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Procalcitonin Trends in the Treatment of Suspected Bacterial Infection

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by

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Abstract:

Introduction and Objective: Infection is a leading cause of death in children. However, clinicians at the bedside still cannot quickly and reliably detect bacterial infection, leading to antibiotic overuse, a modifiable contributor to antibiotic resistance. Biomarkers offer the potential for both the early detection of bacterial infection and the ability to track effective antibiotic treatment. One such biomarker, procalcitonin (PCT), has been demonstrated to safely reduce antibiotic prescription in critically ill adults when used to guide antibiotic initiation and duration. In the current study, we determined if simulation of a similar algorithm in critically ill children would predict a reduction in antibiotic prescription.

Methods: We conducted a prospective, observational, repeated measures, cohort study in patients less than 18 years of age with suspected infection admitted to the pediatric intensive care unit (PICU) between June 2013 and March 2014. We obtained serial PCT measurements on all study subjects while receiving antibiotics. Clinicians were blinded to the PCT measurements, and all decisions regarding antibiotic therapy were at the discretion of the clinical team. The predicted antibiotic duration was determined by retrospectively applying a PCT guided algorithm of antibiotic prescription. The primary outcome was the paired difference in prescribed (as determined by the clinical team) vs. predicted antibiotic days (as determined by the simulated PCT guided algorithm). Additional analyses were performed for diagnostic accuracy of PCT.

Results: The current report presents the findings in the first 40 consecutive subjects enrolled in the study. Subjects had a median age of 5 years (IQR 2.75, 12.25) with a median PICU length of stay of 3 days (IQR 1, 6). The receiver operating characteristic for initial PCT level had an area under the curve (AUC) of 0.76 for clinically defined bacterial infection and an AUC of 0.82 for infection defined by a positive bacterial culture. Twenty-eight patients (75%) would have received a median of 4.5 fewer

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antibiotic days based on the use of our simulated procalcitonin guided algorithm. These patients received a median of 7.5 antibiotic days (IQR 2.8, 13.3). Twelve patients (25%) would have received more antibiotic days based on the simulated model. These patients received a median of only 2 antibiotic days (IQR 1.75, 6). None of these patients had adverse consequence of untreated or undertreated infection. Using the multiple imputation model for missing data, the patients overall would have had a mean reduction of 4.7 days of antibiotic prescription (95% CI 2.8, 6.6, p<0.001).

Conclusion: Procalcitonin had a moderate diagnostic accuracy for bacterial infection in this cohort. Simulating a procalcitonin guided algorithm in critically ill children with suspected infection in combination with a predictive model demonstrates a significant potential for reducing antibiotic days. A randomized controlled trial of a procalcitonin guided algorithm for antibiotic guidance in the critically ill child with suspected infection is warranted to determine the safety of such a method. [Blank Page]

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Tables and Figures

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Abbreviations

РСТ	Procalcitonin
ROC	Receiver Operative Characteristic
PICU	Pediatric Intensive Care Unit
AUC	Area Under the Curve
ССНМС	Cincinnati Children's Hospital Medical Center
PRISM	Pediatric Risk of Mortality

Introduction

Reports of childhood mortality still cite infection as the leading cause of death in children worldwide [1]. However, our ability to diagnose and treat bacterial infection is imperfect. Despite medical advances, we still cannot consistently, reliably, and immediately detect bacterial infections at the bedside, nor can we definitively determine the adequate length of therapy for these same infections. The consequences of an untreated or inadequately treated bacterial infection are potentially fatal. For this reason, many clinicians empirically treat patients with suspected infections. Such a conservative treatment approach likely leads to antibiotic overuse, which is epidemiologically linked to antibiotic resistance. As a result, less than a century after the life-saving discovery of penicillin, pan-antibiotic resistant bacteria kill our patients with unprecedented frequency [2-7].

Unfortunately, the gold standard of detection of bacterial infection, bacterial culture, is both insensitive and can take several days to result. Our current practice for both the diagnosis of bacterial infection and determining the length of antibiotic therapy includes bacterial cultures coupled with clinical assessment. Based on this assessment, empiric antibiotics are initiated and continued for an arbitrarily chosen number of calendar days, with 5, 7, 10, and 14 days being common endpoints.

If we can reduce antibiotic exposure by using novel methods to detect bacterial infection earlier than ever, we can decrease the incidence of antibiotic resistant bacteria [8]. Biomarkers offer tremendous potential for the early detection of bacterial infection, which may offer the dual benefits of earlier diagnosis, and therefore, treatment of life-threatening bacterial infections, as well as potentially reducing the inappropriate utilization of antibiotics.

Procalcitonin (PCT) is a 116 amino acid precursor to calcitonin, a hormone important in calcium regulation, and is an emerging biomarker for bacterial infection that is easily measured in the clinical setting. PCT has been shown to improve upon clinical criteria and blood culture results, thereby

facilitating the early detection of life-threatening bacterial illnesses. Located on the short arm of chromosome 11, the gene for PCT, *Calc-1* is normally expressed only in specific thyroid cells, making PCT barely detectable in human serum. However, during bacterial infection, many cells in the body express *Calc-1*, causing increased serum levels of PCT [9].

Procalcitonin is a relatively sensitive and specific marker of bacterial infection in diverse patient populations, including children [10-32]. The adult and pediatric literature has shown that PCT is a relatively specific marker of bacterial infection that rises with invasive bacterial infection, versus fungal or viral infection, and falls with control of infection. This effect has been noted in multiple patient populations, including burn patients, patients with febrile neutropenia, patients status post cardiopulmonary bypass, and in the transplant population. However, the most effective cut-off does vary based on patient population [10, 11] [12] [13-21] [22-24] [25-31] [32]. In a recent meta-analysis of studies that reported sensitivity and specificity of procalcitonin for bacterial sepsis vs. noninfectious inflammation in the critical care setting for both adult and pediatric patients, the pooled sensitivity was 77% and the pooled specificity was 79%. This resulted in a receiver operating characteristic curve with an area under the curve (AUC) of 0.85. Of relevance to the current study, the AUC was the same for the pediatric studies included. The ideal cut-off point found in these studies varied widely, with a median of 1.1ng/ml (IQR 0.5-2.0) [33].

In addition to aiding the initial diagnosis of bacterial infection, PCT has been used to guide antibiotic duration and treatment. The algorithms used in this context involve initiating antibiotic therapy based on a PCT value above a threshold number, and continuing antibiotics until serial PCT measurements demonstrate a decline in PCT below either this threshold number or below a certain percentage of the peak number. Randomized controlled trials evaluating such protocols have been performed in adults across the outpatient, inpatient and intensive care unit settings[34]. The most robust studies have

demonstrated a safe decrease in antibiotic days in adults with respiratory infections [35] . A similar result has been observed using a PCT guided algorithm for antibiotic prescription for pediatric respiratory infection [36, 37]. In critically ill adults, this strategy also demonstrates a 2-4 day reduction in antibiotic prescription in patients with suspected infection without any increase in adverse outcomes [38-43]. The exception to this trend was a study that focused on antibiotic escalation based on daily PCT measurements of all patients regardless of clinical suspicion of bacterial infection. This particular study found increased antibiotic use with this strategy with resultant harm, including prolonged duration of mechanical ventilation and intensive care unit length of stay [44]. Our long-term goal is to determine whether PCT can be used safely in critically ill children to guide antibiotic initiation and duration of treatment.

Prior to embarking on a randomized controlled trial of a PCT guided algorithm for antibiotic prescription in critically ill children, we sought more information about the trend of PCT with antibiotic treatment in children. The specific objective of this study was to define the temporal kinetics of PCT to determine if a difference exists between the number of days it takes for PCT to fall to a level not concerning for infection and the number of antibiotic days prescribed by the clinician in current practice. Based on the conservative end of the cut-off points used in studies in the critically ill adult population, we defined the PCT level that was not concerning for infection as that between 0.25 to 0.5 ng/ml, or less than 80% of the peak level. We hypothesized that PCT levels will decrease below levels concerning for infection in critically ill children with suspected bacterial infection significantly before the time that clinicians discontinue antibiotics.

Methods

With Institutional Review Board approval, we performed a prospective, repeated measures cohort study

of patients admitted to the Cincinnati Children's Hospital Medical Center (CCHMC) pediatric intensive care unit (PICU) with suspected infection between June of 2013 and March of 2014.

Inclusion Criteria

All patients younger than 18 years of age who presented to the PICU with a suspected infection were eligible for the study. Suspected infection was defined broadly by the action of the clinical team ordering a blood culture on the patient.

Exclusion Criteria

Patients who were non-English speaking or patients with limitations of care were excluded from the study. Patients who already had PCT levels sent before approach for inclusion into the study were also excluded from participation.

Study Procedures

Patients were screened daily for eligibility. After identification, patients and their families were approached for informed consent. After informed consent, PCT was measured within six hours of the blood culture being collected. If antibiotics were initiated or escalated at any point after inclusion in the study, PCT was measured daily until antibiotics were stopped, unless the patient was discharged from the hospital. Clinicians were blinded to the PCT levels.

Data Collection

In addition to the PCT measurements, we collected patient demographic and clinical data, including age, gender, reason for admission, all diagnoses made by the clinical team, Pediatric Risk of Mortality (PRISM-III) score, microbiologic data results and antibiotic agents and duration. Study data were collected and managed using REDCap electronic data capture tools hosted at CCHMC[45].

Procalcitonin Guided Algorithm used for Predicted Duration of Antibiotic Therapy

Based upon the literature of PCT guided antibiotic prescription in critically ill adults, we modified an algorithm for encouragement or discouragement of antibiotic initiation and cessation (see Figure 1). Based upon the initial PCT level, this algorithm either discourages or encourages the initiation of antibiotics. If the initial level is intermediate, it defers to clinician judgment. Once started, antibiotic prescription is recommended until the PCT level drops below either the minimum threshold level of 0.25 ng/ml or <80% of the peak PCT level. This was not an interventional study, therefore the algorithm was not applied to alter antibiotic exposure for any patients. Rather we applied the algorithm via simulation in order to predict antibiotic prescription. For this purpose, we conservatively assumed that the clinician would always choose to prescribe antibiotics whenever the initial PCT level fell into the intermediate range.

Determination of Bacterial Infection

Prior to looking at the PCT measurements, the primary investigator (SS) retrospectively analyzed the charts of each study patient and determined the presence of bacterial infection using culture results and commonly accepted clinical criteria for culture negative bacterial infections, such as pneumonia, cellulitis, or septic arthritis[46-48].

Sample Size Calculation

Analyzing antibiotic prescription for the month of November 2010, preliminary data revealed that our PICU patients with suspected infection received a mean duration of 9.5 antibiotic days (SD 8 days, IQR 2.25-14 days). Sample size was calculated using a t-test statistic for a paired sample, and estimating a moderate correlation (0.5) between the two measurements. To achieve 80% power with an alpha of 0.05 for a 2 tailed alternative hypothesis, we need 129 patients to detect a clinically significant 2-day

difference for our primary outcome. We have approximately 290 eligible patients every year in the PICU. Considering loss to follow up and consent rate, we estimated the duration of this study to be 2 years to collect the data and perform the statistical analysis.

Statistical Analysis

Data were analyzed using R statistical software and SAS 9.3 (SAS Institute Inc., Cary, NC). Continuous variables are reported as median (interquartile range). Categorical variables are expressed as a percentage (%). Comparisons among groups were made using the appropriate non-parametric statistic including the Wilcoxon Rank Sum test, Pearson Chi-squared test, and Fisher's exact test. To determine diagnostic accuracy of PCT for both bacterial culture and defined bacterial infection, a Receiver Operating Characteristic (ROC) curve analysis was performed. For the analysis of our primary endpoint, the paired difference in antibiotic days received versus predicted days, there were three possibilities: patients could either have an equivalent number of received and predicted days, a fewer number of predicted days or a greater number of predicted days. Patients in the last category will, by design, have incomplete data as we did not collect PCT data beyond antibiotic discontinuation (See Figure 2). For these patients, a multiple imputation method with a multivariate regression model was used to predict the duration of antibiotic days for those with missing values. To inform this model, the time to peak PCT, peak PCT and time from peak PCT to drop to 20% of peak levels were predicted for the patients with complete data and then modeled using a linear regression on our demographic characteristics, e.g. age, gender, PRISM score. The multivariate regression model was then used to impute these parameters for the patients with missing information. For each data set, the number of days are computed 10 times for ten sets of possible observations and then aggregated for a summary result [49].

Results

Demographics

A total of 40 patients have been analyzed to date (Table 1). These patients have a median age of 5 years (IQR 2.75,12.25) and stayed in the PICU a median of 3 days (IQR 1, 6). Thirty five percent of included patients were retrospectively determined to have a clinical infection, and 25% were found to have a positive bacterial culture. Patients received overall a median of 5 antibiotic days (IQR 2, 10).

Diagnostic Accuracy

Using the initial PCT value, analysis demonstrates a ROC curve with an AUC of 0.76 (95% CI 0.59, 0.93) for clinically determined bacterial infection (Figure 3) and an AUC of 0.82 (95% CI 0.64, 0.99) for positive bacterial culture (Figure 4). This is consistent with previously published studies on the diagnostic accuracy of PCT.

Predicted Difference in Antibiotic Days based on Simulation of PCT Guided Algorithm

Twenty-eight patients (75%) would have received a median of 4.5 fewer antibiotic days (IQR 2,9) based on a simulated PCT guided algorithm. These patients received a median of 7.5 antibiotic days (IQR 2.75, 13.25). Twelve patients (25%) would have received more antibiotic days based on the simulated model. These patients received a median of only 2 antibiotic days (IQR 1.8, 6.0). Upon chart review, none of these patients had evidence for morbidity of untreated infection, including super-infection or reinfection. Using the multiple imputation model for missing data, the patients overall would have had a mean reduction of 4.6 days of antibiotic prescription (95% CI 2.8, 6.6, p<0.001). Importantly, demographic characteristics of both groups were similar except for a statistically significant shorter PICU length of stay in the group that would have been predicted to receive more antibiotics than what they received based on clinical judgment (discussed above).

Discussion

Our study demonstrates two findings. First, PCT had a moderate diagnostic accuracy for bacterial

infection in this cohort, consistent with the current literature. The current study provides further supportive evidence that PCT measurement can detect infection in critically ill children admitted to the PICU with reasonable sensitivity and specificity. In addition, this is the first study to follow the temporal kinetics of PCT over time in the PICU setting. The majority of series reported to date have limited PCT measurement to only 2-3 days. Critically ill children likely have ongoing inflammation. As such, demonstrating that PCT declines over time even in the setting of critical illness, was an important preliminary step in planning a clinical trial of PCT guided antibiotic initiation <u>and</u> termination. Second, simulating a PCT guided algorithm in critically ill pediatric patients with suspected infection demonstrated a significant potential for fewer days of antibiotic prescription. It is important to note that we did not implement an intervention in this study. However, our study provides new data in the pediatric critically ill population that is consistent with the literature that demonstrates a safe reduction of antibiotic prescription with implementation of a PCT guided algorithm in other patient populations, including the patient with respiratory infections (including pneumonia) and in the adult critically ill patient with suspected infection[35, 43, 50].

Reducing antibiotic exposure safely is a necessary and worthwhile goal. The consequence of unnecessary antibiotic exposure is multifold. Adverse effects to individual patients can result in significant morbidity and mortality, including but not limited to anaphylaxis, cardiotoxicity, nephrotoxicity, and colitis [51]. Furthermore, several antibiotics alter the pharmacokinetics of other commonly used drugs in the PICU[51]. Finally, unnecessary antibiotic use can add further to the already exorbitant costs associated with care in the PICU[52]. More significantly, on a population level, a key modifiable contributor to the increasing burden of antibiotic resistance is antibiotic exposure [53-55]. In addition to the human costs of morbidity and mortality associated with multi-drug and pan-resistant bacteria, the financial cost of treating these morbidities is significant and difficult to account for completely. It includes the cost of more expensive antibiotics, the costs of isolation, cross-infection

control and other healthcare delivery considerations[53]. Therefore, it is important that we explore strategies for more effective antibiotic stewardship, such as the PCT guided algorithm explored in this study.

Not to be ignored, however, are the potential adverse consequences from reduced antibiotic exposure, including morbidity from undertreated infection, re-infection, and superinfection. Although the studies in other populations do not demonstrate an increase in these adverse events, an interventional trial is needed to determine the impact a PCT guided algorithm of antibiotic prescription would have on the pediatric critically ill child with suspected infection and the potential consequences thereof.

It is notable that the 25% of patients who would have received more antibiotics if their clinicians had followed our PCT guided algorithm of antibiotic prescription had a significantly shorter PICU length of stay. Although this may reflect untreated infection, upon further chart review, these patients had no adverse consequence for their lack of antibiotic prescription. This must give pause in considering the specificity of downtrending procalcitonin as a marker for effective antibiotic treatment. Although the overall predicted effect for all patients was a reduction of antibiotic exposure, the potential individual consequence of increased, potentially unnecessary antibiotic exposure cannot be ignored.

Limitations of this study include the number of patients (25%) with incomplete data necessitating a prediction model. This limitation was inherent to the study design given the observational nature of the study and the cessation of PCT measurements with cessation of antibiotic prescription. Additionally, since we had no implemented intervention in this study, we can make no conclusion about safety, including the potential risk for superinfection or reinfection with reduced antibiotic exposure.

In conclusion, the current study shows that a procalcitonin guided algorithm for antibiotic prescription in the critically ill pediatric patient with suspected infection has the potential to reduce antibiotic prescription. This data is consistent with the studies done on critically ill adults and provides significant

support to justify and inform an interventional study. A randomized controlled trial of a PCT guided algorithm for antibiotic guidance in the critically ill pediatric patient with suspected infection is warranted to determine if this strategy can safely reduce antibiotic exposure in this patient population.

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Figure 2: Possibilities of the Primary Outcome and Use of the Prediction Model



Possibility 1 and Possibility 2 have complete data. However, as we stopped measuring PCT after termination of antibiotic prescription, the predicted days in possibility 3 were modeled based on the complete data available from patients in possibility 1 and 2.

Table 1: Demographic Characteristics of Included Patients				
Age (years)	5(2.75-12.25)			
Male(%)	58%			
PICU Length of Stay	3(IQR 1-6)			
PRISM 3 score	6(IQR 2-9)			
Percentage with Clinical infection	35%			
Percentage with Positive Culture	25%			
Median Antibiotic Days	5(IQR 2-10)			





Table 2: Demographic Characteristics of Both Groups							
	Fewer Predicted Antibiotic days	More Predicted Antibiotic days	p value				
Age (years)	5(IQR 2.5-9)	5.5(IQR 3.5-13.25)	0.8				
Male (%)	53%	67%	0.44				
PICU Length of Stay	4(IQR 2-13)	1(IQR 1-2.25)	0.001*				
PRISM 3 score	4(IQR 2-9)	6(IQR 0-8.5)	0.72				
Percentage with Bacterial Infection	40%	25%	0.48				
Percentage with Positive Culture	29%	17%	0.69				