

The Role of Procalcitonin in Patients with Suspected Pulmonary Tuberculosis.

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Introduction

Procalcitonin (PCT) is a 116 amino acid protein with a sequence identical to that of the prohormone of calcitonin (32 amino acids). Under normal metabolic conditions, hormonally active calcitonin is produced and secreted in the C-cells of the thyroid gland after specific intracellular proteolytic processing of the prohormone PCT. Thus, under normal conditions the PCT levels in the circulation are very low (< 0.05 ng/ml). Bacterial infections induce an ubiquitous increase of CALC-1 gene expression and a constitutive release of PCT from all parenchymal tissues and differentiated cell types throughout the body, so that significant concentrations of PCT (up to 1000 ng/ml) can be detected in the blood of patients. The first description of elevated serum PCT concentrations in sepsis was by Assicot in 1993 [3]. This article describes high concentrations of a substance with calcitonin-like immunoreactivity in patients with various bacterial and viral infections. Serum PCT levels decreased rapidly during antibiotic therapy. Bacterial pneumonia has been associated with higher procalcitonin levels than those produced by pulmonary tuberculosis in at least three studies. This study will be conducted to evaluate the role of procalcitonin level in differentiating pulmonary tuberculosis from bacterial pneumonia in patients admitted to respiratory isolation.

Materials and methods

A prospective, blinded and strictly observational study was conducted over a twelve month period (May 8, 2007, through May 12, 2008) at the New York Hospital Medical Center of Queens, Flushing, New York, a 439-bed acute tertiary care teaching hospital, serving nearly 10% of total inpatient discharges for Queens residents, and over 50% in certain regions of Northern Queens. Recruitment consisted of obtaining a list of all patients admitted to respiratory isolation, by the investigators, on a daily basis. All adult patients (<18 years of age), except pregnant patients (which were identified via blood or urine human chorionic gonadotropin (hCG) testing), were enrolled in the study based on the following inclusion and exclusion criteria listed in Tables 1 and 2, respectively. Eligibility criteria included the following three (3) criteria. I) If the patient has had a cough for more than 2 weeks, night sweats, hemoptysis, weight loss, anorexia, or a fever that persists over weeks to months. II) If the patient was among the following groups: elderly, homeless, prisoner at any time in any jail, alcoholic or IVDA, AIDS or HIV infection, foreign born where TB is endemic (Latin America, Asia, India, Caribbean), positive PPD, immunocompromised patients. III) If the patient has respiratory symptoms and a chest X-ray (CXR) suggestive of pulmonary tuberculosis (upper lobe infiltrate, cavitation, granulomata, bronchiectasis and/or scarring). We then recorded the distribution of age, gender, AFB smears, sputum and blood cultures, risks and symptoms, the Pneumonia Severity Index (PSI), and serum PCT levels for each of the patients. A total of 32 patients were included in this study. Patients were excluded from the study based on the following criteria: known tuberculosis, patients not meeting the above inclusion criteria, acute liver disease, recent major trauma, surgery, burns, small cell lung cancer, medullary thyroid carcinoma, patients less than 18 years of age, pregnancy, and known pulmonary Mycobacterium avium intracellulare (MAI) infection, or upon confirmation of bacterial infection of an alternate organ system. A total of 8 patients were excluded due to the criteria listed above.

Procalcitonin (PCT) values were determined by a monoclonal immunoluminometric assay (LUMitest PCT; BRAHMIS Diagnostica, Berlin, Germany), without knowledge of the patients' clinical data. Procalcitonin (PCT) was measured utilizing the Brahmis PCT-Q test in the patients' blood drawn for routine testing within 24 hours of admission. Serum (5-10 mL) was collected from each patient. Plasma was separated, divided and frozen (-70°C) until analysis was performed. No additional venipunctures were performed on the patients for the sole purpose of the study. The medical teams that care for the patients and the patients themselves were blinded to the test results and no decisions were based on them. This study was observational and no actions were taken based on the test results. Patients were divided into two groups the confirmed Mycobacterium group via sputum AFB smear and/or sputum cultures, versus the non-pulmonary tuberculosis (non-Mycobacterium) group that in which subjects were identified as those with negative AFB smear and culture results. This study was approved by the institutional review board of our facility.

Table 1 - Exclusion Criteria:

- o Known tuberculosis
- o Patients not meeting inclusion criteria
- o Patients with known diagnosis of non-pulmonary bacterial/viral infection
- o Patients with acute liver disease
- o Patients with recent trauma, surgery, burns, small cell lung cancer, medullary thyroid carcinoma
- o Patients less than 18 years of age.
- o Pregnancy
- o Patients with known pulmonary MAI infection

Results

The mean age of our patients was 60 years and their gender was divided equally. The median number of symptoms and risk factors for pulmonary tuberculosis was 5 and the median pneumonia severity index (table 6) was 2. Of the total patients (n=32) seventeen (n=17) patients were diagnosed with mycobacterial infections; eleven (n=11) due to *Mycobacterium tuberculosis* and six (n=6) due to *Mycobacterium avium* complex (MAI) (table 3). The remaining 15 patients were diagnosed with bacterial (n=12) and fungal pneumonias (n=3). There was a statistically significant higher rate (p=0.0019) of high procalcitonin levels in the non-mycobacterial group (7/15) versus its mycobacterial counterpart (0/17) (data derived from Table 3). The rapid procalcitonin test was found to be 100% sensitive but 47% specific for diagnosing mycobacterial disease in this patient population (Table 3). The rapid procalcitonin test is most useful when used to rule out the disease since it has a high negative predicted value (100%) but a lower positive predicted value (68%). When excluding the easy to diagnose acid fast bacillus smear positive patients, the sensitivity and specificity of the rapid procalcitonin test did not change (table 5). Of the remaining six patients who were diagnosed with MAI (*Mycobacterium avium intracellulare*), all had AFB smear negative/culture positive results, and all had PCT - Q scores of < 0.5 ng/mL.

Table 2 - Inclusion Criteria:

- I) If the patient has the following symptoms:
 - o Cough (> 2 weeks)
 - o Fever (temp. > 39°C)
 - o Night Sweats (diaphoresis)
 - o Hemoptysis
 - o Respiratory complaints
 - o Anorexia
 - o Weight Loss
- II) And is among the following groups:
 - o Elderly
 - o Homeless
 - o Prisoner at any time in any jail
 - o Alcoholic or IVDA
 - o Person with AIDS or HIV infection
 - o Foreign born where TB is endemic (Latin America, Asia, India, Caribbean)
 - o Positive PPD
 - o Immunocompromised patients
- III) If the patient has respiratory symptoms and a CXR suggestive of pulmonary tuberculosis (upper lobe infiltrate, cavitation, granulomata, bronchiectasis and/or scarring).

Table 3 - Serum PCT (procalcitonin) levels of patients diagnosed with mycobacterial infection vs. non-mycobacterial infection

	PCT Q < 0.5	PCT Q > 0.5	Total
Mycobacterium	17	0	17
Other	0	7	15
Total	25	7	32

Table 4 - Distribution of non-mycobacterial infections and PCT-Q scores

Non-Mycobacterial Infections	PCT - Q scores
<i>Streptococcus viridans</i>	>0.5ng/mL
<i>Candida albicans</i>	<0.5ng/mL
<i>Streptococcus viridans</i>	<0.5ng/mL
MRSA	>0.5ng/mL
E. coli	<0.5ng/mL
P. carinii/C. albicans	<0.5ng/mL
MRSA	>0.5ng/mL
MRSA	>0.5ng/mL
C. albicans	<0.5ng/mL
H. influenzae	<0.5ng/mL
Aspergillus	<0.5ng/mL
E. coli	<0.5ng/mL
Strept pneumoniae	<0.5ng/mL
Pseudomonas	<0.5ng/mL
Acinetobacter	<0.5ng/mL

Discussion

Tuberculosis (TB) is caused by the bacterium *Mycobacterium tuberculosis* and is annually responsible for nearly two million deaths worldwide. A third of the world's population is currently infected with the TB bacillus, and more than eight million new cases are diagnosed each year(1). In total, 13,779 TB cases (a rate of 4.6 cases per 100,000 persons) were reported in the United States in 2006. This represents a 3.1% decline in the rate from 2005. In 2006, the TB rate in foreign-born persons in the United States (22.0 cases per 100,000 persons) was 0.5 times greater than that of U.S.-born persons (2.3 cases per 100,000 persons). In Queens County, New York, the rate of TB was calculated to be 14.2 per 100,000, the highest in the state. The calculated median age for this study was 60 years, and when compared to statewide statistics, the rate per 100,000 population by age group was highest amongst those 60 years or older, 15.8 per 100,000. Per NYSDOH records the number of total reported cases (211953) in 2006 was highest for those aged 60 years or older(1). TB has reemerged as a serious public health threat worldwide because of a significant increase in multiple-drug-resistant TB (MDR-TB) and synergism between Human Immunodeficiency Virus (HIV) and *M. tuberculosis* infection. For unknown reasons, persons co-infected with HIV are particularly susceptible to TB. HIV-positive individuals are more likely to acquire primary TB disease upon initial infection, reactivate a latent TB infection, and experience an accelerated course of fatal disease when infected with a multi-drug resistant strain(8). In a study by Schleicher, G. K., et al., HIV-seropositive patients with pulmonary community acquired pneumonia had a significantly higher procalcitonin and C-reactive protein levels than those with pulmonary tuberculosis despite similar clinical and radiological appearances. The authors found that a procalcitonin level >3 ng/mL and a C-reactive protein level >246 mg/L are both highly predictive of pneumococcal infection and may lead to earlier correct diagnosis, more cost-effective investigations, and less exposure to unnecessary antibiotics. However, elevated procalcitonin levels are also found in a significant proportion of HIV seropositive patients with pulmonary tuberculosis, and may be a marker of severe and disseminated tuberculosis or concomitant infection with other bacterial pathogens(3). In a study by Lawn, S. D., et al., serum procalcitonin was not elevated in patients with post-primary pulmonary tuberculosis at both diagnosis and during treatment. These authors found that of the 20 subjects studied two patients demonstrated slightly elevated PCT scores. The authors concluded that serum PCT may be elevated in those with concurrent debilitating extensive mycobacterial disease, or advanced HIV-coinfection(4). The findings of this study reveal that serum procalcitonin was not elevated (PCT - Q < 0.5 ng/mL), in subjects diagnosed with pulmonary TB (n=11) and all but one patient had negative initial AFB smear (Zahn-Nielsen microscopy) results. The elevated PCT - Q result in our (n=1) may indicate that PCT - Q results may be elevated in the very debilitated or those with extensive mycobacterial disease. Furthermore, concerning the usefulness of PCT concentration as a diagnostic parameter, Polzin, A., et al., demonstrated that patients with pulmonary TB had PCT - Q levels <0.5ng/mL(5). The same was observed by Zarka et al., who investigated PCT levels in 49 patients with CAP, TB, and *Pneumocystis-carini pneumoniae*(9).

Conclusions

In summary, serum negative culture positive tuberculosis patients are often difficult to identify. As in prior studies, many patients with undiagnosed TB on presentation, have either coexisting infections, i.e., CAP, HACP, viral pneumonias with bacterial superinfection, or are in an immunocompromised state (i.e., HIV coinfection). In our study, patients with primary TB infections without coexisting bacterial, viral, or fungal infections all had PCT scores of <0.5ng/mL. One patient who was observed to have a PCT score of >0.5ng/mL was found to have a coexisting infection of another organ system. The present study has some limitations as the sample size in both Mycobacterium (n=17), and non-mycobacterial (n=15), was small. Future studies may incorporate a larger sampling size via a joint multi-center study.

Table 5 - Distribution of AFB negative/culture positive results versus their respective PCT - Q scores

AFB Smear	Culture Result	AFB Culture
Negative	Positive	<0.5ng/mL
Positive	Positive	<0.5ng/mL
Negative	Positive	<0.5ng/mL

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Table 6 - Pneumonia Severity Index:

Demographic Factor	Men	Women	Age	Age - 10
Nursing home resident			+10	
Coexisting illness				
Newly-onset disease			+20	
Liver disease			+20	
Congestive heart failure			+10	
Cerebrovascular disease			+10	
Physical examination findings				
Altered mental status			+20	
Respiratory rate >30/min			+20	
Systolic blood pressure <90mmHg			+20	
Temperature >38°C or >40°C			+10	
Laboratory and radiographic findings				
Arterial blood gas (pH<7.35)			+20	
HbK >30 mmol/L			+20	
Sodium level < 130 mmol/L			+20	
Glucose level >250 mg/dL			+10	
Hematocrit < 30%			+10	
Partial pressure of arterial O2 <60mmHg or O2 saturation < 90mmHg			+10	
Pneumothorax			+10	
Pleural effusion			+10	
				Total
Class				Points
I				< 1
II				1-7.9
III				7.9-10
IV				> 10