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Clinical study of serum interleukin-6 in children with community-acquired pneumonia

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ABSTRACT

Background: Community-acquired pneumonia (CAP) is an important childhood killer. Excessive production of cytokines, including interleukin-6 (IL-6), might be associated with severe disease course but pediatric data is limited.

Aim: To assess value of IL-6 in predicting CAP severity in children.

Methods: A prospective study conducted on 73 children hospitalized for CAP and 15 healthy controls. Pneumonia severity was evaluated according to World Health Organization (WHO) classification, Respiratory Index of Severity Score (RISC), Predisposition, Insult, Response, Organ dysfunction modified (PIROm score), and Pediatric Respiratory Severity Score (PRESS). Serum IL-6 was measured within 24 h of admission. The primary outcome was occurrence of any pneumonia complications or death within 30 days.

Results: IL-6 was significantly higher among patients compared with controls. Unlike CRP, IL-6 was significantly higher among children with severe pneumonia as determined by WHO, PRESS, and RISC ($p = 0.001$ *for all*). IL-6 was significantly higher among children with PICU admission, mechanical ventilation, shock ($p = 0.001$ *for all*), hypoxia ($p < 0.001$), and lobar consolidation ($p = 0.042$). IL-6 had positive correlations with PRESS (r_s=0.8, $P < 0.001$), RISC (r_s=0.6, $p < 0.001$), and PIROm (r_s=0.59, $p < 0.001$) while a negative correlation was found with Oxygen saturation [$r = -0.61$, $p = 0.001$]. IL-6 was not significantly correlated with CRP. Receiver Operating Characteristic curve (ROC) analysis revealed large area under the curve (AUC) of IL-6 for prediction of severe pneumonia as classified by WHO, PRESS, and RISC (*AUC = 0.95, 0.94, and 0.89 respectively*).

Conclusion: IL-6 appears to be valuable for assessment of CAP severity in children compared with conventional biomarkers.

Introduction

Community-acquired pneumonia (CAP) is a common childhood illness associated with significant morbidity and mortality worldwide.[1] In 2016, pneumonia ranked second among the causes of mortality in children under 5 years, accounting for 16% of deaths.[2]

Physicians need to have tools that enable them to know which patient is having severe pneumonia and more likely to experience an adverse outcome so that closer monitoring or referral to a higher center would be made.

Attempts have been made to assess pediatric pneumonia severity based on simple clinical criteria. The most widely used is the WHO classification[3] but in recent years three pediatric pneumonia mortality predictive scores have been developed, namely the Respiratory Index of Severity Score (RISC);[4] the Predisposition, Insult, Response, Organ dysfunction modified (PIROm);[5] and the Pediatric Respiratory Severity Score (PRESS).[6]

For many clinicians, biomarkers are attractive tools for evaluation of pneumonia severity by virtue of their simplicity. These include C-reactive protein (CRP), Procalcitonin, and many cytokines.[7–9] In the early stages of pneumonia, alveolar macrophages produce proinflammatory cytokines, in particular interleukin-6 (IL-6) and tumor necrosis factor-α(TNF-α), which attract polymorphonuclear leucocytes for local defense against bacteria with subsequent rise of the systemic and bronchoalveolar levels of these cytokines.[10,11]

Il-6 is a pleiotropic pro-inflammatory cytokine produced by different kinds of cells, including Lymphocytes and monocytes. IL-6

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regulates host defense mechanisms, acute phase response, inflammation, and hematopoiesis. It also induces production of acute phase proteins, like C-reactive protein (CRP), amyloid protein, haptoglobin, and hemopexin.[12,13].

It is conceivable that the inflammatory reaction is essential for eliminating the respiratory pathogens but an exaggerated inflammatory response may result in lung injury and poor outcome.[14].

Previous studies of IL-6 in CAP have been conducted mostly in adult,[15] rather than pediatric, patients. The aim of the present study was to examine the value of serum IL-6 level in predicting CAP severity and outcome in children particularly in relation to the recently developed pneumonia severity scores.

Materials and methods

Study design and subjects

In this prospective observational study, 73 children with CAP requiring hospitalization were enrolled. The participants were consecutively recruited from Menoufia University Hospital, Menoufia, Egypt from Jaunary 2016 to July 2017. In addition, a control group, consisting of 15 healthy children, was recruited.

The sample size was calculated using Epicalc2000 software, based on a previous study and the following assumptions: α=0.05 and power = 80%. The study protocol was approved by the Menoufia Faculty of Medicine Committee for Medical Research Ethics.

Any child aged 1 month to 18 years with CAP was eligible for inclusion in the study after obtaining a written informed consent from the parents. CAP was defined according to the British Thoracic society guidelines[16] as the presence, in a previously healthy child, of signs and symptoms suggesting lower respiratory tract infection that has been acquired outside the hospital. This was confirmed by the radiological finding of a consolidation. The exclusion criteria included age under 1 month or older than 18 years, cough for greater than 14 days, suspected tuberculosis, underlying chronic respiratory disease, persistent asthma, severe malnutrition, neurologic disease, immunodeficiency, immunosuppressive treatment, prior inpatient admission within 30 days of CAP onset, congenital heart disease, and co-existence of another infection with CAP. Patients with a diagnosis of bronchiolitis were also excluded from the study. Similarly, patients were excluded in the absence of radiographic evidence of consolidation.

For each patient, the vital signs and oxygen saturation were monitored. Hypoxia was defined as a sustained peripheral Oxygen saturation (SPO2) <94%[17]. The diagnostic workup included, besides routine investigations, chest x ray, blood gas analysis, complete blood count (CBC), and blood culture. In addition, IL-6 and CRP were measured for each patient within 24 h of hospital admission. Other investigations, like analysis of pleural fluid and chest Computed Tomography (CT) scan, were requested when clinically indicated.

Pneumonia severity was evaluated at admission by several systems which include the revised WHO guidelines 2014 (for children from 2 months to 5 years),[3] PRESS score (up to 15 years of age),[6] RISC score (under 24 months of age),[4] and PIROm core (up to 15 years of age).[5]

According to the revised WHO guidelines, the presence of tachypnea and/or chest indrawing indicates a diagnosis of pneumonia while the presence of general danger signs (persistent vomiting, lethargy or unconscious, seizures, severe malnutrition, stridor in a calm child, or not able to drink) indicates a diagnosis of severe pneumonia. According to PRESS, pneumonia is deemed severe if the score is 4–5 while a RISC score of 3 or more indicates a poor prognosis. On the other hand, a PIROm score of 5–6 indicates severe pneumonia and a score of 7–10 indicates very severe pneumonia.

Systemic inflammatory response syndrome (SIRS) was diagnosed if a patient fulfilled 2 of the 4 criteria specified by the international pediatric sepsis consensus conference.[18].

Criteria for pediatric intensive care unit (PICU) admission included (1) A need for invasive or non-invasive mechanical ventilation (2) Impending respiratory failure (3) SPO2 < 92% on inspired Oxygen $\geq$ 50% (4) Signs of shock (5) Altered mental status.[19]

The primary outcome measure was the development of any indicator of pneumonia severity like sepsis, shock, respiratory failure, or death within 30 days.

For the control group, history, clinical examination, and routine laboratory investigations were performed besides serum IL-6 measurement.

Laboratory methods

Assay of serum IL-6 was performed within 24 h of hospital admission. In brief, 2 ml venous blood samples were collected from every participant into a plain vacutainer tube and left to clot at room temperature then centrifuged at 3000 rpm for 20 min. Separated sera were kept frozen at −20 °C until analysis. Hemolyzed sera were excluded. Serum IL-6 concentration was determined by enzyme linked immunosorbent assay (ELISA) kit (Shanghai Sunred Biological Technology Co., Ltd, Shanghai, China, Catalogue No. 201-12-0091). The kit employs a double-antibody sandwich ELISA technique. The assay was carried out according to the manufacturer's instructions.

Quantitative CRP was measured by BIOTECNICA BT 3500 FULL AUTOMATED CHEMISTRY ANALYZER, Rome, Italy. A CRP value $\geq$ 6 mg/dL was considered positive.

Statistical analysis

Quantitative data are shown as mean ± standard deviation (SD) or median and range while qualitative data are expressed as frequency and percent. Chi-square test was used to assess the relationship between qualitative variables. Fisher exact test was used for 2×2 qualitative variables when more than 25% of the cells have expected frequencies <5. Student *t*-test was used to compare mean and SD of 2 sets of quantitative normally distributed data, while Mann-Whitney test was used when quantitative data was not normally distributed. Spearman's correlation was used to study the correlations between variables when the data was not normally distributed. The Receiver Operating Characteristic (ROC) curve was used to detect the best cutoff levels of IL-6 and other variables. The larger the area under the curve (AUC) associated with a variable, the greater its predictive power. An AUC $\leq$ 0.5, indicates failure of the test. Univariate logistic regression analysis was used to test the association of IL-6 and other variables with severe pneumonia. Variables which showed significant associations in the univariate analysis were entered in a multivariate logistic regression analysis to identify the independent risk factors of severe pneumonia. A P-value was considered statistically significant when it was <0.05. Statistical analysis was performed using SPSS (Statistical Package for Social Science, version 20; Inc., Chicago. IL).

Results

Characteristics of the study population

The patient group consisted of 73 children with CAP. Their main demographic, clinical, and laboratory characteristics are shown in Table 1.

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