



Procalcitonin Accurately Identifies Hospitalized Children With Low Risk of Bacterial Community-Acquired Pneumonia

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(See the editorial commentary by Shah et al, on pages 54–5.)

Background. Lower procalcitonin (PCT) concentrations are associated with reduced risk of bacterial community-acquired pneumonia (CAP) in adults, but data in children are limited.

Methods. We analyzed serum PCT concentrations from children hospitalized with radiographically confirmed CAP enrolled in the Centers for Disease Control and Prevention's Etiology of Pneumonia in the Community (EPIC) Study. Blood and respiratory specimens were tested using multiple pathogen detection methods for typical bacteria (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*), atypical bacteria (*Mycoplasma pneumoniae* and *Chlamydia pneumoniae*), and respiratory viruses. Multivariable regression was used to assess associations between PCT concentrations and etiology and severity.

Results. Among 532 children (median age, 2.4 years; interquartile range [IQR], 1.0–6.3), patients with typical bacteria had higher PCT concentrations (\pm viruses; $n = 54$; median, 6.10; IQR, 0.84–22.79 ng/mL) than those with atypical bacteria (\pm viruses; $n = 82$; median, 0.10; IQR, 0.06–0.39 ng/mL), viral pathogens only ($n = 349$; median, 0.33; IQR, 0.12–1.35 ng/mL), or no pathogen detected ($n = 47$; median, 0.44; IQR, 0.10–1.83 ng/mL) ($P < .001$ for all). No child with PCT < 0.1 ng/mL had typical bacteria detected. Procalcitonin < 0.25 ng/mL featured a 96% negative predictive value (95% confidence interval [CI], 93–99), 85% sensitivity (95% CI, 76–95), and 45% specificity (95% CI, 40–50) in identifying children without typical bacterial CAP.

Conclusions. Lower PCT concentrations in children hospitalized with CAP were associated with a reduced risk of typical bacterial detection and may help identify children who would not benefit from antibiotic treatment.

Keywords. antibiotic stewardship; children; pneumonia; procalcitonin; risk-stratification.

Respiratory viruses are the most common agents detected in children with community-acquired pneumonia (CAP) [1, 2]. However, because exclusion of bacterial pneumonia is challenging, empirical antibiotics are commonly prescribed. To prevent overprescribing of antibiotics for children at low risk for bacterial CAP, and to assist with discontinuation of empirically prescribed therapy, a rapid and reliable method to identify these patients would be valuable.

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin produced by C cells in the thyroid gland and by neuroendocrine cells in the lung and intestine [3, 4]. Among healthy individuals, serum PCT concentrations are low or undetectable (< 0.1 ng/mL); however, they usually increase markedly in patients with confirmed bacterial infections [5]. In adults, PCT

concentrations have been used to guide the initiation and duration of antibiotic therapy for patients with CAP [6–10].

Results from studies assessing the clinical utility of PCT for children with CAP are conflicting [11–14]. Early studies were limited by the sensitivity of the PCT assays and varying etiological testing methods. The objective of this study was to assess whether serum PCT concentrations were associated with the type of pathogen detected and disease severity in a large, well defined cohort of children hospitalized with radiographically confirmed CAP in the United States [2]. In addition, we sought to evaluate the utility of pediatric-specific PCT thresholds to reliably identify children at low risk for bacterial CAP caused by “typical” pathogens such as *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, and *Staphylococcus aureus*.

METHODS

Study Population

Children enrolled in the Centers for Disease Control and Prevention's (CDC) Etiology of Pneumonia in the Community (EPIC) Study [2] at Primary Children's Hospital in Salt Lake City,

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Utah, and the Monroe Carrell Jr Children's Hospital at Vanderbilt in Nashville, Tennessee, were included. The EPIC study was a multicenter, population-based, prospective active surveillance study of radiographically confirmed CAP in children performed between January 1, 2010 and June 30, 2012 [2]. Of the 1397 children enrolled in the EPIC study in Salt Lake City and in Nashville, 532 (38%) had residual sera obtained at the time of hospitalization available. The study protocol was approved by the institutional review board at each site and at the CDC.

Diagnostic Testing

Diagnostic testing used in the EPIC study has been previously described [2]. In brief, a "typical" bacterial pathogen was defined as *S pneumoniae*, *S pyogenes*, *H influenzae*, *S aureus*, specific viridans group streptococci, or Gram-negative bacteria detected in blood, high-quality endotracheal aspirates (except viridans group streptococci), bronchoalveolar-lavage specimens, or pleural fluid by culture, or in whole blood or pleural fluid by polymerase chain reaction (PCR) [2]. "Atypical" bacteria were defined as *Chlamydophila pneumoniae* or *Mycoplasma pneumoniae* detected in combined nasopharyngeal/oropharyngeal (NP/OP) swabs by PCR. A viral pathogen was defined as adenovirus, coronavirus, human metapneumovirus (hMPV), rhinovirus, influenza virus, parainfluenza virus, or respiratory syncytial virus (RSV) detected in an NP/OP swab by PCR or a 4-fold increase in agent-specific antibody titer between the acute-phase and convalescent-phase serum specimen obtained 3–10 weeks after discharge for each aforementioned virus, except for coronavirus and rhinovirus.

Etiologic Classification

Participants were classified into 4 categories based on pathogens detected: (1) typical bacterial pathogen(s) (with/without viral and/or atypical detection); (2) atypical bacterial pathogen(s) (with/without viral detection); (3) only viral pathogen(s); and (4) no pathogen detected. All of the children with residual sera in groups 1 and 2 were included in this analysis. A random sample of children with residual sera from groups 3 and 4 was included (396 of 1160 [24%]).

Procalcitonin Testing

Residual sera were frozen at -70° until PCT testing was performed using the VIDAS BRAHMS PCT assay (bioMérieux, Marcy, L'Etoile, France; assay detection range from 0.05 to 200 ng/mL). All PCT testing was performed retrospectively. Procalcitonin results were not available to the treating clinicians. Clinical information was not available to personnel performing the PCT assay.

Measures of Severe Outcomes

We examined several outcome measures including intensive care unit (ICU) admission, invasive mechanical ventilation,

parapneumonic empyema, and total hospital length of stay (LOS). Empyema was defined by presence of a pleural effusion and drainage by chest tube or surgical procedure. Laboratory testing results were not used to confirm that drained pleural fluid was truly empyema, and thus this is a proxy definition.

Statistical Analyses

We calculated median PCT values and compared groups using the Mann-Whitney *U* test. We examined the discriminatory performance of PCT using cutoffs from decision algorithms used for adults with CAP [6, 8, 15, 16]. Diagnostic test measures including sensitivity, specificity, positive and negative predictive values, and diagnostic likelihood ratios were calculated for PCT cutoffs of <0.1, <0.25, <0.5, <1, and <2 ng/mL. Due to frequent use of the <0.25 ng/mL cutoff in the adult literature, this threshold was selected for a majority of the comparisons. To assess the discriminatory power of PCT concentration in distinguishing patients with typical bacterial from other pathogen detections, multivariable logistic regression models were developed in which the dependent variable was defined as the presence or absence of a typical bacterial detection. Ten-fold cross-validation was performed. In brief, this involved splitting the dataset into 10 equal partitions. The model was fitted using 9 of the partitions and tested on the remaining partition. This process was repeated 10 times with each partition tested exactly once. Model results were then averaged across the 10 runs to produce a single estimate. Receiver operating curve (ROC) plots were also developed. All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographics, microbiological findings and clinical characteristics for children included in this analysis are shown in Table 1. Typical bacteria (with/without viral and/or atypical bacterial codetection) were detected in 54 (10%) children, atypical bacteria (with/without viral codetection) were detected in 82 (15%) children, and viruses alone were detected in 349 (66%) children. Bacterial detections included blood culture ($n = 19$), blood PCR ($n = 21$), pleural fluid culture or PCR ($n = 25$), bronchoalveolar lavage culture ($n = 2$), and culture of high-quality endotracheal aspirates ($n = 1$) (numbers sum to more than 100% due to detection by multiple methods). No pathogen was detected in 47 (9%) children. Severe outcomes included ICU care in 185 (35%) children, invasive mechanical ventilation in 57 (11%) children, and parapneumonic empyema in 34 (6%) children. Most children (87%) received inpatient antibiotics, and 25% received outpatient antibiotics. Children included in this study were more likely to have a typical or atypical bacterial pathogen detected, have empyema or be admitted to ICU, and less likely to have no pathogen identified compared with children

Table 1. Demographics, Clinical Characteristics, and Microbiological Findings Among Children Hospitalized With CAP in this Study

Parameter	Combined (n = 532)	Salt Lake City, Utah (n = 377)	Nashville, Tennessee (n = 155)
Demographics			
Male	289 (54%)	200 (53%)	89 (57%)
Median age (IQR), years	2.4 (1.0–6.3)	2.2* (0.9–6.2)	3.2* (1.3–6.8)
Microbiological findings			
Typical bacterial pathogens ^b	54 (10%)	42 (11%)	13 (8%)
Atypical bacterial pathogen(s) ^b	82 (15%)	60 (16%)	22 (14%)
Viral pathogen(s) only ^c	349 (66%)	241 (64%)	107 (69%)
No pathogen detected	47 (9%)	34 (9%)	13 (8%)
Clinical characteristics			
Parapneumonic empyema	34 (6%)	24 (6%)	10 (6%)
Intensive care unit admission	185 (35%)	120 (32%) ^d	65 (42%) ^d
Invasive mechanical ventilation	57 (11%)	31 (8%) ^e	26 (17%) ^e
Median length of stay (IQR), days	3.0 (1.9–5.5)	3.1 (2.0–5.8)	2.9 (1.8–5.0)
Death	0 (0%)	0 (0%)	0 (0%)

Abbreviations: CAP, community-acquired pneumonia; IQR, interquartile range.

* $P = .04$ via Wilcoxon-Mann-Whitney U test.

^bIncludes bacterial detections with and without viral codetection.

^cThe viruses tested for in this study included the following: adenovirus, coronavirus 229E, coronavirus HKU1, coronavirus OC43, coronavirus NL63, influenza A, influenza B, human metapneumovirus, human rhinovirus, parainfluenza viruses 1–4, and respiratory syncytial virus.

^d $P = .03$ via the χ^2 test.

^e $P = .004$ via the χ^2 test.

enrolled in the EPIC study who were not included in this analysis (Supplemental Table 1).

Median PCT concentrations were higher in those with typical bacterial pathogens detected (6.10 ng/mL; IQR, 0.84–22.79) compared with those with atypical bacteria detected (0.10 ng/mL; IQR, 0.06–0.31), only viral pathogens detected (0.33 ng/mL; IQR, 0.12–1.35), or no pathogen detected (0.44 ng/mL; IQR, 0.10–1.83) ($P < .001$ for each comparison) (Figure 1). Procalcitonin concentrations were similar in children with typical bacterial infection alone ($n = 17$; median, 2.98 ng/mL; IQR, 0.93–12.48) compared with those with bacterial and viral codetection ($n = 37$; median, 6.64 ng/mL; IQR, 0.80–26.63) ($P = .53$) (Table 2).

Among 120 children (23% of cohort) with PCT concentrations <0.1 ng/mL, none had a typical bacterial pathogen detected (Table 3). Of 127 children with a PCT concentration ranging from 0.1 to <0.25 ng/mL, only 9 (7%) had a typical bacterial pathogen detected. In contrast, 17% of children with a PCT concentration ≥ 0.25 ng/mL had a typical bacterial pathogen detected ($P = .03$).

Using a cutoff of <0.25 ng/mL, the sensitivity of PCT for the identification of children with typical bacterial CAP was 85% (95% CI, 72–93), with a specificity of 45% (95% CI, 40–50), a positive predictive value of 17% (95% CI, 13–23), and a negative predictive value of 96% (95% CI, 91–98) (Table 4). Lowering the cutoff to <0.1 ng/mL increased the sensitivity to 100% (95% CI, 92–100%) but decreased specificity (20%; 95% CI, 17–25) and the positive predictive value (15%; 95% CI, 11–19). However, negative predictive value was 100% (95% CI, 94–100). A PCT concentration <0.25 ng/mL was associated with a 5-fold lower odds of typical bacterial detection (odds ratio [OR], 0.20; 95% CI, 0.09–0.41). This association remained after adjustment for pretreatment with antibiotics (based on inpatient

administration timing of the first dose), time from symptom onset to specimen collection, age, and detection of influenza, RSV, or hMPV (adjusted OR, 0.21; 95% CI, 0.09–0.42).

Table 5 shows clinical outcomes for children with CAP, stratified by PCT concentration. The median PCT concentration was significantly higher for children admitted to the ICU (0.61 ng/mL;

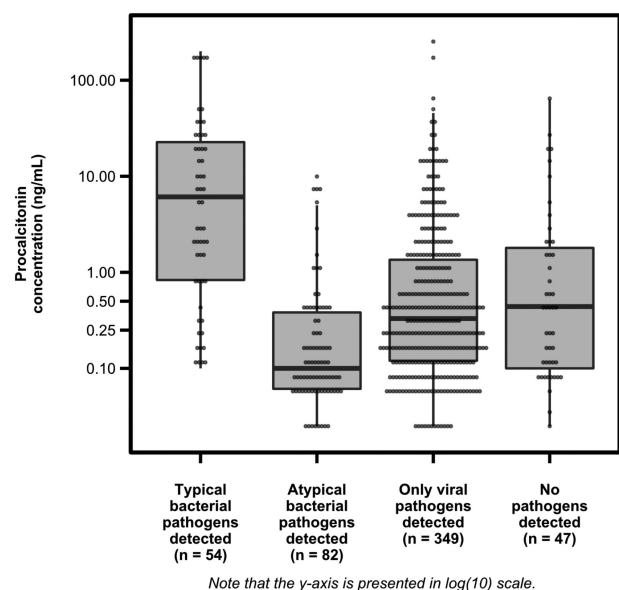


Figure 1. Procalcitonin concentrations among children hospitalized with community-acquired pneumonia stratified by patterns of microbiological detection. The solid gray lines inside the boxes denote the median, and the borders of the boxes denote the interquartile range. Vertical lines extending above and below the boxes are 1.5 times the interquartile range. Individual observations are represented by small gray dots.

Table 2. Procalcitonin Concentrations Stratified by Pathogen Detection Among 532 Children Hospitalized With CAP

Pathogen	Median Procalcitonin Concentration (IQR)
Typical bacterial pathogen detected (<i>n</i> = 54)	6.10 (0.84–22.79)
Bacterial pathogen alone (<i>n</i> = 17)	2.98 (0.93–12.48)
Bacterial/viral codetection (<i>n</i> = 37)	6.64 (0.80–26.63)
Atypical bacterial pathogen detected (<i>n</i> = 82)	0.10 (0.06–0.31)
Atypical pathogen detected alone (<i>n</i> = 58)	0.09 (0.06–0.21)
Atypical pathogen/viral codetection (<i>n</i> = 24)	0.13 (0.07–0.50)
Viral pathogen detected alone (<i>n</i> = 349)	0.33 (0.12–1.34)
Respiratory syncytial virus only (<i>n</i> = 102)	0.30 (0.11–0.95)
Human rhinovirus only (<i>n</i> = 30)	0.38 (0.15–1.56)
Human metapneumovirus only (<i>n</i> = 49)	0.43 (0.15–0.65)
Influenza only (<i>n</i> = 23)	0.62 (0.13–2.51)
No pathogen identified (<i>n</i> = 47)	0.44 (0.10–1.83)

Abbreviations: CAP, community-acquired pneumonia; IQR, interquartile range.

IQR, 0.16–4.32) compared with children not in the ICU (0.24 ng/mL; IQR, 0.09–0.95) ($P < .001$) (Supplemental Figure 1). Procalcitonin was significantly higher among children with empyema (2.94 ng/mL; IQR, 0.70–32.06) compared with those without empyema (median, 0.27 ng/mL; IQR, 0.10–1.33) ($P < .001$). Among 120 children with a PCT concentration <0.1 ng/mL, 26 (22%) were admitted to the ICU and 1 had empyema. After adjustment for age and detection of a typical bacterial pathogen, PCT concentrations <0.25 ng/mL were associated with a reduced odds of ICU admission (adjusted OR, 0.48; 95% CI, 0.30–0.78). A PCT concentration <0.25 ng/mL was also associated with a 2.3-day (95% CI, 1.4–3.2) decrease in the average hospital LOS.

To assess the discriminatory power of PCT concentrations in identifying children without typical bacterial pneumonia, ROC curves were constructed (Figure 2A). The area under the curve was 0.80 (95% CI, 0.73–0.86). The diagnostic accuracy of PCT for typical bacterial detections is shown in Figure 2B.

DISCUSSION

We evaluated the association between serum PCT concentrations, pathogens detected, and severity within a large, well

Table 3. Pathogens Identified From 532 Children Hospitalized With CAP and Serum Procalcitonin Concentration Ranges

PCT Range	Total, <i>n</i>	Typical Bacteria ^{a,b}	Atypical Bacteria ^{a,b}	Viral Alone ^a	No Pathogen Detected ^a
<0.1 ng/mL	120	0 (0%)	39 (33%)	70 (58%)	11 (9%)
0.1–0.24 ng/mL	127	9 (7%)	20 (16%)	91 (72%)	8 (6%)
0.25–0.49 ng/mL	75	3 (4%)	11 (15%)	53 (71%)	8 (11%)
0.5–0.99 ng/mL	44	4 (9%)	3 (7%)	33 (75%)	4 (9%)
1–1.99 ng/mL	44	6 (14%)	3 (7%)	31 (70%)	4 (9%)
≥ 2 ng/mL	122	32 (26%)	6 (5%)	71 (58%)	12 (10%)

Abbreviations: CAP, community-acquired pneumonia; PCT, procalcitonin.

^aThe number (and row percent) are presented.

^bIncludes bacterial detections with and without viral codetection.

defined cohort of hospitalized children with radiographically confirmed CAP using comprehensive diagnostics for pathogen detection [2]. Procalcitonin concentrations <0.25 ng/mL were strongly associated with a decreased likelihood of detecting typical bacteria and decreased disease severity. Higher serum PCT concentrations were associated with an increased likelihood of ICU admission, empyema, and increased hospital LOS; these associations remained when controlling for age and detection of a bacterial pathogen. Procalcitonin concentrations <0.1 ng/mL had a very high negative predictive value, effectively excluding typical bacterial CAP.

In adults, studies have shown a correlation between higher PCT concentrations and the isolation of typical bacterial pathogens [8, 15, 17, 18]. Elevated serum PCT concentrations have been most strongly associated with bacteremic CAP [17, 18]. Studies in children have been less conclusive. Two pediatric studies from Sweden [19, 20] found limited association between PCT concentrations and detected pathogens in CAP; however, other studies have shown a reasonable correlation, with the highest levels again in bacteremic CAP [13, 21]. Limitations to earlier studies include reliance on insensitive methods such as culture or bacterial serology for etiologic diagnosis and the use of first generation PCT assays with a detection limit of 0.5 ng/mL, above the range in which viral pneumonia and mild bacterial disease can be distinguished [22]. More recent studies, including ours, have used PCT assays with an improved range, but only a few have combined this with modern methods of pathogen detection [23]. Our study extends prior works by evaluating the predictive value of PCT for CAP etiology using a highly sensitive PCT assay in a cohort of children with CAP with extensive laboratory testing including modern molecular methods [2].

Procalcitonin concentrations in children in our study with *M pneumoniae* or *C pneumoniae* infections were lower than those seen in children with either typical bacterial or viral CAP. This has been reported in previous studies of both adults and children [21, 24]. The Infectious Diseases Society of America/Pediatric Infectious Diseases Society CAP guidelines emphasize the use of empirical β -lactam antibiotics for children hospitalized with CAP and de-emphasize empirical therapy for atypical bacteria [1]. The guidelines recommend testing for *M pneumoniae* and the use of macrolides when infection is documented by testing or strongly suspected if testing is not available. The value of routine treatment of atypical pathogens remains controversial; however, many patients, particularly those requiring hospitalization, may benefit [25, 26].

Similar to other studies, our data show overlap in PCT values between bacterial and viral causes of CAP. Of note, 65% of children with PCT concentrations ≥ 0.5 ng/mL had only a viral or atypical pathogen detected. Current methods to identify typical bacteria causing nonbacteremic pneumonia are limited. For children with PCT concentrations ≥ 0.5 ng/mL and only viral or atypical pathogens detected, we cannot be certain

Table 4. Discriminatory Performance of Varying Procalcitonin Cutoff Values in Identifying Typical Bacterial Infections Among 532 Children Hospitalized With CAP

PCT Cutoff Values (ng/mL)	Number (%) of Children With a PCT Concentration Above the Cutoff	Sensitivity ^a	Specificity ^a	Positive Predictive Value ^a	Negative Predictive Value ^a	Positive Likelihood Ratio ^a	Negative Likelihood Ratio ^a
<0.1	412 (77%)	1.00 (0.92–1.00)	0.20 (0.17–0.25)	0.15 (0.11–0.19)	1.00 (0.94–1.00)	1.26 (1.20–1.32)	0.00 (0.00–∞)
<0.25	290 (55%)	0.85 (0.72–0.93)	0.45 (0.40–0.50)	0.17 (0.13–0.23)	0.96 (0.91–0.98)	1.55 (1.35–1.79)	0.33 (0.17–0.63)
<0.5	226 (42%)	0.80 (0.66–0.89)	0.60 (0.55–0.65)	0.22 (0.16–0.28)	0.96 (0.92–0.98)	2.00 (1.68–2.41)	0.34 (0.20–0.57)
<1	167 (31%)	0.72 (0.58–0.83)	0.70 (0.65–0.75)	0.25 (0.18–0.32)	0.95 (0.92–0.97)	2.42 (1.94–3.03)	0.40 (0.26–0.61)
<2	123 (23%)	0.61 (0.47–0.74)	0.79 (0.75–0.83)	0.28 (0.21–0.38)	0.94 (0.90–0.96)	2.92 (2.19–3.88)	0.49 (0.35–0.69)

Abbreviations: CAP, community-acquired pneumonia; PCT, procalcitonin.

^aPoint estimates are presented on the top line, and 95% confidence intervals are presented on the second line in parentheses. Confidence intervals were derived using the continuity-corrected efficient-score method.

that the elevated PCT does not represent undetected bacterial coinfection; in some studies, PCT concentrations ≥ 0.5 ng/mL have been considered presumptive evidence of bacterial CAP [27]. Despite the overlap at the high end of the PCT concentration range, however, at the low end (<0.1 ng/mL) there were no detections of typical bacterial pathogens. More importantly, children with bacterial-viral codetections had elevated PCT concentrations, which were actually higher (but not statistically different) than those in children with bacterial detections alone. With only 54 patients with typical bacteria detected, our data do not exclude the possibility that viral coinfection could lower PCT concentrations in children with bacterial coinfection. However, our data suggest that a very low PCT concentration can accurately identify children at extremely low risk of typical bacterial infection. Furthermore, only 9 children with a PCT concentration 0.1 to <0.25 ng/mL had a typical bacterial pathogen detected (Table 6). Although PCT results were not available to the clinicians, 4 of these 9 children did not receive antibiotic therapy for CAP; none were readmitted to the same healthcare system after discharge. Thus, the role of the identified bacteria in the illness of these children is uncertain.

Lower PCT concentrations were associated with less severe disease in our cohort based on ICU admission, parapneumonic empyema, and hospital LOS. High PCT was associated with parapneumonic empyema; 82% of children requiring a drainage procedure had a PCT concentration ≥ 0.5 ng/mL.

Table 5. Disease Severity Among Hospitalized Children With CAP and Serum Procalcitonin Concentration Ranges

PCT Range	Total, n	Admitted to an Intensive Care Unit ^a	Empyema Requiring Drainage ^a	Median (IQR) Length of Stay, Days
<0.1 ng/mL	120	26 (20%)	1 (1%)	2.5 (1.5–3.6)
0.1–0.24 ng/mL	127	39 (31%)	1 (1%)	2.9 (1.9–5.0)
0.25–0.49 ng/mL	75	23 (31%)	4 (5%)	3.2 (2.0–4.3)
0.5–0.99 ng/mL	44	16 (36%)	4 (9%)	3.1 (1.9–5.2)
1–1.99 ng/mL	44	21 (48%)	4 (9%)	4.1 (2.9–6.7)
≥ 2 ng/mL	122	60 (49%)	20 (17%)	5.0 (2.8–8.9)

Abbreviations: CAP, community-acquired pneumonia; IQR, interquartile range; PCT, procalcitonin.

^aThe number (and row percent) are presented.

The use of PCT as a biomarker to guide antibiotic therapy has been investigated in a number of settings among adults, including sepsis, acute lower respiratory tract infection (LRTI), acute exacerbation of chronic obstructive pulmonary disease, and pneumonia [15]. In adult trials, PCT-based algorithms for LRTI have proven to be safe and to result in significant reductions in overall antibiotic use [6, 8, 10, 15]. Most trials used similar cutoffs for patients requiring antibiotic therapy: “definitely” for PCT >0.5 ng/mL, “probably” for PCT 0.26 to 0.5 ng/mL, “probably not” for PCT 0.1 to 0.25 ng/mL, and “definitely not” for PCT <0.1 ng/mL.

The experience with clinical trials to date using PCT-guided antibiotic therapy in pediatric CAP is limited but suggestive [11, 12]. The “Procalcitonin Guidance to Reduce Antibiotic Treatment of Lower Respiratory Tract Infection in Children and Adolescents” (ProPAED) study included 337 children diagnosed with LRTI or CAP in 2 Swiss Emergency Departments. Children were randomized (1) to receive therapy based on a PCT-guided algorithm (similar to the adult algorithm described above) or (2) to follow standard clinical guidelines [11]. Among children with CAP in the PCT-guided algorithm, there was a significant reduction in length of antibiotic therapy (5.7 vs 9.1 days; $P = .001$), but rates of antibiotic initiation were similar (71% vs 79%) in both groups.

Esposito et al [12] enrolled 319 children with uncomplicated CAP in a randomized trial using a simpler PCT algorithm. Antibiotics were not administered to children if their PCT concentration was <0.25 ng/mL, and if started, antibiotics were stopped when the PCT fell below 0.25 ng/mL. Controls were treated according to the Italian Society of Pediatrics’ guidelines, which recommends antibiotic therapy for all hospitalized children with CAP [28]. Clinical cure rates were equivalent in both groups. Significantly fewer patients in the PCT arm started antibiotics (86% vs 100%), and the overall antibiotic duration was shorter (5.4 vs 11 days) ($P < .05$ for both).

Pediatric guidelines currently emphasize antibiotics for most children hospitalized with CAP, even though most do not have confirmed bacterial pneumonia [1]. In the EPIC study, bacterial pathogens were detected in 15% of children with CAP, and only 8% were typical bacterial pathogens [2], yet 88% received

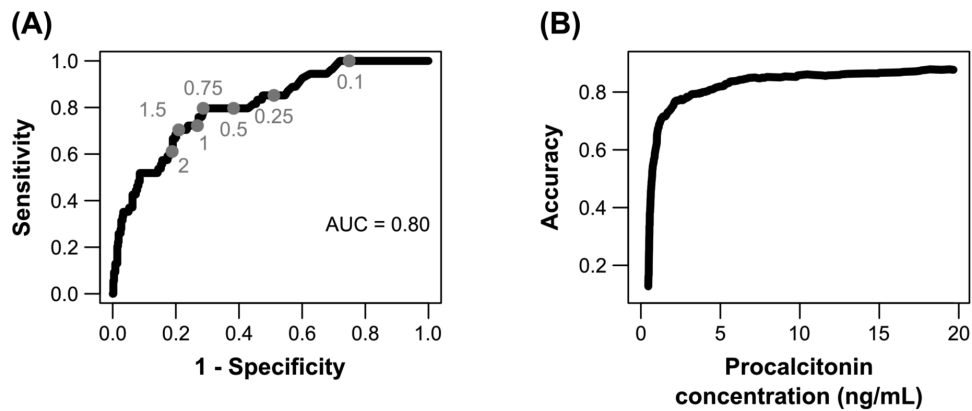


Figure 2. Discriminatory performance of several procalcitonin cutoffs in identifying children hospitalized without typical bacterial community-acquired pneumonia (CAP). (A) Receiver operating curve depicting the classifier performance of procalcitonin cutoffs of <0.1, <0.25, <0.5, <0.75, <1, <1.5, and <2 ng/mL. (B) Accuracy in identifying typical bacteria at procalcitonin concentrations ranging from 0 to 20 ng/mL. Accuracy measures how correct a diagnostic test identifies and excludes patients with a condition (in this case, typical bacterial CAP). Accuracy is calculated using the following equation:

$$\text{Accuracy} = \frac{(\text{True negative} + \text{True positive})}{(\text{True negative} + \text{True positive} + \text{False negative} + \text{False positive})}$$

inpatient antibiotics. In the current analysis, 46% of children had a PCT <0.25 ng/mL, 84% of whom received inpatient antibiotics. A PCT <0.1 ng/mL had a negative predictive value

of 100% (95% CI, 94–100), potentially preventing antibiotic exposure in 23% of children. The negative predictive value of a PCT concentration <0.25 ng/mL was 96% (95% CI, 91–98),

Table 6. Characteristics of Children Hospitalized With CAP, Low PCT, and Typical Bacterial Pathogens Detected

Patient Number	Age (Months)	PCT (ng/mL)	Intensive Care Unit Admission	Length of Stay (Days)	Bacterial Pathogen(s) Detected	Site of Isolation	Viral Pathogen(S) Detected	Treated for Bacterial CAP? If Yes, Therapy and Duration	Other
1	121	0.10	No	2.6	<i>Staphylococcus intermedius</i>	Lung abscess	hMPV	Yes Ceftriaxone and clindamycin initially, then clindamycin (4 weeks)	
2	3	0.11	Yes	11.4	<i>Streptococcus pneumoniae</i> ; MRSA	Tracheal aspirate	RSV	No	48 hours antibiotics (cefotaxime) for "rule out sepsis", then discontinued
3	28	0.11	Yes	5.8	<i>Streptococcus salivarius</i>	Blood culture	No	Yes Ceftriaxone initially, then amoxicillin/clavulanate (10 days)	Trisomy 21
4	69	0.12	No	4.2	<i>S pneumoniae</i>	Blood PCR* (culture negative)	Parainfluenza	Yes Ceftriaxone initially, then cefdinir (10 days)	
5	8	0.16	No	2.0	<i>S salivarius</i>	Blood culture	Parainfluenza	Yes Amoxicillin/ clavulanate (10 days)	Treated, although notes report treatment for otitis media, not CAP
6	2	0.17	Yes	13.1	<i>Haemophilus influenzae</i>	Protected brush	RSV	Yes Ceftriaxone (7 days)	
7	7	0.18	Yes	6.1	<i>S pneumoniae</i>	Blood PCR* (culture negative)	hMPV	No	
8	19	0.20	No	1.1	<i>S pneumoniae</i>	Blood culture	RSV; Coronavirus	No	Culture reported after discharge, no readmission, and no treatment documented
9	0.5	0.21	No	6.7	<i>S salivarius</i>	Blood culture	hMPV	No	

Abbreviations: CAP, community-acquired pneumonia; CDC, Centers for Disease Control and Prevention; hMPV, human metapneumovirus; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; RSV, respiratory syncytial virus; PCR, polymerase chain reaction; PCT, procalcitonin.

*Polymerase chain reaction assay for *S pneumoniae* (lytA) performed at the CDC. Results were not available to clinicians at the time of the hospitalization.

potentially limiting antibiotic use in 46% of children. To optimize the treatment of children hospitalized with CAP while reducing unnecessary and potentially harmful antibiotic use, clinicians will likely need to integrate PCT with other predictors of outcome and rapid etiologic diagnosis. Patterns of immune response identified by expression profiling may ultimately replace individual biomarkers to differentiate viral from bacterial and mixed infections [29, 30].

Our study has a number of strengths, including prospective enrollment, radiographic confirmation of pneumonia, and comprehensive diagnostic testing, but it also has several limitations. Not all children enrolled in EPIC were included in this study; however, all children with typical bacteria detected from the 2 children's hospitals participating in this study were included. Despite extensive testing, 9% of children with CAP had no etiology determined. Based on the continued difficulty in identifying bacterial causes of CAP, it is possible that some children without a typical bacterial pathogen detected were infected with bacteria, particularly those with high PCT. Over 87% of patients in this study received inpatient antibiotics, including 83% of those with only a viral pathogen detected, which may have hampered bacterial detection. Many children did not have residual serum available for PCT analysis; children with residual serum available were more frequently admitted to the ICU than other EPIC enrolled children. Because the prevalence of bacterial detections and severe disease were higher in our study sample, our estimate of the positive predictive value of PCT for these characteristics may be higher than what would have been observed for the entire EPIC cohort. Because PCT testing was not standard of care, serum collection occurred a median of 1 day (IQR, 0–1) after admission; we observed no correlation between time of serum collection and PCT concentrations overall and when stratified by etiology (data not shown). Finally, some studies suggest serial testing increases accuracy in the correlation between PCT concentration and etiologic diagnosis, but we did not perform serial monitoring.

CONCLUSIONS

In this large cohort of 532 prospectively enrolled children with strictly defined, radiographically confirmed CAP who underwent extensive testing for etiology, PCT cutoffs of <0.1 and <0.25 ng/mL accurately identified children at lower risk of typical bacterial CAP. Our findings suggest that PCT may safely be incorporated into treatment algorithms for children with CAP to reduce antibiotic administration and duration. Implementation studies and clinical trials of PCT-guided therapy could significantly improve the care of children with CAP by decreasing the use of unnecessary antibiotics.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online.

In Memoriam

The authors wish to dedicate this paper to the memory of Chris Stockmann PhD, who died tragically in a rock climbing accident on July 25, 2016. He was 28 years old. Chris's brief career was remarkable in many ways. He was prolific; with the publication of this paper, he has authored 87 peer-reviewed papers (35 as first author), including seven published in *The Journal of the Pediatric Infectious Disease Society*. His skills and interests were wide ranging, focusing on the epidemiology and prevention of infectious diseases, antimicrobial stewardship, pharmacology and pharmacogenomics, clinical decision support, and advanced statistical modeling. He made many contributions to the health of children through his research.

Chris completed his Masters of Science in Clinical Investigation in 2010 and his PhD in Pharmacology and Toxicology in 2015, both at the University of Utah. He joined the University of Utah's Division of Pediatric Infectious Diseases as a Research Assistant Professor in July of 2015. Chris was known not only for his brilliance, passion for research, and incredible productivity, but even more for his warm, humble, and unpretentious style. He was extraordinarily generous with his time and expertise and had innumerable friends and collaborators within the University of Utah, the Centers for Disease Control and Prevention, and across the country. Chris was also a passionate backcountry skier, mountain biker, hiker, canyoneer, and rock climber.

The Department of Pediatrics at the University of Utah has created the *Chris Stockmann Memorial Scholarship Fund* in his honor to foster the career of other brilliant and passionate scientists dedicated to the care of children. For information about donating to the fund, please contact Denise Begue in the University of Utah Development Office at (801) 581-6874; E-mail: denise.begue@hsc.utah.edu.

Notes

Disclaimer. The views expressed in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC). bioMérieux had no role in the study design, data collection, data analysis, data interpretation, writing of this report, or the decision to submit this report for publication.

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Potential conflicts of interest. A. J. B. collaborates with BioFire Diagnostics, LLC on federally funded studies and has intellectual property licensed to BioFire Diagnostics through the University of Utah. A. J. B. has received research funding from BioFire Diagnostics for investigator-initiated research and has acted as a paid advisor to BioFire Diagnostics and BioFire Defense regarding risk assessment for the US Food and Drug Administration-cleared products. A. J. B. has also received research funding from Gilead Sciences and Merck for investigator-initiated research. For work unrelated to this study, C. S. was supported by grants from Merck, the Thrasher Research Fund, and the Primary Children's Hospital Foundation.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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