Prospective Observational Study to Determine Kinetics of Procalcitonin in Hospitalized Children Receiving Antibiotic Therapy for Non-Critical Acute Bacterial Infections

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ABSTRACT

Introduction: The kinetics of procalcitonin in pediatric patients with non-critical acute bacterial infections receiving appropriate antibiotic therapy are not well described.
Methods: We performed a single-center, prospective observational pilot study of children admitted to a tertiary care children's hospital who were receiving antibiotics for treatment of a non-critical acute bacterial infection, and we prospectively measured serial procalcitonin levels daily for 4 days during hospitalization.
Results: Among the 46 children with baseline procalcitonin levels enrolled in the study, procalcitonin kinetics followed a half-life of approximately 24 h in most patients. Procalcitonin declined faster than C-reactive protein over the first 48 h of appropriate antibiotic treatment. There was variation in biomarker levels among participants with the same infection type, especially in participants with bacteremia, musculoskeletal infection and skin/soft tissue infection.
Conclusion: Utility of procalcitonin as a biomarker to follow every 24–48 h in non-critically ill children receiving antibiotic therapy for bacterial infections as an objective measure of clinical improvement is promising.

Keywords: Kinetics; Pediatric; Procalcitonin

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Key Summary Points
Among hospitalized children with serious bacterial infections, PCT declined faster than CRP over the first 48 h of appropriate antibiotic treatment.
Proclacitonin kinetics followed a half-life of approximately 24 h in most pediatric patients.
There was variation in biomarker levels among participants with the same infection type.
The inclusion of single or serial procalcitonin values could strengthen pediatric prediction scoring systems.

DIGITAL FEATURES

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INTRODUCTION

Procalcitonin (PCT) has been investigated as a biomarker for prediction of serious bacterial infection in febrile infants and critically ill adult patients with pneumonia and sepsis [1–8]. In adults with microbiologically confirmed bacterial infections, PCT levels have been shown to rise early in infection (2–4 h after a bacterial stimulus), peak after 12–24 h and decrease with initiation of effective antibiotic therapy with a half-life of around 24 h [9, 10]. In the event that PCT is measured too early in the disease course, it can be falsely low and should be repeated in patients with other signs and symptoms consistent with bacterial infection. In adults, clinical syndromes with the most data supporting use of PCT include sepsis, pneumonia and chronic obstructive pulmonary disease [11, 12]. The 2019 Infectious Diseases Society of America (IDSA) Community Acquired Pneumonia guidelines suggest that PCT can be used to decrease duration of therapy for pneumonia but should not be used to determine need to initiate antibiotics in someone with clinical suspicion of pneumonia [12]. Similarly, the 2016 Surviving Sepsis Campaign guidelines recommend the use of PCT for antibiotic de-escalation but not for determining need to initiate antibiotics [13]. There are fewer data to support the use of PCT use in meningitis or in infectious complications of trauma, burns and pancreatitis [11]. Recent studies have evaluated the role of PCT in identifying bacterial infection in children with pneumonia, musculoskeletal infection, central line and fever and urinary tract infections, with varying utility of PCT to predict bacterial vs. non-bacterial infection [14–18].

Causes of falsely elevated procalcitonin levels have been described and include massive stress (i.e., severe trauma, surgery, cardiac shock, burns or cardiopulmonary bypass), prolonged severe cardiogenic shock or organ perfusion abnormalities, malaria and some fungal infections, systemic vasculitis and acute graft vs. host disease, treatment with agents that stimulate cytokines (i.e., OKT3, anti-lymphocyte globulins, alemtuzumab, IL-2 or granulocyte transfusion), end-stage renal disease or peritoneal dialysis and paraneoplastic syndromes due to medullary thyroid and small cell lung cancer [19].

Although clinicians with access to PCT use serial measurements to determine clinical improvement and response to antibiotics, data describing the kinetics of PCT in children are lacking [20–23]. To determine whether PCT can be used as a surrogate of clinical response to help guide antibiotic de-escalation in non-critically ill children, we evaluated the kinetics of PCT among children with non-critical acute bacterial infections who are receiving effective antibiotic therapy.

METHODS

Study Design

We performed a single-center, prospective observational pilot study of children admitted to a tertiary care children's hospital who were receiving antibiotics for treatment of a non-critical acute bacterial infection.

Study Setting and Population

Children between ages 1 week to ≤ 19 years who were hospitalized at Vanderbilt Children's Hospital with an acute, non-critical bacterial infection from March 2018 through April 2019 were eligible for study inclusion. Each day, participants with initiation of antibiotics in the prior 24 h were identified through the electronic medical record. Acute, non-critical bacterial infection was defined as culture-proven bacteremia or urinary tract infection, or non-culture confirmed diagnoses (based on clinical and/or radiographic findings), which included antibiotic pre-treated urinary tract infection,

retropharyngeal abscess, peritonsillar abscess, orbital cellulitis, septic arthritis and osteomyelitis. Exclusion criteria included children younger than 7 days of age or children admitted to the neonatal intensive care unit. This study was approved by the Vanderbilt University institutional review board. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All subjects provided informed consent to participate in the study.

Biomarker Measurements

The first plasma sample for PCT testing was collected as leftover blood from routine laboratory testing obtained in a lithium heparin gel tube at the time of hospital presentation and prior to antibiotic administration. Serial plasma samples were then prospectively collected daily for 4 days or until hospital discharge. Samples were refrigerated within 3 h of collection, centrifuged and separated into two aliquots within 72 h of collection, and the plasma was then frozen at -80° C, until PCT testing was performed using a bioMérieux Vidas® 3 platform. Samples underwent one freeze-thaw cycle prior to testing. Results of PCT testing were not shared with providers and were not used for clinical care. Results of C-reactive protein (CRP), white blood cell count, other laboratory tests obtained for routine clinical care and blood, urine and cerebrospinal fluid bacterial, viral and fungal cultures were abstracted from the electronic medical record. Percent change from baseline was calculated for each participant's biomarker levels each day by subtracting their PCT or CRP level from baseline, divided by the baseline biomarker level and multiplying by 100. For the subset of 20 patients who had all five PCT levels drawn, we additionally calculated daily rate of change.

Clinical Outcomes

Clinical and demographic characteristics at enrollment and during the study period were obtained through electronic medical record review and included diagnosis, age, sex, race/ ethnicity, underlying chronic medical diagnoses, hospital unit on admission and surgical procedure. An antibiotic was considered effective if the organism was susceptible to it or when a participant demonstrated clinical improvement while receiving antibiotic therapy in the absence of susceptibility data. An infectious syndrome was characterized as one of the following: bacteremia, brain abscess, meningitis, osteomyelitis or myositis without bacteremia, osteomyelitis or myositis with bacteremia, skin/soft tissue infection without bacteremia or urinary tract infection.

Statistical Analysis

Paired t-tests and Wilcoxon signed-rank tests were used to compare mean/median PCT and CRP levels and change from baseline. All analyses were performed using Stata version 15.1 for Mac.

RESULTS

A total of 50 children were enrolled during the 13-month study period. After enrollment, four children had no leftover blood for initial PCT sample testing and were excluded from further data analysis, leaving a total sample size of 46 children. Demographic data are shown in Table 1, with a mean age of 6.9 years (range 1.04 weeks to 18.2 years), and 25 (54.4%) participants were female. All participants were started on effective antibiotic therapy immediately after baseline labs were obtained. The majority (38/46, 83%) of participants had culture-confirmed bacterial infection. Aside from surgery, none of the patients had or were exposed to any potential causes of falsely elevated PCT including massive stress, shock, systemic vasculitis, treatment that stimulates cytokines, end-stage renal disease, peritoneal dialysis or paraneoplastic syndromes. Median baseline PCT levels were similar for participants with gram-positive infection ($n = 24$) and gram-negative infection ($n = 12$) at 1.22 and 1.25 µg/l, respectively ($p = 0.8$). When comparing mean baseline PCT levels by clinical syndrome, meningitis (55.4 µg/l, $n = 2$) and

Table 1 Cohort demographics

	All subjects (n = 46)	Bacteremia (n = 21)	SSTI (n = 9)	MSK infection (n = 11)
Age (years) (median, IQR)	5 (2.5, 10.5)	3.6 (2.5, 13)	4.2 (3.9, 8.3)	7.2 (1.6, 11.4)
Male sex	21 (46%)[a]	10 (48%)	4 (44%)	5 (45%)
Race/ethnicity				
White	37 (80%)	15 (71%)	7 (77%)	10 (91%)
Black	7 (15%)	4 (19%)	2 (22%)	1 (9%)
Hispanic/Latino	4 (9%)	2 (10%)	0	2 (18%)
Chronic disease				
Heart disease	2 (4%)	2 (10%)	0	0
Gastrointestinal	7 (15%)	7 (33%)	0	0
Oncologic	9 (20%)	9 (43%)	0	0
None	21 (46%)	2 (10%)	9 (100%)	8 (73%)
ICU admission	5 (11%)	2 (10%)	0	1 (9%)
Surgical procedure[b]	16 (34%)	4 (19%)	3 (33%)	7 (64%)
Baseline PCT (mean ± SD) (median; IQR)	6.41 ± 13.62 (0.76; 0.11, 5.96)	4.26 ± 5.95 (0.91; 0.4, 5.9)	1.73 ± 3.7 (0.27; 0.11, 0.54)	7.11 ± 10.41 (2.12; 0.09, 10.98)

SSTI skin/soft tissue infection, *MSK* musculoskeletal, *ICU* intensive care unit, *PCT* procalcitonin, *SD* standard deviation, *IQR* interquartile range

[a] Percent represents percent of participants in each column

[b] Participant underwent surgical procedure during the study period (on or after the day of enrollment)

musculoskeletal infection (7.1 μg/l, *n* = 11) were higher than other infection types. Median PCT levels declined faster than median CRP levels (Fig. 1). Of the 11 participants with musculoskeletal infection, 7 (64%) underwent surgery during the study time period (3 participants on the day that the baseline PCT level was obtained and 4 participants on day 1). Procalcitonin kinetics followed a half-life of approximately 24 h in most patients (Fig. 2). Of the 39 patients who had PCT levels drawn at baseline and on day 1, 8 (21%) had a decrease of at least 50% in their PCT value on day 1, and 14 of the 37 patients (37.8%) who had PCT levels drawn at baseline and on day 2 had a decrease of at least 50% on day 2. Restricting only to patients with initial PCT levels > 0.5 μg/l, 8 of 25 patients (32%) with PCT levels drawn on baseline and day 1 had at least 50% decline in PCT on day 1,
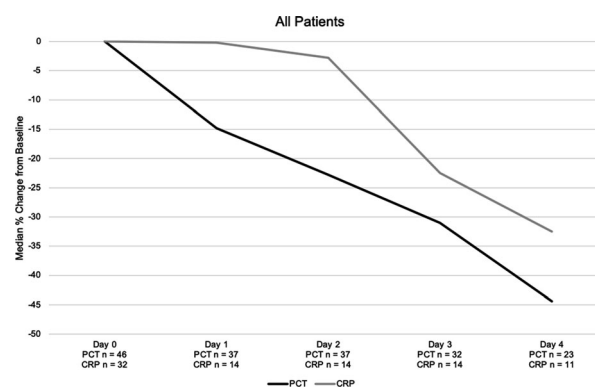

Fig. 1 Median percent change in biomarker levels during treatment. Black line indicates median percent change in procalcitonin levels from baseline, and gray line indicates median percent change in C-reactive protein levels from baseline over the study period. *PCT* procalcitonin, *CRP* C-reactive protein
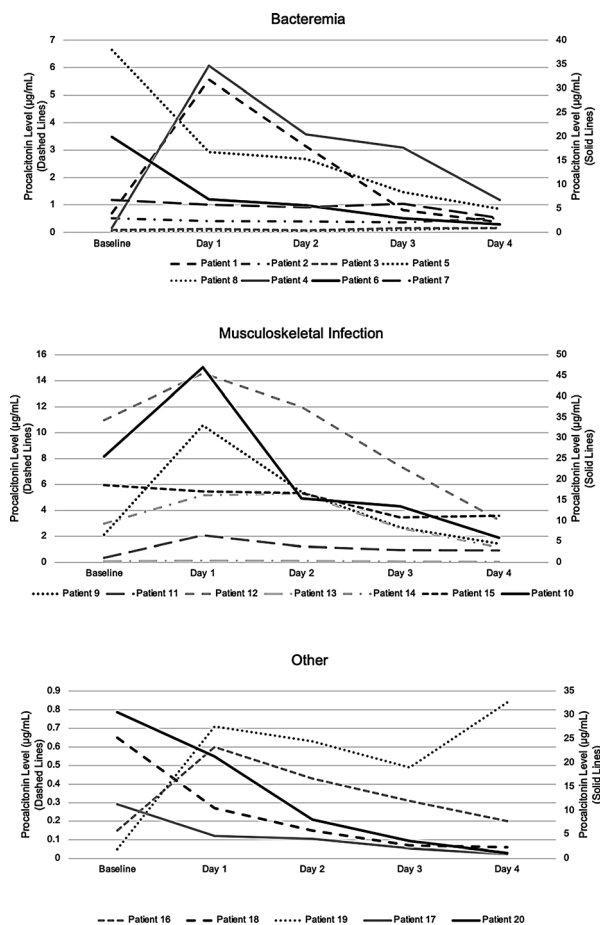
Fig. 2 Daily procalcitonin levels among 20 participants with levels measured per protocol. Each line represents a unique participant. 'Other' diagnoses include skin/soft tissue infection (*n* = 2), urinary tract infection (*n* = 2) and meningitis (*n* = 1)

and 12 of 24 patients (50%) with PCT levels drawn on baseline and day 2 had a decline in PCT value of at least 50%. There was variation in biomarker levels among participants with the same infection type, especially in participants with bacteremia, musculoskeletal infection and skin/soft tissue infection (Fig. 2 and Table 2). Most participants had declining PCT levels throughout the study, but some had stable or rising levels throughout the study duration. Most participants with stable or rising levels had low PCT levels (< 1 µg/l) throughout the duration of the study (Fig. 2).

DISCUSSION

Although PCT is commonly used in the clinical setting to predict severe bacterial infection and to guide antibiotic de-escalation in both adults and children, the utility of PCT to predict response to antibiotic therapy is unclear, especially in children. Comparisons of serial PCT and CRP in this prospective cohort of hospitalized children with serious bacterial infections revealed that mean baseline PCT was high in all participants and highest for those with meningitis and musculoskeletal infections. PCT declined faster than CRP over the first 48 h of appropriate antibiotic treatment in all participants, including those with musculoskeletal infection who underwent surgery within the first 48 h of enrollment. Due to small sample size, we were not able to determine whether PCT declined faster than CRP in participants with bacteremia or skin/soft tissue infection.

If PCT normalizes faster than CRP, trending PCT instead of CRP could be cost saving in the long term because fewer tests would be needed. A recent study demonstrated that CRP outperformed PCT in diagnosing pediatric musculoskeletal infection, so measurement of PCT alone on initial evaluation may not be sufficient [14]. Another possible use for PCT is in reducing the duration of antibiotic courses for non-critical bacterial infections or facilitating earlier conversion from intravenous to oral antibiotics, although more research is needed on this topic before recommendations to support this clinical application can be made.

The decline in PCT levels that we noted among participants receiving adequate antibiotic therapy provides supporting evidence that PCT may add useful information to clinical prediction scores, especially for musculoskeletal infection. PCT is currently used, along with other laboratory and clinical characteristics, in the "step-by-step" approach, a prediction score that aids clinicians to safely avoid lumbar punctures in febrile infant evaluations [1]. Low PCT values have also been associated with reduced odds of ICU admission and shorter length of hospital stay compared with higher PCT concentrations in the Etiology of

Table 2 Detailed information on organism and surgery date among 20 participants with procalcitonin levels measured per protocol

ID	Infection type	Organism	Surgery (yes or no), day of surgery
1	Bacteremia	*E. coli*	No
2	Bacteremia	*E. coli*	No
3	Bacteremia	*Enterococcus* spp.	No
4	Bacteremia	*P. aeruginosa*	No
5	Bacteremia	*E. coli*	No
6	Bacteremia	*S. pneumoniae*	No
7	Bacteremia	*S. aureus*	Yes, day 4
8	MSKI	*S. aureus*	Yes, day 3
9	MSKI	Negative	Yes, day 1
10	MSKI	Negative	No
11	MSKI	MSSA	No
12	MSKI	MRSA	Yes, day 2
13	MSKI	MSSA	Yes, day 2
14	MSKI	*H. influenzae*	Yes, day 2
15	MSKI	MRSA	Yes, day 2
16	SSTI	MRSA	Yes, day 2
17	SSTI	*S. pyogenes*	Yes, day 2
18	UTI	*E. coli*	No
19	UTI	Negative (culture was pre-treated with antibiotics)	Yes, day 2
20	Meningitis	*S. pneumoniae*	No

MSKI musculoskeletal infection, *SSTI* skin/soft tissue infection, *UTI* urinary tract infection

Pneumonia in the Community (EPIC) study, a multicenter study of 532 hospitalized children with pneumonia [24]. Recent prediction scores developed to identify complications of acute hematogenous osteomyelitis in children include biomarkers such as total leukocyte count, erythrocyte sedimentation rate (ESR) and CRP along with clinical characteristics [25, 26]. The inclusion of single or serial PCT values could further strengthen these prediction scoring systems and warrants further research. A recent meta-analysis demonstrated only moderate diagnostic accuracy of PCT for diagnosis of bacterial pneumonia in children, highlighting the fact that PCT should not be used in isolation to diagnose bacterial infections in children [16].

This study has several limitations. It was a single-center study with a small sample size (increasing probability of a type II error and decreasing generalizability), and we had difficulty obtaining all five blood draws among enrolled participants. We enrolled participants with a variety of bacterial infections, which increases generalizability but also decreases the ability to draw meaningful conclusions for individual diagnoses. We could not evaluate the utility of PCT as a marker of treatment failure or poor clinical outcome as we did not have any

participants whose infection did not respond to antibiotic therapy, and all had good outcomes. Not all patients enrolled had culture-confirmed bacterial diagnoses, so it is possible that these patients' elevated PCT levels may have been due to a cause other than bacterial infection. Finally, CRP levels were drawn as part of routine clinical care and were not directed by the study protocol, so corresponding levels were only available for 32/46 (70%) participants at baseline and 11/46 (24%) on day 4. Participants with CRP levels drawn on day 4 were also more likely to be sicker than those without CRP levels as they had longer hospital stays and clinicians chose to monitor their inflammatory biomarkers. We expected all participants with bacteremia to have high PCT levels and were surprised to see that some did not. It is possible that participants with lower levels had low-level colonization of their central lines without systemic bacteremia. Despite these limitations, this study is one of only a few evaluating serial PCT levels among pediatric patients and provides valuable insight into the kinetics of PCT in children receiving effective therapy for non-critical, acute bacterial infection.

CONCLUSION

PCT is a promising biomarker to follow every 24–48 h to monitor response to antibiotic therapy and appears to decline more quickly than CRP in response to effective therapy. More research is needed to determine the optimal monitoring frequency for PCT and to understand its utility as a prognostic biomarker in children with a variety of infections.

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