# Value of Procalcitonin Measurement for Early Evidence of Severe Bacterial Infections in the Pediatric Intensive Care Unit

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**Objectives** To determine whether peak blood procalcitonin (PCT) measured within 48 hours of pediatric intensive care unit (PICU) admission can differentiate severe bacterial infections from sterile inflammation and viral infection and identify potential subgroups of PICU patients for whom PCT may not have clinical utility.

**Study design** This was a retrospective, observational study of 646 critically ill children who had PCT measured within 48 hours of admission to an urban, academic PICU. Patients were stratified into 6 categories by infection status. We compared test characteristics for peak PCT, C-reactive protein (CRP), white blood cell count (WBC), absolute neutrophil count (ANC), and % immature neutrophils. The area under the receiver operating characteristic curve was determined for each biomarker to discriminate bacterial infection.

**Results** The area under the receiver operating characteristic curve was similar for PCT (0.73, 95% CI 0.69, 0.77) and CRP (0.75, 95% CI 0.71, 0.79; $P = .36$), but both outperformed WBC, ANC, and % immature neutrophils ($P < .01$ for all pairwise comparisons). The combination of PCT and CRP was no better than either PCT or CRP alone. Diagnostic patterns prone to false-positive and false-negative PCT values were identified.

**Conclusions** Peak blood PCT measured close to PICU admission was not superior to CRP in differentiating severe bacterial infection from viral illness and sterile inflammation; both PCT and CRP outperformed WBC, ANC, and % immature neutrophils. PCT appeared especially prone to inaccuracies in detecting localized bacterial central nervous system infections or bacterial coinfection in acute viral illness causing respiratory failure. *(J Pediatr 2016;179:74-81).*

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Difficulty in distinguishing bacterial infections from noninfectious systemic inflammatory illness exposes many patients to unnecessary antibiotic therapy in the intensive care unit.[1-6] There remains an unmet need to identify early biomarkers of severe bacterial infections in critically ill pediatric patients that can help to optimize antibiotic utilization. Procalcitonin (PCT) is an emerging biomarker with demonstrable utility to guide antibiotic utilization in adults.[7-12] Several trials in adults have shown that serum PCT level is higher with invasive bacterial infections than with viral or sterile inflammatory conditions and can help to optimize antibiotic utilization without increasing morbidity or mortality.[13-15]

In critically ill children, however, the utility of PCT to augment early recognition of severe bacterial infections compared with routinely available laboratory tests remains unclear. Prior pediatric studies have reported mixed results, and few studies have specifically examined the use of PCT in the pediatric intensive care unit (PICU).[16-19] In some cases, PCT has yielded superior test characteristics than routinely used laboratory tests, such as measurement of C-reactive protein (CRP), white blood cell count (WBC), and % immature neutrophils, but the optimal cut point reported for PCT to guide clinical decision-making remains highly variable across studies.[20-24] One common limitation of prior studies has been the relatively small sample size of subjects analyzed. In addition, although few diagnostic tests perform universally well in all patient subgroups, prior PICU-based studies of PCT have not attempted to consider diagnostic patterns for which PCT testing may have more or less clinical utility. Along these lines, one

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| ANC | Absolute neutrophil count |
| AUROC | Area under the receiver operating characteristic curve |
| CNS | Central nervous system |
| CRP | C-reactive protein |
| NPV | Negative predictive value |
| PCT | Procalcitonin |
| PICU | Pediatric intensive care unit |
| PPV | Positive predictive value |
| WBC | White blood cell count |

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recently published prospective study suggested that there may be subgroups of patients in the PICU for whom PCT measurement is less useful, but the study but had too few patients to draw firm conclusions.[19]

We sought to determine if peak blood PCT measured within 48 hours of PICU admission could differentiate severe bacterial infections from severe viral illness and systemic sterile inflammation and identify potential subgroups of critically ill children for whom PCT may not have clinical utility. We hypothesized that a low PCT cut point may perform as well as or better than routinely available laboratory tests to identify PICU patients with a low likelihood of bacterial infection who required prolonged treatment with antibiotics, and there are identifiable diagnostic patterns of PICU disease that are prone to false-positive and false-negative PCT results for whom PCT testing may be less useful.

## Methods

We performed a retrospective, observational study of all patients ages 29 days to 21 years admitted to a 55-bed PICU at an academic medical center between August 1, 2012, and February 15, 2014. Patients were included if blood PCT was sent as part of routine care within 48 hours of PICU admission, and the maximum measured PCT within this timeframe was used. For patients with multiple PICU admissions, only data from the first episode were included. We also excluded patients with superficial (ie, noninvasive) bacterial infections, those transferred from another unit or hospital with established antibiotic therapy for >48 hours, or those whose final infection status could not be determined because of transfer out to another institution before all diagnostic testing was complete. This study was approved by the Institutional Review Board at The Children's Hospital of Philadelphia, and a waiver of consent was granted.

Study design and data collection followed published guidelines for chart reviews.[25] A review of the electronic medical record was completed for all eligible patients. Demographics, comorbid conditions, duration of hospitalization, and laboratory and microbiologic data were collected, and any missing data were noted. Recognizing that patients may come to attention at different time points in their courses of illness, the maximum values of PCT, CRP, and WBC within 48 hours prior to and 48 hours after PICU admission were recorded as (measured) biomarker peaks. The absolute neutrophil count (ANC) and % immature neutrophils corresponding to the highest WBC also were recorded. Severity of illness was determined by the Pediatric Risk of Mortality-III and Pediatric Index of Mortality-2 scores.[26,27] Definitions of types of infections were adapted from guidelines by the Centers for Disease Control and Prevention and the National Healthcare Safety Network.[28] All data were recorded onto a standardized case report form using the web-based Research Electronic Data Capture system.[29] The case-report form, a glossary of terms, and a coding sheet for infection categorization were developed with collaborative input from all study group members. Four abstractors were trained to collect data and categorize patients in a similar manner.

Patients were classified into 1 of 6 mutually exclusive categories of infection (**Table I**; available at www.jpeds.com): (1) no infection; (2) viral infection; (3) suspected bacterial infection without shock; (4) documented bacterial infection without shock; (5) bacterial infection with shock (bacterial septic shock); and (6) septic shock without definitive microbiologic evidence of bacterial infection ("culture-negative septic shock"). Patients categorized as having no infection had no pathogenic organisms identified and no imaging suggestive of infection. Patients with viral infection had either an identified viral pathogen or a documented strong suspicion of viral infection without concurrent bacterial infection. Criteria for bacterial infection without shock included a clinical syndrome consistent with a likely bacterial infection, with (for documented infection) or without (for suspected infection) isolation of a bacterial or fungal pathogen from a sterile site.[28] For example, most patients with pneumonia who did not have shock were categorized as suspected bacterial infection without shock. Patients with bacterial septic shock had a documented bacterial or fungal pathogen and met criteria for severe sepsis or septic shock.[30] Culture-negative septic shock included patients with suspected infection (including documented viral infection) without isolation of a bacterial or fungal pathogen but who met criteria for severe sepsis or septic shock. Although culture-negative septic shock likely included some patients with undocumented bacterial infection, we a priori determined to analyze this group separately from documented bacterial septic shock because it was not possible to differentiate these patients from nonbacterial (eg, viral) septic shock and because their severity of illness justified empiric antibiotic administration regardless of pathogen.[7,20]

Interrater reliability testing was undertaken to ensure congruent classification of infection. Fifteen charts were randomly selected for all abstractors to review. The mean percent agreement across all abstractors to determine the infection category was 83% (Kappa 0.71). When categories of infection were conservatively grouped by presence or absence of bacterial infection (ie, no infection and viral infection vs bacterial with/without shock and culture-negative septic shock), the mean percent agreement increased to 87%. Following consensus review, agreement of the final assigned infection category reached 100%. Because interrater reliability for infection category did not reach 100% until after consensus review, abstractors continued to flag any cases for which the category of infection was not clear during the remainder of the chart review process. Regular meetings were held to monitor overall performance and to establish final categorization by consensus agreement for all cases with uncertainty. In total, 24% of patients were reviewed for consensus agreement. Abstractors were blinded to PCT values during chart abstraction, categorization, and consensus review. PCT values were separately provided by the institution's Department of Biomedical and Health Informatics. Other laboratory values, including CRP and WBC, were directly abstracted from the medical

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