Role of Procalcitonin in Pediatric Patients with Pneumonia

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Abstract

Background: The alveoli, the tiniest air sacs in the lungs, are particularly vulnerable to damage from the inflammation caused by pneumonia. For young children in the poor world, childhood community-acquired pneumonia (CAP) is the leading cause of death. CAP is an infection of the lower respiratory tract that spreads easily from person to person. The 116-amino-acid peptide procalcitonin (PCT) is the calcitonin precursor and has no known hormonal property. The levels of PCT in the serum of healthy people are either very low or undetectable. The inflammatory biomarker procalcitonin is of great importance. The CALC-I gene on chromosome 11 codes for a protein that serves as a precursor to calcitonin, a hormone that controls calcium levels in the body. Serum PCT levels may rise by a factor of 1000 due to induction by inflammatory cytokines and bacterial endotoxin in lung, liver, kidney, and adipose tissue during bacterial infections. In 2005, the FDA of the United States authorized PCT for use as a diagnostic tool for sepsis.

Objectives: Assessing the use of serum procalcitonin as a diagnostic and prognostic marker in children with pneumonia.

Conclusion: procalcitonin should be considered as a useful diagnostic and prognostic biomarker in pediatric patients with pneumonia. It may have some utility in predicting the most severe outcomes.

Keywords: Childhood community-acquired pneumonia (CAP), Procalcitonin (PCT), CRP

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Introduction

To infect the lung parenchyma is considered pneumonia. Healthcare providers should not treat pneumonia as a single illness but rather as a range of syndromes caused by different organisms and resulting in different clinical presentations and outcomes.**(Prina et al., 2015)**

Throughout the globe, pneumonia is the top infectious killer of children. There are an estimated 120 million instances of pneumonia among children less than 5 years old each year across the globe, with an estimated 1.3 million fatalities. Worldwide, severe pneumonia has an estimated case fatality ratio of 8.7 percent. The youngest age bracket has the highest fatality rate. In fact, 81 percent of pneumonia-related fatalities occur in children less than 2 years old. Since the 1980s, when respiratory tract diseases killed 4-5 million children annually, these numbers have greatly improved.**(Tramper-Stranders, 2018)**

Precursor of Calcitonin is a hormone called procalcitonin. The human calc-1 gene on chromosome 11 is the locus of development. Pre-procalcitonin is the first translation product when CT-DNA is translated into mRNA; PCT is then modified in a series of processes. **(Le moullee et al., 1984)**

Some research has shown that PCT does not rise in viral infections and that after treatment with antibiotics, PCT levels in the blood drop. The specificity of existing inflammatory biomarkers like C-reactive protein (CRP) is inadequate for distinguishing bacterial from non-bacterial illnesses. PCT tests with a specificity of 79% have now been developed and used to more reliably establish whether a particular bacterial species is the root cause of a patient's systemic inflammatory response.**(Lippi & Sanchis-Gomar., 2017)**

Epidemiology of childhood pneumonia:

Differences in risk factor prevalence and infectious agent types account for most of the global variation in the epidemiology of pediatric pneumonia. The continents of Southeast Asia and Africa have the highest rates of pneumonia. Significantly, although just 19% of the world's under-5 population lives in sub-Saharan Africa, the region accounts for 43% of pneumonia mortality. Over the last decade, the incidence has dropped by 25% in LMIC, to a rate of 0.22 incidents per kid year.**(Tramper-Stranders, 2018)**

Viruses account for up to 90% of all cases of pneumonia in infants and young children under the age of two. Respiratory syncytial virus, parainfluenza 1, 2, and 3, influenza A and B viruses, adenoviruses, rhinoviruses, and, less often, herpes simplex virus and enteroviruses have all been linked to this condition**(le Roux & Zar, 2017)**

Although pneumonia becomes less common as people age, bacterial infections including Streptococcus pneumoniae, Mycoplasma pneumoniae, and Chlamydia pneumoniae become more common.**(Naito et al., 2016)**

Procalcitonin (biochemistry, action):

In 1984, Le Moullee et al. originally described the 116-amino-acid residue known as PCT; nevertheless, its diagnostic importance was not recognized until 1993. For early diagnosis of (systemic) bacterial infections, procalcitonin (PCT) has emerged as a potential novel biomarker in recent years.**(Le Moullec et al., 1984)**

In 1993, Assicot et al. confirmed a connection between elevated PCT levels in the blood and the presence of

bacterial illness or sepsis in patients (e.g., positive blood cultures).**(Assicot et al., 1993)**

Concentrations of PCT rise between 3 and 4 hours, peak between 6 and 24 hours, and then level down**. (Groothius et al., 2000)**.

Half-life estimates for PCT range from 25-30 hours, due to its degradation by a specific protease. **(Carrol et al., 2002).**

The concentration of serum PCT rapidly decreases throughout the course of antibiotic medication, making repeated testing a useful method for monitoring the patient's response to treatment. (**Reidel, 2012**). Systemic inflammatory response syndrome is described by a number of medical characteristics, but PCT was shown to have greater predictive value for microbial infections and death (abnormal temperature, tachycardia, tachypnea, and abnormal white blood cell counts). **(Bossink et al., 1999)**An elevated PCT concentration over time is indicative of an ongoing infection.

Twenty-five studies showed that procalcitonin for bacterial pneumonia had an overall sensitivity of 0.64, specificity of 0.72, positive likelihood ratio of 2.3 and negative likelihood ratio of 0.50**. (Po-yang T et al., 2020)**

Evidence of association between procalcitonin and pneumonia:

Procalcitonin's clinical relevance stems from its predictive value, which gives doctors insight into the relationship between illness severity and high PCT serum levels, which is particularly true for septic patients.**(Liu et al., 2015)**

Lee et al. reported that Lobar pneumonia may be diagnosed using a serum PCT level, which is superior to CRP and ESR in distinguishing between bacterial and viral illnesses. Based on their analysis of the literature, they concluded that PCT may be used to enhance clinical information to help evaluate whether or not the illness is likely bacterial in origin. **(Lee et al., 2012)**

According to **El-Shafey et al**. Serum levels of CRP and PCT were found to be considerably elevated after analysis of findings from 40 children with CAP. Using a cutoff value of 24 (mg/dl), CRP was 100% sensitive and 70% specific, while PCT was 67% sensitive and 97.5% specific when used as a cutoff value of 530 (pg/ml). **(El-shafey et al., 2015)**

In recent case-control study **Rashed et al** this research involved testing on 90 babies and children ranging in age from 2 months to 5 years (60 months). Group I consisted of sixty in patients with CAP, while group II consisted of thirty healthy controls of similar age and gender who were seen in the outpatient clinics of the same hospitals for regular treatment. WBCs count, neutrophil percentage, CRP level, and procalcitonin concentration were all found to be significantly higher in the patients group compared to the controls (13.43.4 vs. 8.31.7; 54.515.4 vs. 37.26.7; 57.530.1 vs. 5.75.6; 0.50.47 vs. 0.070.04). The existence of CAP in patients may be predicted with 83.3%, 85%, 86.7% sensitivity and 76.6%, 100%, 96.7% specificity using the AUROC test for white blood cell count, C-reactive protein, and procalcitonin, respectively. (**Rashed et al., 2020**)

Abu Elkhashab et al. in their analysis of 15 patients where HAP was highly suspected. Clinical criteria of a lung infection and the presence of radiological abnormalities are necessary to make a diagnosis of HAP. At admission and again 2 weeks later, we took a full blood count, cultured and tested sputum, measured ESR, CRP, and PCT, and performed a pulmonary function test. They discovered that a Serum PCT level of more than 0.5 ng/ml was clinically significant for the diagnosis of HAP.

After two weeks, it has dropped to 1.0 1.91 ng/ml from the 2.72 1.72 ng/ml seen upon admission. Antibiotic treatment resulted in a statistically significant drop in serum procalcitonin levels (P = 0.002). Furthermore, patients with poor result had a PCT that was between 2.11 and 6.0 ng/ml, while those with a good outcome had a PCT that was 1.76 ng/ml, on average. **(Abu Elkhashab et al., 2013)**

Similarly **Fonseca et al.** reviewed the correlation between pneumonia and procalcitonin concentration. Among the infants (12-29 months old), 60% were male. Many different types of infections, including those caused by viruses (49.5%), common bacteria (38%), atypical bacteria (12.5%), and perhaps pneumococcal bacteria (26%), were identified. Eighty-four percent of the kids were afebrile after 48 hours of therapy. The median blood procalcitonin (ng/ml) level on admission was greater in children who remained febrile after 48 hours of therapy (2.1[0.8-3.7] vs. 0.6[0.1-2.2]; P = 0.025) compared to those who recovered quickly. Pneumococcal infections were more prevalent in the children who responded slowly to treatment (71% vs. 17%; P 0.001). Children with pneumococcal pneumonia had greater procalcitonin concentrations at admission (2[0.7-4.2] vs. 0.5[0.08-2.1]; P = 0.002) than children with non-pneumococcal pneumonia. Serum procalcitonin levels below 0.25 ng/ml demonstrated a strong negative predictive value (93% [95%CI: 80%-99%]) for pneumococcal infection, as seen by the ROC curve. All children admitted with a procalcitonin level above 0.25 ng/ml on entry were still experiencing fever after 48 hours of therapy. Most children in underdeveloped countries who are diagnosed with pneumonia and treated with antibiotics will recover to afebrile status within 48 hours. **(Fonseca et al., 2017)**

Jeong et al. conducted the study on 147 kid volunteers. Mycoplasma-related pneumonia could only be diagnosed after many rounds of IgM antibody testing and/or polymerase chain reaction. Clinical illness severity was correlated with CRP, PCT, LDH, and WBC levels. Using multivariate logistic regression analysis, they compared the middle five quintiles of PCT levels to the bottom quintile to determine the odds ratio for protracted fever (>3 days after admission) and hospital stay (> 6 days). Children whose fever persisted for more than three days after arrival and whose hospital stays were less than six days had higher serum PCT and CRP values. Increased likelihood of persistent fever and/or inpatient care was seen at the highest PCT levels compared to those at the lowest. In conclusion, children with Mycoplasma pneumonia who had elevated serum PCT and CRP levels on the day of admission were more likely to have a protracted course of fever and hospitalization. (**Jeong et al., 2017)**

Nobre and Borges shown that research assessing the predictive usefulness of early procalcitonin levels in patients with community-acquired pneumonia have produced more consistent and practically relevant findings; in this example, low procalcitonin levels indicate those individuals with a low chance of bad outcomes. **(Nobre and Borges, 2016)**

TSENG et al. examined the predictive power of PCT on Twenty-two patients with CAP-related ARDS were participated in the trial, and by day 14, 17 (77.3%) were still alive whereas 5 (22.7%) had passed away. The plasma PCT was lower at baseline (9.83 3.54 vs. 106.70 67.86, P = 0.004), 24 hours later (10.51 5.39 vs. 81.32 57.68, P = 0.014), and 72 hours later (2.03 0.76

vs. 19.57 6.67, P = 0.005) among the survivors compared to the non-survivors. Patients with ARDS due to severe CAP had a higher risk of dying if their PCT was evaluated within 72 hours after ARDS onset. **(TSENG et al., 2007**)

Trippella et al. revealed in a Medline comprehensive literature review spanning 2007-2017. Twelve studies were included in the meta-analysis evaluating PCT's diagnostic efficacy, examining data from 7,260 children with unexplained fever. A total of four meta-analyses were conducted to calculate the sensitivity, specificity, diagnostic odds ratio, and summary receiver operating characteristic curve of PCT for detecting severe bacterial infection and invasive bacterial infection at two different thresholds. The sensitivity and specificity of PCT for detecting invasive bacterial infection were 0.82 and 0.86 at a threshold of 0.5 ng/mL, respectively, but declined to 0.61 and 0.94 at a threshold of 2 ng/mL. With a sensitivity of 55% and a specificity of 85% at a threshold of 0.5 ng/mL and a sensitivity of 30% and a specificity of 95% at a threshold of 2 ng/mL, respectively, PCT performed poorly in the identification of severe bacterial infection**. (Trippella et al., 2017)**

Jacobs et al. Seventy-five individuals were enrolled in the study, and 28 (37%) had a severe bacterial infection (Median PCT = 6.48 ng/mL), compared with 47 (63%) in the non infection group (median PCT = 0.23 ng/mL, P .0001). Accurate prediction of severe bacterial infection was achieved using PCT (AUC-ROC = 0.83, 95% CI 0.74-0.93; P .0001), and a PCT 1.28 ng/mL was the best threshold for detecting Sever bacterial infection, with a positive predictive value of 76.7% and a negative predictive value of 88.9%. Predictive challenge testing (PCT) was able to accurately predict severe bacterial infection in a diverse PICU group, suggesting it may be effective for reducing unnecessary antibiotic usage. **(Jacobs et al., 2017)**

Al-Zahrani et al concluded that PCT had a greater diagnostic utility than hsCRP and IL-6, and the combination of markers (hsCRP, IL-6 and PCT) was better than a single marker to diagnose neonatal sepsis.

Table 1. Diagnostic value of procalcitonin in patients with pneumonia:

Study	Study design	Participants	Procalcitonin level	Results
Rashed et al., 2020	Case-control study	90 infants and children aged from 2 months to 5 years (60 months)	From the same serum sample of CRP, 50 µl of serum was obtained for PCT analysis. Analysis was done by commercial kits (NOVA ELISA kits) using sandwich-ELISA method	Diagnosis of CAP in infants and children relies heavily on evaluation of white blood cell count, serum CRP, and serum procalcitonin levels.
Jacobes et al., 2017	Retrospective cohort study	Seventy-five patients	The concentration of PCT was determined with the use of the BRAHMS test.	PCT has been shown to be an accurate predictor of bacterial infection, with a cutoff of 1.28 ng/mL being the optimal level at which to identify severe bacterial infection.
Abu Elkhashab et al., 2017	Cross-sectional study	15 patients	Patients' serum procalcitonin levels were measured upon admission and again after 2 weeks of treatment.	In cases of HAP, procalcitonin served as a reliable etiological and predictive marker. In comparison to other biomarkers, PCT offers the highest level of specificity and many additional benefits.

Table 2. Prognostic value of procalcitonin in patients with pneumonia:

Study	Study design	Participants	Procacitonin level	Results
Welange W et al., 2020	Cohort study	264 pediatric patients	ELISA was used to measure procalcitonin (PCT) in the serum.	PCT proved to be a useful biomarker for the diagnosis and treatment of HAP in children, and hence should be included into treatment algorithms for this condition.
Angello L et al., 2015	Cross sectional study	119 children , aged from 1 - 14 years	Serum CRP and PCT were determined in blood samples obtained on admission**.** Serum PCT was measured by ELISA**.**	The primary inflammatory indicators in CAP children are associated with PCT.
Tseng et al., 2008	Cohort study	22 patients	At enrollment, 24 and 72 hours later, the plasma PCT was evaluated by ELISA.	PCT analyzed within 72 hours of the onset of ARDS predicted mortality of patients with ARDS caused by severe CAP**.**
Fonseca et al., 2017	A prospective cohort study	89 patients, 12–29 months.	Upon admission, blood samples were taken and analyzed for PCT levels using an immunoluminometric assay.	Serum procalcitonin < 0.25 ng/ml predicted rapid clinical response and nonpneumococcal etiology
Jeonge et al., 2018	prospective cross-sectional study	147 children	A blood sample was taken to check the PCT concentration. The BRAHMS PCT kit was used for the electrochemiluminescence immunoassay.	Hospitalization and/or protracted fever were substantially more likely in the highest PCT quintile compared to the lowest PCT quintile.

Conclusion

Procalcitonin was shown to be a good etiological and prognostic biomarker in children with pneumonia, according to the evidence that was available. It may be included into treatment algorithms for pediatric patients with HAP.

Conflict of Interest: No conflict of interest.

List of abbreviations

ARDS: acute respiratory distress syndrome
AUROC: area under ROC curve
CAP: childhood community acquired pneumonia
CRP: C reactive protein
ESR: erythrocyte sedimentation rate
FDA: food & drug administration
HAP: hospital acquired pneumonia
LDH: lactate dehydrogenase
LMIC: low & middle income country
MPP: mycoplasma pneumonia
PCT: procalcitonin
WBCS: white blood cell count

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