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Utility of serum procalcitonin and C-reactive protein in severity assessment of community-acquired pneumonia in children

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ABSTRACT

Objectives: Although the importance of serum Procalcitonin (PCT) levels at diagnosis is well established in adult Community-Acquired Pneumonia (CAP), its use remains controversial in pediatric CAP. The aim of our study is to investigate the role of PCT and C-Reactive Protein (CRP) in the assessment of pediatric CAP severity defined by the extent of consolidation on chest X-rays and the presence of pleural effusion. In this particular setting, no clinical severity score is available at present and chest X-ray, although important for diagnosis confirmation, is not recommended as routine test.

Design and methods: The study involved 119 children admitted to the Department of Pediatric Infectious Disease for radiographically documented CAP aged 1 year to 14 years, without chronic diseases. Baseline PCT, CRP and routine laboratory tests were performed on admission.

Results: The median PCT (μg/L) and CRP (mg/L) were 0.11 (0.05–0.58) and 21.3 (4.2–48.1), respectively. PCT showed a good correlation with CRP, neutrophils and WBC ($r = 0.538$, $P < 0.001$; $r = 0.377$, $P < 0.001$; $r = 0.285$, P0.002, respectively). CRP, but not PCT, was associated with lobar consolidation ($P = 0.007$) and pleural effusion ($P = 0.002$). Logistic regression analysis revealed that only CRP was a predictor of lobar consolidation (OR: 1.078; 95% CI: 1.017–1.143; $P = 0.011$) and pleural effusion (OR: 1.076; 95% CI: 1.005–1.153; $P = 0.036$).

Conclusion: Our findings revealed that PCT is correlated to the main inflammatory markers in children with CAP. CRP, unlike PCT, is able to predict the extent of chest X-ray infiltration and ultimately the severity of the disease confirming its usefulness in the management of pneumonia.

1. Introduction

Community-acquired pneumonia (CAP) is a significant cause of respiratory morbidity and mortality in children. It can be defined as the presence of signs and symptoms of peumoniae due to an infection acquired in community, in previously healthy children without predisposing factors. CAP is one of the most common pediatric diseases, being the second cause of death in children in developing countries and one of the most frequent causes of hospitalization in industrialized countries with an incidence of 10–40/10,000 cases in the first 5 years of life and 11–16/10,000 cases aged between 5 and 14 years [1,2].

Streptococcus pneumoniae is the most common bacterial cause of pneumonia, even if a significant number of cases (30–50%) is due to a mixed bacterial/viral infection and in many cases the pathogen remains unknown [3,4].

Although the diagnosis of CAP is suggested by clinical features, such as fever and respiratory symptoms, chest radiography is the gold standard for confirming diagnosis and for severity assessment. However, current guidelines recommend that chest radiography should not be considered a routine investigation in children thought to have CAP [5]. So, it could be useful to identify serum markers that could predict pulmonary involvement otherwise identified by chest radiography in order to stratify children who should undergo further radiographic investigation. Moreover, while disease severity can easily be assessed in adults by a disease severity score, such as Pneumonia Severity Index (PSI) [6], it is not the case for children, for whom no clinical scoring system is yet available.

Procalcitonin (PCT), a member of the calcitonin gene-related family peptide-amylin-procalcitonin-adreno-medullin (CAPA) family, is a 116 amino acid protein encoded by *CALC-1* gene which is located on chromosome 11 [7]. The precursor pre-PCT is converted into the pro-hormone PCT which, in turn, is cleaved into calcitonin, known to be involved in calcium homeostasis. Normally, neuro-endocrine cells in the thyroid gland and the lung produce PCT at a very low rate so it is not detectable in serum [8]. The overexpression of *CALC1* gene is

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induced by inflammation and infections; in these conditions serum PCT increases and its synthesis and secretion become ubiquitous [9,10,11]. Furthermore, in animal models and in humans high levels of serum PCT have been associated with the severity of the condition, especially in adults [12].

Several studies investigated the role of Procalcitonin (PCT) in comparison with the known marker C-Reactive Protein (CRP) in children with CAP, but conflicting results have been obtained [13,14,15]. Although the significance of serum PCT levels at diagnosis is well established in adult systemic inflammation, its use has not been fully elucidated in pediatric CAP and particularly in its severity assessment. Currently, few evidences regarding the association of PCT with radiographic findings of CAP are present [16,17], so the aim of our study is to investigate the role of PCT in the evaluation of pediatric CAP severity in relation to clinical and radiographic findings.

2. Material and methods

2.1. Study group

From September 2013 to September 2014, 119 children admitted to the Department of Pediatric Infectious Diseases of ARNAS Di Cristina Hospital (Palermo) for CAP were included in this cross-sectional study. Ethical approval was obtained from the Ethics Committee of the hospital and an informed consent to use data retrospectively was obtained from all the children's parents. The inclusion criteria for participating in the study were: an age of >1 year and <14 years and a radiographically confirmed diagnosis of community-acquired pneumonia. A pediatric radiologist reviewed chest X-rays that were performed on admission. In particular, patients were classified for the presence and the extent of consolidation, interstitial infiltrates, and pleural effusion according to standard criteria [18]. Children were excluded if they had received antibiotics for more than 48 h before admission, if they were suffering from an underlying chronic respiratory disease, or if they were hospitalized for more than 48 h.

Demographic and clinical data were recorded on admission in an electronic chart together with the results of the laboratory tests and chest radiography. CAP was defined as the presence of signs and symptoms of pneumonia (fever and respiratory symptoms) and pulmonary condensation on chest radiography in a previously healthy child caused by an infection that was acquired outside the hospital [5].

2.2. Laboratory methods

White blood cell (WBC) count, serum CRP and PCT were determined in blood samples obtained on admission. WBC count was assessed within 3 h by flow cytometry (Beckman coulter, Pasadena, CA, USA), according to the manufacturer's instructions, while serum was stored at −20 °C until CRP and PCT analysis. Serum PCT was measured by an enzyme-linked fluorescence assay (miniVIDAS® BRAHMS PCT assay; Biomerieux, Lyon, France); the detection limit was less than 0.05 μg/L and the upper limit for normal serum PCT was 0.5 μg/L. Serum CRP was assayed by an immunoturbidimetric method using the ARCHITECT cSystems (MULTIGENT CRP Vario assay); the limit of quantitation was 0.2 mg/L and the upper limit for normal serum was 5 mg/L.

Identification of *S. pneumoniae* was performed by routine sputum culture and *Mycoplasma pneumoniae* by serologic investigation. Viral infections were diagnosed by molecular analysis on a nasal swab sample (xTAG Respiratory Viral Panel, Luminex). Etiology was classified as pneuomococcal, atypical (*M. pneumoniae*), viral, mixed (pneumococcal and viral), and unknown.

2.3. Statistical analysis

Categorical data were expressed as percentages and continuous variables as mean ± standard deviation when normally distributed. Not-normally distributed variables are expressed as median and interquartile range. Normality was assessed by Kolmogorov–Smirnov test. Differences in clinical, radiographic and laboratory findings across PCT or CRP quartiles were evaluated by analysis of variance, chi-square test or exact Fisher's test, when appropriate. Differences of PCT or CRP levels according to the presence of lobar consolidation, pleural effusion and BT > 38.5 °C were assessed by Mann–Whitney U test. Correlation analysis between CRP or PCT and percentage of neutrophils or WBC were performed by non parametric Spearman's test. Multivariate logistic regression was used to assess the association of CRP, O_2 saturation, age, respiratory rate, heart rate and fever with severity of pneumonia evaluated by the extent of chest X-ray infiltration (lobar vs segmental consolidation) and the presence of pleural effusion.

Statistical significance was considered for $P < 0.05$. Statistical analysis was performed by SPSS 15.0.

3. Results

Demographic features, clinical, laboratory and radiographic findings on admission are described in Table 1. Eleven percent had respiratory distress, defined according to Ranieri VM, et al. [19]. Segmental and lobar consolidation on chest radiography were detected in 76% and 17%, respectively. Etiology was pneumococcal in 9%, atypical in 5%, viral in 36%, mixed in 27% and unknown in 23%. The median PCT (μg/L) and CRP (mg/L) were 0.11 (0.05–0.58) and 21.3 (4.2–48.1), respectively.

Correlation analysis revealed a significant correlation between serum PCT levels and the main markers of inflammation, namely CRP,

Table 1
Demographic, clinical, laboratory and radiographic findings on admission.

Demographic features	
Patients, *n*	119
Males, *n* (%)	61 (51.3)
Age, yrs	5.25 ± 3.61
Clinical findings	
BT ≥ 38.5 °C, *n* (%)	77 (64.7)
Respiratory distress, *n* (%)	14 (11.76)
Rhonchi, *n* (%)	31 (26.05)
Wheeze, *n* (%)	100 (84.03)
Whistle, *n* (%)	34 (28.57)
RR, bpm	42.17 ± 15.37
HR, bpm	124.57 ± 30.48
SpO_2 <92%, *n* (%)	9 (7.6)
Dyspnoea, *n* (%)	14 (11)
Radiographic findings. n (%)	
Lobar consolidation	21 (17.64)
Segmental consolidation	91 (76.47)
Alveolar consolidation	8 (6.72)
Interstitial consolidation	8 (6.72)
Bilateral consolidation	25 (21)
Pleural effusion	13 (10.92)
Laboratory findings. mean value ± SD	
WBC, cell/mm^3	12.242 ± 5.837
Platelets, cell/mm^3	362.084 ± 350.000
Neutrophils, %	65.78 ± 68.09
Etiology, *n* (%)	
Pneumococcal	11 (9)
Atypical (*M. pneumoniae*)	6 (5)
Viral	43 (36)
Mixed	32 (27)
Unknown	27 (23)
PCT, μg/L	0.11 (0.05–0.58)
CRP, mg/L	21.3 (4.2–48.1)

BT, body temperature; HR, heart rate; RR, respiratory rate; SpO_2, peripheral oxygen saturation; WBC, white blood cell count; PCT, serum procalcitonin; CRP, serum C-reactive protein; SD, standard deviation.