Is Procalcitonin Better than C-Reactive Protein for Early Diagnosis of Bacterial Pneumonia in Children?

Dilshad Ahmad Khan,* Aisha Rahman, and Farooq Ahmad Khan

¹Department of Pathology, Army Medical College, National University of Sciences and Technology, Rawalpindi, Pakistan

Early diagnosis of bacterial pneumonia plays a pivotal role in the management. We evaluated the diagnostic accuracy of procalcitonin (PCT) as compared with C-reactive protein (CRP) for the early diagnosis of bacterial pneumonia in children. In total, 92 children consisting of 46 patients of bacterial pneumonia were admitted in the Military hospital, Rawalpindi, Pakistan and equal number of controls were included. Patient's investigations were carried out at admission. PCT and CRP were analyzed on Vidas analyzer and Immulite 1000, respectively. Out of 46 pneumonia patients, 28 were male and 18 female, with a median age of 4 years. PCT levels were significantly high median (range) of 2.69 ng/ml

(0.30–13.00) vs. 0.45 ng/ml (0.10–2.00) in controls. Serum CRP levels were moderately elevated with median (range) 6.5 mg/l (0.30–60) vs. 0.30 mg/l (0.30–5.0) in controls. The area under receiver characteristic curves for PCT and CRP were 0.89 (95% CI = 0.83–0.96) and 0.79 (95% CI = 0.70–0.88), respectively. In total, 38 patients were diagnosed to have bacterial pneumonia with PCT (sensitivity 83% at cutoff ≥ 1 ng/ml) and 26 children with CRP (sensitivity 57% at cutoff ≥ 6 mg/L). PCT has better diagnostic accuracy than CRP and can be utilized for early diagnosis of bacterial pneumonia in children. *J. Clin. Lab. Anal.* 24:1–5, 2010. © 2010 Wiley-Liss, Inc.

Key words: procalcitonin; C-reactive protein; bacterial pneumonia; diagnostic accuracy; sensitivity; specificity; children

INTRODUCTION

Pneumonia is an inflammation of the lung parenchyma, which is often caused by bacterial or viral agents. It is responsible for 19% of deaths in children under 5 years of age worldwide. According to World Health Organization, the incidence of pneumonia is highest in South Asia as compared to the other regions (1). Early diagnosis and prompt initiation of antimicrobial therapy are necessary to decrease mortality in children. Accurate differentiation of clinically relevant bacterial pneumonia from viral is pivotal. It is recommended that blood cultures should be performed in all children suspected of having bacterial pneumonia, although the positive growth on culture is very low (2).

Several biomarkers such as cytokines, interleukins and acute-phase reactants such as C-reactive protein (CRP) have been introduced for the diagnosis of infections during last decade (3). CRP is an acute-phase reactant synthesized by the liver in response to inflammation. However, elevated CRP concentration also occurs in

viral infections and other inflammatory conditions. Owing to its nonspecific nature, it has limited utility in differentiating bacterial from viral pneumonia (4). Keeping in view the limitations and drawbacks associated with the use CRP in pediatric population; researchers have strived hard to find out a new biomarker for the diagnosis of bacterial infections.

Procalcitonin (PCT) is 116-amino acid prohormone of calcitonin. Microbial infection induces a ubiquitous increase in CALC-I gene expression and release of PCT from all parenchymal tissues throughout the body (5). PCT levels rise rapidly after a bacterial challenge.

Grant sponsor: National University of Sciences and Technology, Rawalpindi, Pakistan; Grant number: 0986/10/AMC/R&D/NUST.

*Correspondence to: Dilshad Ahmad Khan, Department of Pathology, AM College, Abid Majeed Road, Rawalpindi, Pakistan. E-mail: dilshad@nust.edu.pk, dilshad56@yahoo.com

Received 12 December 2008; Accepted 4 June 2009

DOI 10.1002/jcla.20333

Published online in Wiley InterScience (www.interscience.wiley.com).

Therefore, it can be used as a biomarker for diagnosis of bacterial infection when the blood culture reports are still unavailable (6).

The role of PCT in the diagnosing of bacterial pneumonia in children remains controversial. Several researchers have reported varying sensitivity and specificity of PCT for the diagnosis of bacterial pneumonia (7–9). Moulin et al. (9) reported that PCT had more sensitivity and predictive values than CRP for differentiating bacterial from viral community-acquired pneumonia (CAP) in admitted children. It was demonstrated by another group that PCT had a little value in the diagnosis of bacterial pneumonia in children (4).

The early identification of bacterial infection in children is a challenge in our country. Furthermore, diagnostic accuracy of PCT for diagnosis of bacterial pneumonia is not yet conclusively established in children. There is a need for early and sensitive markers for the diagnosis of bacterial pneumonia as current blood culture fails to identify many affected patients. We aimed to evaluate the diagnostic value of serum PCT as compared with CRP for early diagnosis of bacterial pneumonia in children admitted in the tertiary-care hospital at Rawalpindi. This study will help in the improvement of the diagnostic process of pneumonia and better management in pediatric clinical practice.

MATERIALS AND METHODS

Subjects

Eighty-nine children of suspected pneumonia were included after informed parental consent on a prospective sequential basis. They were admitted from January to September 2008 in the pediatric unit of in Military hospital tertiary, National University of Sciences and Technology, Rawalpindi, Pakistan. However, 43 patients were excluded from the final analysis because of incomplete characterization of bacterial pneumonia in 27 children, 5 had primary tuberculosis, and 11 had already taken antibiotic. Therefore, the total study population comprised 46 patients of bacterial pneumonia with age ranging from 1 to 12 years. Equal numbers ($n = 46$) of healthy children were included from Rawalpindi as controls. This study was approved by the Ethics Committee of the Army Medical College, Rawalpindi, Pakistan.

Diagnosis of Bacterial Pneumonia

All children of CAP of bacterial origin were diagnosed by a qualified pediatrician on the basis of respiratory symptoms, i.e., cough, sputum production, dyspnea, tachypnea, pleuritic pain plus one auscultatory finding, core body temperature $>38.0^{\circ}\text{C}$ and leukocyte count

$>15 \times 10^9/\mu\text{l}$ cells (2). Chest radiography was reported by an independent radiologist and pneumonia was identified by the presence of infiltrate. The children who were diagnosed to have chronic infection, recurrent viral infection, and cystic fibrosis were not enrolled in the study.

Laboratory Methods

All samples were collected in separator vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ) when the patients arrived in the wards. Blood samples were allowed to clot and then centrifuged for 10 min at 10000 g. The serum was separated and stored at -80°C until assayed for PCT and CRP. All the routine investigations including blood count were carried out in the Pathology Department of the Army Medical College, Rawalpindi. Blood cultures and sputum cultures were set up immediately; Pathogens were identified by positive blood culture and serological tests. *Streptococcus pneumoniae* was diagnosed by significant increases in IgG antibodies to pneumolysin and/or pneumococcal capsular C-polysaccharide in paired sera, measured by enzyme immunoassay on ELISA Reader Diamate, Orpington UK (10). Mycoplasma pneumonia was diagnosed by significant increase in IgM antibodies by using ELISA test designed for the detection and quantitative determination of specific antibodies against Mycoplasma (11).

Serum hS-CRP was analyzed by solid-phase, two-site sequential chemiluminescent immunometric high sensitivity CRP assay kit based on Reference (12) on Immulite-1000 (Immulite, Diagnostic Product Corporation, Los Angeles, CA). Serum PCT levels were measured by two monoclonal antibodies, by a VIDAS BRAHMS PCT. It is an automated test for use on the VIDAS instrument (BRAHMS Diagnostica, Berlin, Germany) for the determination of human PCT in human serum using the enzyme-linked fluorescent assay (ELFA) technique. Coefficient of variance (CV) for PCT and CRP were 3.8 and 4.5%, respectively.

Statistical Analysis

Statistical analysis was performed by SPSS version 16 (Chicago, IL). Exploratory data analysis revealed that PCT and CRP concentrations were not normally distributed. Therefore, the results are presented as medians and ranges. The area under receiver operator curves (AUROC) of serum PCT and CRP were calculated for diagnosing bacterial pneumonia in children. Receiver operator characteristic curves were used to evaluate the diagnostic values and compared by the Hanley and McNeil test (13). The diagnostic accuracy values of sensitivity (SN), specificity (SP),

and likelihood ratio (LR) were calculated. We set the optimal cutoff value for the diagnosis of bacterial pneumonia. The concentrations of PCT and CRP at admission in the patients were compared with controls by Mann–Whitney *U*-test. A *P* value of less than 0.05 was considered significant.

RESULTS

Forty-six children were diagnosed as cases of bacterial pneumonia in the pediatric unit of tertiary-care hospital with reference tests. They consisted of 28 (61%) male and 18 (39%) female with a median age of 4 ranging from 1 to 12 years. At admission, most of the children had temperature above 38°C. They presented with severe respiratory symptoms predominately cough 42 (91%), chest pain 34 (74%), tachypnea 18(39), and wheeze 12(26).

Chest X-ray revealed notable alveolar infiltration among the pneumonia patients. Bacteremia was detected in 8 (17%) patients, *S. pneumoniae* in 6 children, and *Staphylococcus aureus* in 2 children. Sputum cultures revealed bacterial growth of *S. pneumoniae* (34%), *Haemophilus influenzae* (9%), and *Klebsiella* species (7%) children. The bacterial pneumonia in the remaining children was confirmed by increase in IgG antibodies to pneumolysin and/or pneumococcal capsular C-polysaccharide in paired sera, measured by enzyme immunoassay on ELISA reader Diamate. A cutoff of limit of ≥ 3 fold increase in antibodies to C-polysaccharide and >2 fold increase in antibodies to pneumolysin were considered to be diagnostic for probable bacterial pneumonia. Three patients of mycoplasma pneumonia were diagnosed by a cutoff value of

IgM antibodies titer ≥ 32 by the ELISA method. Bacterial antibody assays provide a useful tool in the study of the etiology of acute lower respiratory tract bacterial infection in young children.

Early Diagnosis of Bacterial Pneumonia by PCT

The children with bacterial pneumonia had significantly ($P = <0.01$) high median (range) serum PCT levels of 2.69 ng/ml (0.300–13.00) as compared with controls 0.45 ng/ml (0.10–2.00) at admission (Fig. 1a). Serum CRP levels were moderately elevated at admission with median (range) 6.5 mg/l (0.30–60.00) as compared with controls 0.30 mg/l (0.30–5.00) (Fig. 1b).

Receiver operator characteristic curves at admission for serum PCT for bacterial pneumonia are shown in Figure 2. The AUROC at admission for the PCT (0.89) (95% CI = 0.83–0.96) was significantly high ($P = <0.01$) as compared with CRP (0.79) (95% CI = 0.70–0.88). The optimum diagnostic cutoff point for PCT levels in this study population was found to be 1 ng/ml by the receiver operating character analysis (Fig. 2). Diagnostic accuracy parameters of PCT revealed a maximum sensitivity of 83% and a specificity of 72% at the cutoff of ≥ 1 ng/ml.

The AUROC at admission for CRP was 0.79 (95% CI = 0.70–0.88). The optimum diagnostic cutoff point for CRP levels in this study population was found to be 6 mg/l by the receiver operating character analysis (Fig. 2). Diagnostic accuracy of CRP demonstrated a sensitivity of 57% and a specificity of 82% for the diagnosis of bacterial pneumonia at a cutoff of 6 mg/l.

Comparison of diagnostic accuracy parameters of PCT and CRP at two different cutoffs for diagnosis of

Fig. 1. Scatter plot showing comparison of PCT (a) and CRP (b) levels in the patients of bacterial pneumonia with controls ($n = 92$). PCT, procalcitonin; CRP, C-reactive protein.

Fig. 2. ROC curves of serum PCT (AUC 0.89; 95% CI = 0.83–0.96) and CRP (AUC 0.79; 95% CI = 0.70–0.88) concentrations at admission. PCT, procalcitonin; ROC, receiver operating characteristic.

TABLE 1. Diagnostic Accuracy of Serum Procalcitonin and Serum C-reactive Protein in Children with Bacterial Pneumonia at Admission ($n = 46$)

Biochemical markers (cutoff value)	SE (%)	SP (%)	LR+	LR–	DOR
PCT ≥ 0.5 (ng/ml)	87	59	2.12	0.22	9.63
PCT ≥ 1 (ng/ml)	83	72	2.96	0.24	12.33
CRP ≥ 4 (mg/L)	65	74	2.50	0.47	5.30
CRP ≥ 6 (mg/L)	57	82	3.17	0.52	6.10

SE, sensitivity; SP, specificity; LR, likelihood ratio; DOR, diagnostic odds ratio.

bacterial pneumonia is given in Table 1. The study has demonstrated that PCT had maximum LRs and diagnostic odds ratio for diagnosis of bacterial pneumonia at a cutoff of ≥ 1 ng/ml. PCT had maximum LRs and diagnostic odds ratio for diagnosis of bacterial pneumonia than CRP at a cutoff of 1 ng/ml. In total, 38 children out of 46 were correctly identified as having bacterial pneumonia by PCT at the time of admission in the hospital. Serum CRP correctly identified 26 children out of 46 patients of bacterial pneumonia at admission. Thus, PCT had better diagnostic odds ratio for the diagnosis of bacterial pneumonia than CRP. Diagnostic values of PCT were better than the serum CRP for diagnosis of bacterial pneumonia.

DISCUSSION

The diagnosis of pneumonia in critically ill children remains an area of much uncertainty. The classic symptom complex of pneumonia consists of fever,

tachypnea, and cough. However, symptoms can vary widely and are often nonspecific. There is considerable overlap in the presentations of viral, bacterial, and atypical bacterial pneumonias (14). During the past decade, there has been unprecedented progress in the field of medical diagnostics and newer biomarkers for the diagnosis of bacterial infection.

This study has shown for the first time that PCT is a sensitive biomarker for the identification of bacterial pneumonia in patients presenting to the pediatric wards. The sensitivity and specificity of PCT for the diagnosis of bacterial pneumonia are significantly greater than that of CRP. This early prediction by a biochemical marker of infection is important, as it may improve our ability to recognize and differentiate bacterial pneumonia and use PCT-guided therapeutic trials. In this study, both PCT and CRP values were significantly higher in patients with bacterial pneumonia compared with controls. Our observation also supports the study by others (9,15). We found that the receiver operating characteristic area of serum PCT was greater than that of serum CRP at admission and the areas under receiver operating characteristic curve of serum PCT and CRP were significantly different AUROC 0.89 (95% CI = 0.83–0.96) vs. 0.79 (95% CI = 0.70–0.88), respectively ($P < 0.001$). This finding proves that serum PCT is a better marker than serum CRP for the diagnosis of bacterial pneumonia.

Similar results were reported that the overall diagnostic accuracy of PCT was better than CRP for differentiation of bacterial infections from other non-infective causes of systemic inflammation in clinical practice (16). In our study, PCT at a cutoff of ≥ 1 ng/ml had best sensitivity (83%) and specificity (72%). This is in accordance with the previous observation (9). They found that PCT concentration, with a threshold of 1 μ g/L, had greater positive and negative predictive values than CRP for diagnosis of CAP in the admitted children. In a recent study, PCT at a cutoff of ≥ 0.5 ng/ml was found to be more useful than CRP in CAP in adults (17). A Finnish study reported high values of PCT in patients with bacterial pneumonia but with a large overlap between bacterial and viral pneumonia (18). However, our study has demonstrated that PCT rises earlier and can be utilized for the identification of bacterial pneumonia.

CRP although is routinely used for the differentiation of bacterial from nonbacterial infections. CRP performed better at a cutoff value of ≥ 6 (mg/dl), with a sensitivity and specificity of 57 and 82%, respectively, in our study. A recent meta-analysis in children with fever and bacterial infections has shown similar finding that CRP had moderate sensitivity in predicting bacterial infections in children (19). Few studies have reported the

limited role of CRP in the diagnosis of bacterial infections (20,21).

According to a study in bacterial pneumonia, PCT and CRP were not sufficiently sensitive and specific to be used in clinical pediatric practice (22). A Finnish study reported a large overlap between bacterial and viral pneumonia (18). Recently, a study reported that the AUC for distinguishing bacterial from viral infection was 0.838 for CRP and was 0.770 for PCT (17). Our results are different from a few cited above reports in CAP because we included only admitted children with severe bacterial pneumonia. The above-mentioned study was a population-based study. Moreover, they utilized different assays that had low sensitivities (15,18).

These initial results are promising, but the study has several important limitations. We used healthy children for the comparison of diagnostic accuracy of PCT with CRP for the early diagnosis of bacterial pneumonia. Healthy children were enrolled instead of nonbacterial cases because of the nonavailability of confirmatory diagnostic tests for viral pneumonia in our laboratory and also because serum CRP levels also increase in nonbacterial infections. In addition, healthy controls helped us to establish a cutoff value of these biomarkers for the diagnosis of bacterial pneumonia. However, comparisons of these biomarkers in the patients of bacterial pneumonia with nonbacterial cases are recommended in our clinical setting. In our study, the sample size was small. Future multicenter study with a larger population should be conducted before generalizing the results of this study.

Despite the limitations of this study, we have shown that PCT has potential as a diagnostic biomarker for bacterial pneumonia. Significantly more bacterial pneumonia patients were recognized at admission by PCT than by CRP. If the present results are confirmed by further studies, the use of PCT may improve current diagnostic strategies for bacterial pneumonia in children in pediatric clinical practice.

CONCLUSION

Our study has demonstrated that PCT can serve as an early biomarker than CRP for diagnosing bacterial pneumonia. PCT has emerged as a reliable diagnostic marker and can be used in combination with clinical evaluation for proper management of our children.

REFERENCES

- World Health Organization, Health Report 2004. www.who.org.
- BTS Guidelines for the Management of Community Acquired Pneumonia in Childhood. Thorax 2002;57:1–24.
- Gendrel D, Raymond J, Coste J, et al. Comparison of procalcitonin with C-reactive protein, interleukin 6 and interferon-alpha for differentiation of bacterial vs. viral infections. *Pediatr Infectious Dis J* 1999;18:875–881.
- Thayyil S, Shenoy M, Hamaluba M, Gupta A, Frater J, Verber IG. Is procalcitonin useful in early diagnosis of serious bacterial infections in children? *Acta Paediatr* 2005;94:155–158.
- Dandona P, Nix D, Wilson MF, et al. Procalcitonin increase after endotoxin injection in normal subjects. *J Clin Endocrinol Metab* 1994;79:1605–1608.
- Christ-Crain M, Muller B. Procalcitonin in bacterial infections—Hype, hope, more or less? *Swiss Med Wkly* 2005;135:451–460.
- Brunkhorst FM, Heinz U, Forycki ZF. Kinetics of procalcitonin in iatrogenic sepsis [letter]. *Intensive Care Med* 1998;24:888–889.
- Nijsten MW, Olinga P, The TH, et al. Procalcitonin behaves as a fast responding acute phase protein in vivo and in vitro. *Crit Care Med* 2000;28:458–461.
- Moulin F, Raymond J, Lorrot M, et al. Procalcitonin in children admitted to hospital with community-acquired pneumonia. *Arch Dis Child* 2001;84:332–336.
- Nohynek H, Eskola J, Kleemola M, Jalonen E, Saikku P, Leinonen M. Bacterial antibody assays in the diagnosis of acute lower respiratory tract infection in children. *Pediatr Infect Dis* 1995;14:478–484.
- Kenny GE, Grayston JT. Eaton pleuropneumonia-like organism (*Mycoplasma pneumoniae*) complement-fixing antigen: Extraction with organic solvents. *J Immunol* 1965;95:19–25.
- Roberts WL, Sedrick R, Moulton L, Spencer A, Rifai N. Evaluation of four automated high-sensitivity C-reactive protein methods: Implications for clinical and epidemiological applications. *Clin Chem* 2000;46:461–468.
- Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;148:839–848.
- Jean-Paul M, Adeline M, Pierre-Regis B. The role of biomarkers in community-acquired pneumonia: predicting mortality and response to adjunctive therapy. *Critical Care* 2008;12:S5.
- Don M, Fasoli L, Paldanius M, et al. M. Aetiology of community-acquired pneumonia: Serological results of a pediatric survey. *Scand J Infect Dis* 2005;37:806–812.
- 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.
- Ip M, Rainer HT, Lee N, et al. Value of serum procalcitonin, neopterin, and C-reactive protein in differentiating bacterial from viral etiologies in patients presenting with lower respiratory tract infections. *Diagn Microbiol Infect Dis* 2007;59:131–136.
- Toikka P, Irjala K, Juven T, et al. Serum procalcitonin, C-reactive protein and interleukin-6 for distinguishing bacterial and viral pneumonia in children. *Pediatr Infect Dis J* 2000;19:596–602.
- Sanders S, Barnett A, Correa-Velez I, Coulthard M, Doust J. Systematic review of the diagnostic accuracy of C-reactive protein to detect bacterial infection in nonhospitalized infants and children with fever. *J Pediatr* 2008;153:570–574.
- Heiskanen-Kosma T, Korppi M, Jokinen C, et al. Etiology of childhood pneumonia: Serological results of a prospective, population-based study. *Pediatr Infect Dis J* 1998;17:986–991.
- Flood RG, Badik J, Aronoff SC. The utility of serum C-reactive protein in differentiating bacterial from nonbacterial pneumonia in children: A meta-analysis of 1230 children. *Pediatr Infect Dis J* 2008;27:95–99.
- Korppi M. Non-specific host response markers in the differentiation between pneumococcal and viral pneumonia: What is the most accurate combination? *Pediatr Int* 2004;46:545–550.