# Clinical Progress Note: Procalcitonin in the Management of Pediatric Lower Respiratory Tract Infection

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Procalcitonin (PCT) is a biomarker that has shown promise to identify bacterial etiology in acute infections, including bacterial lower respiratory tract infection (LRTI). In 2017, the United States Food and Drug Administration (FDA) approved the use of PCT as a diagnostic aid to guide the decisions around antibiotic therapy in acute LRTI.[1] Although most of the data supporting the use of PCT for LRTI stems from adult studies, the high disease burden, predominance of viral etiologies, and frequent diagnostic uncertainty resulting in antibiotic overuse make pediatric LRTI an ideal target for the use of PCT as a diagnostic aid. This review evaluates and summarizes the current evidence regarding the role of PCT in the clinical care of pediatric LRTI, including its use in guiding antibiotic use and prognosticating disease severity.

## THE ROLE OF PROCALCITONIN IN GUIDING INITIATION OF ANTIBIOTICS

The commonly used PCT cut points for withholding or stopping antibiotics in adults and children are 0.1 μg/L (very low risk of bacterial etiology) or 0.25 μg/L (low risk of bacterial etiology).[2-4] Among the 532 children enrolled in the multicenter study of Etiology of Pneumonia in the Community (EPIC), a PCT threshold of 0.25 μg/L demonstrated an approximate sensitivity of 85%, specificity of 45%, positive likelihood ratio of 1.55, and negative likelihood ratio of 0.33 for community acquired pneumonia (CAP) caused by typical bacterial pathogens.[5] Lowering the cutoff to <0.1 μg/L increased PCT sensitivity to 100%, decreased specificity, positive likelihood ratio, and negative likelihood ratio to 20%, 1.26, and 0, respectively. Although the EPIC study obtained culture and performed PCR testing on any blood sample, pleural fluid specimen, endotracheal aspirate, or bronchoalveolar–lavage specimens obtained during the study period, currently available laboratory methods show poor sensitivity for defining bacterial LRTI. Thus, bacterial etiologies may have been underestimated. The highly negative predictive value demonstrated in this study highlights the potential of PCT as a biomarker for ruling out bacterial diseases, including LRTI.

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Published online first September 18, 2019.

**Received**: June 6, 2019; **Revised**: August 5, 2019; **Accepted**: August 8, 2019

 **DOI 10.12788/jhm.3301**

Multiple studies have evaluated the potential utility of PCT in guiding antibiotic initiation in adults with LRTI, but data on pediatric patients are sparse.[4] In a randomized, single-center Italian study comparing a PCT-guided algorithm (withholding antibiotics when PCT < 0.25 μg/L) versus usual care among 319 hospitalized children with pneumonia, the PCT group experienced fewer antibiotic initiations (15.5% vs 100%, $P < .05$) without significant differences in recurrence of respiratory symptoms or new antibiotic prescriptions in the month following enrollment.[2]

A similar randomized trial using a PCT-guided algorithm for the initiation of antibiotics conducted among 337 Swiss children presented to the emergency department (ED) with pneumonia and other LRTIs failed to demonstrate decreases in antibiotic initiation.[3] This study used an algorithm that categorized the likelihood of requiring antibiotic treatment for bacterial LRTI as "definitely" if PCT was >0.5 μg/L, "probably" if PCT was 0.26–0.5 μg/L, "probably not" if PCT was 0.1–0.25 μg/L, and "definitely not" if PCT was <0.1 μg/L. In the PCT group, 104 out of 168 (62%) patients received antibiotics within 14 days compared with 93 out of 165 (56%) patients in the control group (odds ratio [OR]: 1.26, 95% CI: 0.81, 1.95). In the subgroup analyses, the odds of administering antibiotics to those with nonpneumonia LRTI was significantly higher than those of the PCT group and control group (OR: 4.09, 95% CI: 1.8, 9.93); the odds of receiving antibiotics also showed no difference in the subgroup of children with pneumonia (OR: 0.66, 95% CI: 0.35, 1.23).

The benefit of PCT for informing decisions around the initiation of antibiotics likely varies based on perceived risk of bacterial diseases. When the pretest probability of bacterial disease is extremely high, the use of PCT is unlikely to alter treatment decisions. Similarly, PCT should not be used in situations where the pretest probability for bacterial pneumonia is very low—in these instances, an elevated PCT may lead to unnecessary antibiotic use among children presenting to the ED. However, the risk of bacterial pneumonia is often equivocal, and in these situations, PCT may provide clinicians with useful insights, primarily for ruling out bacterial disease.

## THE ROLE OF PROCALCITONIN IN GUIDING DISCONTINUATION OF ANTIBIOTICS

In the study by Esposito et al., the PCT levels were additionally measured every two days until discharge and during two scheduled follow-up visits; the antibiotics were discontinued when PCT < 0.25 μg/L.[2] The PCT-guided group experienced

TABLE. **Causes of Falsely Elevated and Falsely Decreased Procalcitonin Levels**[12,15]

| Falsely Elevated | Falsely Decreased |
|---|---|
| Newborns <48–72 hours of age | Localized infections (osteomyelitis, abscess, subacute endocarditis, empyema) |
| Massive stress (severe trauma, surgery, cardiac shock, burns) | Procalcitonin checked early in course of illness |
| Treatment with agents that stimulate cytokines (OKT3, anti-lymphocyte globulins, alemtuzumab, IL-2, granulocyte transfusion) | *Mycoplasma pneumoniae* pneumonia |
| Malaria and some fungal infections | |
| Prolonged, severe cardiogenic shock or organ perfusion abnormalities | |
| Systemic vasculitis and acute graft vs host disease | |
| End-stage renal disease | |
| Paraneoplastic syndromes due to medullary thyroid and small cell lung cancer | |

Abbreviations: IL-2, interleukin 2; OKT3, murine monoclonal antibody of the immunoglobulin IgG2a isotype.

shorter antibiotic duration (mean 5.4 vs 11.0 days, $P < .05$), shorter length of hospital stay (mean 4.7 vs 5.61 days for mild LRTI and 5.01 vs 5.93 for severe LRTI), and fewer antibiotic-related adverse events (3.9% vs 25.2%, $P < .05$). Similarly, in the study by Baer et al., the PCT-guided group had PCT levels repeated on days three and five after enrollment, and the antibiotics were discontinued when PCT was less than 0.25 μg/L. The duration of antibiotic administration was significantly lower in the PCT-guided group (mean difference: 1.8 days, 95% CI: −3.1, −0.).[3] The rates of hospitalization, duration of hospital stay, and mean impairment of daily activities attributable to LRTI were similar between groups.

Considering the adult studies and the small number of pediatric LRTI research published to date, the use of PCT to safely reduce antibiotic treatment duration is encouraging.[4] Although the studies on the kinetics of PCT are limited, the biomarker has been shown to rise two to four hours after a bacterial stimulus, peak in 24-48 hours and achieve a half-life of 24-36 hours.[6,7] As such, serial PCT measurements at 24-hour intervals for three to five days may be more beneficial than stand-alone PCT tests. Nonetheless, additional studies are needed to better define groups of patients who will most likely benefit from PCT testing and to understand how to best integrate testing into clinical practice.

## PROCALCITONIN FOR SEVERITY PREDICTION IN LRTI

PCT has also been explored as a marker of LRTI disease severity. In a 2008 multicenter cohort encompassing 1,651 adults with pneumonia, PCT < 0.1 μg/L was associated with a decreased 30-day mortality, shorter length of stay, and decreased admission to the intensive care unit (ICU) compared with those with PCT ≥ 0.1 μg/L.[8] In a 2017 study of 317 adults hospitalized with pneumonia, the PCT level was significantly higher in those with bacteremia and in those admitted to intensive care.[9] When used in combination with the pneumonia severity index (PSI), the addition of PCT resulted in improved prognostic performance compared with the PSI alone for both outcomes, increasing the area under the receiver operating characteristic curve from 0.67 to 0.85 for bacteremia and from 0.58 to 0.64 for intensive care. Similarly, in the adult EPIC cohort, the addition of PCT contributed significant prognostic information beyond existing severity scores for predicting the need for invasive respiratory or vasopressor support; each 1 μg/L increase in PCT was associated with a 1% to 2% absolute increase in the need for this outcome.[10]

A European study of 100 children with pneumonia also demonstrated higher PCT values among hospitalized children (n = 26, median PCT 17.8 μg/L) compared with outpatient children (n = 73, median PCT 0.72 μg/L, $P < .01$).[11] Among the 532 children from the EPIC study, a PCT < 0.25 μg/L was associated with the reduced odds of ICU admission (adjusted OR: 0.48; 95% CI: 0.30, 0.78) and a 2.3-day (95% CI: 1.4, 3.2) decrease in the average length of stay compared with those with higher PCT concentrations.[5] Of the 34 children with empyema requiring drainage, 28 (82%) showed a PCT concentration ≥0.5 μg/L. Additional pediatric studies are needed, but the limited data to date suggest that PCT may play a role in predicting pediatric LRTI disease severity, including the need for mechanical ventilatory support and ICU-level care.

## LIMITATIONS TO CLINICAL APPLICATION

Although PCT shows promise as a biomarker to reliably rule out bacterial infection, several potential limitations exist in assessing its role in pediatric LRTI. Atypical bacterial infections (ie, *Mycoplasma pneumoniae*) and localized bacterial infection may not induce significant PCT production, as has been shown in adults and children with tonsillitis, localized skin infections, endocarditis, or empyema (Table).[12] The majority of clinical trials in LRTI have been conducted in the adult population,[4] with the number of pediatric trials remaining small.[2,3] Given the predominance of viral LRTI in children compared with adults, the utility of PCT may differ in these populations.[13,14] Further-

more, existing studies demonstrate mixed results regarding the magnitude of benefits that PCT may provide in terms of limiting antibiotic use. Another concern is the potential of PCT to increase unnecessary antibiotic use in those with viral LRTI,[3] as PCT may also be increased in populations with systemic inflammation from nonbacterial causes.[12,15]

## CONCLUSIONS AND CLINICAL APPLICATION

The misuse of antibiotics is a public health crisis resulting in the emergence of antibiotic-resistant pathogens and adverse outcomes, including *Clostridioides difficile* infection, drug toxicities, and increased healthcare costs.[16] Pneumonia is responsible for more days of antibiotics than any other disease in children's hospitals and is an important target for stewardship efforts.[17] PCT is a promising biomarker for distinguishing bacterial from viral infection, and its use may help in making informed antibiotic decisions and predicting disease outcomes in pediatric LRTI. Although PCT has been cleared by the FDA for assisting with antibiotic decisions in pediatric LRTI, the majority of evidence supporting this indication is drawn from adults. Additional studies are needed prior to the widespread implementation in the pediatric population, but the results of available pediatric studies show promise. The clinical context and severity of patient presentation are important when considering whether or not to use PCT and how to best interpret PCT levels when making clinical management decisions. The utility of PCT for antibiotic initiation in the pediatric population is encouraging given the predominance of viral etiologies in pediatric LRTI. Currently available data demonstrate the value of serial PCT measurements in antibiotic de-escalation and promoting antibiotic stewardship for children and adults.[2-4] As with all new diagnostic modalities, provider education is paramount to ensure a safe and value-driven implementation.

Disclosures: Dr. Katz received investigator-initiated grant funding from Roche and bioMérieux to conduct research involving procalcitonin in the past three years. Dr. Sartori has nothing to disclose. Dr. Williams received investigator-initiated grant funding from bioMérieux to conduct research involving procalcitonin in the past three years.

Funding: This work was supported by the National Institute of Health (1T32AI095202-07).

Disclaimer: This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, Roche, or bioMérieux.

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