable mortality rate of 38.4%, and Al-Tawfiq and Abed [22] reported that VAP increases the in-hospital mortality of ventilated patients to 46% compared with 32% for ventilated patients who do not develop VAP.

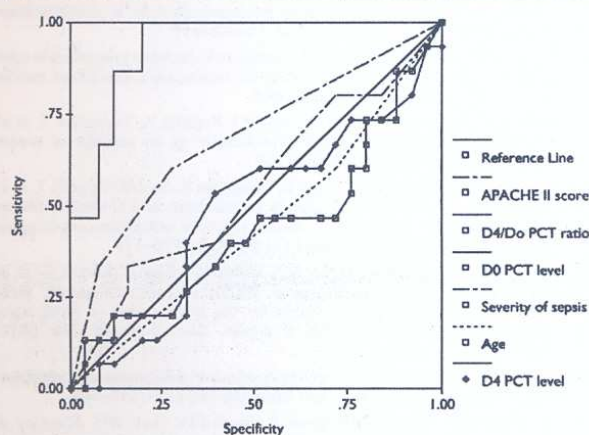
The mean PCT plasma levels estimated at D0 were significantly higher in VAP patients, irrespective of the outcome, which indicates that plasma PCT was elevated in response to the presence of infection, and its detection on the first day of diagnosis implies that it could be used

Table 2 ROC curve analysis of evaluated parameters as independent predictors for mortality assessed by AUC arranged in descending order

	AAC	SE	P	95% confidence interval	
				Lower	Upper
D4/D0 plasma PCT ratio	0.933	0.037	<0.001*	0.860	1.006
Severity of sepsis	0.683	0.091	=0.036*	0.504	0.861
APACHE II score	0.544	0.097	>0.05	0.353	0.735
D4 plasma PCT level	0.533	0.095	>0.05	0.347	0.720
Age	0.476	0.097	>0.05	0.285	0.667
Time till development of VAP	0.464	0.095	>0.05	0.277	0.651
Sex	0.440	0.096	>0.05	0.253	0.627
D0 plasma PCT level	0.429	0.099	>0.05	0.236	0.623

AUC, area under curve; PCT, plasma procalcitonin; ROC, receiver operating characteristic; VAP, ventilator-associated pneumonia.

*Significant versus the null hypothesis.

Figure 2

ROC curve analysis of evaluated parameters as specific predictors of mortality of VAP patients. ROC, receiver operating characteristic; VAP, ventilator-associated pneumonia.

as a primary phase reactant to infection. These findings were in agreement with those reported previously on the diagnostic validity of the estimation of plasma PCT in various infectious diseases in comparison with other primary phase reactants. Aikawa *et al.* [23] reported significantly higher serum levels of PCT, endotoxin, interleukin-6 (IL-6), and C-reactive protein (CRP) in patients with bacterial infectious diseases than in those with nonbacterial infectious diseases, but PCT showed higher discriminating power with higher AUC than other parameters. Hirakata *et al.* [24] found that the PCT level might be more useful for the estimation of the severity of community-acquired pneumonia than the CRP level at the first visit. Recently, Haasper *et al.* [25] reported that in the development of sepsis, PCT was superior to IL-6, showing significantly higher plasma levels in the group positive for sepsis from the first day after trauma, and concluded that serum levels of IL-6 and PCT may be useful in the early identification of patients at a high risk for developing post-traumatic multiorgan dysfunction syndrome; however, for sepsis, PCT is a better prognostic factor.

On the fourth day after the diagnosis of VAP, the mean PCT plasma levels were significantly higher compared with

both the control levels and the D0 levels; however, the mean plasma PCT levels estimated at D4 were significantly higher in nonsurvivors compared with survivors. The progressive increasing plasma levels of PCT indicate the progress of the inflammatory process. Estimation of plasma PCT despite being higher in survivors compared to their D0 levels, the plasma PCT levels in survivors being significantly lower compared to non-survivors. These findings are in agreement with the previously reported data that serum markers, in particular procalcitonin, represent a promising strategy in the clinical decision-making process in patients in whom pneumonia is suspected, and can be used to guide management and to monitor the clinical course, adjust the duration of antibiotic therapy, and identify nonresponders [3,26,27]. The reported increased D4 levels compared with D0 levels, irrespective of the outcome, indicate the diagnostic value of sequential estimation for monitoring of patients and are in agreement with the study by Gibot *et al.* [28], which emphasized the need for more than an estimation of PCT and with the study by Ramirez *et al.* [29], which found that sequential measurements of PCT showed the best sensitivity and specificity (78 and 97%, respectively) compared with CRP and clinical scoring for predicting the outcome of VAP.

However, statistical analyses of the survival predictability of single PCT estimation and clinical variables versus the null hypothesis that true AUC = 0.5 defined only the severity of septic status as a significant prognostic indicator for mortality and plasma PCT levels were nonsignificant. Evaluation of the D4/D0 ratio as a prognostic parameter versus the severity of septic status indicated a high D4/D0 plasma PCT ratio as the most specific predictor for the possibility of estimating high mortality and showed AUC = 0.949, which was highly significant ($P < 0.001$) compared with the null hypothesis, followed by the severity of sepsis, which showed AUC = 0.683, which was significantly higher than ($P = 0.036$) but lower than the D4/D0 ratio. These data showed that persistently elevated or elevating plasma levels of PCT correlated with the septic state before the development of VAP and indicated a poor prognosis.

VAP is associated with a high mortality rate irrespective of its type, cause, or duration of ICU admission. Estimated

levels of plasma PCT were significantly higher in non-survivors despite treatment compared with survivors, and a high D4/D0 ratio of plasma PCT levels was found to be a highly specific predictor of mortality among VAP patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

- Wanner GA, Keel M, Steckholzer U, Beier W, Stocker R, Ertel W. Relationship between procalcitonin plasma levels and severity of injury, sepsis, organ failure and mortality in injured patients. *Crit Care Med* 2000; 28: 950-957.
- Floriańczyk B. Structure and diagnostic value of procalcitonin. *Ann Univ Mariae Curie Skłodowska Med* 2003; 58:338-342.
- Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. *J Clin Microbiol* 2010; 48:2325-2329.
- El Solh AA, Choi G, Schultz MJ, Pineda LA, Mankowski C. Clinical and hemostatic responses to treatment in ventilator-associated pneumonia: role of bacterial pathogens. *Crit Care Med* 2007; 35:490-496.
- Lisboa T, Rello J. Diagnosis of ventilator-associated pneumonia: is there a gold standard and a simple approach? *Curr Opin Infect Dis* 2008; 21:174-178.
- Lisboa T, Seligman R, Díaz E, Rodríguez A, Teixeira PJZ, Rello J. C-reactive protein correlates with bacterial load and appropriate antibiotic therapy in suspected ventilator-associated pneumonia. *Crit Care Med* 2008; 36:166-171.
- Viallon A, Guyomarc'h S, Marjollet O, Berger C, Carricajo A, Robert F, et al. Can emergency physicians identify a high mortality subgroup of patients with sepsis: role of procalcitonin. *Eur J Emerg Med* 2008; 15:26-33.
- Barati M, Alinejad F, Bahar MA, Tabrisi MS, Shamshiri AR, Bodouhi NO, et al. Comparison of WBC, ESR, CRP and PCT serum levels in septic and non-septic burn cases. *Burns* 2008; 34:770-774.
- Maier M, Wutzler S, Lehnert M, Szermutzky M, Wyen H, Bingold T, et al. Serum procalcitonin levels in patients with multiple injuries including visceral trauma. *J Trauma* 2009; 66:243-249.
- Castelli GP, Pognani C, Cita M, Paladini R. Procalcitonin as a prognostic and diagnostic tool for septic complications after major trauma. *Crit Care Med* 2009; 37:1845-1849.
- De Kruij MD, Limper M, Gerritsen H, Spek CA, Brandjes DPM, Ten Cate H, et al. Additional value of procalcitonin for diagnosis of infection in patients with fever at the emergency department. *Crit Care Med* 2010; 38:457-463.
- Luyt CE, Guérin V, Combes A, Trouillet JL, Ayed SB, Bernard M, et al. Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171:48-53.
- Fàbregas N, Ewig S, Torres A, El-Ebary M, Ramirez J, De la Bellacasa JP, et al. Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. *Thorax* 1999; 54:867-873.
- Langer M, Cigada M, Mandelli M. Early onset pneumonia: a multicenter study in intensive care units. *Intensive Care Med* 1987; 13:342-346.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13:818-829.
- 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* 1992; 20:864-874.
- Dwenger A. Radioimmunoassay: an overview. *J Clin Chem Clin Biochem* 1984; 22:883-894.
- Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002; 165:867-903.
- Nseir S, Di Pompeo C, Soubrier S, Cavestri B, Jozefowicz E, Saulnier F, et al. Impact of ventilator-associated pneumonia on outcome in patients with COPD. *Chest* 2005; 128:1650-1656.
- Uno H, Takezawa J, Yatsuya H, Suka M, Yoshida K. Impact of intensive-care-unit(ICU)-acquired ventilator-associated pneumonia(VAP) on hospital mortality: a matched-paired case-control study. *Nagoya J Med Sci* 2007; 69: 29-36.
- Zilberberg MD, Mody SH, Chen J, Shorr AF. Cost-effectiveness model of empiric doripenem compared with imipenem-cilastatin in ventilator-associated pneumonia. *Surg Infect* 2010; 11:409-417.
- Al-Tawfiq JA, Abed MS. Decreasing ventilator-associated pneumonia in adult intensive care units using the Institute for Healthcare Improvement bundle. *Am J Infect Control* 2010; 38:552-556.
- Aikawa N, Fujishima S, Endo S, Sekine I, Kogawa K, Yamamoto Y, et al. Multicenter prospective study of procalcitonin as an indicator of sepsis. *J Infect Chemother* 2005; 11:152-159.
- Hirakata Y, Yanagihara K, Kurihara S, Izumikawa K, Seki M, Miyazaki Y, 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* 2008; 61:170-174.
- Haasper C, Kalmbach M, Dikos GD, Meller R, Müller C, Krettek C, et al. Prognostic value of procalcitonin (PCT) and/or interleukin-6 (IL-6) plasma levels after multiple trauma for the development of multi organ dysfunction syndrome (MODS) or sepsis. *Technol Health Care* 2010; 18:89-100.
- Póvoa P. Serum markers in community-acquired pneumonia and ventilator-associated pneumonia. *Curr Opin Infect Dis* 2008; 21:157-162.
- Schneider CP, Yilmaz Y, Kleespies A, Jauch KW, Hartl WH. Accuracy of procalcitonin for outcome prediction in unselected postoperative critically ill patients. *Shock* 2009; 31:568-573.
- Gibot S, Cravoisy A, Dupays R, Barraud D, Nace L, Levy B, et al. Combined measurement of procalcitonin and soluble TREM-1 in the diagnosis of nosocomial sepsis. *Scan J Infect Dis* 2007; 39:604-608.
- Ramirez P, Garcia MA, Ferrer M, Aznar J, Valencia M, Sahuquillo JM, et al. Sequential measurements of procalcitonin levels in diagnosing ventilator-associated pneumonia. *Eur Respir J* 2008; 31:356-362.