Use of Procalcitonin for Identification of Cobacterial Pneumonia in Pediatric Patients

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OBJECTIVE To evaluate the utility of procalcitonin (PCT) in identifying cobacterial pneumonia in pediatric patients with known viral respiratory infection.

METHODS A retrospective cohort study was conducted in a stand-alone children's hospital during 2 time periods (period 1: October 1, 2014, to March 31, 2015; period 2: October 1, 2015, to March 31, 2016). Patients admitted with any upper respiratory tract infection were included. Exclusion criteria included any condition compromising lung function, age <30 days or >18 years, or lack of PCT (period 2). PCT values of <0.5 ng/mL were considered normal, whereas values of >1.5 ng/mL were used to identify cobacterial pneumonia. Receiver-operator characteristic curves were used with multiple logistic regression to evaluate patient variables.

RESULTS Of the 374 pediatric patients evaluated, 64% were classified as having viral pneumonia and 23% as having cobacterial pneumonia across both study time periods. Non-significant predictors of cobacterial pneumonia included temperature ($p = 0.0795$, $p = 0.1466$), WBC count ($p = 0.8774$, $p = 0.6675$), and C-reactive protein ($p = 0.7115$, $p = 0.3835$). Median initial PCT for patients with viral pneumonia was 0.14 ng/mL compared with 1.41 ng/mL in patients with cobacterial pneumonia; median second PCTs were 0.26 ng/mL (viral pneumonia) and 4.55 ng/mL (cobacterial pneumonia). Patients with an elevated PCT had 17.5 times (95% CI, 5.2, 59.1) greater odds of having a cobacterial pneumonia.

CONCLUSIONS PCT was found to be strongly associated with cobacterial pneumonia with an underlying viral etiology. Temperature, WBC, and C-reactive protein failed to be significant predictors in differentiating between viral and cobacterial pneumonia.

ABBREVIATIONS CRP, C-reactive protein; PCT, procalcitonin; PICU, pediatric intensive care unit; WBC, white blood cell

KEYWORDS biomarkers; communicable diseases; pediatrics; procalcitonin

J Pediatr Pharmacol Ther 2020;25(5):445–450

DOI: 10.5863/1551-6776-25.5.445

Introduction

Pneumonia is the leading cause of hospitalization in pediatric patients in the United States and accounted for almost \$1 billion in medical expenditures in 2009. The most common cause of pneumonia among pediatric patients is respiratory viruses, followed by bacterial infections.¹ The reported cobacterial pneumonia infection rate in pediatric patients with an underlying viral respiratory infection is estimated to be 23% to 35%.^{2,3} However, there remains a lack of reliable clinical, laboratory, or radiologic methods to definitively diagnose a cobacterial pneumonia in pediatric patients without the use of invasive measures. The lack of reliable non-invasive tests for pneumonia-causing bacteria, such as sputum cultures in pediatric patients, often leads to empiric antibiotic initiation and the overuse of antibiotics. Recent literature suggests that procalcitonin (PCT) can be useful in predicting cobacterial pneumonia in

pediatric patients with a concurrent viral pneumonia.^{4–6}

Procalcitonin was first described in the 1980s,⁷ and during the past several decades there have been numerous studies conducted to best identify its use. This marker is the precursor of calcitonin and is produced in the neuroendocrine cells of the thyroid and lungs under normal homeostasis.^{8,9} During a serious bacterial infection, transcription of the PCT gene is upregulated, causing a several thousand-fold increase in the amount of PCT produced in the body.^{8–10} Minor infections, including acute otitis media and cystitis, have not been shown to increase PCT serum levels.¹¹ There are situations in which PCT can be falsely elevated, including burns, trauma, and malignancies, such as small cell lung cancer.⁸ Serial PCT values have a high positive predictive value for an infection and have the most clinical utility. Upon initiation of treatment with antibiotics, a fall in PCT within 24 hours has been associated with favorable outcomes.^{8,12} As a result, PCT has been strongly

Table 1. Baseline Characteristics for Period 1 and Period 2 (N = 374)

	Period 1 (n = 299)	Period 2 (n = 75)
Age, mean (IQR)	2.4 yr (4 days, 17 yr)	2.2 yr (10 days, 17 yr)
Female, n (%)	130 (43)	35 (47)
Days of illness on presentation, median (IQR)	4 (3, 6)	4 (2, 5)
Temperature in emergency dept, median (IQR), °C	37.4 (36.9, 38)	37.4 (37.0, 37.7)
Length of stay, median (IQR), days	4 (3, 6)	6 (4, 10)

predictive of cobacterial infections and may decrease unnecessary antibiotic use.⁴⁻⁶ The primary objective of this study was to determine whether PCT can serve as a biomarker to identify cobacterial pneumonia in pediatric patients with a known viral respiratory infection.

Materials and Methods

This was a single-center, retrospective, cohort study of pediatric patients admitted for any upper respiratory tract illness during 2 time periods at a midsized, stand-alone children's hospital located in the Midwestern United States. To evaluate the effect of PCT, a preanalysis and a postanalysis were conducted. Baseline data (period 1) were collected from October 1, 2014, to March 31, 2015, prior to the hospital's initial use of PCT. Staff education regarding the use of PCT was conducted prior to the start of the viral respiratory season in October 2015. Postanalysis data (period 2) were collected from October 1, 2015, to March 31, 2016. Data were collected from the patient's electronic medical record using Epic (Epic Systems Corporation, Verona, WI).

Patients were included if they were between the ages of 31 days and ≤18 years, admitted for any upper respiratory tract illness, and had at least 1 PCT value obtained during their admission (period 2 only). These patients were identified using International Classification of Diseases (ICD-9) and/or Diagnosis Related Group (DRG) codes upon discharge. Exclusion criteria were met if the patient had any condition that compromised lung function (e.g., cystic fibrosis, chronic lung disease, immunosuppressed state, muscular dystrophy, or other chromosomal abnormalities affecting lung function),

malignancy, a recent surgery or trauma, or resided in a long-term care facility.

Patients were categorized into 1 of 3 patient groups: viral, bacterial, or cobacterial. Initial patient classification was based on the clinical diagnosis provided by the attending physician, and final classification was done based on the results of viral respiratory FilmArray (i.e., Biofire Diagnostics FilmArray multiplex PCR molecular testing, Salt Lake City, UT) and/or sputum culture(s), if available. If a viral respiratory FilmArray or sputum culture was not available, then classification was based on the initial classification from the attending physician's clinical diagnosis. A PCT value of <0.5 ng/mL was considered normal, whereas a cutoff value of >1.5 ng/mL was considered to be elevated and was used to classify the possible presence of a cobacterial pneumonia. For the purpose of this study, patients were included regardless of the antibiotic that was used (if any). Broad-spectrum antibiotics were defined as any antibiotic other than ampicillin or amoxicillin.

Descriptive statistics were conducted to determine the percentage of patients treated for viral, bacterial, or cobacterial pneumonia and to review baseline characteristics (Table 1). Patient variables were compared between these infection classifications using Kruskal-Wallis tests or χ^2 tests. The predictive value of patient variables on viral or cobacterial classifications, dependent variable, was determined using a multiple logistic regression model and presented using receiver-operator characteristic (ROC) curves. Variable selection (i.e., temperature, WBC, and PCT) for modeling was based on study clinician experience and parsimony.

Table 2. Comparison of Patient Data Values for Period 1 (n = 299)

Patient Variable	Viral	Bacterial	Cobacterial	p value*
Patients, n (%)	197 (66)	43 (14)	59 (20)	
Temperature, median (IQR), °C	37.4 (36.9, 37.9)	37.7 (37.0, 38.6)	37.4 (37.0, 38.1)	0.0795
WBC count, median (IQR), $\times 10^3/\text{mm}^3$	10.9 (8.6, 15.0)	11.0 (7.8, 15.1)	10.5 (8.4, 13.9)	0.8774
CRP, median (IQR), mg/dL	2.9 (0.7, 4.5)	2.8 (1.0, 3.8)	1.6 (0.5, 4.7)	0.7115
Patients with chest x-ray, n (%)	124 (63)	43 (100)	58 (98)	<0.0001
Viral FilmArray, n (%)	151 (76)	33 (76)	51 (85)	0.3490
Sputum culture, n (%)	4 (2)	0 (0)	18 (30)	<0.0001

CRP, C-reactive protein

* Overall omnibus: Kruskal-Wallis or χ^2 test.

Figure 1. Receiver operating characteristic curve (ROCC) for co-bacterial infection classification in patients within Period 1 (n = 120).

ROC, receiver-operator characteristic.

Figure presents the sensitivity and 1 – specificity values for the reviewed variables of white blood cell count (red; ROCC area: 0.53) and temperature (blue; ROCC area: 0.51) along with the 45-degree line of non-discrimination.

Figure 2. Receiver operating characteristic curve (ROCC) for co-bacterial infection classification in patients within Period 2 (n = 63).

ROC, receiver-operator characteristic.

Figure presents the sensitivity and 1 – specificity values for the reviewed variables of white blood cell count (red; ROCC area: 0.46), temperature (blue; ROCC area: 0.64), and procalcitonin (purple; ROCC area: 0.94) along with the 45-degree line of non-discrimination.

All analyses were based on a 0.05 significance level, 2-sided, and conducted with SAS 9.4M6 (SAS Institute, Cary, NC).

Results

In period 1 of the study there were 299 patient records evaluated (Table 1). Most (66%) were classified as viral infections (bacterial, 14%; cobacterial, 20%). When comparing commonly used laboratory values (temperature, WBC, or C-reactive protein [CRP]) among infection groups, data illustrated a lack of utility in distinguishing between cobacterial pneumonia and viral pneumonia (Table 2). Of note, patients with a diagnosis of viral pneumonia were less likely to have a chest x-ray ordered compared with patients with a diagnosis of a bacterial or cobacterial pneumonia, whereas a contrasting difference was not found in the incidence of obtaining a viral respiratory FilmArray (Table 2).

When comparing the antibiotic spectrum among patient groups in period 1, approximately 52% of patients with a diagnosis of cobacterial pneumonia received broad-spectrum antibiotics, compared with 26% with viral pneumonia and 42% with bacterial pneumonia. Graphical representation of the logistic model is presented as Figure 1 and controlled for WBC and temperature. It was revealed from the graph that of the 2 incorporated covariates, neither WBC (accuracy, 0.53; 95% CI, 0.42, 0.63) nor temperature (accuracy, 0.51; 95% CI, 0.40, 0.62) had high sensitivity or specificity values with regard to classification of cobacterial

pneumonia. Of note, there were not enough patients with CRP values in the sample for it to be included in the model or graphed, because about 78% (n = 236) of the patients did not have a CRP obtained.

In period 2, a total of 75 patients were evaluated. Most (57%) received a diagnosis of viral pneumonia (bacterial, 7%; cobacterial, 36%; Table 3). None of the commonly used laboratory markers (temperature, WBC, or CRP) were found to be different between the 3 patient groups. The PCT values were significantly different between patients with a diagnosis of viral pneumonia and those with a cobacterial pneumonia diagnosis (Table 3). There was also a difference in the likelihood of patients having a chest x-ray obtained in period 2 (Table 3). The median second PCT value for patients with a cobacterial pneumonia was 4.55 ng/mL (0.61–10.42 ng/mL) compared with 0.26 ng/mL (0.14–0.80 ng/mL) for those with a viral pneumonia.

Approximately 55% of the patients with a clinical diagnosis of a viral pneumonia received broad-spectrum antibiotics, compared with 89% of patients with a clinical diagnosis of a cobacterial pneumonia. Graphical representation of period 2 is presented in Figure 2, which controlled for WBC, temperature, and PCT, when modeling cobacterial pneumonia status. Patients with an elevated PCT had 17.5 (95% CI, 5.2, 59.1) times greater odds of having a cobacterial pneumonia than patients with a normal PCT value. Additionally, PCT had high sensitivity and specificity values for the presence of a cobacterial pneumonia (Figure 2).

Table 3. Comparison of Patient Data Values for Period 2 (n = 75)

Patient Variable	Viral	Bacterial	Cobacterial	p value*
Patients, n (%)	43 (57)	5 (7)	27 (36)	
Temperature, median (IQR), °C	37.2 (36.8, 37.7)	37.7 (37.1, 38.3)	37.6 (37.2, 38.3)	0.1466
WBC, median (IQR), $\times 10^3/\text{mm}^3$	11.5 (9.0, 13.2)	13.0 (9.9, 13.2)	10.4 (5.7, 17.2)	0.6675
CRP, median (IQR), mg/dL	3.9 (2.5, 4.9)	5.1 (4.2, 9.0)	4.7 (0.9, 8.9)	0.3835
First PCT, median (IQR), ng/mL	0.14 (0.09, 0.28)	0.25 (0.18, 0.56)	1.41 (0.28, 5.58)	<0.0001
Patient with chest x-ray, n (%)	35 (81)	4 (80)	27 (100)	0.0272
Viral FilmArray, n (%)	39 (91)	2 (40)	26 (96)	0.0055
Sputum culture, n (%)	7 (16)	2 (40)	17 (63)	0.0001

CRP, C-reactive protein; PCT, procalcitonin

* Overall omnibus: Kruskal-Wallis or χ^2 test.

Discussion

Several studies have documented the clinical utility of PCT in pediatric patients with pneumonia and viral bronchiolitis.^{4–6} However, the best way to use PCT has yet to be determined. The present study aimed to evaluate the utility of PCT in pediatric patients with cobacterial pneumonia and determine whether PCT could serve as a biomarker for cobacterial pneumonia. We evaluated clinical variables and the utility of PCT during 2 time periods. Period 1 was used as baseline data prior to the implementation of PCT use, whereas period 2 was focused on evaluating the role and utility of PCT. Most of the patients evaluated in both time periods had viral pneumonia, and the number of patients who were classified as having a cobacterial pneumonia aligned with the reported national average of 23% to 35%.^{2,3}

Clinical variables of WBC, CRP, and temperature were all found not to be associated with cobacterial pneumonia across both study periods, which is consistent with a previous study by Laham et al.⁵ That study retrospectively examined infants admitted to the PICU with a primary diagnosis of acute bronchiolitis, 75% of whom tested positive for respiratory syncytial virus. About 38% of the patients evaluated were found to have a cobacterial pneumonia, determined by positive cultures or chest x-ray findings. Most patients with a cobacterial pneumonia were found to have initial PCT values greater than the study cutoff of 1.5 ng/mL; the mean PCT for those with positive bacterial cultures was 8.3 ng/mL. When directly comparing WBC and PCT of patients in the study, it was found that PCT was more reliable than WBC as a marker for cobacterial pneumonia. This was demonstrated when all of the patients without a cobacterial pneumonia were found to have a PCT value less than 1.5 ng/mL, whereas these same patients had WBC counts that ranged from $5 \times 10^3/\text{mm}^3$ to greater than $25 \times 10^3/\text{mm}^3$. This information guided the use of a cutoff value of 1.5 ng/mL for determining an elevated/positive PCT result in the presented study. Similarly, the present study found that patients with an

elevated PCT had greater odds of having a cobacterial pneumonia than patients with a normal PCT value, illustrating that PCT could be used to aid in the prediction and clinical diagnosis of patients with a cobacterial pneumonia. Although the initial median PCT value of patients with a cobacterial pneumonia was 1.41 ng/mL, the second PCT value had a median of 4.55 ng/mL, which was above the threshold of 1.5 ng/mL. Based on the ROC curves, the PCT cutoff had an approximately 80% accuracy in classifying cobacterial pneumonia status in the sample; this is consistent with the results of Laham et al,⁵ which suggested that PCT was a more reliable marker of infection than WBC. The Laham et al study also found the use of PCT could result in a 45% reduction in unnecessary use of antibiotics. When comparing antibiotic use between the 2 time periods of our study, period 2 demonstrated a greater level of antibiotic use (period 1, 26%–52%; period 2, 55%–89%). It is important to note that although this number is high, this included patients who received a minimum of 1 dose of an antibiotic, such as ceftriaxone, either in the emergency department or in the physician's office for the concern of or continued treatment of acute otitis media or pneumonia, who were then later identified as having a viral pneumonia.

A study conducted by Cies and Chopra⁴ reviewed all patients (201 patients) admitted to the PICU during a 4-month period. Unlike Laham et al,⁵ Cies and Chopra⁴ used a lower cutoff value of 1 ng/mL as a predictor of serious bacterial infection. It is important to note that the Cies and Chopra⁴ study did include patients in whom PCT values could have been falsely elevated, such as trauma patients, burn patients, and patients on extracorporeal membrane oxygenation. When evaluating those results, the authors found a positive correlation between a PCT value of ≥ 1 ng/mL and positive bacterial cultures. Of the 201 patients evaluated, 75 (37%) had a PCT value of ≥ 1 ng/mL, of whom 28 (37%) had positive bacterial cultures. Of the patients with positive bacterial cultures 7 (25%) had positive blood cultures, and these 7 patients had a mean PCT of 26.6 ng/mL.

A total of 53 of the patients evaluated in the Cies et al⁴ study (26%) had a PCT value obtained for the purpose of determining whether antibiotics needed to be initiated or whether current antibiotic coverage needed to be expanded. Of these patients, 46 (87%) did not have antibiotics started or coverage expanded, based on the results of PCT values, and they did not experience clinical deterioration.⁴ Like the results from Laham et al⁵ and Cies and Chopra,⁴ our data showed elevated PCT values were associated with cobacterial pneumonia. The median initial PCT value for patients with a viral pneumonia was 0.14 ng/mL, which is about 10-fold less than the 1.41 ng/mL for those with a cobacterial pneumonia; whereas the median second PCT for patients with viral pneumonia was 0.26 ng/mL, compared with 4.55 ng/mL in patients with cobacterial pneumonia. Although our providers did not use PCT values as the sole determining factor for initiating antibiotics or expanding coverage, it was an important clinical tool used to assist in the guidance of therapy.

Although the presented results are promising, the study was not without limitations. During period 2, a concurrent quality improvement project was conducted in the pediatric emergency department and with the pediatric hospitalist service. The project was aimed at using the American Academy of Pediatrics standard of care guidelines to diagnose and treat respiratory illnesses, such as viral bronchiolitis. As a part of this standard of care, one aim was to reduce the number of viral respiratory FilmArrays and chest x-rays that were obtained for pediatric patients. Our study also had a limited number of patients (47%) with serial PCT values, which limited our ability to fully assess the utility of PCT. Additionally, patients were classified into 1 of 3 groups based on the clinical diagnosis by the attending physician, rather than having a confirmed bacterial or viral culture in all patients. Also, our region experienced a more severe viral season in period 2 compared with period 1, which may have affected the number of patients that were classified and treated as viral pneumonia. As a retrospective study design, the information obtained was through chart review; therefore, some clinical information may not have been thoroughly documented in the provider's notes, which could have affected the classification of the patients into viral, bacterial, and cobacterial groups.

Despite the above limitations, study data suggested PCT as a useful non-invasive marker to identify pediatric patients who present with a viral upper respiratory illness who may also have a cobacterial pneumonia. Based on the correlation of PCT with cobacterial pneumonia, the use of PCT may help identify patients needing antibiotics earlier in their course and prevent empiric initiation of antibiotics in a patient who is clinically worsening secondary to only a viral cause. Further studies are needed in pediatric patients evaluating the

utility of PCT. This study adds to current literature aimed at determining the utility of PCT in pediatric patients with upper respiratory tract infections.

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Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data and take responsibility for the integrity and accuracy of the data analysis.

Ethical Approval and Informed Consent The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation. Institutional review board approval was granted for both time periods of this study and informed consent was deemed unnecessary.

Acknowledgments Results from completed period 1 data were presented at the Iowa Pharmacy Association's 2/2/2 Meeting on April 12, 2016, in Des Moines, Iowa. Completed results and poster presentation were presented at the Midwest Pharmacy Residents Conference in May 2016 in Omaha, Nebraska, and the Iowa Pharmacy Association's Annual Meeting in June 2016 in Des Moines, Iowa, respectively. The authors of this article would like to thank the pediatric hospitalists, pediatric intensivists, and pediatric emergency providers for their contributions to the project.

Accepted January 14, 2020

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