



American Journal of Microbiology and Immunology
(ISSN:2474-2910)



Elevated Serum Procalcitonin an Adjunct for Early detection of Infant Tuberculosis in Paediatric HIV/AIDS

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ABSTRACT

In countries with a high tuberculosis (TB) burden, Mycobacterium tuberculosis is a frequent cause of acquired pneumonia (AP) amongst people living with HIV/AIDS and the differential and early diagnosis of TB from common bacterial pneumonia is difficult. The varying clinical and radiographic presentation of Acquired Pneumonia and Tuberculosis according to patient age and comorbidity and the low sensitivity of acid-fast bacillus microscopy make it even more difficult to distinguish TB from common bacterial pneumonia. Therefore, an adjunct diagnostic method that can determine early pulmonary tuberculosis in infants living with HIV/AIDS in order to differentiate it from other bacterial pathogens causing acquired pneumonia. Although a confirmatory microscopy test for Tuberculosis detection was carried out which would have a clinical role in terms of isolating patients with TB and administering appropriate anti-TB medication or antibiotic treatment at an early stage. The use of serum procalcitonin (PCT) for early detection of pulmonary tuberculosis (TB) from infants with paediatric HIV/AIDS in Adamawa state, Nigeria a country with an intermediate TB burden and one with the highest number of people living with HIV/AIDS in West-Africa. A prospective study, enrolling 50 infants with paediatric HIV/AIDS with suspected Pulmonary Tuberculosis in a community-based

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How to cite this article:

Ibeh Isaiah Nnanna. Elevated Serum Procalcitonin an Adjunct for Early detection of Infant Tuberculosis in Paediatric HIV/AIDS. American Journal of Microbiology and Immunology, 2016,1:8.

eSciencePublisher

eSciPub LLC, Houston, TX USA.

Website: <http://escipub.com/>

referral hospital. A clinical assessment was performed before treatment, serum and PCT were measured. The test results were compared to the final diagnoses 50 patients, 35 had Pulmonary Tuberculosis and 15 had bacterial associated pneumonia TB. The median PCT level was 0.564 ng/mL (range, 0.01 to 27.75) with bacterial acquired pneumonia and 0.044 ng/mL (range, 0.01 to 0.87) with pulmonary TB ($p < 0.001$). No difference was detected in the discriminative values of PCT ($p = 0.733$). The concentrations of PCT differed significantly in patients with pulmonary TB and bacterial acquired Pneumonia. The high sensitivity and negative predictive value for early detection pulmonary TB when compared to bacterial acquired pneumonia suggest a supplementary role of PCT in the diagnostic exclusion of pulmonary TB from bacterial AP in areas with an intermediate prevalence of pulmonary TB.

Keyword. Pulmonary Tuberculosis, Paediatric, Procalcitonin, Pneumonia

INTRODUCTION

In critically ill neonates, septicemic infection is generally associated with an increased risk of death and a greater length of hospital stay [1]. Outcome can be improved if prompt and appropriate antibiotic therapy is administered [4]. In neonates with community-acquired sepsis, in Paediatric HIV/AIDS who develop infection are under close supervision through iterative clinical assessment and monitoring of various blood markers. The onset of infection should, therefore, be identified more easily and more quickly in this setting. However, the usual infection-related symptoms can be missing in such patients due to deep alterations in their immune status as well as the exposure to specific therapies and procedures.

In countries with a high tuberculosis (TB) burden, *Mycobacterium tuberculosis* is a frequent cause of AP [2-4], and the differential diagnosis of TB

from common bacterial pneumonia is difficult. The varying clinical and radiographic presentation of CAP and TB according to patient age and comorbidity and the low sensitivity of acid-fast bacillus microscopy make it even more difficult to distinguish TB from common bacterial pneumonia [5-7]. Therefore, an adjunct diagnostic method that can determine whether CAP is caused by pulmonary TB or other bacterial pathogens would have a clinical role in terms of isolating patients with TB and administering appropriate anti-TB medication or antibiotic treatment at an early stage. Acquired pneumonia (AP) is a major cause of hospital admission and the most important infectious cause of death [1]. A rapid diagnosis and appropriate antibiotic treatment are essential to reduce the morbidity and mortality from AP. PCT (Procalcitonin) a 116 amino acid protein is a biomarker of severe systemic infectious bacterial disease [8-11]. Recently, PCT has also been introduced as a promising alternative to CRP in guiding the antibiotic treatment of CAP and acute exacerbations of chronic obstructive pulmonary disease [12,13] based on the ability of PCT to discriminate between patients with or without bacterial infection.

Therefore, we investigated the utility of serum PCT for differentiating pulmonary TB from other bacterial AP Paediatric HIV/AIDS in Benin Metropolis (Nigeria), a country with an intermediate TB burden and second largest outbreak of people living with HIV/AIDS.

PATIENTS AND METHOD

Patients:

Of the 50 children enrolled in the study 35 were classified with pulmonary TB the other 15 had bacterial AP, the patients in this study were known Paediatric HIV/AIDS.

Patients were recruited between October 2015 and January 2016 after the study protocol had been approved by the Ethics Review Committee. Adult patients who visited the emergency department or outpatient clinic with respiratory symptoms and chest radiograph abnormalities were eligible for enrollment in this study.

Patients were considered to have pulmonary TB when *M. tuberculosis* was cultured from their sputum or lavage fluid, and the concentration of adenosine deaminase in the effusion was >65 IU/

dL in lymphocyte-predominant exudative pleural effusions combined with a lung parenchymal lesion. Bacterial CAP was diagnosed when the subjects had clinical signs of pneumonia and a new infiltrate on chest X-ray, and these resolved completely with antibiotic treatment and cultures of sputum or lavage fluid were negative for *M. tuberculosis* during follow-up. For the microbiologic evaluation of the patients with AP, sputum Gram stains and cultures was performed, two blood cultures, and urinary antigen assays to detect *Legionella pneumophila* and *Streptococcus pneumoniae*.

Additionally, demographic data, a white blood cell (WBC) count and differential, and the Pneumonia Patient Outcomes Research Team (PORT) [24] score were collected. The results of these tests were compared to the final diagnostic group scores.

Methods:

The PCT level was measured using a monoclonal immunoluminometric assay (LIA PCT sensitive; BRAHMS Diagnostica, Berlin, Germany). After separating the serum, it was aliquoted and frozen at -70°C until analyzed. The functional assay sensitivity for PCT with a 20% inter-assay variation coefficient was 0.05 ng/mL.

Statistics:

Differences between the two groups were tested using the nonparametric Mann-Whitney *U*-test for continuous variables. Pearson's χ^2 test or Fisher's exact test was used for categorical variables, and the Spearman rank correlation coefficient was calculated. Optimal cutoffs for predicting pulmonary TB or bacterial AP were investigated using receiver-operating characteristics (ROC) analysis, and the diagnostic accuracy was assessed from the area under the ROC curves (AUCs). A $p < 0.05$ was regarded as statistically significant, and analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 50 patients who met the inclusion criteria, 15 had bacterial AP and 35 had pulmonary TB. The median age of the bacterial AP and pulmonary TB groups was 0-1 year old respectively. The responsible pathogen was determined in 15 patients (30%) with bacterial AP.

35 (70%) with pulmonary TB had positive respi-

ratory specimen cultures for *M. tuberculosis*. The patients' demographic characteristics, symptoms, and laboratory results are compared in Table 1.

The respective median PCT level was 0.528 ng/mL (range, 0.013 to 27.754) and 0.042 ng/mL (range, 0.01 to 0.873) ($p < 0.001$). A significant positive correlation was detected with the PCT concentrations ($r = 0.648$, $p = 0.01$).

Diagnostic accuracy for discriminating TB from bacterial AP

discriminative value of 0.857 (95% confidence interval [CI], 0.778 to 0.936), and the PCT concentration had a discriminative value of 0.872 (95% CI, 0.792 to 0.951). No difference was found in the discriminative value of PCT ($p = 0.733$). At a cutoff value of 12.5 mg/dL, the PCT concentration had a sensitivity of 93.1% and a specificity of 59.6% (Table 2).

DISCUSSION

The results of this study is suggestive that PCT can help to discriminate between pulmonary TB and other common bacterial AP in a setting of intermediate TB prevalence most especially amongst immunocompromised infants with know Paediatric HIV/AIDS status. Significantly lower PCT serum concentrations were found with pulmonary TB compared to the other bacterial AP in the initial diagnosis stage. About 46,000 cases of TB are newly diagnosed annually in South Korea [25], and the rapid, accurate differential diagnosis of TB from common bacterial AP has important public health implications for the isolation care of Paediatric TB and early appropriate anti-TB medication or antibiotic treatment. Discriminating pulmonary TB from bacterial AP is frequently impossible based on patient history, physical examination, and radiographic findings. Therefore, PCT might have a role in the diagnostic algorithm as rapid, noninvasive tests.

There was no difference observed in the discriminating power of PCT for differentiating pulmonary TB and other bacterial infections in this study. PCT has also been investigated as a predictor of bacterial infection and is considered a more accurate marker of various bacterial infections [16,27]. Therefore, the absence of a difference of PCT in our study should be considered in light of several factors. First, the low yield of a causative pathogen

Table 1 Anthropometric details

Bacterial pneumonia (n=15)	Tuberculosis (n=35)	p value
Demographic characteristics		
Age, 0-1 YEAR	0-1YEAR	<0.001*
Sex, male/female 36/21	18 / 12	0.77†
History of tuberculosis 14 (24.6)	6 (20.0)	0.63†
Symptoms		
Cough 62 (63.2)	48 (93.0)	0.10†
Fever 52 (91.2)	15 (50.0)	<0.001†
Dyspnea 34 (59.6)	12 (40.0)	0.08†
Night sweats 0 (0)	7 (23.3)	<0.001‡
Weight loss 1 (1.8)	15 (30.0)	0.001‡
Laboratory test		
White blood cell, $\times 10^3/\mu\text{L}$ 15.21 (2.30-39.92)	8.38 (5.07-22.99)	<0.001
Neutrophils, $\times 10^3/\mu\text{L}$ 11.06 (1.70-37.92)	5.85 (3.07-20.23)	<0.001*
Monocyte, μL 503 (0-1210)	535 (253-5009)	0.053*
Procalcitonin, ng/mL 0.528 (0.013-27.754)	0.042 (0.01-0.873)	<0.001*
Upper lobe dominance 18 (28.1)	23 (76.7)	<0.001†
Cavitary lesion 0 (0)	11 (36.7)	<0.001‡
Effusion 11 (19.3)	9 (30.0)	0.26†
PORT score 94 (18-187)	76.4 (10-126)	<0.001*
Values are presented as number (%) or median (range).		
PORT, Pneumonia Patient Outcomes Research Team.		
* Mann-Whitney U-test.		
† Pearson χ^2 test.		
‡ Fisher's exact test.		

Table 2.0 PCT data across the Paediatric known HIV/AIDS cases

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
PCT, ng/mL				
<0.1	86.2	78.9	67.6	91.8
<0.25	93.1	59.6	54.0	94.4
<0.5	93.1	50.9	49.1	93.5
<1.0	100.0	31.6	42.6	100.0

in bacterial AP (24.7%) suggests the possibility of including bacterial AP with an atypical etiology, such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and respiratory viruses. These atypical pathogens produce lower PCT levels than classical bacterial pneumonia such as pneumococcal pneumonia [11,28]. Second, because the hospital in which this study was conducted is a secondary referral hospital, although it is a community-based hospital, more than 24 hours had passed from the onset of symptoms to the time some patients visited the hospital. The variable time interval from the onset of symptoms before evaluating PCT might have affected the results because of the kinetics of each inflammatory marker [29,30].

Conclusion:

In conclusion, serum PCT concentrations differed significantly in Paediatric HIV/AIDS related pulmonary TB and those with bacterial AP at the initial diagnosis stage. The high sensitivity and negative predictive value for differentiating the diagnosis of pulmonary TB from bacterial AP suggest a supplementary role for PCT in the diagnostic exclusion of pulmonary TB from bacterial AP in areas with an intermediate prevalence of active pulmonary TB.

Acknowledgement:

We are indebted to the intensive care unit nursing staff for their invaluable contribution to the management of the neonates and also the National Academy for the Advancement of Science, Nigeria, for their financial contribution and academic tutelage.

Conflict of interest:

There were no conflict of interest

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