Review Article:

Procalcitonin in sepsis and bacterial infections

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ABSTRACT

The differentiation of sepsis and systemic bacterial infections from other causes of systemic inflammatory response is crucial from the therapeutic point of view. The clinical signs and symptoms are non-specific and traditional biomarkers like white cell count, erythrocyte sedimentation rate and C-reactive protein are not sufficiently sensitive or specific to guide therapeutic decisions. Procalcitonin (PCT) is considered a reliable marker for the diagnosis and prognosis of moderate to severe bacterial infections, and it has also been evaluated to guide the clinicians in the rational usage of antibiotics. This review describes the diagnostic and prognostic role of PCT as a biomarker in various clinical settings along with the laboratory aspects and its usefulness in risk stratification and antibiotic stewardship.

Key words: *Procalcitonin, Biomarker, Sepsis*

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INTRODUCTION

Sepsis is systemic inflammatory response syndrome (SIRS), due to bacterial infection[1] and this condition requires prompt institution of antibiotic therapy. On the other hand, indiscriminate use of antibiotics in critically ill patients with SIRS due to other causes leads to overuse of antibiotic with risk of rise in antibiotic resistance. The search for a biomarker for sepsis which is highly specific and sensitive with the minimum turnaround time which can reliably distinguish between bacterial infection from other infections, such as, viral, fungal, or protozoal infections as well as non-infectious causes of SIRS have been ongoing. It has also been felt that the biomarker should also be able to determine the infection severity and response to treatment, thus acting as an effective prognostic indicator (Table 1).[2]

Traditional markers of sepsis like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and leucocyte count have been widely used worldwide but these lack specificity. Novel biomarkers which hold promise include procalcitonin (PCT), interleukins, low eosinophil count , adrenomedullin, interferon-γ (IFN-γ), resistin, natriuretic peptides, and copeptin; and the list is ever expanding.[3] However, during the last two decades, PCT has attracted universal attention and is the most studied biomarker for sepsis. This review highlights the diagnostic and prognostic utility of PCT in sepsis and other infections and its role in antibiotic stewardship, particularly in the field of critical care.

Table 1: Features of an ideal sepsis biomarker

Objective parameter
Easy to use and interpret
Reproducible
Readily available
High sensitivity and specificity
Should show rapid increase and decrease
Should show appropriate response with effective therapy
Should co-relate with disease severity
Should show sustained rise in any subsequent infection
Inexpensive

Source: *reference 2*

Procalcitonin: structure and synthesis

The first mention of PCT in sepsis appeared in a report of 1983[4] mentioning its elevated levels in toxic shock syndrome (TSS) caused by *Staphylococcus aureus*. However, it was Assicot et al[5] who in 1993 first described PCT as a new marker for infection. PCT is a 116 amino acid long peptide having a molecular weight of 13 KDa.[6] As the

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name suggests, it is a precursor of calcitonin, produced by the C-cells of thyroid under the control of the calcitonin gene related peptide 1 *(CALC-1)* gene.[7] Normally, the expression of the gene is found in the neuroendocrine cells of the thyroid and the lung. However, during microbial infections there is increased *CALC-1* gene expression in various extra-thyroid tissues and cells including kidneys, liver, pancreas, leucocytes, and adipose tissue with concomitant release of PCT throughout the body.[8] The normal physiological level of PCT in serum is less than 0.1 ng/mL which can increase several folds in systemic bacterial infections.[9]

The pathophysiological role of PCT in sepsis is imperfectly understood.[10] It has been proposed that in inflammation, the release of PCT may be a two way process: direct and indirect.[11,12] The toxins and lipopolysaccharides released by microbes can induce the release of PCT in a direct manner; or alternately the inflammatory cytokines like interleukin (IL) 1b, IL-6, tumour necrosis factor-α (TNF-α) etc may indirectly influence PCT production.

IFN-γ released in response to viral infection can cause a down-regulation of PCT. This makes PCT a more specific marker for bacterial infection.[13] Thus, during severe bacterial infections, the level of PCT may rise several hundred-folds and may even reach a level of 1000 ng/mL without any change in serum calcitonin level.[11,14] However, it is important to keep in mind the following situations while interpreting PCT reports: (i) Gram negative bacteraemias cause higher elevation of PCT than those caused by Gram positive pathogens;[15] (ii) there is a low or negligible rise in PCT levels in localized infections, and in infections caused by viruses or intracellular bacteria;[16,17] and (iii) in the neonatal period, particularly in the first 48-72 hours of life, serum PCT levels increase to a high level and then gradually fall during the first week. This is possibly due to initial establishment of gut flora.[18]

Procalcitonin as a diagnostic marker of bacterial sepsis

A large number of studies have investigated the diagnostic role of PCT in bacterial infections, particularly in critically ill patients; and also to differentiate bacterial sepsis from SIRS. However, the results have been conflicting. To resolve this issue, a few systematic reviews and meta-analyses of representative studies have been attempted. One such meta-analysis compared 25 studies comprising of 2966 patients.[19] This analysis found a global diagnostic accuracy odd ratio (OR) of 15.7 for PCT [95% confidence intervals (CI) 9.1-27.1] compared to 5.4 for CRP (95% CI, 3.2-9.2). The performance of PCT was significantly higher than CRP (Q-values 0.78 versus 0.71, p=0.02) In a similar systematic review of 18 studies,[20] the mean sensitivity and specificity for PCT as a diagnostic marker for bacterial infections was found to be 71% (95% CI, 67-76) with a Q- value of 0.72. In another study[21] in a series of 103 intensive care patients, it was found that PCT with an area under receiver operating curve (AUROC) of 0.81 and sequential organ failure assessment (SOFA) score with AUROC of 0.82 were the only independent predicators for infections; and not CRP.[21] In a recent meta-analysis[22] that assessed the usefulness of PCT as a diagnostic marker for sepsis, 30 reports out of a total search of 3487 reports fulfilled their inclusion criteria, accounting for 3244 patients. Bivariate analysis yielded a mean sensitivity of 0.77 (95% CI, 0.72-0.81) and a specificity of 0.79 (95% CI, 0.74-0.84), with an AUROC of 0.85 (95% CI, 0.81-0.88). The authors[22] concluded that PCT was a helpful biomarker for early diagnosis of sepsis in critically ill patients, but cautioned that the results should be interpreted in the context of medical history, physical examination and microbiological assessments.

A number of formats are available for the detection and quantification of PCT in serum and plasma. These include semi-quantitative as well as sensi-

tive quantitative assays with variable detection limits. Table 2 gives the relevant information regarding the different platforms for PCT detection.

Knowledge of the various cut-off values for PCT and their interpretation is important for the clinicians and the laboratory may mention it when reporting PCT results (Table 3A). Moreover, like any other biomarker, false-positive and false-negative results (Table 3B) are also seen with PCT.

Published evidence suggests that PCT appears to have a distinct advantage over CRP in diagnosis of sepsis.[17,20] However, clinicians regard it as a relatively non-specific marker of inflammation. This is reflected by the recommendations of American College of Critical Care Medicine (ACCM) and the Infectious Diseases Society of America (IDSA). The ACCM and IDSA have graded PCT as a level 2 evidence (reasonably justifiable by available scientific evidence and strongly supported by expert critical care opinion), and recommended that PCT can be used as an adjunctive diagnostic tool for discriminating infection as the cause for fever or sepsis presentation while evaluating new fever in critically ill patients.[16] However, the Surviving Sepsis Campaign guidelines 2012[23] mention that the utility of procalcitonin levels or other biomarkers (such as CRP) to discriminate the acute inflammatory pattern of sepsis from other causes of generalized inflammation (e.g. postoperative, other forms of shock) has not been demonstrated. These guidelines mention that no recommendation can be given for the use of these markers to distinguish between severe infection and other acute inflammatory states.[23]

Procalcitonin for the diagnosis of bacterial infections in special settings

Apart from its usefulness in the diagnosis of bacterial sepsis in the critical care area, the utilityof

Table 2: Assay techniques for PCT detection and quantification

Assay Technique	Assay principle	Time to result (hours)	Measurement range (ng/mL)	Instrumentation
Semi-quantitative rapid assay(BRAHMS PCT-Q)	Immunochromatographic test using monoclonal mouse anti-calcitonin antibody conjugated with colloidal gold (tracer) and a polyclonal sheep anti-calcitonin antibody (solid phase)	0.5	< 0.5 0.5 - <2 2-<10 ≥ 10	No
Quantitative manual assay (BRAHMS PCT-LIA)	Sandwich type luminescence immunoassay. Uses two monoclonal antibodies directed against the C-terminal and mid-regional calcitonin sequences. The anti-calcitonin antibody is labeled with a luminescent acridine derivative	2	0.3-500	Yes. Luminometer
Quantitative automated assay (BRAHMS PCT KRYPTOR)	Uses time resolved amplified cryptate emission technology based on a non-radiative transfer of energy between two fluorescent tracers (Europium cryptate donor and XL665 acceptor) attached to two different antibodies which capture the PCT	0.5	0.02-50 (Direct range) Up to 1000 (Extended range)	Yes. KRYPTOR system (Random access immune analyzer)
Quantitative automated system (LIASION System)	Two site immunoluminometeric assay (sandwich technique) where two different highly specific monoclonal antibodies are used for coating the solid phase (magnetic particles) and for the tracer	1	0.3-500	Yes. LIASION random access analyzer.
VIDAS®BRAHMS PCT Test	Enzyme linked fluorescent assay based on a one step immunoassay sandwich method and a final fluorescent detection step	0.3	0.05-200	VIDAS or mini-VIDAS system

PCT=procalcitonin
Source: http:// www.procalcitonin.com

Table 3A: Reference values of PCT

Reference values (ng/mL)	Interpretation
<0.05	Normal
<0.5	Localized infection possible. Re-test after 6-24 hours
≥0.5-<2	Systemic bacterial infection possible. Re-test after 6-24 hours
≥2-<10	Systemic bacterial infection is likely. High risk for severe sepsis
≥10	Severe bacterial sepsis, septic shock

PCT=procalcitonin
Source : *references 9,17*

Table3B: Causes of false-positive and false-negative PCT results

False positive Results
Neonates <48 hrs age
First days after major surgery, trauma, burn
Treatment with OKT3 antibodies, interleukins, TNF-α
Invasive fungal infections, acute attack of falciparum malaria
Prolonged or severe cardiogenic shock
Malignancies: e.g., medullary C-cell carcinoma of thyroid, small cell cancer of lung, bronchial carcinoid
False negative results
Early course of infection
Localized infections
Sub acute bacterial endocarditis

PCT=procalcitonin; OKT3=orthoclone monoclonal antibody; TNF-α=tumor necrosis factor - alpha

PCT in some other bacterial infection settings has also been evaluated.

Respiratory tract infections

PCT has been extensively studied for the diagnosis of ventilator associated pneumonias (VAP) and community acquired pneumonia (CAP). A multinational study from 10 academic hospitals in Canada, The United States, and two European countries (Germany, Belgium) included 175 patients [57 with CAP, 61 with VAP, and 57 with hospital acquired pneumonia (HAP)].[24] Initial PCT levels were higher in CAP than VAP patients, but not significantly different from the levels seen in HAP patients. The initial and maximum PCT levels also showed agreement with the SOFA scores. On the basis of the various studies, it has been concluded that PCT remains the best validated biomarker, as compared to CRP and others, in differentiating viral and bacterial causes of pneumonia.[25]

Neonatal and paediatric infections

A systematic review[26] which included studies on infections among the newborns (up to 59 days age) found that PCT was a useful diagnostic marker in early stages of bacterial infections (sensitivity=77%-93%, specificity=81%-84% at a cut off value of 8.92 ng/mL) compared to CRP (sensitivity=66%, specificity=86%, cut off value of 17 mg/L). However, it should be noted that there is a surge of PCT in the first 24-48 hours of life which returns to normal over the next 3-7 days.[18] In older children with more invasive bacterial infections like sepsis and meningitis, levels of PCT were significantly higher compared to CRP; and moreover during the period of evolution of fever (<8 hours), PCT performed better than CRP with a more rapid rise in its level.[27] Another study which involved children with bacterial and viral pneumonia revealed that on admission 100% of the children with bacterial pneumonia had high levels of PCT (0.94-6210 ng/mL), while only 34% of the children with viral pneumonia had PCT levels between 0.5-2.13 ng/mL.[28] In this study, it was concluded that PCT concentration of greater than 2.0 ng/mL had 100% sensitivity, 98% specificity, and a positive predictive value of 93% for bacterial pneumonia. CRP levels were elevated in 100% and 88% cases of bacterial and viral pneumonia respectively, giving a specificity of 38% and positive predictive value of 42% for bacterial pneumonia. In a study[29] of 359 children it was observed that PCT was superior to CRP and PCT levels increased significantly with the severity of illness (AUROC=0.91), but CRP could not mirror the change effectively (AUROC=0.75). In conclusion it may be said that

serum PCT levels appears to be a significant improvement over CRP.[30]

Neutropenic and/or immunosuppressed patients

Early diagnosis of bacterial infection, particularly in febrile neutropenic patients is difficult because the typical clinical features and routine laboratory tests used to diagnose such infections lack diagnostic accuracy.[31,32] In studies in children with haematological malignancies, using a cut-off level of 2.0 ng/mL, PCT was found to have a sensitivity and specificity of 94% and 96.5% respectively for predicting bacteraemia.[17] In a study[33] of 286 episodes of febrile neutropenia, PCT was considered to be an useful early diagnostic marker for the detection of bacteraemia and was found to have a better profile than CRP. A systematic review[34] evaluated 30 studies and found that PCT was a valuable diagnostic tool in febrile neutropenic patients.[34] One attractive aspect of PCT is that its level is not influenced by corticosteroid use.[35] In a study[36] with 102 critically ill patients with systemic bacterial infections receiving parenteral prednisolone 20-1500 mg/day, while appropriately high PCT levels were observed, significantly lower levels of CRP and IL-6 were observed.[36]

Dialysis patients

In a recent study,[37] the usefulness of PCT, CRP, IL-6, and white cell count for detecting bacterial infection in patients on haemodialysis was investigated. The AUROC for PCT was 0.921, which was significantly higher than the AUROC for CRP (0.853, $p<0.01$), IL-6 (0.739, $p<0.01$), and white cell count (0.692, $p<0.01$). Among continuous ambulatory peritoneal dialysis (CAPD) patients presenting with peritonitis, conflicting reports are available. In a report from Turkey,[38] among 50 patients on CAPD related peritonitis, increased levels of PCT was found in 42% patients while bacterial culture was positive in 74% cases.[38] In a study[39] of 35 patients on CAPD with peritonitis although serum PCT was elevated in some patients at the time of peritonitis, its value in making a diagnosis and predicting long term prognosis was observed to be doubtful.

Procalcitonin as a prognostic marker of bacterial infections

PCT level have been observed to be definitely increased with increasing severity of sepsis and organ dysfunction.[40] PCT was also found to be a predictor of mortality in a study involving 472 critical care patients.[41] PCT measurement was done daily in these patients and both high PCT levels and the increase in the levels following the first reading of greater then 1.0 ng/mL were independent predictors of 90 day mortality. White cell count and CRP were not found to be predictors of mortality in this study.[41] On the other hand, in another study[42] there was a significant difference in PCT values between survivors and non-survivors, but only the Acute Physiology and Chronic Health Evaluation (APACHE II) score and male gender were found to be independent predictors for death. In another recent study, CRP, SOFA score, age, and gender could predict mortality, but not PCT.[21]

APACHE II and SOFA scores have been well validated for mortality risk stratification, but they are more commonly used for audit and research purposes rather than for clinical decision making. Thus a point-of-care rapid test which can provide prognostic information can be very useful for the clinician in decision making regarding early intervention. PCT may be helpful to assess the severity of the infection.[38] The favourable kinetic profile of PCT makes it a useful clinical marker. PCT promptly increases within 6-12 hours after an infection trigger and the levels halve daily when the infection is controlled.[43] A decrease in PCT level by more than 30% after the first 24 hrs from the onset of antimicrobial therapy is indication of appropriate treatment and control of infection.[44]

Role of procalcitonin in antibiotic stewardship

Antibiotic stewardship has been defined as the optimal selection, dosage,and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infec-

tion, with minimal toxicity to the patients and minimal impact on subsequent resistance.[45] Thus the 4 Ds of optimal antimicrobial therapy are: right drug, right dosage, de-escalation to pathogen directed therapy, and right duration of therapy.[46]

In a meta-analysis of 14 randomized controlled trials comprising 4211 patients[47] that studied the role of PCT in guiding antibiotic therapy in acute respiratory infections, it was seen that PCT guided antibiotic therapy reduced treatment failures but not mortality, compared with usual care. The PCT guided group had less antibiotic exposure than the usual care group (median 4 days Vs 8 days). Similar observations were noted for respiratory tract infections[48]; and critically ill patients.[49] In a large randomized trial[50] conducted in eight French intensive care units patients with elevated PCT had significantly more days without antibiotic exposure than control patients and received significantly fewer days of antibiotics.[50] To date, the most comprehensive analysis which examined 18 randomized controlled trials focusing on PCT-guided antibiotic therapy among 5 patient populations was published in 2012.[51] The salient findings were as follows: (i) PCT guidance reduces antibiotic use when used to discontinue antibiotics in adult intensive care patients; (ii) PCT reduces antibiotic use when used to initiate or discontinue antibiotics (high evidence) without increasing morbidity (moderate evidence) and mortality (low evidence) in respiratory tract infections; (iii) PCT guidance reduces antibiotic use (moderate evidence), without sufficient evidence on morbidity and mortality outcomes in early neonatal sepsis; and (iv) regarding utility of PCT in fever of unknown origin in children 1-36 months age and in post-surgical patients evidence was insufficient to draw any meaningful conclusions.

Apart from these, it has been opined that in certain units where antibiotics are used for 10-14 days or more, PCT may be a highly cost-effective strategy to give the confidence to clinicians to stop antibiotics earlier.[3] Similarly, the Surviving Sepsis Campaign Group[23] recommends the use of low PCT levels to help clinicians in the discontinuation of empiric antibiotics in patients who appeared to have sepsis, but do not have final evidence of infection.

Other novel biomarkers for sepsis on the horizon

A number of molecules are in the evaluation stage as biomarkers in the diagnosis and prognosis of sepsis and bacterial infections. Some of these are described below. Pro-adrenomedullin (p-ADM) is the precursor protein of adrenomedullin first discovered in 1993.[52] In a study of 99 septic shock patients, both p-ADM and pro-vasopressin (copeptin) were significantly elevated in the first week in those who died and were found to be significantly associated with mortality on bivariate analysis.[52] Interestingly, these two molecules have competing biological properties but when used as a combination improved the predictive ability. It is felt that there is need for further evaluation to find out whether they reflect an adaptive response to shock since both the molecules partly reflect the level of stress in an individual.[53]

In an analysis of 12 studies[54] using brain natriuretic peptide (BNP) and N-terminal pro-B type natriuretic peptide (NT-pro BNP) comprising of 1865 sepsis patients, both were found to be significantly associated with increased risk of mortality (OR 8.65, 95% CI 4.94-15.13, $p<0.00001$). The pooled sensitivity was 79% and specificity was 60%. It was concluded that these may prove to be a powerful predictor of mortality.[54] A review[55] of ten papers revealed that soluble urokinase-type plasminogen activator receptor (suPAR) had little diagnostic value in critically ill patients with sepsis, SIRS, or bacteraemia. But mortality prediction by other biological markers, or severity of disease classification system scores improved when combined with suPAR.[55]

Levels of both matrix metalloproteinase (MMP) and tissue inhibitor of MMP (TIMP) were significantly elevated in a series of 37 patients with severe sepsis compared to similar number of healthy controls, and TIMP was found to be at higher lev-

els in those who died, compared to the survivors.[56] Other markers like IL-6,IL-8,IL-18, transforming growth factor β-1, interferon-γ, resistin, cluster of differentiation 64 (CD-64), serum lactate etc., have also been evaluated in various studies[30,57-59] to find out their diagnostic and prognostic potentials in sepsis with variable results.

PCT thus, appears to be promising as a biomarker for diagnosis and prognosis of moderate to severe bacterial infections and as a guide for antibiotic therapy. Further studies in field-conditions from tropical countries may help in establishing PCT as a point-of-care diagnostic test.

The other potential biomarkers need additional studies using larger number of patients before their use can be validated. The scenario which is emerging seems to suggest that any single biomarker is unlikely to identify and stratify all patients adequately,[30] and a combination of such markers may reveal a clearer picture.

REFERENCES

1. Borc RC. Sepsis, the sepsis syndrome, multi-organ failure: a plea for comparable definitions. Ann Intern Med 1991;114:332-3.
2. Pavoa P, Salluh JI. Biomarker guided antibiotic therapy in adult critically ill patients: a critical review. Ann Intensive Care 2012;2:32.
3. Kibe S, Adams K, Barlow G. Diagnostic and prognostic biomarkers of sepsis in critical care. J Antimicrob Chemother 2011;66 Suppl 2:i33-40.
4. Chesney RW, McCarren DM, Haddad JG, Hawker CD, DiBella FP, Chesney P, et al. Pathogenic mechanisms of the hypocalcemia of the staphylococcal toxic-shock syndrome J Lab Clin Med 1983;101:576-85.
5. Assicot M, Gendrel D, Cassin H, Raymond J, Guilband J, Bohoun C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993;341:515-8.
6. Le Moullec JM, Julienne A, Chenais J, Lasmoles F, Guiliana JM, Milhaud J, et al. The complete sequence of human procalcitonin. FEBS Lett 1984;167:93-7.
7. Becker K, Miller R, Nylen E, Cohen R, Siliva O, Snider R. Calcitonin gene family of peptides. In: Principles and Practice of Endocrinology and Metabolism. Ed. Becker K. 2001. Lippincott, Philadelphia. pp 520-34.
8. Muller B, White JC, Nylen E, Snider R, Becker K, Hebner JF. Ubiquitous expression of the calcitonin-1 gene in multiple tissues in response to sepsis. J Clin Endocrinol Metab 2001; 86:396-404.
9. Schneider HG, Lam QT. Procalcitonin for the clinical laboratory: a review. Pathology 2007;39:383-90.
10. Christ-Crain M, Opal SM. Clinical review: the role of biomarkers in the diagnosis and management of community acquired pneumonia. Crit Care 2010;14:203.
11. Oberhoffer M, Stonans I, Russwurm S, Stonane E, Vogelsang H, Junker U, 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 1999;134 :49-55.
12. Gogos CA, Drosou E, Bassaris HP, Skoutelis A. Pro-versus anti-inflammatory cytokine profile in patients with severe sepsis: a marker for prognosis and future therapeutic options. J Infect Dis 2000;181:176-80.
13. Christ-Crain M, Muller B. Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. Eur Respir J 2007;30:556-73.
14. Nijsten MW, Olinga P, The TH, de Vries EG, Koops HS, Groothuis GM, et al. Procalcitonin behaves as a fast responding acute phase protein in vivo and in vitro. Crit Care Med 2000;28:458-61.
15. Charles PE, Ladoire S, Aho S, Quenot JP, Doise JM, Prin S, et al. Serum procalcitonin elevation in critically ill patients at the onset of bacteremia caused by either Gram negative or Gram positive bacteria. BMC Infect Dis 2008;8:38.
16. Shehabi Y, Seppelt I. Pro/con debate: is procalcitonin useful for guiding antibiotic decision making in critically ill patients? Crit Care 2008;12:211-6.
17. Hatzistilianou M. Diagnostic and prognostic role of procalcitonin in infections. Scientific World Journal 2010;10:1941-6.
18. Sachse C, Dressler F, Henkel E. Increased serum procalcitonin in newborn infants without infections. Clin Chem 1998;44:1343-4.
19. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a

systematic review and meta-analysis. Crit Care Med 2006;34:1996-2003.

20. 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;7:210-7.
21. Ruiz-Alvarez MJ, García-Valdecasas S, De Pablo R, Sanchez García M, Coca C, Groeneveld TW et al. Diagnostic efficacy and prognostic value of serum procalcitonin concentration in patients with suspected sepsis. J Intensive Care Med 2009;24:63-71.
22. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis 2013;13:426-35.
23. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.
24. Bloos F, Marshall JC, Dellinger RP, Vincent JL, Gutierrez G, Rivers E, et al. Multinational, observational study of procalcitonin in ICU patients with pneumonia requiring mechanical ventilation: a multicenter observational study. Crit Care 2011;15:R88.
25. Kruger S, Welte T. Biomarker in community acquired pneumonia. Expert Rev Respir Med 2012;6:203-14.
26. Meem M, Modak JK, Mortuza R, Morshed M, Islam MS, Saha SK. Biomarkers for the diagnosis of neonatal infections: A systematic analysis of their potential as a point-of-care diagnostics. J Global Health 2011;1:201-9.
27. Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt L. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. Pediatr Infect Dis J 2007;26:672-7.
28. Hatzistilianou M, Hitoglou S, Gougoustamou D, Rekliti A, Tzouvelekis G, Nanas C, et al. Serum procalcitonin, adenosine deaminase and its isoenzymes in the aetiological diagnosis of pneumonia in children. Int J Immunopathol Pharmacol 2002;15:119-27.
29. Rey C, Los Arcos M, Concha A, Medina A, Prieto S, Martinez P, et al. Procalcitonin and C-reactive protein as markers of systemic inflammatory response syndrome severity in critically ill children. Intensive Care Med 2007;33:477-84.
30. Standage SW, Wong HR. Biomarkers for paediatric sepsis and septic shock. Expert Rev Anti Infect Ther 2011;9:71-9.
31. Hatzistilianou M. The role of procalcitonin in febrile neutropenic children with haematological malignancies. US Pediatr 2008;4:77-9.
32. Massaro KS, Costa SF, Leone C, Chamone DA. Procalcitonin (PCT) and C-reactive protein (CRP) as severe systemic infection markers in febrile neutropenic adults. BMC Infect Dis 2007;7:137.
33. Kim DY, Lee YS, Ahn S, Chun YH, Lim KS. The usefulness of procalcitonin and C-reactive protein as early diagnostic markers of bacteremia in cancer patients with febrile neutropenia. Cancer Res Treat 2011;43:176-80.
34. Sakr Y, Sponholtz C, Tuche F, Brunkhorst F, Reinhart K. The role of procalcitonin in febrile neutropenic patients: review of the literature. Infection 2008;36:396-407.
35. de Kruif MD, Lemaire LC, Giebelen IA, Struck J, Morgenthaler NG, Papassotiriou J, et al. The influence of corticosteroids on the release of novel biomarkers in human endotoxemia. Intensive Care Med 2008;34:518-22.
36. Müller B, Peri G, Doni A, Perruchoud AP, Landmann R, Pasqualini F, et al. High circulating levels of the IL-1 type II decoy receptor in critically ill patients with sepsis: association of high decoy receptor levels with glucocorticoid administration. J Leukoc Biol 2002;72:643-9.
37. Mori K, Noguchi M, Sumino Y, Sato F, Mimata H. Use of procalcitonin in patients on chronic haemodialysis : procalcitonin is not related with increased serum calcitonin. ISRN Urol 2012;2012:431859.
38. Bulut C, Ozturk R, Yilmaz GR, Parpucu H, Irmak H, Kinikli S, et al. Evaluation of the epidemiological, clinical and laboratory findings in continuous ambulatory peritoneal dialysis related peritonitis attacks. Microbiyol Bul 2008;42:255-64.
39. Lam MF, Leung JC, Lam CW, Tse KC, Lo WK, Lui SL, et al. Procalcitonin fails to differentiate inflammatory status or predict long term outcomes in peritoneal dialysis associated peritonitis. Perit Dial Int 2008;28:377-84.

40. Giamarellos-Bourboulis EJ, Mega A, Grecka P, Scarpa N, Koratzanis G, Thomopoulos G, et al. Procalcitonin: a marker to clearly differentiate systemic inflammatory response syndrome and sepsis in the critically ill patient? Intensive Care Med. 2002;28:1351-6.

41. 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 2006;34:2596-602.

42. Pettilä V, Hynninen M, Takkunen O, Kuusela P, Valtonen M. Predictive value of procalcitonin and interleukin 6 in critically ill patients with suspected sepsis. Intensive Care Med 2002;28:1220-5.

43. Becker KL, Nylen ES, White JC, Muller B, Snider RH Jr. Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: A journey from calcitonin back to its precursor. J Clin Endocrinol Metab 2004;89:1512-25.

44. 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;59:339-47.

45. Gerding DN. The search for good antimicrobial stewardship. Jt Comm J Qual Improv 2001;27:403-4.

46. Joseph J, Rodvold KA. The role of carbapenems in the treatment of severe nosocomial respiratory tract infections. Expert Opin Pharmacother 2008;9:561-75.

47. Jagminas L. Meta-analysis: procalcitonin-guided antibiotic therapy reduces treatment failure in acute respiratory infections. Ann Intern Med 2013;158:JC 2-5.

48. Schuetz P, Briel M, Mueller B. Clinical outcomes associated with procalcitonin algorithm to guide antibiotic therapy in respiratory tract infections. JAMA 2013;309:717-8.

49. Matthaiou DK, Ntani G, Kontogiorgi M, Poulakou G, Armaganidis A, Dimopoulos G. An ESICM systematic review and meta-analysis of procalcitonin-guided antibiotic therapy algorithms in adult critically ill patients. Intensive Care Med 2012;38:940-9.

50. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010;375:463-74.

51. Soni NJ, Samson DJ, Galaydick JL, Vats V, Pitrak DL, Aronson N. Procalcitonin-guided antibiotic therapy. Rockville: Agency for Healthcare Research and Quality (US); 2012.

52. Guignant C, Voirin N, Venet F, Poitevin F, Malcus C, Bohé J, et al. Assessment of pro-vasopressin and pro-adrenomedullin as predictors of 28-day mortality in septic shock patients. Intensive Care Med 2009;35:1859-67.

53. Roch A. Increased levels of pro-AVP and pro-ADM in septic shock patients: what could it mean? Intensive Care Med 2009;35:1827-9.

54. Wang F, Wu Y, Tang L, Zhu W, Chen F, Xu T, et al. Brain natriuretic peptide for prediction of mortality in patients with sepsis: a systematic review and meta-analysis. Crit Care 2012;16:R74.

55. Backes Y, Van der Sluijs KF, Mackie DP, Tacke F, Koch A, Tenhunen JJ, et al. Usefulness of suPAR as a biological marker in patients with systemic inflammation or infection; a systematic review. Intensive Care Med 2012;38:1418-28.

56. Hoffmann U, Bertsch T, Dvortsak E, Liebetrau C, Lang S, Liebe V, et al. Matrix-metalloproteinases and their inhibitors are elevated in severe sepsis: prognostic value of TIMP-1 in severe sepsis. Scand J Infect Dis 2006;38:867-72.

57. Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med 2001;164:396-402.

58. Wu HP, Chen CK, Chung K, Jiang BY, Yu TJ, Chuang DY. Plasma transforming growth factor-beta1 level in patients with severe community-acquired pneumonia and association with disease severity. J Formos Med Assoc 2009;108:20-7.

59. Sundén-Cullberg J, Nyström T, Lee ML, Mullins GE, Tokics L, Andersson J, et al. Pronounced elevation of resistin correlates with severity of disease in severe sepsis and septic shock. Crit Care Med 2007;35:1536-42.