Procalcitonin as a Marker for Bacterial Infection in Febrile Infants and Young Children

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Abstract

Early detection of bacterial infections in infants and young children is important. An appropriate acute phase reactant to differentiate between fever from a bacterial source and fever from a non-bacterial source is essential to pediatricians in inpatient, outpatient, and emergency departments. We compared the white blood cell count (WBC), C-reactive protein (CRP), and procalcitonin (PCT) values in febrile infants and young children who were admitted to a pediatric ward in a regional teaching hospital. PCT showed a significant difference between the bacterial and non-bacterial infection groups (P=0.002). WBC and CRP showed no significant differences between groups. PCT with a cutoff value of 0.4 ng/mL could be an important tool for detecting bacterial infections in febrile infants and young children.

Key Words : children, procalcitonin, bacterial. infection

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Introduction

Procalcitonin (PCT) is a precursor of the hormone calcitonin and is synthesized in the C-cells of the thyroid gland. Also as a acute phase reactant, PCT levels showed good correlation with the severity of invasive bacterial infection on patients in ICU.[1] Early rapid assessment and diagnosis of bacterial infections is important for young children because the clinical course would deteriorate soon if appropriate treatment is not initiated promptly. To determine which biomarker was the best for detecting bacterial infection in the ward, we compared the white blood cell count (WBC), CRP, and PCT levels in patients who were admitted to a pediatric ward in a regional teaching hospital.

Methods

Between July 2008 and May 2009, 76 patients between the ages of 1.7 months and 6.4 years were admitted to Cheng-Ching Hospital due to fever greater than 38°C. This hospital is a regional teaching hospital in central Taiwan and all of the patients were admitted via outpatient department or emergency department. Initial laboratory tests for these patients included: CBC, DC, CRP, blood culture, and PCT (VIDAS® B・R・A・H・M・S PCT). Urinalysis, urine culture, X-rays, other laboratory tests, and other image modalities were checked if needed. All of these 76 patients were healthy without documented congenital or acquired diseases before admission. After the patients were discharged, two pediatricians reviewed their charts and hospital courses; of the two, one is a pediatric infectious diseases

sub-specialist. Laboratory data (WBC, CPR and PCT) were deliberately omitted when charts were presented for review. Patients were assigned into bacterial and non-bacterial groups only when there was a consensus between the two pediatricians, according to viral antigen identification, bacterial culture, 4-fold change in antibody titer or clinical diagnosis. If a discrepancy occurred or if one pediatrician was unsure which group a patient belonged to, the patient in question was excluded from this study.

26 patients were categorized into a bacterial infection group and another 25 patients were categorized into a non-bacterial infection group. Diagnoses of the bacterial infection group included: lobar pneumonia (12), urinary tract infection with or without acute pyelonephritis (7), salmonellosis (3), cellulitis (2), sepsis (1) and sinusitis (1). Diagnoses of the control group included: acute pharyngitis (7, recovered without antibiotics), Kawasaki disease (KD) (4), RSV bronchiolitis (3), croup (3), rotaviral enterocolitis (3), herpangina (3), and adenoviral infection (2). The rest of the 25 patients whose fever sources were equivocal (e.g., acute gastroenteritis, pharyngitis, purulent tonsillitis, or bronchopneumonia with empiric antibiotic treatment) were excluded from this study. Statistical analysis was performed with *SPSS, Version 10.0 for Windows* (SPSS, Chicago, IL, USA). Data of these two groups were compared with independent samples t-test and chi-square test. Significance was assumed when $P < 0.05$.

Results

Demographic characteristics and laboratory findings of patients are summarized in Table. Age was a significant factor but only because of the 12 cases of lobar pneumonia in the bacterial infection group with a mean age of 4.0 years. Among these three laboratory data values, WBC and CRP showed no significant difference between the bacterial and non-bacterial infection groups. The *P* values of WBC and CRP were 0.18 and 0.55 respectively. PCT revealed a significant difference between these two groups ($P = 0.002$). Receiver operating characteristic (ROC) analysis was carried out for PCT, CRP and WBC (Figure). Area under the ROC curve is 0.731, 0.715 and 0.565 respectively. PCT prevailed over CRP and WBC with significance between these 2 groups and higher value of ROC area. The cutoff level of PCT for bacterial infection is 0.4 ng/mL, with a sensitivity of 73% and specificity of 72%. The positive likelihood ratio is 3.04 and the negative likelihood is 0.35.

Discussion

An acute phase reactant is a useful parameter for clinical physicians to monitor disease activity, especially in inflammatory diseases. CRP is one of the most frequently used reactant and has come into wide use in evaluating patients with fever. However, the specificity of CPR for detecting bacterial infection, which is important for infants and young children, is controversial.[2] PCT has been noted as a marker for severe infection since 1993.[1] Some physicians suggest the extrathyroidal PCT comes from peripheral blood mononuclear cells, liver and the other organs with the purpose of suppressing LPS-induced TNF production in bacterial infection.[3, 4] The relative rapid response and short plateau of PCT make it feasible for early detecting bacterial infection and monitoring disease activity, comparing to CRP. (rise: 4 hr v.s. 12-24 hr; plateau: 8-24 hr v.s. 20-72) [5] Routine testing of PCT in critical patients in ICU is FDA approval and now performed widely.[4]

Literatures regarding early detection for bacterial infection have been reported but few focused on patients in the ward. Most reports focused on critically ill children in ICU, patients in ER, and the correlation of PCT levels with the severity of infection.[6] Deviating from previous studies, we investigated patients admitted to the ward due to fever, as these patients are more reflective of the daily work of physicians in a clinic setting. Neonates were excluded from our study due to naturally high PCT levels in the early postpartum period.[4]

Patients with false negative PCT values were patients diagnosed with: lobar pneumonia (5), urinary tract infection (1) without acute pyelonephritis, and

periorbital cellulitis (1). The 5 patients with lobar pneumonia presented with a mild to moderate pneumonia patch (RUL: 1; RLL: 2; LUL: 2). All of the patients received empirical antibiotics treatment. 4 patients received Aqueous Penicillin G and Azithromycin; 1 patient (2.5 years old) received Ampicillin/Sulbactam and Azithromycin. The lower PCT value of these patients may be due to a less severe infection by atypical bacterial pathogens, such as Mycoplasma or Chlamydia. False positive values were noted in patients: with KD (3 false positive values out of four patients diagnosed with KD), rotaviral enterocolitis (1), herpangina (1), and pharyngitis (1). Okada et al. stated that high PCT levels were noted in patients with KD disease, and this may help to differentiate KD from other systemic autoimmune diseases in its early stages,[7] though not from bacterial infection.[8] The correlation between serum PCT level and development of coronary aneurysm is still under debate.[9] None of our three cases developed coronary aneurysm during outpatient follow-up.

The reference value of PCT is generally acknowledged.[4] PCT≧2 ng/mL suggests bacterial infection; PCT≧0.5 but<2 ng/mL suggests only probable bacterial infection. In children, the cutoff value of PCT for bacterial infection has been reported for differentiating bacterial from viral infection in children in emergency department.[10-12] One study reported a PCT cutoff value of 1 ng/mL;[11] another study reported 0.53 ng/mL.[12] In our study, we focused on patients in the pediatric ward, with age ranging from 1 month to 6 years old. Our cutoff value is 0.4 ng/mL, which is lower than values previously reported as well as the generally acknowledged reference. The limitation of our study is the inclusion of patients with clinical diagnosis of bacterial infection without pathogen proved, such as patients with lobar pneumonia, cellulitis or sinusitis. But good response to antibiotics was the reason to include them in the group of bacterial infection, which were agreed by the two chart reviewers.

Conclusion

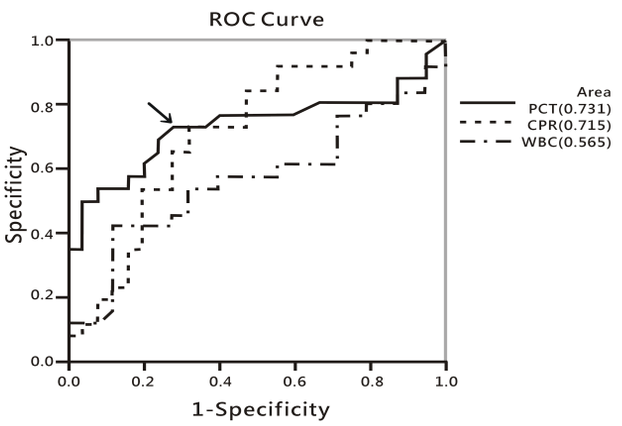
PCT prevailed over CRP in detecting bacterial infection in infants and children younger than 6 years old in our study. We therefore suggest replacing CRP with PCT in clinical practice for evaluating febrile infants and young children, especially in the future when the cost of rapid PCT assay may decrease.

Table : Data of patients in bacterial infection and non-bacterial infection groups

	Bacterial Infection (Study Group)	Non-Bacterial Infection (Control Group)	P value
Case No.	26	25	
Gender (M/F)	18/8	21/4	0.889
Age (year)*	2.9 (± 2.0)	1.8 (± 1.4)	0.024
PCT (ng/mL)*	5.34 (± 7.17)	0.55 (±0.99)	0.002
WBC (10^3/uL)	15.2 (± 11.6)	11.7 (± 5.6)	0.180
CRP (mg/dL)	9.9 (± 10.0)	5.1 (± 7.6)	0.055
Fever days before admision	3.6 (± 2.9)	3.7 (± 3.8)	0.912
Hospital days*	8.5 (± 3.6)	6.4 (± 3.8)	0.047

*P < 0.05

Figure :
ROC curve of PCT, CRP and WBC for bacterial infection. Cutoff point (arrow) is 0.4 ng/mL with a sensitivity of 73% and specificity of 72% in PCT. Area under the curve is also described.



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降鈣素原為住院發燒嬰兒及幼童之細菌感染的指標

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摘要

在區域醫院兒科工作所碰到的病患大多屬於一般兒科(General Pediatrics)的範疇，其中以發燒而轉診至門急診的病患為大宗。快速的鑑別其是否為危險的細菌性感染是有其必要的，而這也是轉診醫師，家長及臨床醫師亟欲所知的。在急性反應物質(acute phase reactant)的檢測上，由近來的研究我們知道降鈣素原(procalcitonin)在1.住進加護病房敗血症病患的預測其預後；2.疑似敗血症病患初到急診時的追蹤預後，這兩方面有其價值。本研究簡短的在此拋磚引玉探討是否在一般兒科病房收治的發燒幼童其procalcitonin值跟其臨床疾病尤其是細菌感染的疾病是否有相關性，並且跟傳統臨床上常測的C-reactive protein和白血球計數值做比較。

關鍵字:幼童、降鈣素原、細菌感染