PROCALCITONIN AS BIOMARKER OF ANTIBIOTIC EFFECTIVITY IN COMMUNITY-ACQUIRED PNEUMONIA

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ABSTRAK

Procalcitonin merupakan marker spesifik infeksi akut yang ditandai peningkatan kadar procalcitonin sehingga procalcitonin digunakan sebagai marker efektifitas terapi antibiotika. Penelitian ini bertujuan mengkaji procalcitonin sebagai marker efektifitas terapi antibiotika pada pasien pneumonia komunitas. Penelitian ini merupakan penelitian kohort prospektif pada pasien pneumonia komunitas di Instalasi Rawat Inap SMF Pulmonologi dan Ilmu Kedokteran Respirasi RSUD Dr. Soetomo Surabaya. Procalcitonin dan parameter SIRS sebelum, hari ke-3 dan hari ke-5 terapi antibiotika dianalisis secara deskriptif. Didapatkan 19 pasien pneumonia komunitas dengan penyakit penyerta TB paru, sepsis, pneumothorax dan efusi pleura. Procalcitonin pada pasien pneumonia komunitas sebelum terapi antibiotika adalah 0,51± 0,19 (0,28-0,89) ng/ml, sesudah terapi antibiotika hari ke-3 0,53 ± 0,24 (0,08-0,93) ng/ml dan pada hari ke-5 mencapai kadar 0,43± 0,24 (0,00-0,83) ng/ml. Procalcitonin pada pasien pneumonia komunitas dengan sepsis adalah 0,48 ± 0,24 (0,29-0,89) ng/ml; 0,40 ± 0,26 (0,08-0,74) dan 0,22 ± 0,13 (0,00-0,32) ng/ml. Procalcitonin pada pasien pneumonia komunitas dengan TB paru adalah 0,52 ± 0,18 (0,38-0,83) ng/ml; 0,55 ± 0,25 (0,23-0,89) ng/ml dan 0,57 ± 0,16 (0,41-0,82) ng/ml. Procalcitonin pasien pneumonia komunitas dengan TB paru dan sepsis sebelum terapi antibiotika, hari ke-3 dan hari ke-5 terapi antibiotika adalah 0,55 ± 0,12 (0,38-0,70) ng/ml, 0,56 ± 0,15 (0,42-0,73) ng/ml dan 0,47 ± 0,15 (0,33-0,64) ng/ml. Terdapat 60% pasien pneumonia komunitas dengan sepsis, 20% pasien pneumonia komunitas dengan efusi pleura dan tidak ada pasien pneumonia komunitas dengan TB Paru yang mencapai kadar procalcitonin < 0,26 ng/ml pada hari ke-5 sesudah terapi antibiotika. Procalcitonin tidak dapat digunakan sebagai marker efektifitas terapi antibiotika pada pasien pneumonia komunitas. ***(FMI 2015;51:96-100)***

Kata kunci: *procalcitonin, pneumonia komunitas, antibiotika, biomarker*

ABSTRACT

Major therapy for community-acquired pneumonia (CAP) is antibiotics. Procalcitonin used as the measure of antibiotics effectiveness. Procalcitonin is specific biomarker that elevates in acute bacterial infection. This study aimed to analyze procalcitonin as effective antibiotics biomarker in CAP patients hospitalized at Pulmonology Department Dr. Soetomo Teaching Hospital. This study was performed by cohort prospective data and analyzed by descriptively. Data were assessed at before antibiotics, day 3 and day 5 after antibiotics therapy. Nineteen community-acquired pneumonia were enrolled. Serum procalcitonin before antibiotic therapy , day 3 and day 5 antibiotics therapy in CAP are 0.51± 0.19 (0.28-0.89) ng/ml, 0.53± 0.24 (0.08-0.93) ng/ml and 0.43± 0.24 (0.00-0.83) ng/ml. Serum procalcitonin in CAP with sepsis patients are 0.51± 0.19 (0.28-0.89) ng/ml (before antibiotic therapy), 0.40 ± 0.26 (0.08-0.74) ng/ml (day 3) and 0.22 ± 0.13 (0.00-0.32) ng/ml (day 5). Serum Procalcitonin in CAP with pulmonary TB are 0.52 ± 0.18 (0.38-0.83) ng/ml, 0.55 ± 0.25 (0.23-0.89) ng/ml dan 0.57 ± 0.16 (0.41-0.82) ng/ml. Serum procalcitonin in CAP with sepsis and pulmonary TB are 0.55 ± 0.12 (0.38-0.70) ng/ml, 0.56 ± 0.15 (0.42-0.73) ng/ml dan 0.47 ± 0.15 (0.33-0.64) ng/ml. Procalcitonin of 60% CAP with sepsis patients, 20% CAP with pleural effusion patients and no patients of CAP with pulmonary TB reach <0.26 ng/ml. In conclusion, procalcitonin is not useful biomarker in CAP. ***(FMI 2015;51:96-100)***

Keywords: *procalcitonin, community-acquired pneumonia, antibiotic therapy, biomarker*

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INTRODUCTION

Community-acquired pneumonia is an infection of the pulmonary parenchyma that develops outside the hospital (Marrie 2008). The clinical manifestations are frequently febrile with a tachycardic response and may have chills or sweats and cough that are either nonproductive or productive of mucoid, purulent, or blood-tinged sputum (Wunderink 2010). Many physiological changes occur in the host in order to restore the impaired homeostasis during bacterial and viral. The release of inflammatory mediators, such as interleukin (IL) 1 and tumor necrosis factor (TNF), results in fever. Chemokines, such as IL-8 and

granulocyte colony-stimulating factor, stimulate the release of neutrophils and their attraction to the lung, producing both peripheral leukocytosis and increased purulent secretions (Wunderink 2010).

White blood cell (leukocyte) count and other parameter SIRS are the most frequently used markers of acute phase responses in clinical practice. Classical diagnostic instruments including leukocyte count, chest x ray and sputum culture do not have sufficient specificity in differentiating between bacterial infections, non-infectious systemic inflammations or viral infections. Therefore, more specific and reliable markers that might be helpful in deciding the treatment are needed in these community-acquired pneumonia patients.

Procalcitonin, a protein of 116 amino-acids with molecular weight of 13 kDa, is prohormone of calcitonin produced by C-cells of thyroid gland and intracellulary cleaved by proteolytic enzymes into the active hormone. The production of procalcitonin during inflammation is linked with a bacterial endotoxin and with inflammatory cytokines (TNF, IL-6) (Meissner 2000). The aim of this study was to analyze procalcitonin as effective biomarker of antibiotics community-acquired pneumonia patients who hospitalized at the Pulmonology Department Dr. Soetomo Teaching Hospital.

MATERIALS AND METHODS

A cohort prospective study was conducted at Pulmonology Department Dr. Soetomo Teaching Hospital during September to December 2014. Patient selection based on inclusion and exclusion criteria. Inclusion criteria (1) patient diagnose with community-acquired pneumonia aged 18-75 years old; (2) patient or their family agreed to follow the study. Patient hospital-acquired pneumonia, thyroid carcinoma, pulmonary carcinoma, received corticosteroids or antibiotic therapies before come to Emergency Department were excluded.

Blood samples were collected from all patients before antibiotic therapy in order to perform complete blood count and routine biochemistry, as well as to analyze serum procalcitonin. Procalcitonin levels were reassessed after 3 and 5 d. culturing of the sputum specimens that were obtained from patients with sputum production were performed. The blood collected for serum PCT measurement was centrifuged and kept at -20°C until the time of the measurement. PCT measurement was performed by the Bio-Rad iMark device. In this study, we used Biotech Human PCT ELISA Kit made in the China. Descriptive analyses were performed to determine the demographic patients, profile of procalcitonin and parameter SIRS at before and after antibiotic therapy. Correlation between procalcitonin and parameter SIRS (pulse, respiratory rate, body temperature and leukocyte) was measured by the Spearman's correlation test and Pearson's correlation test. A probability value of 0.05 was regarded as significant.

RESULTS

During the study period, 24 consecutive patients with CAP were screened for eligibility. Of these, 19 were eligible. Baseline characteristic on admission are shown in Table 1. The most age of the patient was 19-59 years and included 9 females and 10 males. The classic triad of dyspnea, cough, and sputum, as reported by the patients, was present in 90%, 90% and 58% of cases. The most coexisting illnesses in patients are pulmonary TB (63%) and sepsis (57%).

Eleven patients had purulent sputum. In 8 of those with purulent sputum, a causative microorganism was identified in 6 patients. Bacterial growth was shown in sputum culture. The results were as follows: Diplococcus in 4 patient, *Acinobacter baumannii* in 1 patients and *Aeromonas hydrophila* in 1 patient. On the day of admission, serum procalcitonin levels were 0.26 to 0.5 ng/mL in 12 patients and >0.5 ng/mL in 7 patients. The results of PCT before and after antibiotic therapy are shown in Figure 1. Serum PCT levels in all patients were >0.25 ng/ml. Results of PCT after 3 days and 5 days of antibiotic therapy shows that the number of patients seemed to have decreased from >0.25 at diagnosis to <0.1 ng/mL (2 patients).

There was no statistically significant correlation between procalcitonin and parameter SIRS (leukocyte, pulse, respiratory rate and the body temperature) in all community-acquired pneumonia patients coexisting illnesses group.

Table 1. Characteristics of CAP patients

Characteristic (n=19)		n (%)
Sex	Female	9 (47)
	Male	10 (53)
Age	13 – 18 years	1 (5)
	19 – 59 years	12 (63)
	>59 years	6 (32)
Procalcitonin (ng/ml)	<0.1	0 (0)
	0.1 – 0.25	0 (0)
	0.26 – 0.5	12 (63)
	>0.5	7 (37)
Leukocyte counts	4 – 10	3 (16)
	>10	16 (84)
Coexisting illnesses*	Pulmonary TB	12 (63)
	Sepsis	11 (57)

	Hypertension	2 (11)
	Diabetes mellitus	2 (11)
	Pleural effusion	2 (11)
	Fluidopneumothorax	2 (11)
	Pyopneumothorax	1 (5)
	Heart failure	1 (5)
Clinical manifestations	Dyspnea	17 (90)
	Cough	17 (90)
	Sputum	11 (58)
Antibiotics	Ceftazidime	11 (58)
	Levofloxacine	11 (58)
	Anti TB	10 (53)
	Ceftriaxone	4 (21)

* One patient may have one or more coexisting illnesses

As expected, high levels of WBC, pulse, respiratory rate and temperature were decrease after 3 and 5 days antibiotic therapy (Figure 2 and 3).

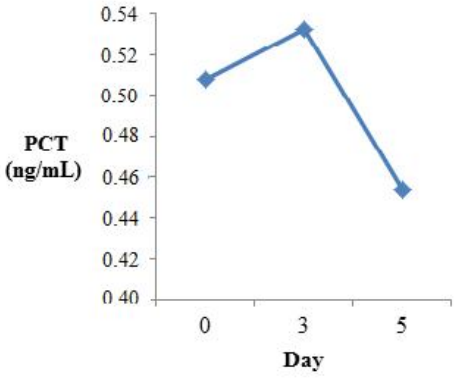

Figure 1. Serum procalcitonin before and after antibiotic therapy

Table 2. Correlation in CAP with PTB

Parameter	Procalcitonin			
	Day 3		Day 5	
	p	r	p	r
Pulse	1.000	0.000	0.946	0.042
RR	0.004	0.979	0.511	-0.395
Temp	0.586	-0.331	0.627	0.297
Leukocyte	0.121	-0.779	0.588	0.330

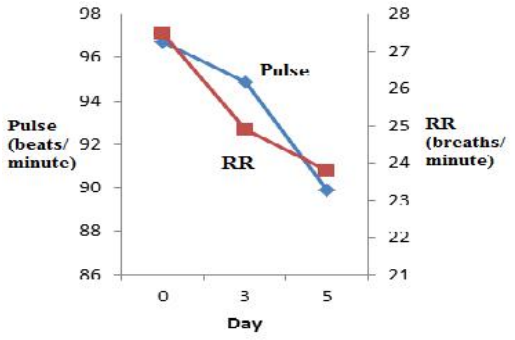

Figure 2. Pulse and RR before and after antibiotic therapy

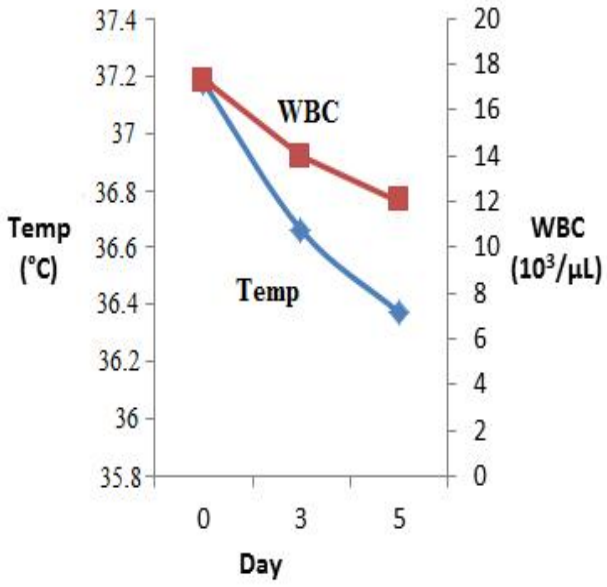

Figure 3. Temperature and WBC before and after antibiotic therapy

Table 3. Correlation in CAP with sepsis

Parameter	Procalcitonin			
	Day 3		Day 5	
	p	r	p	r
Pulse	0.926	0.058	0.355	0.533
RR	0.638	-0.289	0.105	0.799
Temp	0.880	-0.94	0.810	-0.150
Leukocyte	0.320	-0.565	0.405	-0.487

Table 4. Correlation in CAP with PTB and sepsis

Parameter	Procalcitonin			
	Day 3		Day 5	
	p	R	p	r
Pulse	0.199	0.689	0.741	0.205
RR	0.149	0.744	0.347	-0.541
Temp	0.870	0.102	0.391	-0.500
Leukocyte	0.332	-0.555	0.180	0.709

DISCUSSION

PCT is a protein having a molecular weight of 13 kD and it consists of 116 amino acid residues (Meissner 2002). In healthy humans, its normal serum level is 0.1 ng/ml (Carrol et al 2002). In a previous study, administration of bacterial endotoxin to healthy individuals resulted in an increase in PCT levels starting two hours after administration, with a peak value

Table 5. Procalcitonin before and after antibiotics therapy

PCT (ng/ml)	Criteria*	Patients		
		Before Antibiotics Therapy	After Antibiotics Therapy	
		Day 0	Day 3	Day 5
		n (%)	n (%)	n (%)
< 0.1	Bacterial infection very unlikely	0 (0)	0 (0)	2 (10)
0.1 – 0.25	Bacterial infection unlikely	0 (0)	1 (6)	0 (0)
0.26 – 0.5	Bacterial infection likely	12 (63)	9 (47)	10 (59)
> 0.5	Bacterial infection very likely	7 (37)	9 (47)	7 (41)
Total		19 (100)	19 (100)	19 (100)

*Based on algorithm for procalcitonin-guided antibiotic therapy (Crain et al 2010, Albrich et al 2012)

reached in 12 hours (Linscheid et al 2004). Consequently, the serum level remains constant for another 12 hours and decreases back to normal level in 20-24 hours. PCT gives rapid response to bacterial infections (Müller et al 2007, Kibe et al 2011). Following the administration of bacterial endotoxin, PCT levels increase faster and return to normal range more rapidly compared to the levels of CRP (Linscheid et al 2004).

In this study, we have demonstrated that serum PCT levels increase in day 3 antibiotic therapies and decrease in day 5 antibiotic therapy. Serum procalcitonin levels remain high after 5 days antibiotic therapy because of pulmonary TB. Studies have shown that after 2 months of intensive phase of treatment, the number of pulmonary TB patients with an increase in PCT was more than those with decrease or no change in the procalcitonin levels. Although a clearly conclusive statement on the prognostic utility of PCT cannot be made at the end of 2 months of intensive treatment, the procalcitonin seems to be a good prognostic marker for the efficacy of the 6 months treatment, because at the end of 6 months, PCT in all patients had decreased (Rohini et al 2013). A similar result was found in another study that PCT level reduced significantly ($P < 0.001$) after 6 months treatment anti-TB (Ghobadi et al 2014). PCT levels increase with the increasing severity of the inflammatory response to infection and may help in assessing the severity of infection, the prognosis of disease, and the response to therapeutic measures. In this study, procalcitonin is not useful biomarker biomarker of antibiotic effectivity in community-acquired pneumonia with pulmonary TB.

Serum procalcitonin levels decrease until < 0.26 ng/mL in community-acquired pneumonia with sepsis. Procalcitonin decrease as parameter SIRS to response antibiotic therapy. Serum PCT levels are elevated in patients with sepsis. A decrease in PCT concentrations was associated with a favorable outcome in patients with sepsis. Based on this data, procalcitonin is useful biomarker of antibiotic effectivity in community-acquired pneumonia with sepsis.

Studies have shown that the diagnostic efficacy of leukocyte count is not high; it has either moderate or low efficacy. In this study, we also were unable to find any significant relationship between PCT and leukocyte count. This suggests that WBC count is not a significant factor in identifying a bacterial infection. In another study, it was shown that PCT has no significant correlation with leukocyte (TAŞÇI 2008, Ugajin et al 2011).

Our study has several limitations. First, since outpatients were excluded, the enrolled patients might have had relatively severe conditions. As a result, serum PCT was elevated compared with previous studies. Secondly, community-acquired pneumonia patients could be associated with bacterial coinfection (pulmonary TB and sepsis). Third limitations of this study are the low sample size (because of lesser prevalence of community-acquired pneumonia that meets inclusion). A further study with a larger sample size and no coexisting illnessess is suggested.

CONCLUSION

The results of procalcitonin in 19 patients of community-acquired pneumonia with coexisting illnessess suggest that procalcitonin is not useful biomarker in community-acquired pneumonia.

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