Int J Clin Exp Med 2016;9(2):3173-3178
www.ijcem.com /ISSN:1940-5901/IJCEM0015966

Original Article

Diagnostic value of dynamic serum PCT testing in patients with recurrent infections

Yuejing Mu*, Weijia Wang*, Youye Yang, Shengnan Xu, Haili Lan, Haizhong Yan, Quanzhong Xu, Lijuan Kan, Xiuming Zhang

*Department of Laboratory Medicine, Sun Yat-sen University Affiliated Zhongshan Hospital, Zhongshan, Guangdong Province, China. *Equal contributors.*

Received September 10, 2015; Accepted December 10, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Objective: To investigate the diagnostic value of dynamic serum procalcitonin (PCT) level in recurrent infection and cut-off value for PCT. Method: From which such cases as voluntary discharge, death and generally accepted conditions affecting PCT levels were ruled out, leaving 300 cases taken into our research, including 200 cases of recurrent infection and 100 cases of effective treatment. The PCT levels for the recurrent cases were compared with those receiving effective treatment simultaneously. Furthermore, differences between PCT rebound points for the recurrent and those from 60 control cases were compared. The diagnostic performance of PCT, WBC count, and IL-6 for recurrent infection cases was evaluated using ROC curve. Results: The PCT level differed for cases with recurrent infections and those receiving effective treatment. The former demonstrated a rebound in PCT level. The PCT rebound point for recurrent cases was higher than that of the normal controls. The area under the ROC of PCT for the diagnosis of recurrent infection was 83.5%. The cut-off level corresponding to the optimal sensitivity (89%), specificity (83%), positive predictive value (84%), and negative predictive value (88.3%) was 2.29 $ng{\cdot}ml^{-1}$. However, the WBC count and IL-6 level had little diagnostic value for recurrent infection, and the area under the ROC curve was 55.1% and 61.0%, respectively. Conclusion: Dynamic monitoring of serum PCT levels had an important diagnostic and discriminatory value for recurrent infection induced by bacteria.

Keywords: Procalcitonin (PCT), recurrent infection, white blood cells (WBC), interleukin 6 (IL-6)

Introduction

Bacterial infections are common clinical diseases, for which the procedures of etiological diagnosis are usually time-consuming. So the timely diagnosis of bacterial infections remains a challenge [1]. Before obtaining the microbiological reports, the physicians prescribe antibiotics based on their experience, which increases the risk of inducing drug-resistant bacteria and the probability of aggravation, recurrence or infection. Procalcitonin was described as a new and innovative marker for infection for the first time in 1993 [2]. It closely related to the severity of infection, for which inducers of PCT are bacterial endotoxins and exotoxins, as well as inflammatory cytokines, e.g., TNF, IL-2 and IL-6 [3]. PCT has emerged as a promising marker for the diagnosis of bacterial infections because higher levels of PCT are found in severe bacterial infections relative to viral infections and nonspecific inflammatory diseases. During bacterial infections, levels of PCT reach plateau value within 8-24 h [4, 5]. Hence, PCT may be used to support clinical decisions regarding the initiation or discontinuation of antibiatic therapy [6, 7]. Also applied in the scoring of severity [8], dynamic PCT level can indicate whether to terminate antibiotic use. It was recently suggested that monitoring PCT levels could be a valuable tool for guiding antibiotic treatment in patients with bacterial infection in an intensive care unit [9]. We assessed the diagnostic application of dynamic serum PCT level in recurrent infection as a warning indicator to guide antibiotic use.

Materials and methods

Reagents and equipments

An automatic immunochemical analyzer Cobas E601 (Roche) was used. Roche provided the calibration solution, reagents, and quality con-

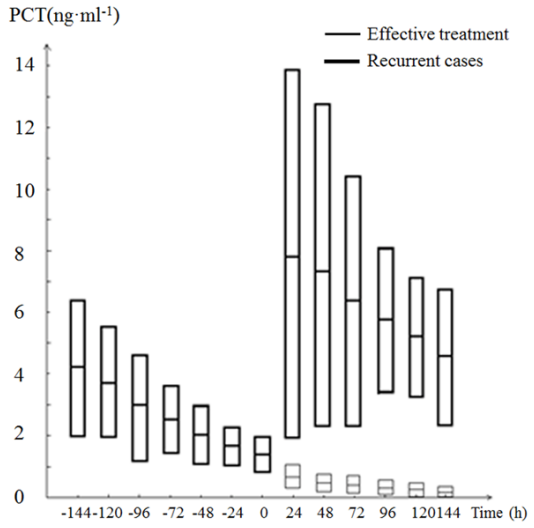

Figure 1. Variations in serum PCT levels.

trol substances. The laboratory for implementing the protocol had passed an inspection. Blood culture was performed using a BacT/ALERT® 3D Automated Rapid Microbial Detection System with matching culture bottles (aerobic and anaerobic), and Vitek analyzer (bioMerieux, UK) was applied to identify the bacteria.

Sample collection

Blood samples were collected from 804 hospitalized adult patients with bacterial infection at the Affiliated Zhongshan Hospital of Sun Yat-sen University from January 2012 to May 2015, from which such cases as voluntary discharge, death and generally accepted conditions affecting PCT levels were ruled out, leaving 300 cases taken into our research, including 200 cases of recurrent infection and 100 cases of effective treatment. Also 60 samples were collected as healthy controls. Infants were excluded considering the probability of a transient increase in PCT level [10]. Inclusion criteria were as follows: positive for bacterial culture and clinically confirmed simple bacterial infection. Dynamic monitoring of serum PCT levels was performed for all 300 cases with a bacterial infection at 24-h intervals. Since variation rates and trends for PCT levels differed depending on pathogenic bacteria, antibiotic use and treatment effect, a reference time point (0 h) was chosen as the point corresponding to the rebound in PCT levels for recurrent cases (**Figure 1**), as compared with cases receiving effective treatment. The serum PCT levels within 144 hours before and after "0 h" were monitored. Exclusion criteria were as follows: trauma, surgery, burn injuries, small cell lung cancer, medullary thyroid carcinoma, and heart failure (because they are considered causes for increased PCT levels). Furthermore, samples from patients with severe hemolysis, lipidemia, and jaundice were excluded.

Variations in PCT levels among the three groups

Recurrent cases: After antibiotic use, 200 adult cases with bacterial infections experienced a return to a normal body temperature, as well as symptom alleviation. Serum PCT levels declined significantly in these cases but did not reach the criterion for stopping antibiotic therapy (PCT ≤ 0.1 ng·ml-1), or the duration of antibiotic therapy was less than 2 weeks, which a sudden rebound in PCT levels occurred. Symptom aggravation, bacterial count increasing in blood cultures, bacterial species changing, and the formation of drug resistant bacteria were observed subsequently. A total of 100 cases were receiving effective treatment and demonstrated symptom alleviation after antibiotic use, with PCT levels meeting the criterion for stopping antibiotic therapy. The healthy control group consisted of 60 normal adults according to a physical examination; we had no gender limitations. Variations in serum PCT levels were analyzed for the three groups.

Plotting an ROC curve for evaluation of the diagnostic performance of PCT, WBC, and IL-6 for recurrent infections

ROC curves were plotted using the reference (0 h) and rebound (24 h) point in PCT levels for recurrent cases, and the diagnostic performance of PCT for recurrent infection was evaluated. In addition, serum PCT, WBC, and IL-6 were detected for the 200 recurrent cases receiving effective treatment during the same period, and ROC curves were plotted for each indicator with a comparison of diagnostic performance of the three indicators.

Statistical analysis

Statistical analysis was performed using SPSS 19.0 software. The means between the two

Table 1. Comparison of PCT levels between recurrent cases and cases receiving effective treatment

Group	Cases	Mean ($ng \cdot ml^{-1}$)	Standard deviation	F
1 Bacterial infection (0 h)	150	1.37	0.57	80.71
2 Recurrent (24 h)	100	7.88	5.94	
3 Effective (24 h)	50	0.71	0.42	
P value	1 vs 2 P < 0.05	1 vs 3 P < 0.05	2 vs 3 P < 0.05	

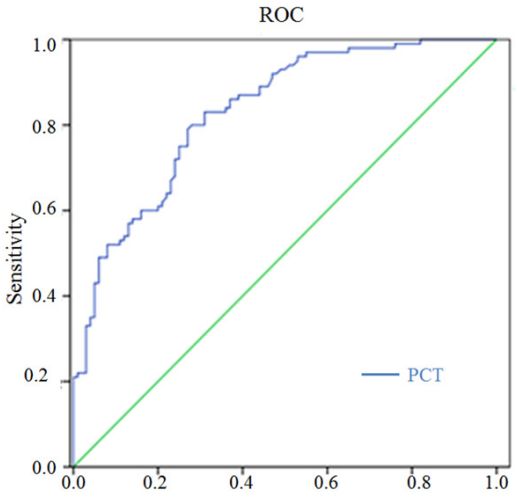

Figure 2. Receiver operating characteristic curve for the procalcitonin diagnosis of recurrent infections.

groups were compared using a *t* test, and one-way analysis of variance test was adopted for comparing the means of multiple groups. ROC curves were plotted for evaluation of diagnostic performance, and a *P* of < 0.05 was considered significant.

Results

Variations in serum PCT levels

Dynamic serum PCT levels were monitored for 300 cases with bacterial infections, and the results are shown in **Figure 1**. Considering the differences in types of infection, treatment efficacy, time of hospital visit and intra-individual differences, a reference time (0 h) was chosen as the rebound point in PCT levels for recurrent cases. Observations were performed at -144 h to 0 h and 0 h to +144 h, at 24-h intervals. Serum PCT levels demonstrated a continuous decline for 100 cases, while 200 cases had a rebound in their PCT level at 1.37 ± 0.57 $ng \cdot ml^{-1}$, which was the mean rebound level, rather than the diagnostic cut-off point.

Comparing the PCT levels between recurrent cases and cases receiving effective treatment

It can be seen from **Figure 1** that the PCT levels for cases receiving effective treatment at 0 h to +24 h were obviously lower than those at 0 h. The PCT levels for recurrent cases at 0 h to +24 h were obviously higher than those at 0 h and demonstrated an increasing trend. The serum PCT levels for the three groups differed significantly (**Table 1**). One way ANOVA was employed to evaluate the difference among the means of recurrent cases and cases receiving effective treatment at 0 h and 0 h to +24 h.

Comparing the PCT levels of cases before recurrence with those of normal controls

At 0 h, the serum PCT levels for 200 recurrent cases were 1.37 ± 0.57 $ng \cdot ml^{-1}$ and those of the normal controls were 0.03 ± 0.02 $ng \cdot ml^{-1}$. The means of the two groups were compared using *t* test. The PCT level at the reference point for recurrent cases was significantly higher than that of normal controls ($t = 6.877$; $P < 0.05$), indicating the need to redesign the diagnostic PCT cut-off points for recurrent infection patients.

Comparing the diagnostic performance of PCT, WBC, and IL-6 for recurrent infections

ROC curves were plotted using the serum PCT levels before and after recurrence (**Figure 2**). The AUC for PCT was 83.5% (95% CI: 76%-99.1%; $P < 0.01$), indicating that PCT is a good diagnostic value for recurrent infections. At the best cut-off point, which was 2.29 $ng \cdot ml^{-1}$, the sensitivity, specificity, positive predictive value, and negative predictive value were 89%, 83%, 84%, and 88.3%, respectively. The ROC curves for PCT, WBC, and IL-6 were plotted (**Figure 3**). The AUC for the WBC count and IL-6 level was 55.1% (95% CI: 44%-66.3%) and 61% (95% CI: 50.2%-71.8%), respectively, indicating that the two indicators have a low diagnostic value.

Discussion

PCT is the propeptide of calcitonin, a glycoprotein without hormonal activity [11]. Karzai et al. reported a significant elevation in the PCT level

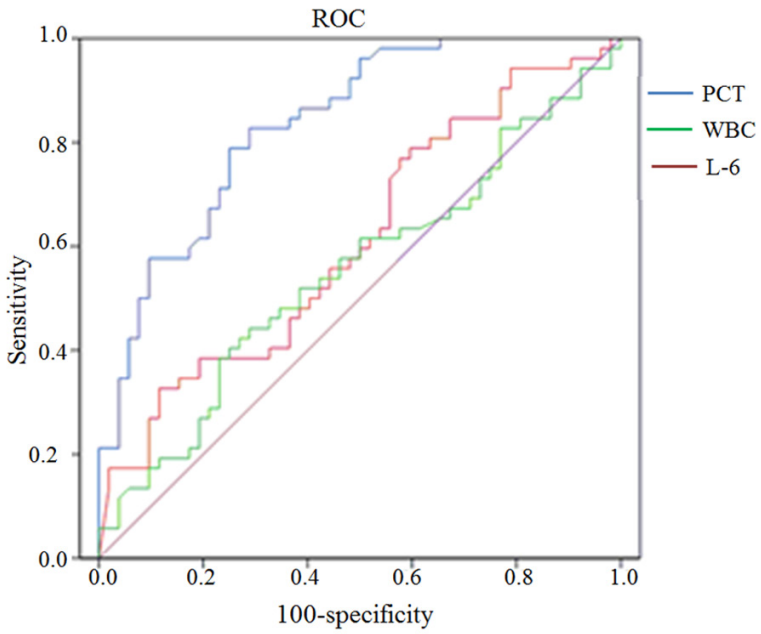

Figure 3. Comparison of PCT, the WBC, IL-6 detection performance to the diagnosis of bacterial infection recurrence.

of patients with bacterial infections in the 1990s [12]. After that, PCT has been applied for distinguishing among bacterial infections, nonbacterial infections, localized mild infections, and serious systemic infections and for guiding antibiotic use [13]. However, little research has been conducted regarding the diagnostic value of dynamic serum PCT levels for recurrent infections. We determined the diagnostic cut-off point for PCT in recurrent infections in the present study and made comparisons with other indicators including WBC and IL-6. The findings are valuable for differentiating diagnosis of recurrent infection and for discrimination between effective treatment and recurrence.

According to the results, the serum PCT levels for recurrent cases were obviously higher than those of normal controls before recurrence. Thus, cases with recurrent infections were chosen as the focus of research. In clinical practice, the use of wide-spectrum antibiotics may lead to dysbacteria, and conditioned pathogens have gradually become the main culprit in refractory infections. Bacterial cultures for those with recurrent infections usually reveal altered *Candida* species, variations, or multidrug resistant bacteria. A few cases may have negative bacterial cultures, probably as a result of extensive antibiotic use, which inhibits bacterial growth. So, two days after drug withdrawal, the specimen cultivation result is positive. Considering the impact of antibiotics on bacterial culture, it is of great significance to perform dynamic monitoring of PCT levels. Proven as a reliability indicator, PCT can be used to identify false positive results secondary to blood culture contamination. We compared the serum PCT levels between recurrent cases and cases receiving effective treatment to determine the diagnostic cut-off point for PCT. The recommended threshold for the use and termination of antibiotics is 0.25 μg/L for PCT, as a countermeasure for avoiding antibiotic misuse [14]. Efforts have been made to determine the diagnostic cut-off point for PCT in different diseases. By plotting an ROC curve, the diagnostic cut-off point was preliminarily determined to be 2.29 $ng{\cdot}ml^{-1}$ in the present study. The diagnostic cut-off point for PCT was also studied in a variety of bacterial infections due to its high performance, including simplex infection, sepsis, and concurrent bacterial infections in various diseases. Research shows that PCT levels of ≥0.85 $ng{\cdot}ml^{-1}$ could be used as an independent predictor of infections [15]. The diagnostic threshold of PCT for sepsis is 0.47 $ng{\cdot}ml^{-1}$ and that for severe sepsis is 2.28 $ng{\cdot}ml^{-1}$ [16]. For infections in patients who have class II, III, and IV heart failure, the best diagnostic cut-offs for PCT are 0.086, 0.192, and 0.657 $ng{\cdot}ml^{-1}$, respectively [17]. However, diagnostic cut-off values for PCT may show great variability because of different causes of septic shock and are 9.7 $ng{\cdot}ml^{-1}$ for surgical cases and 1.00 $ng{\cdot}ml^{-1}$ for internal medicine cases [18]. Setting diagnostic cut-off values for PCT should be based on patients' primary diseases, surgical impact, and the timing of biomarker measurements. In the present study, we presented a preliminary diagnostic cut-off value for PCT. As shown by many studies, PCT is more reliable than conventional indicators such as body temperature, WBC, CRP and cytokines (IL-6, IL-8)

[19, 20]. Dandona et al. showed that a PCT elevation might be attributed to the action of IL-6 [21]. Whang et al. demonstrated with animal experiments that interleukin induced an increase in PCT levels, but did not result in the upregulation of cytokines [22]. According to the results of the present study, PCT might be used as a diagnostic indicator of recurrent infections, while WBC and IL-6 have little diagnostic value. Combined with other existing research, PCT seems to have an irreplaceable diagnostic value for recurrent infection.

PCT could indicate the progression of infections and the effects of antibiotics, while dynamic serum PCT levels combined with a blood culture might improve diagnostic accuracy and provide guidance for antibiotic use. As an important indicator, PCT could help reduce the adverse impact of the emergence of superresistant bacteria. Dynamic monitoring of serum PCT levels could provide more reliable evidence for the diagnosis and treatment of recurrent infections, which represent a new clinical application for PCT levels.

Acknowledgements

This research was supported by the key projects of Zhongshan City Science and Technology Plan 2014A1FC005 and by a grant from Roche Diagnostics.

Disclosure of conflict of interest

None.

Address correspondence to: Xiuming Zhang, Department of Laboratory Medicine, Sun Yat-sen University Affiliated Zhongshan Hospital, Zhongshan 528403, Guangdong Province, China. Tel: +86-760-89880351; Fax: +86-760-89880351; E-mail: XiumingZhangcn@163.com

References

[1] Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. BMC Med 2011; 9: 107-110.

[2] Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993; 341: 515-518.

[3] Dandona P, Nix D, Wilson MF, Love J, Assicot M, Bohuon C. Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab 1994; 79: 1605-1608.

[4] Al-Nawas B, Shah PM. Procalcitonin in patients with and without immunosuppression and sepsis. Infection 1996; 24: 434-436.

[5] 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 2009; 59: 229-347.

[6] Schuetz P, Briel M, Christ-Crain M, Stolz D, Bouadma L, Wolff M, Luyt CE, Chastre J, Tubach F, Kristoffersen KB, Wei L, Burkhardt O, Welte T, Schroeder S, Nobre V, Tamm M, Bhatnagar N, Bucher HC, Mueller B. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. Clin Infect Dis 2012; 55: 651-662.

[7] 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: 940-949.

[8] Vincent J, Beumier M. Diagnostic and prognostic markers in sepsis. Expret Rev Ant Infect Ther 2013; 11: 265-275.

[9] Hochreiter M, Kohler T, Schweiger AM, Keck FS, Bein B, von Spiegel T, Schroeder S. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. Crit Care 2009; 13: R83.

[10] Elenius V, Peltola V, Ruuskanen O, Ylihärsilä M, Waris M. Plasma procalcitonin levels in children with adenovirus infection. Arch Dis Child 2012; 97: 582-583.

[11] Linscheid P, Seboek D, Nylen ES, Langer I, Schlatter M, Becker KL, Keller U, Müller B. In vitro and in vivo calcitonin I gene expression in parenchymal cells: a novel product of human adipose tissue. Endocrinology 2003; 144: 5578-5584.

[12] Karzai W, Oberhoffer M, Meier-Hellmann A, Reinhart K. Procalcitonin a new indicator of the systemic response to severe infections. Infection 1997; 25: 329-334.

[13] Bottner F, Wegner A, Winkelmann W, Becker K, Erren M, Götze C. Interleukin-6, procalcitonin and TNF-alpha: markers of peri-prosthetic infection following total joint replacement. J Bone Joint Surg Br 2007; 89: 94-99.

[14] Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trails and recommendations for clinical algorithms. JAMA 2011; 171: 1322-1331.

[15] Contou D, d'Ythurbide G, Messika J, Ridel C, Parrot A, Djibré M, Hertig A, Rondeau E, Fartoukh M. Description and predictive factors of infection in patients with chronic kidney disease admitted to the critical care unti. J Infect 2014; 68: 105-115.

[16] Zhao D, Zhou J, Haraguchi G, Arai H, Mitaka C. Procalcitonin for the differential diagnosis of infectious and non-infectious systemic inflammatory response syndrome after cardiac surgery. J Intensive Care 2014; 2: 35-38.

[17] Weijia W, Xiuming Z, Ne G, Liu J, Yuan H, Zhang P, Liu W, Wen D. PCT testing for diagnosis and short-term prognosis in bacterial infection complicated by congestive heart failure: a multicenter analysis of 4698 cases. Critical Care 2014; 18: R4.

[18] Clec'h C, Foses JP, Karoubi P, Vincent F, Chouahi I, Hamza L, Cupa M, Cohen Y. Differential diagnostic value of procalcitonin in surgical and medical patients with septic shock. Crit Care Med 2006; 34: 102-7.

[19] Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, Vadas L, Pugin J; Geneva Sepsis Network. 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.

[20] Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis 2004; 39: 206-217.

[21] Dandona P, Nix D, Wilson MF, Aljada A, Love J, Assicot M, Bohuon C. Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab 1994; 79: 1605-8.

[22] Whang KT, Vath SD, Becker KL, Snider RH, Nylen ES, Muller B, Li Q, Tamarkin L, White JC. Procalcitonin and proinflammatory cytokine in interactions in sepsis. Shock 2000; 14: 73-8.