Association of Procalcitonin Value and Bacterial Coinfections in Pediatric Patients With Viral Lower Respiratory Tract Infections Admitted to the Pediatric Intensive Care Unit

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OBJECTIVE Our primary objective was to determine the utility of procalcitonin (PCT) in detection of bacterial coinfection in children < 5 years admitted to the pediatric intensive care unit with viral lower respiratory tract infection (LRTI).

METHODS Electronic medical record review of children < 5 years admitted to the pediatric intensive care unit with a viral LRTI who also had at least 1 PCT concentration measurement.

RESULTS Seventy-five patients were admitted to the intensive care unit and met the inclusion criteria for this investigation. The PCT threshold concentrations of 0.9, 1, 1.4, and 2 ng/mL were found to be statistically significant in determining the presence of a bacterial coinfection. The PCT concentration with the most utility was 1.4 ng/mL with sensitivity, specificity, positive and negative predictive values of 46%, 83%, 68%, and 76%, respectively. For patients with serial PCTs, the second PCT correctly influenced treatment decisions for 11 of 25 patients (44%).

CONCLUSIONS A PCT value of 1.4 ng/mL determined the presence of a bacterial coinfection primarily owing to the high specificity and negative predictive value. Our data add evidence to the relatively high negative predictive value of PCT concentrations in identifying patients with bacterial coinfection, specifically in the case of viral LRTI. In addition, our preliminary data indicate serial PCT measurements may help further influence correct treatment decisions. Prospective, controlled studies are warranted to validate an appropriate PCT threshold concentration to help in identifying bacterial coinfection as well as to further explore the role of serial PCT values in determining the absence or presence of a bacterial coinfection.

ABBREVIATIONS CXR, chest radiograph; ICU, intensive care unit; LOS, length of stay; LRTI, lower respiratory tract infections; PCT, procalcitonin; PICU, pediatric intensive care unit

KEYWORDS lower respiratory tract infection; pediatric; procalcitonin

J Pediatr Pharmacol Ther 2018;23(6):466–472

DOI: 10.5863/1551-6776-23.6.466

Introduction

Viral lower respiratory tract infections (LRTIs), including bronchiolitis, are a common cause of hospitalization in children < 5 years of age in the United States, with one source estimating approximately 236,000 LRTI hospitalizations in the United States per year.^{1–3} While pediatric hospitalizations in the United States for LRTIs such as bronchiolitis have declined overall, there has been an increase in the proportion of these patients requiring an increased level of care. An estimated 14% of viral LRTI admissions require pediatric intensive care unit (PICU) level of care or mechanical ventilation.^{1,4} Bacterial coinfection has been reported in a significant proportion of patients admitted to the PICU with a viral LRTI, with recent studies reporting rates of 38% to 44%,^{5,6} creating diagnostic and treatment dilemmas

for the multidisciplinary team caring for these patients. Clinicians may obtain bacterial cultures and initiate empiric antimicrobial therapy that may subsequently be deemed unnecessary. Usual biomarkers (i.e., white blood cell count or C-reactive protein) are not sensitive or specific for bacterial infection and cannot be used to independently differentiate bacterial from viral infection.⁶

Prior data have indicated procalcitonin (PCT) may be a more useful biomarker for determining the absence or presence of bacterial infection in children^{7–12} primarily owing to the high negative predictive value.⁹ Multiple studies have demonstrated the utility of PCT concentrations in predicting bacterial infection in varying neonatal and pediatric clinical scenarios, including sepsis,¹¹ the febrile neonate,^{12,13} and critically ill patients.^{7,14} There have recently been studies demonstrating the potential

utility of PCT in identifying bacterial coinfection in patients with viral bronchiolitis and its ability to potentially reduce health care costs.⁶

Therefore, the purpose of this investigation was to evaluate if PCT would aid in determining bacterial coinfection in patients with a viral LRTI. The primary outcome was to analyze the clinical utility of PCT (i.e., sensitivity, specificity, positive and negative predictive values, and likelihood ratios) to determine the absence or presence of a bacterial coinfection in children < 5 years admitted to the PICU with viral LRTI. The secondary aim was to evaluate the utility of serial PCT concentrations to determine the absence or presence of bacterial coinfection in the same cohort.

Materials and Methods

This was a retrospective electronic medical record review of data between January 25, 2010, and September 28, 2015, at St. Christopher's Hospital for Children. Patients were initially screened on the basis of a database (TheraDoc, Premier Inc, Charlotte, NC) of patients admitted to one of the critical care units with an *International Classification of Diseases, Ninth Revision* code (ICD-9) for acute bronchiolitis. Inclusion criteria for the study were a diagnosis of a viral LRTI, age < 5 years, and at least 1 PCT value obtained upon presentation and/or during the acute LRTI admission. The medical record was then reviewed to record the presence of viral culture(s), viral antigen testing, or polymerase chain reaction for 17 viral pathogens, chest radiograph (CXR), and bacterial culture results (i.e., urine, blood, cerebrospinal fluid, bronchoalveolar lavage, and respiratory). Confirmed bacterial infections were defined as 1) bacteremia assessed from final culture results; 2) urinary tract infections (UTIs) assessed from final culture results; and 3) bacterial pneumonia defined as a) a culture-positive bronchoalveolar lavage, b) a positive respiratory culture with at least moderate leukocytes on Gram stain and a positive CXR finding consistent with an attending physician's clinical diagnosis, c) a positive CXR finding consistent with an attending physician's clinical diagnosis, or d) a discharge summary with a final diagnosis of bacterial pneumonia.

The analyzed population was subdivided into 2 groups: a single PCT concentration or serial PCT concentration (defined as > 1 PCT concentration measurement obtained during the acute illness course). Procalcitonin measurements were performed by using the VIDAS BRAHMS PCT assay on the Mini-Vidas instrument (bioMérieux Inc, Durham, NC). Based on previous internal data and a review of the literature, the diagnostic utility of 5 PCT concentrations (0.5, 0.9, 1, 1.4, and 2 ng/mL) was evaluated between patients with and without bacterial coinfections. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated for each of the PCT concentrations. The utility of serial PCT values in influ-

Figure 1. Patient selection diagram (334 patients screened from TheraDoc).

Serial PCT concentration defined as >1 PCT concentration obtained during admission.

encing treatment decisions was also evaluated. To be included in the analysis for serial PCT, the concentrations had to be obtained ≥ 12 hours apart. These cases were coded as an appropriate intervention on the basis of whether the PCT values were below a specific threshold and antimicrobials were discontinued or withheld, or whether the PCT values were above a specific threshold and antimicrobials were continued. If the opposite occurred, these cases were coded as an inappropriate intervention. All coding was done blinded to the PCT concentrations. A receiver operating characteristic curve was also generated to determine if additional PCT concentrations other than the ones selected *a priori* should also be evaluated for clinical utility. Demographic and clinical characteristics were compared between the groups, with a Student *t* test for continuous variables and a χ^2 test, Fisher exact test, or Mann-Whitney *U* test for non-continuous variables. A 2-sided significance level of $p = 0.05$ was used to determine statistical significance. All analyses were performed by using IBM SPSS Version 24 (SPSS Inc, Chicago, IL). The institutional review board at the Drexel University College of Medicine approved the study.

Results

Study Population. A total of 334 patients were screened on the basis of ICD-9 data (Figure 1). Baseline demographic information is presented in Table 1. Seventy-five patients met full inclusion criteria with a

Table 1. Baseline Demographic Information

Variables	Procalcitonin		
	Combined (N = 75)	Single (n = 50)	Serial (n = 25)
Male sex, n (%)	49 (65)	36 (72)	13 (52)
Age, mo, median (range)	9 (1–55)	12 (2–55)	7 (1–49)
LOS in hospital, days, mean $\pm$ SD	14 $\pm$ 17.3	7.8 $\pm$ 8	26.4 $\pm$ 24.5
LOS in ICU, days, mean $\pm$ SD	11.2 $\pm$ 16.1	6 $\pm$ 7.9	21.4 $\pm$ 22.4
Antibiotics >5 days, n (%)	34 (45.3)	17 (34)	17 (68)

ICU, intensive care unit; LOS, length of stay

diagnosis of viral LRTI, based on review of the electronic medical record, and with at least 1 PCT value obtained during their acute viral illness hospitalization. A single PCT value was obtained in 50 of 75 patients (67%), and >1 PCT value (“serial PCT”) was obtained in 25 of 75 patients (33%). The total cohort of 75 patients (“combined PCT”), was composed of 49 males (65%) and 26 females (35%). The median age was 9 months with an age range of 1 month to 4.5 years. The mean hospital length of stay (LOS) was 14 $\pm$ 17.3 days with a mean intensive care unit (ICU) LOS of 11.2 $\pm$ 16.1 days. In the single PCT cohort (n = 50), there were 36 males (72%) and 14 females (28%). The median age was 12 months with a range of 2 months to 4.5 years. The mean hospital LOS was 7.8 $\pm$ 8 days with a mean ICU LOS of 6 $\pm$ 7.9 days. In the serial PCT group (n = 25), there were 13 males (52%) and 12 females (48%). The median age was 7 months with a range of 1 month to 4 years. The mean hospital LOS was 26.4 $\pm$ 24.5 days with a mean ICU LOS of 21.4 $\pm$ 22.4 days. Overall, 34 of 75 patients (45%) received an antibiotic course >5 days, with 17 of 50 patients (34%) in the single PCT group and 17 of 25 patients (68%) in the serial PCT group receiving an antibiotic course >5 days.

Viral Infection. Seventy-one of the 75 total patients (95%) underwent viral testing during their admission. Sixty-one of 71 patients (86%) tested positive for a virus. Thirteen of the 61 patients (21%) with a documented viral infection tested positive for multiple viruses. Rhinovirus was the most common virus, present in 35 of 61 patients (57%). Human metapneumovirus was present in 19 of 61 patients (31%), parainfluenza type 3 in 10 of 61 patients (16%), adenovirus in 6 of 61 patients (9.8%), coronavirus

in 3 of 61 patients (5%), parainfluenza 4 in 2 of 61 patients (3%), and parainfluenza 2 in 1 of 61 patients (1.6%).

Bacterial Coinfection. During the acute viral illness course in the PICU, varying combinations of either blood, urine, cerebrospinal fluid, or respiratory cultures were obtained from 71 of the 75 patients (95%). A CXR was also obtained from 71 of the 75 patients (95%). Bacterial coinfection was diagnosed in 33 of 75 patients (44%) in the combined PCT group. Overall, the 33 patients accounted for 36 bacterial infections; 3 patients in the serial PCT group were diagnosed with both bacterial pneumonia and UTI.

In the single PCT group, 16 of 50 patients (32%) were diagnosed with bacterial coinfection and in the serial PCT group, 17 of 25 patients (68%) were diagnosed with bacterial coinfection (Table 2). Bacterial pneumonia was diagnosed in 30 of 75 (40%) of the combined cohort, with 13 of 50 (26%) in the single PCT group and 17 of 25 (68%) in the serial PCT group. A UTI was diagnosed in 4 of 75 patients (5.3%), with 1 of 50 (2%) in the single PCT group and 3 of 25 (12%) in the serial PCT group. Bacteremia was diagnosed in 2 of 75 patients (2.7%), both in the single PCT group. There were no cases of meningitis in the 8 patients tested.

Bacterial Organisms. Overall, bacterial cultures were obtained from 71 of 75 patients (95%) and 21 of 71 patients (30%) had a positive bacterial culture. There were 9 positive bacterial cultures in the single PCT group, and 17 positive bacterial cultures in the serial PCT group (3 patients had concomitant UTI and a positive tracheal aspirate). Of the 17 positive cultures in the serial PCT group, 12 were documented positive cultures and 5 were considered to have a bacterial infection as

Table 2. Bacterial Coinfection Data by Diagnosis

Coinfection	Procalcitonin		
	Combined (N = 75)	Single (n = 50)	Serial (n = 25)
Positive bacterial infection, n (%)	33 (44)	16 (32)	17 (68)
Bacteremia	2 (2.7)	2 (4)	0 (0)
Urinary tract infection	4 (5.3)	1 (2)	3 (12)
Pneumonia	30 (40)	13 (26)	17 (68)
Meningitis	0 (0)	0 (0)	0 (0)

Table 3. Bacterial Organisms Isolated on Tracheal Aspirate

Organism Name	No. of Positive Cultures (Percentage of Total)
<i>Staphylococcus aureus</i> (methicillin sensitive)	5 (16)
<i>Pseudomonas aeruginosa</i>	5 (16)
<i>Moraxella catarrhalis</i>	4 (13)
<i>Stenotrophomonas maltophilia</i>	4 (13)
<i>Staphylococcus aureus</i> (methicillin resistant)	2 (6)
<i>Haemophilus influenzae</i>	2 (6)
<i>Klebsiella pneumoniae</i>	2 (6)
<i>Serratia marcescens</i>	2 (6)
<i>Streptococcus pneumoniae</i>	1 (3)
<i>Klebsiella oxytoca</i>	1 (3)
<i>Enterobacter cloacae</i>	1 (3)
<i>Enterobacter aerogenes</i>	1 (3)
<i>Prevotella melaninogenica</i>	1 (3)
<i>Bacteroides tectum</i>	1 (3)

based on a clinical diagnosis of bacterial pneumonia by CXR. *Staphylococcus aureus* and *Klebsiella pneumoniae* were the most common causative pathogens of bacteremia. *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Citrobacter koseri* (x2) were responsible for the UTIs. No patient had a bronchoalveolar lavage culture positive for a bacterial organism, and there were numerous patients with multiple organisms isolated on tracheal aspirate, which are listed in Table 3.

PCT Testing. Procalcitonin values were obtained for the entire 75-patient cohort. The median PCT value for the entire cohort was 0.78 ng/mL (IQR, 0.25–1.94 ng/mL). The median PCT value for those diagnosed with bacterial infection was 1 ng/mL (IQR, 0.41–3.83 ng/mL). The median PCT value for those without evidence of bacterial infection was 0.61 ng/mL (IQR, 0.2–0.97 ng/mL). In the single PCT group (n = 50), the median PCT value was 0.66 ng/mL (IQR, 0.19–0.98 ng/mL). The median PCT value for those diagnosed with bacterial infection was 0.85 ng/mL (IQR, 0.17–2.35 ng/mL), and the median PCT value for those without evidence of bacterial infection was 0.61 ng/mL (IQR, 0.2–0.88 ng/mL). In the serial PCT group (n = 25), the median PCT value, including a first and second PCT value obtained 12 to 24 hours from the first value, was 1.03 ng/mL (IQR, 0.43–4.4 ng/mL). The median PCT value for those diagnosed with bacterial infection was 1.22 ng/mL (IQR, 0.55–4.54 ng/mL), and the median PCT value for those without evidence of bacterial infection was 0.69 ng/mL (IQR, 0.26–4.36 ng/mL).

The sensitivity, specificity, positive and negative predictive values of PCT in predicting the presence or absence of a bacterial coinfection were analyzed for the combined PCT group (N = 75). Threshold concentrations of 0.5, 0.9, 1, 1.4, and 2 ng/mL were tested, and the

results are shown in Table 4. A threshold concentration of >1.4 ng/mL demonstrated the best utility with a sensitivity of 46%, a specificity of 83%, a positive predictive value of 68%, and a negative predictive value of 76%.

The utility of a second PCT value obtained (“serial PCT”) within 24 hours from the first PCT value was evaluated regarding its influence on treatment decisions. A second PCT value correctly influenced treatment decisions in 44% of cases. Similar PCT threshold concentrations (0.5, 0.9, 1, 1.4, and 2 ng/mL) were also tested for the second PCT value, and these results are demonstrated in Table 5. A receiver operating characteristic curve was generated to evaluate other potential PCT threshold points, and it is shown in Figure 2. No additional PCT thresholds were identified for further analysis, based on the results of the receiver operating characteristic curve.

Discussion

In this study of 75 patients < 5 years of age admitted to the PICU with a diagnosis of viral LRTI, we found PCT to have a high negative predictive value for identifying the presence of a bacterial coinfection. A threshold concentration of 1.4 ng/mL demonstrated the best utility of the PCT concentrations tested with a combined specificity of 83% and a negative predictive value of 76%. This was similar to the negative predictive value of a PCT threshold concentration of 2 ng/mL, but with a slightly better sensitivity and similar likelihood ratios. The negative predictive value for a threshold concentration of 1.4 ng/mL is similar to that reported in a recent study performed by Cies and Chopra,⁹ demonstrating a negative predictive value of 93% for a threshold concentration of 1.45 ng/mL in a population of “all comers” to the PICU.

Table 4. Test Characteristics for Varying PCT Threshold Concentrations in the Combined 75-Patient PCT Cohort in Determining the Presence of Bacterial Infection (N = 75)

PCT, ng/mL	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	(+) LR (95% CI)	(-) LR (95% CI)
0.5	73 (55–87)	41 (26–57)	49 (41–57)	65 (49–79)	1.2 (0.9–1.7)	0.67 (0.4–1.3)
0.9	62 (43–78)	68 (52–82)	61.8 (49–73)	68 (57–78)	1.95 (1.2–3.3)	0.56 (0.4–0.9)
1	55 (36–72)	76 (61–88)	64 (49–77)	68 (59–76)	2.29 (1.2–4.3)	0.6 (0.4–0.9)
1.4	46 (28–64)	83 (69–93)	68 (50–82)	76 (68–83)	2.73 (1.3–5.9)	0.65 (0.47–0.9)
2	39 (23–58)	86 (71–95)	68 (48–84)	65 (53–76)	2.8 (1.2–6.5)	0.71 (0.5–0.96)

LR, likelihood ratio; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value

There has been significant variability in the utility of PCT in predicting bacterial infections. A study by Laham et al⁶ in 2014 demonstrated a specificity of 100% in predicting bacterial infection in patients with bronchiolitis, using a threshold concentration of 1.5 ng/mL, while other studies have shown high false-negative rates approaching 13% to 18%.¹⁴ In addition to this study, our previous study demonstrated poor specificity in predicting bacterial infection with the primary benefit being the relatively high negative predictive value.⁹ The specificity of PCT in predicting the presence of bacterial coinfection was good in this investigation at a threshold concentration of 1.4 and 2 ng/mL. Some of the highest PCT values were observed in patients with no confirmed bacterial infection, which contradicts findings in some studies⁶ yet is similar to findings in others.¹⁴ This could be a result of the lack of a good “gold standard” methodology for diagnosing bacterial pneumonia. LRTIs are commonly diagnosed from the presence of fever (core body temperature $\geq 38^{\circ}\text{C}$ measured in hospital or at home) and at least 1 symptom (cough, sputum production, pleuritic pain, poor feeding) and at least 1 sign (tachypnea, dyspnea, wheezing, late inspiratory crackles, bronchial breathing, pleural rub).¹⁴ None of these signs and symptoms are specific to a bacterial source or a viral source of infection, which makes overtreating with antimicrobials common and the need for better diagnostic measurements paramount. While these patients may represent false negatives, they may also be representative of a population of pa-

tients with culture-negative infection, such as those with pneumonia, where it is difficult to isolate a pathogen, and who may be misdiagnosed as having an isolated viral infection. While some of these patients received antimicrobials, attempting to determine whether they clinically responded to antimicrobial therapy or had clinical improvement despite receiving antimicrobial therapy was not possible in a retrospective manner. The conclusion we drew from our data supports the idea that PCT may aid clinicians to rule out bacterial coinfection in the setting of viral LRTI.

Serial PCT concentrations have been recently studied (by Mandell et al¹⁵ in 2016) in the pediatric population in regard to sepsis. They suggested that patients with confirmed viral infections in the absence of bacterial infections demonstrated rising PCT concentrations and concluded that the trend in PCT concentrations could not accurately be used to predict the presence or absence of bacterial infection. In our study, a second PCT value helped correctly influence treatment decisions in 44% of cases by stopping or not starting antimicrobials in patients with consecutive low PCT values or continuing antimicrobials in patients with consecutive high PCT values who subsequently had a confirmed bacterial infection. While this is less than half of the patients, the benefit can be in confirming the correct diagnosis of bacterial infection if the PCT is above a certain threshold concentration but more likely in discontinuing antibiotics in patients with PCT concentrations consistently below thresholds. We did not

Table 5. Test Characteristics for Varying PCT Threshold Concentrations in the 25-Patient Serial PCT Cohort in Determining the Presence of Bacterial Infection (n = 25)

PCT, ng/mL	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	(+) LR (95% CI)	(-) LR (95% CI)
0.5	88 (64–99)	38 (9–76)	75 (63–84)	60 (24–88)	1.41 (0.8–2.5)	0.31 (0.06–1.5)
0.9	77 (50–93)	50 (16–84)	77 (61–87)	50 (25–75)	1.53 (0.7–3.2)	0.47 (0.16–1.4)
1	65 (38–86)	50 (16–84)	73 (56–86)	40 (21–63)	1.29 (0.6–2.8)	0.71 (0.27–1.82)
1.4	53 (28–77)	63 (25–92)	75 (53–89)	39 (23–57)	1.41 (0.52–3.84)	0.75 (0.36–1.6)
2	53 (28–77)	63 (25–92)	75 (53–89)	39 (23–57)	1.41 (0.52–3.84)	0.75 (0.36–1.6)

LR, likelihood ratio; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value

Figure 2. Receiving operating characteristic (ROC) curve for combined PCT data (n = 75).

PCT, procalcitonin.

explore these scenarios in further detail, but the utility of serial PCT concentrations does warrant further study.

Limitations to the study include the retrospective, single center nature of the study, the reliance on coding data with chart review for the diagnosis of a viral LRTI, the lack of strict guidelines for ordering PCT studies, and the reliance on clinical judgment for the diagnosis of bacterial pneumonia in the absence of strict CXR criteria. The presence of an elevated PCT concentration with equivocal CXR findings may influence the clinician to diagnose a bacterial superinfection, leading to a confirmation bias of a high PCT concentration as predictive of a bacterial superinfection in the absence of positive culture results when this may in fact not be the case.

Our data add evidence to the relatively high negative predictive value of PCT concentrations in identifying patients with bacterial coinfection, specifically in the case of viral LRTI. In addition, our preliminary data indicate serial PCT measurements may help further influence correct treatment decisions, although the small sample size of the serial PCT patients limits the usefulness of the data obtained from this subgroup. Prospective, controlled studies are warranted to validate an appropriate PCT threshold concentration to help in identifying bacterial coinfection as well as to further explore the role of serial PCT in determining the absence or presence of a bacterial coinfection.

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Disclosures Dr Cies is a consultant for Atlantic Diagnostic Laboratories and has received grants and/or honoraria from Allergan, Merck, and Thermo Fisher Scientific. The other authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. This work was supported by a grant from Thermo Fisher Scientific. The authors had full access to all the data and take responsibility for the integrity and accuracy of the data analysis.

Acknowledgment This work, in part, was presented as an oral presentation at the 46th Society of Critical Care Medicine Annual Congress, Honolulu, Hawaii, February 2017.

Accepted June 8, 2018

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