Evaluation of procalcitonin as a biomarker for bacterial and nonbacterial community-acquired pneumonia in children

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Background/aim
The aims of the present study were to investigate the role of procalcitonin (PCT) as a diagnostic biomarker for community-acquired pneumonia (CAP) in children and its value to distinguish between bacterial and nonbacterial infections.
Patients and methods
The study enrolled 64 children admitted to the Department of Pediatrics at El-Helal Specialized Hospital of Pediatrics, Cairo, for clinical and radiological evidence of CAP, aged from 1 month to 7.5 years. They were divided into two groups according to pathogen detection: group I comprised bacterial pneumonia (33 cases) and group II included nonbacterial pneumonia (31 cases). In addition, 37 healthy children were also enrolled as a control group. Full clinical examination was conducted, and venous blood samples were taken from all participants for the assessment of complete blood count, serum levels of PCT by ELISA, and C-reactive protein (CRP) by latex agglutination technique.
Results
PCT and CRP levels in peripheral blood were significantly higher ($P<0.001$) in all children with pneumonia compared with controls (357.4±70.8, 18.8±5.1, vs. 121.5± 21.3, 5.61±1.82, respectively). Serum PCT level was higher in the bacterial pneumonic group compared with those with nonbacterial pneumonia ($P<0.001$). There was also a positive correlation between PCT level and both CRP ($P\leq0.05$), and leukocytic count ($P<0.05$).
Conclusion
PCT can be considered as an important indicator for CAP and can be used for differentiation between bacterial and nonbacterial pneumonia.

Keywords:
children, community-acquired pneumonia, C-reactive protein, procalcitonin

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Introduction

Respiratory disease is a common and significant cause of morbidity and mortality all over the world, being the most common cause of hospital admission in children. Approximately 1 billion 'common colds' occur yearly. In 2010, there were ~6.8 million visits to the critical care units for respiratory disorders in the USA among pediatric age group [1,2].

Respiratory tract infections can affect any part of the respiratory system. It may be upper respiratory tract infections, represented as common cold, or lower respiratory tract infections, represented as pneumonia, which is usually caused by bacteria, particularly *Streptococcus pneumonia*; however, the etiology of this lower respiratory tract infection in children younger than 2 years is mostly viral [3,4].

It is difficult to determine accurately the cause of community-acquired pneumonia (CAP), whether caused by viral or bacterial agents, whereas the diagnosis is based on clinical symptoms and signs [5,6]. As a result of missed diagnosis of being viral or bacterial, the most guidelines indicate treatment directly with antibiotics [7,8], but unfortunately, empirical treatment with these antibiotics may lead to antibiotic resistance [9,10].

In 2016, the Federal Government in the USA allocates 1.2 billion dollars for the development and dissemination of diagnostic tests that distinguish between bacterial and viral infections in 20 min or less [6]. Diagnostic tests used as biomarkers of bacterial infection already exist as white blood cell count and C-reactive protein (CRP), but one of the most recent biomarker for CAP detection is procalcitonin (PCT) [11,12].

Procalcitonin, a protein containing 116 amino acids, corresponds to a group of proteins related to the calcitonin gene, calcitonin gene-related peptide I and II [11]. The transcription of the *CALC 1* gene generates PCT and consequently mature calcitonin. Normally PCT is produced by neuroendocrine cells in the thyroid and lungs with low rate and is undetectable in serum. Inflammation stimulates the increase in the secretion of PCT in serum [13,14].

There was a debate on whether PCT is increased through bacterial infection and if it can be used as a diagnostic tool to help distinguish viral from bacterial CAP [14,15]. Studies have shown that use of PCT level is needed when antibiotics are introduced. It is used as guidance for initiation and duration of antibiotic treatment [16,17]. Thus, it represents a great headway that the PCT test will be used as a tool for reducing the empirical use of antibiotics in respiratory tract infections [18,19].

The present study aims to investigate the role of PCT as a diagnostic biomarker for CAP in children and its value to distinguish between bacterial and nonbacterial infections.

Patients and methods

Study design and patients characteristics

Sixty-four children, who were hospitalized in the NICU, PICU, or Department of Pediatrics of El-Helal Specialized Hospital of Pediatrics in the period between January 2016 and January 2017 were enrolled in the study. The inclusion criteria were as follows: age between 1 and 15 years, clinical signs suggestive of CAP such as tachypnea, abnormal breath sounds, and a radiological confirmation of CAP in accordance with the WHO criteria for the standardized interpretation of pediatric chest radiographs for a diagnosis of pneumonia [20]. Children were excluded if they had received antibiotics for more than 48 h before admission or if they were experiencing underlying chronic respiratory disease. Culture and sensitivity test were done to confirm the etiology whether bacterial or nonbacterial pneumonia. Cases were divided into two groups according to pathogen detection: group I included 33 cases of bacterial pneumonia (22 males and 11 females) and group II included 31 cases of nonbacterial pneumonia (16 male and 15 females). Thirty apparently healthy children of matched age and through physical examination were enrolled as a healthy control group. The demographic, clinical history, and clinical disease characteristics of each child were recorded.

Anthropometric measurements

Anthropometric evaluation was carried out on all children. Children were weighed (kg) using a calibrated Seca scale to the nearest 0.1 kg (Seca, Hamburg, Germany), whereas height (cm) was measured using a Seca 225 stadiometer (Seca) to the nearest 0.1 cm. BMI was calculated by weight (kg)/height (m).

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional (National Research Centre) committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Blood sampling

Venous blood samples (3 cm) were taken from each child participating in the study, and divided into two aliquots. The first aliquot was ~1 ml of venous blood for determination of CBC. The second aliquot was 2 ml of venous blood that was left to clot, and then the serum was separated by centrifugation and stored at −20°C for biochemical assays.

Hematological and biochemical assays

Complete blood count was determined using Coulter Counter T890 (Coulter Counter, Harpenden, UK). CRP was determined using latex agglutination technique according to the method of Wadsworth and Wadsworth [21], whereas procalcitonin was determined using Human ELISA Kit (Bioassay Technology Laboratory Co., Shanghai, China). The detection range of this kit was 5–20 000 pg/ml according to the method of Arkader *et al.* [22].

Statistical analysis

Data were statistically analyzed with SPSS 20.0 software (SPSS Inc., Chicago, Illinois, USA). The measurement data were presented as mean±SD. χ^2-test was done for qualitative data, which were represented by numbers and percentages. *T*-test was done for comparison between two means. Simple linear correlation (Pearson's correlation) for quantitative data was also done. *P* value was considered statistically significant when less than 0.05 and considered statistically highly significant when less than 0.001.

Results

The study group consisted of 64 children with a mean age of 3 years, ranging from 1 month to 7.5 years old, with a male predominance (60% of cases). Thirty age-matched and sex-matched children served as control.

Forty (62%) cases lived in urban areas, whereas 24 (37.5%) cases lived in rural areas (data not shown).

All cases were divided into two groups according to pathogen detection: group I included 33 cases of bacterial pneumonia, of which 22 were males and 11 were females. Group II included 31 cases of nonbacterial pneumonia, of which 16 were male and 15 were females. Thirty apparently healthy children of matched age and sex through physical examination were enrolled as healthy control group.

The data obtained in Table 1 showed a highly statistically significant difference between cases and control regarding PCT level and CRP level ($P<0.01$). Moreover, white blood cell and neutrophil count were significantly higher in cases compared with control ($P<0.05$).

The results presented in Table 2 revealed that PCT level in the bacterial pneumonic group was higher than those of the nonbacterial pneumonia group with a statistically significant difference ($P<0.001$), whereas CRP levels were statistically indifferent between both pneumonic groups (Table 3).

Discussion

CAP is a common disease in children, being the major cause of respiratory morbidity and mortality, with etiological causes being either bacteria, viruses, fungi, or combination of these infectious agents [8]. It is of importance to differentiate between types of CAP for early diagnosis to prescribe the most effective treatment that can reduce the mortality rate and adverse effects in infected children [23,24].

Although CAP diagnosis is mostly achieved by clinical manifestations of fever and respiratory symptoms, chest radiography, and some valuable hematological indicators such as white blood cell and neutrophils, it is necessary to find new serum markers to replace the old diagnostic tools to help in the early and accurate diagnosis of the disease and its etiological cause [25,26].

Some of the inflammatory biomarkers are used not only for identifying the etiological diagnosis of CAP in children but also for a possible differentiation between two types, either bacterial or nonbacterial infections [27,28].

The study group included 64 children enrolled for clinical signs suggestive of CAP, with a mean age of 3 years, ranging from 1 month to 7.5 years.

The results of this study revealed that white blood cells and percentage of neutrophils were significantly higher in pneumonic cases compared with control group ($P<0.04$). These could be explained by the physiological immune response of the circulating leukocytes to various stressful events, which is characterized by increased total leuokocytic and neutrophil count against an inflammatory reaction caused by any bacterial infection. Total leukocytic count and neutrophil percentage could be considered as the traditional indicators for screening bacterial infection in children with CAP. These results fit those found by Ning *et al.* [14] and Nikaido *et al.* [29] who found a significant increase in hematological parameters such as leukocytic count in Chinese children with CAP.

Table 1 Anthropometric and laboratory results of all children with community-acquired pneumonia and healthy control group

Variables	All cases (*N*=64)	Controls (*N*=30)
Weight (kg)	13.7±4.0	15.6±5.4
Height (cm)	88.7±19.7	95.7±22.4
HC (cm)	46.6±6.8	45.7±5.9
Hb (g/dl)	9.9±1.6	11.1±1.7
WBC (10^9 cell/l)	14.8±4.6*	9.7±3.4
Neutrophil (%)	61.4±18.8*	37.3±9.7
CRP (mg/l)	18.8±5.1**	5.61±1.82
Procalcitonin (pg/ml)	357.4±70.8**	121.5±21.3

All data are expressed as mean±SD; CRP, C-reactive protein; Hb, hemoglobin; HC, hematocrit; WBC, white blood cells; *Significant difference than control group at *P* value ≤0.05; **Highly significant difference than control group at *P* value ≤0.01.

Table 2 Serum levels of procalcitonin and C-reactive protein in bacterial pneumonic group and nonbacterial pneumonic group

	Group I bacterial group (*N*=33)	Group II nonbacterial group (*N*=31)
Procalcitonin (pg/ml)	469.7±86.3**	245.1±25.8
CRP (mg/l)	24.1±6.5	22.47±3.21

All data are expressed as mean±SD; CRP, C-reactive protein; **Highly significant difference than nonbacterial group at *P* value≤0.01.

Table 3 Correlation between procalcitonin and laboratory data in children with community-acquired pneumonia

Items	Procalcitonin in all cases (*N*=64)	
	r	*P*
CRP (mg/l)	0.4	0.03*
WBC (10^9 cell/l)	0.6	0.001*
Neutrophils (10^9 cell/l)	0.6	0.002*
Hb (g/dl)	–0.6	0.7

CRP, C-reactive protein; Hb, hemoglobin; WBC, white blood cells; *Significant difference using Pearson's correlation at $P<0.05$.

This study showed that there was a highly statistically significant difference between cases and control regarding PCT level, which was higher in cases, with *P* less than 0.001. These results could be explained by the fact that inflammation stimulates the increase in the secretion of PCT in serum and that CAP, marked by inflammatory and infectious injuries, stimulates overexpression of the CALCI gene, consequently increasing serum PCT. These findings go with Pierce *et al.* [15] and Engelmann *et al.* [30] who found a significantly higher level of PCT in a group of pneumonic children compared with normal ones [15,30].

Our results revealed also that PCT level of the group I (bacterial pneumonia) was significantly higher than those of group II (nonbacterial pneumonia) ($P<0.001$), whereas CRP levels were statistically indifferent between both pneumonic groups. PCT is more specific, being highly increased in bacterial infections but lower in nonbacterial infections, whereas CRP increases independent of infection type. This result matched findings of Meili *et al.* [16] and Esposito *et al.* [17] who stated that PCT but not CRP was found to be specific for bacterial infection [16,17]. On the contrary, Schuetz *et al.* [31] and Angello *et al.* [32] reported that CRP is better than PCT for assessment of CAP and that both biomarkers PCT and CRP are poor predictors for the etiology of pneumonia.

Conclusion

PCT can be used as an important diagnostic marker for CAP and for differentiation between its various etiological factors in children. Further studies are recommended for assessment of PCT in a larger study group and its prognostic value in the treatment of CAP in children.

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Conflicts of interest

There are no conflicts of interest.

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