African Journal of Biotechnology Vol. 11(33), pp. 8167-8171, 24 April, 2012
Available online at http://www.academicjournals.org/AJB
DOI: 10.5897/AJBX11.075
ISSN 1684–5315 © 2012 Academic Journals

Review

Procalcitonin, C-reactive protein and prognosis in septic patients

Yoshan Moodley

Department of Anaesthetics, University of Kwazulu-Natal, South Africa. E-mail: moodleyyo@ukzn.ac.za. Tel: +27 31 240 1729.

Accepted 3 February, 2012

Sepsis is of major importance worldwide, placing economic burden on healthcare systems and often resulting in morbidity and mortality in affected patients. The use of rapid, effective prognostic laboratory tests will no doubt improve decision-making on the part of the physician. We describe prospective observational studies of two commonly used biomarkers when monitoring the clinical course of sepsis, procalcitonin and C-reactive protein, herein.

Key words: Procalcitonin, C-reactive protein, sepsis.

INTRODUCTION

Infection by microorganisms may develop into systemic manifestations, namely sepsis (Figure 1). Sepsis may place significant economic burden on the healthcare systems of some countries and accounts for a substantial proportion of morbidity and mortality in affected patients (Martin et al., 2003). There remains a need for rapid, effective methods to predict outcomes in septic patients. Advances in medical biotechnology have yielded a number of biological markers (biomarkers), such as procalcitonin (PCT) and C-reactive protein (CRP), which address this need.

PCT is a 116 amino acid prohormone encoded for by the *CALC-1* gene on chromosome 11 (Figure 2). In healthy individuals, PCT is produced by C-cells in the thyroid (Carrol et al., 2002; Maruna et al., 2000; Michael, 2002). During sepsis/infection, parenchymal cells produce PCT in large quantities (up to 100,000 times normal physiological levels) following the onset of sepsis/infection (Niederman, 2008). The cytokines interleukin-1β and tumor necrosis factor-α, as well as bacterial cell wall components such as lipopolysaccharide, are known inducers of PCT synthesis (Maruna et al., 2000). The role played by PCT during infection remains unknown; however its application as a biomarker is well established. PCT levels may be used to differentiate between Systemic Inflammatory Response Syndrome (SIRS) and sepsis, as well as differentiate between different degrees of sepsis (Carrol et al., 2002).

CRP belongs to a group of phyllogenetically ancient proteins known as pentraxins(Black et al., 2004). CRP is encoded by a gene *CRP* mapped to chromosome 1, and is produced by the liver during the acute phase (following trauma/infection) (Volanakis, 2001). Serum concentrations of CRP may increase 1000-fold within 2 days following induction by the pro-inflammatory cytokine interleukin-6 (Ablij and Meinders, 2002). Structurally, CRP consists of 206 amino acids arranged as five non-covalently linked protomers (Figure 3). CRP was first described in 1930, following its observed reaction with cell wall components of the bacterium *Streptococcus pneumoniae*. In addition to phosphocholine on bacterial cell walls, which it binds in a calcium-dependant manner, chromatin and nuclear proteins have also been identified as ligands for CRP (Black et al., 2004). CRP plays an important role during the innate immune response to infection. It activates the complement system via the classical pathway through direct interactions with complement proteins. CRP may also activate phagocytic cells by interacting with receptors on the cell surface. Other functions of CRP include its roles in the removal of apoptotic cells, atherosclerosis, and the mediation of tissue damage during myocardial infarction (Ablij and Meinders, 2002).

PROSPECTIVE STUDIES COMPARING PCT AND CRP

Zhang and colleagues evaluated the prognostic potential

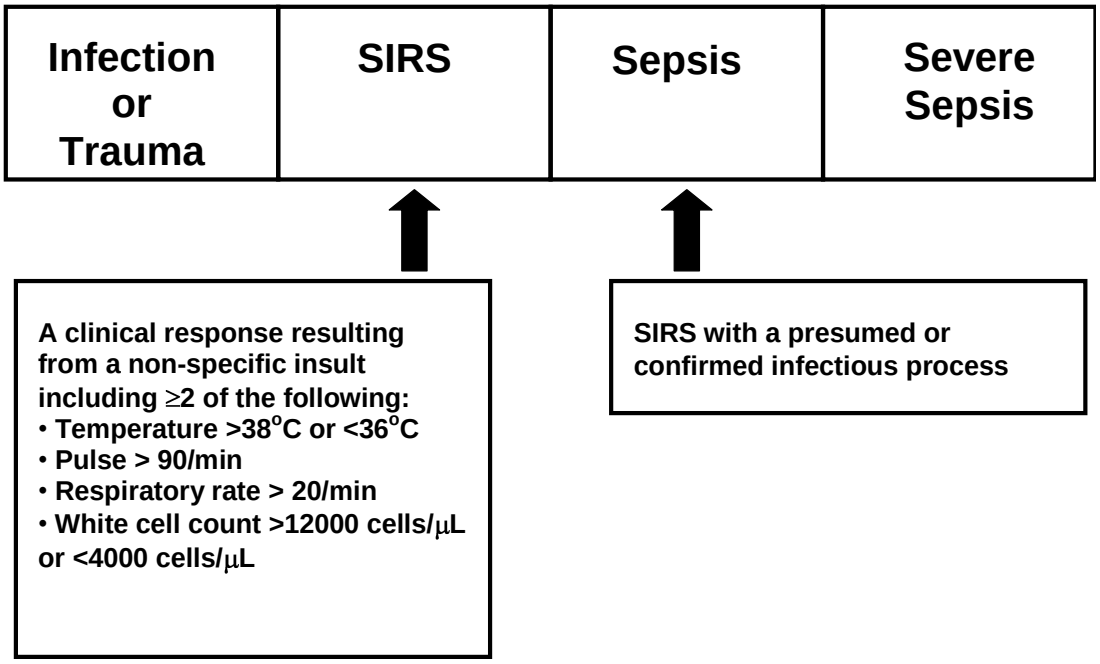

Figure 1. Definitions of SIRS and Sepsis (Qureshi and Rajah, 2008).

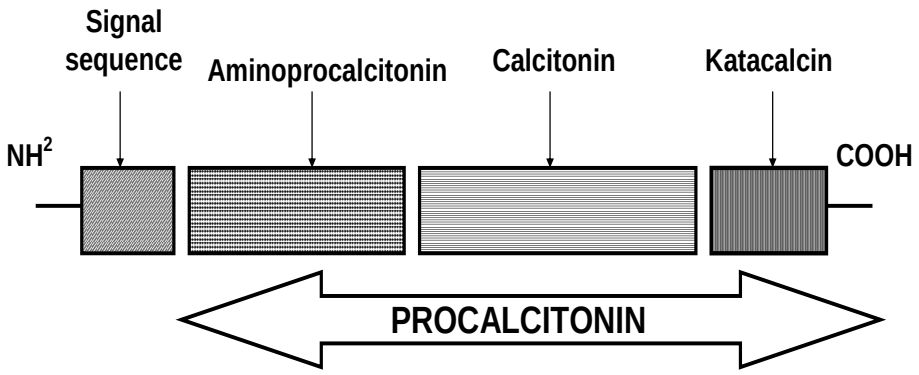

Figure 2. Schematic illustration of PCT (Carrol et al., 2002).

of serum soluble proteins such as: Triggering receptor expressed on myeloid cells-1 (sTREM-1), CRP and PCT in 52 patients with varying degrees of sepsis. It was found that within 7 days of admission to an intensive care unit (ICU), there was no significant difference in CRP and PCT levels between survivors and non-survivors. However, CRP and PCT levels were found to be significantly different between the two groups at days 10 and 14 post-ICU admission. Patients with higher serum levels of PCT and CRP had poorer prognoses, with CRP levels tending to be higher than PCT levels in patients diagnosed with sepsis based on 28-day survival. Correlation co-efficients between the physiological sequential organ failure assessment (SOFA) score and PCT levels was higher than that between SOFA scores and CRP levels ($r = 0.257$ vs. $r = 0.406$) (Zhang et al., 2011). A similar study showed that baseline CRP did not differ significantly between survivors and non-survivors. PCT levels in non-survivors were almost 4 times higher than PCT levels in survivors (Gibot et al., 2005).

The prognostic value of pro-atrial natriuretic peptide, proadrenomedullin, CRP and PCT was evaluated in 51 critically ill patients (Wang and Kang, 2010). In concurrence with the findings of Zhang et al. (2011), CRP and PCT levels were not significantly different between survivors and non-survivors on the day of admission to ICU ($p = 0.75$ and $p = 0.08$, respectively). Receiver operating characteristic (ROC) curve analysis showed that PCT was of more prognostic value than CRP. The area under curve (AUC) for PCT and CRP were

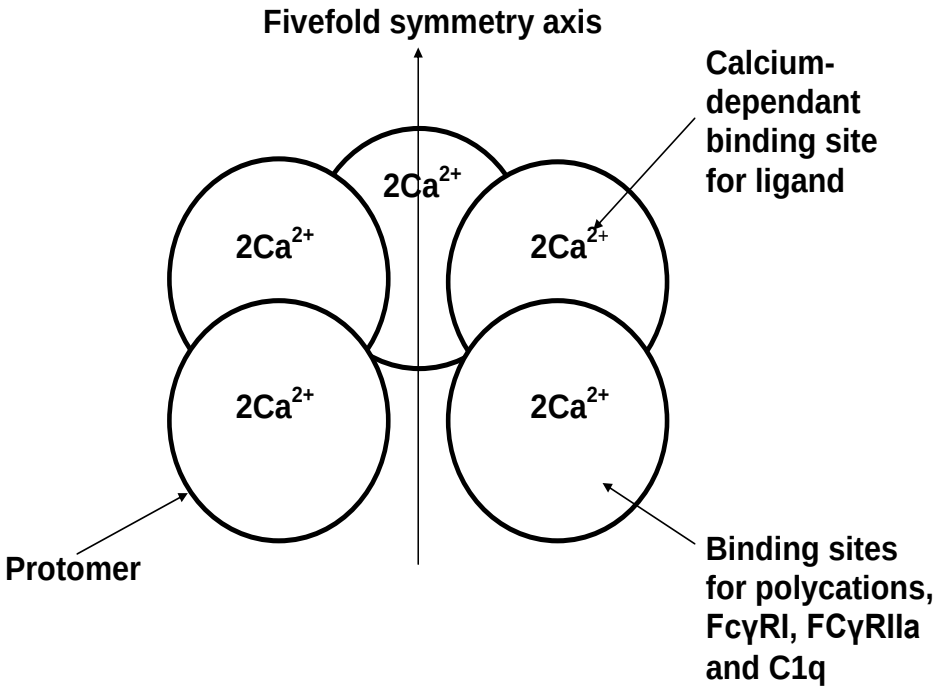

Figure 3. Schematic illustration of CRP (Ablij and Meinders, 2002)

calculated as 0.81 and 0.53, respectively. In a smaller study of 20 patients with sepsis and severe sepsis, both PCT and CRP were higher in non-survivors with sepsis versus survivors (Piechota et al., 2007).

In another study, PCT and CRP levels were elevated on day 1 of sepsis, and decreased steadily by day 7 in both survivors and non-survivors. Following day 7 of sepsis, an increase in circulating PCT was associated with a lethal outcome. Similar increases in CRP levels were observed in non-survivors after 7 days. However, serial CRP measurements did not adequately reflect sepsis severity or outcomes in septic patients. Also, CRP measurements in this study were not able to differentiate between sepsis and uneventful post-operative course (Tschaikowsky et al., 2002).

In a study of 281 patients with community-acquired pneumonia (Schuetz et al., 2008), CRP levels measured at baseline where higher than PCT levels measured at the corresponding point in time. ROC analysis suggested that the ability of PCT to predict death was better when compared to CRP (AUC = 0.59 vs. 0.51). ROC analysis also showed that the ability of PCT to predict adverse outcomes tended to be better than that of CRP (AUC = 0.65 vs. 0.58). When combined with clinical severity scores, both CRP and PCT could not reliably predict death/adverse outcomes. The authors concluded that PCT was more of a diagnostic tool rather than a prognostic tool. In another two studies of community-acquired pneumonia, PCT showed improved performance at predicting death/organ failure than CRP (Christ-Crain et al., 2006, 2007). Brunkhorst et al. (2002) demonstrated that elevated CRP levels in patients with severe pneumonia were not prognostic, while PCT had a slight prognostic value. It was also found that in the latter stages of disease, non-survivors had higher PCT levels than survivors.

Rau et al. (2007a) found that elevated PCT in patients with peritonitis was more likely to be associated with multi-organ dysfunction syndrome (MODS). Persistent PCT elevation was observed after 7 days in non-survivors. These findings were in contrast to CRP levels, which was not significantly different between survivors and non-survivors. A PCT level of >1 ng/ml was established as a suitable predictor of mortality in the week following the onset of symptomatic peritonitis. In a similar study, PCT was again shown to be a better prognostic tool than CRP in patients with severe acute pancreatitis (Rau et al., 2007b).

Pettila et al. (2002) conducted a prospective cohort study to establish the predictive value of PCT and interleukin-6 in critically ill patients with suspected sepsis. CRP was also included for comparison. PCT was higher in non-survivors on days 1 and 2 post-admission ($p = 0.007$ and 0.003, respectively). For CRP, there was no significant difference observed in non-survivors and survivors on days 1 and 2 post-admission ($p = 0.15$ and 0.52, respectively). For PCT, reasonable discriminative power related to hospital mortality was observed on day 2 post admission (AUC > 0.75). AUC analysis for CRP did not yield similar results (AUC = 0.533). It should be noted that both PCT and CRP were not independently associated with mortality in this study.

In a study of 101 critically ill patients admitted to an ICU, there was no significant difference between PCT levels in survivors (p = 0.38) and non-survivors (p = 0.05) on the day following ICU admission. The authors also stated that there was also a significant difference in CRP levels between survivors and non-survivors on the day following ICU admission, although this data was not presented. ROC/AUC plot analysis suggested PCT was better at predicting mortality than CRP (AUC = 0.67 vs. 0.51) (Morgenthaler et al., 2005).

Between May 1998 and April 2000, Meisner et al. (2006) studied the kinetics of CRP and PCT in 90 adult trauma patients. Forty of these patients had proven infection, with PCT levels of days 1 and 2 post-trauma significantly higher in those who subsequently developed infection or those with suspected infection. CRP measurements at the same time points did not differ significantly amongst those developing a proven infection or in patients with suspected infection.

Maruna et al. (2011) compared PCT with other inflammatory markers (including CRP) to determine its prognostic value following pulmonary artery endarterectomy. ROC/AUC analysis for PCT to predict post-operative infection was 0.83. No ROC/AUC analysis for CRP was presented. The discriminatory ability of PCT, CRP and physiological scores (MEDS) to predict mortality was evaluated by Lee and colleagues. The physiological scoring system was better than the two biomarkers at predicting early/late mortality. ROC analysis showed that there was a larger AUC for PCT in predicting early mortality than CRP (AUC = 0.76 vs. 0.68, respectively). C-statistics were also significantly different between CRP and PCT (P = 0.031). For late mortality, AUC obtained for PCT and CRP were 0.73 and 0.674, respectively. C-statistics were once again significantly different between CRP and PCT (P = 0.030). Overall, there was a recommendation that PCT/CRP should be combined with physiological scoring systems for improved predictive accuracy (Lee et al., 2008).

In a pilot study, comparing macrophage migration inhibitory factor (MIF), CRP and PCT in cardiac surgery patients with sepsis, PCT levels in non-survivors were significantly higher than those measured in survivors (P = 0.007). An AUC of 0.656 was obtained for PCT. No significant association between CRP and mortality/organ dysfunction was observed. Unfortunately, no ROC/AUC data for CRP was presented (de Mendonca-Filho et al., 2005).

Clec'h et al. (2004) conducted a prospective controlled trial to determine whether PCT is a reliable diagnostic/prognostic marker in septic shock versus non-septic shock. In patients with septic shock, non-survivors had higher levels of PCT that survivors measured on days 1, 3, 7 and 10 of septic shock (P = 0.045; 0.03; 0.003; and 0.02, respectively). PCT was shown to be of little value in predicting outcomes in cardiogenic shock. CRP levels were not correlated with outcomes on days 1, 3, 7, and 10 of septic shock. On day 1 of septic shock, a PCT level of 6 ng/ml predicted death (sensitivity = 87.5%, specificity = 45%). The authors stated that caution should be exercised when interpreting high PCT levels, as these may be associated with reduced specificity

In a study by Claeys et al. (2002), both CRP and PCT proved to be poor predictors of outcome in terms of survival. PCT levels showed a decreasing trend in survivors versus non-survivors within 2 days of acute septic shock (P = 0.047). CRP levels in survivors also showed a decreasing trend, however after a longer time period of 120 h (P = 0.037). Christ-Crain and colleagues showed that there was no significant difference in PCT and CRP levels between survivors and non-survivors on admission to ICU. In those patients with diagnosed sepsis, PCT showed better prognostic ability than CRP (AUC = 0.68 vs. 0.60, respectively) (Christ-Crain et al., 2005). Similarly, PCT levels on day 3 of sepsis were superior to CRP in predicting mortality in critically ill patients (AUC = 0.81 vs. 0.63, respectively) (Chopin et al., 2006).Castelli et al. (2009) established that a PCT level of 1 to 1.5 ng/ml admission was the optimal cutt-off value for prognosis of sepsis versus SIRS. PCT, but not CRP at admission correlated with SOFA scores (p < 0.001). PCT was a superior maker for identifying patients at risk of organ dysfunction.

A study of meningococcal septic shock in children showed that PC and CRP levels on admission were not significantly different between survivors and non-survivors. The AUC for prediction of septic shock for PCT and CRP were 0.85 and 0.428, respectively. The AUC for PCT in predicting the need for ventilation was 0.72, whilst CRP was not able to discriminate between children requiring ventilation and those who did not. PCT was also able to discriminate children requiring prolonged ICU stay exceeding 10 days (AUC = 0.97), whereas CRP could not (Carrol et al., 2005).

CONCLUSION

Biomarkers have proven to be a suitable method for predicting clinical outcomes in septic patients. Both CRP and PCT levels are commonly measured in septic patients, however, PCT is shown in many studies to have superior prognostic value when compared with CRP. Although there is a trend to a better prognostic value of PCT, many of the studies described in this paper are limited by small sample size. Further research with larger cohort sizes is required.

REFERENCES

Ablij H, Meinders A (2002). C-reactive protein: history and revival. Eur. J. Int. Med. 13: 412.

Black S, Kushner I, Samols D (2004). C-reactive Protein. J. Biol. Chem. 279: 48487-48490.

Brunkhorst FM, Al-Nawas B, Krummenauer F, Forycki ZF, Shah PM (2002). Procalcitonin, C-reactive protein and APACHE II score for risk evaluation in patients with severe pneumonia. Clin. Microbiol. Infect.

8: 93-100.
Carrol ED, Newland P, Thomson AP, Hart CA (2005). Prognostic value of procalcitonin in children with meningococcal sepsis. Crit. Care Med. 33: 224-225.
Carrol ED, Thomson APJ, Hart CA (2002). Procalcitonin as a marker of sepsis. Int. J. Antimicrob. Agents, 20: 1-9.
Castelli GP, Pognani C, Cita M, Paladini R (2009). Procalcitonin as a prognostic and diagnostic tool for septic complications after major trauma. Crit. Care. Med. 37: 1845-1849.
Chopin N, Floccard B, Sobas F, Illinger J, Boselli E, Benatir F, Levrat A, Guillaume C, Crozon J, Negrier C, Allaouchiche B (2006). Activated partial thromboplastin time waveform analysis: a new tool to detect infection? Crit. Care Med. 34: 1654-1660.
Christ-Crain M, Morgenthaler NG, Stolz D, Muller C, Bingisser R, Harbarth S, Tamm M, Struck J, Bergmann A, Muller B (2006). Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia [ISRCTN04176397]. Crit. Care, 10: R96.
Christ-Crain M, Morgenthaler NG, Struck J, Harbarth S, Bergmann A, Muller B (2005). Mid-regional pro-adrenomedullin as a prognostic marker in sepsis: an observational study. Crit. Care, 9: R816-824.
Christ-Crain M, Stolz D, Jutla S, Couppis O, Muller C, Bingisser R, Schuetz P, Tamm M, Edwards R, Muller B, Grossman AB (2007). Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. Am. J. Respir. Crit. Care. Med. 176: 913-920.
Claeys R, Vinken S, Spapen H, ver Elst K, Decochez K, Huyghens L, Gorus FK (2002). Plasma procalcitonin and C-reactive protein in acute septic shock: clinical and biological correlates. Crit. Care. Med. 30: 757-762.
Clec'h C, Ferriere F, Karoubi P, Fosse JP, Cupa M, Hoang P, Cohen Y (2004). Diagnostic and prognostic value of procalcitonin in patients with septic shock. Crit. Care. Med. 32: 1166-1169.
De Mendonca-Filho HT, Gomes GS, Nogueira PM, Fernandes MA, Tura BR, Santos M, Castro-Faria-Neto HC (2005). Macrophage migration inhibitory factor is associated with positive cultures in patients with sepsis after cardiac surgery. Shock, 24: 313-317.
Gibot S, Cravoisy A, Kolopp-Sarda MN, Bene MC, Faure G, Bollaert PE, Levy B (2005). Time-course of sTREM (soluble triggering receptor expressed on myeloid cells)-1, procalcitonin, and C-reactive protein plasma concentrations during sepsis. Crit. Care Med. 33: 792-796.
Lee CC, Chen SY, Tsai CL, Wu SC, Chiang WC, Wang JL, Sun HY, Chen SC, Chen WJ, Hsueh PR (2008). Prognostic value of mortality in emergency department sepsis score, procalcitonin, and C-reactive protein in patients with sepsis at the emergency department. Shock, 29: 322-327.
Martin GS, Mannino DM, Eaton S, Moss M (2003). The epidemiology of sepsis in the United States from 1979 through 2000. N. Engl. J. Med. 348: 1546-1554.
Maruna P, Kunstyr J, Plocova KM, Mlejnsky F, Hubacek J, Klein AA, Lindner J (2011). Predictors of infection after pulmonary endarterectomy for chronic thrombo-embolic pulmonary hypertension. Eur. J. Cardiothorac. Surg. 39: 195-200.
Maruna P, Nedelnikova K, Gurlich R (2000). Physiology and genetics of procalcitonin. Physiol. Res. 49(1): S57-61.
Meisner M, Adina H, Schmidt J (2006). Correlation of procalcitonin and C-reactive protein to inflammation, complications, and outcome during the intensive care unit course of multiple-trauma patients. Crit. Care, 10: R1.
Michael M (2002). Pathobiochemistry and clinical use of procalcitonin. Clin. Chimica Acta. 323: 17-29.
Morgenthaler NG, Struck J, Christ-Crain M, Bergmann A, Muller B (2005). Pro-atrial natriuretic peptide is a prognostic marker in sepsis, similar to the APACHE II score: an observational study. Crit. Care, 9: R37-45.
Niederman MS (2008). Biological markers to determine eligibility in trials for community-acquired pneumonia: a focus on procalcitonin. Clin. Infect. Dis. 47(3): S127-132.
Pettila V, Hynninen M, Takkunen O, Kuusela P, Valtonen M (2002). Predictive value of procalcitonin and interleukin 6 in critically ill patients with suspected sepsis. Intensive Care Med. 28: 1220-1225.
Piechota M, Banach M, Irzmanski R, Misztal M, Rysz J, Barylski M, Piechota-Urbanska M, Kowalski J, Pawlicki L (2007). N-terminal brain natriuretic propeptide levels correlate with procalcitonin and C-reactive protein levels in septic patients. Cell. Mol. Biol. Lett. 12: 162-175.
Qureshi K, Rajah A (2008). Septic shock: A review article. BJMP. 1: 7-12.
Rau BM, Frigerio I, Buchler MW, Wegscheider K, Bassi C, Puolakkainen PA, Beger HG, Schilling MK (2007a). Evaluation of procalcitonin for predicting septic multiorgan failure and overall prognosis in secondary peritonitis: a prospective, international multicenter study. Arch. Surg. 142: 134-142.
Rau BM, Kemppainen EA, Gumbs AA, Buchler MW, Wegscheider K, Bassi C, Puolakkainen PA, Beger HG (2007b). Early assessment of pancreatic infections and overall prognosis in severe acute pancreatitis by procalcitonin (PCT): a prospective international multicenter study. Ann. Surg. 245: 745-754.
Schuetz P, Stolz D, Mueller B, Morgenthaler NG, Struck J, Mueller C, Bingisser R, Tamm M, Christ-Crain M (2008). Endothelin-1 precursor peptides correlate with severity of disease and outcome in patients with community acquired pneumonia. BMC Infect. Dis. 8: 22.
Tschaikowsky K, Hedwig-Geissing M, Schiele A, Bremer F, Schywalsky M, Schuttler J (2002). Coincidence of pro- and anti-inflammatory responses in the early phase of severe sepsis: Longitudinal study of mononuclear histocompatibility leukocyte antigen-DR expression, procalcitonin, C-reactive protein, and changes in T-cell subsets in septic and postoperative patients. Crit. Care Med. 30: 1015-1023.
Volanakis JE (2001). Human C-reactive protein: expression, structure, and function. Mol. Immunol. 38: 189-197.
Wang RL, Kang FX (2010). Prediction about severity and outcome of sepsis by pro-atrial natriuretic peptide and pro-adrenomedullin. Chin. J. Traumatol. 13: 152-157.
Zhang J, She D, Feng D, Jia Y, Xie L (2011). Dynamic changes of serum soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) reflect sepsis severity and can predict prognosis: a prospective study. BMC Infect. Dis. 11: p. 53.