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Procalcitonin as a Marker of Etiology in Adults Hospitalized With Community-Acquired Pneumonia

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(See the Editorial Commentary by Bergin and Tsalik on pages 191–3.)

Background. Recent trials suggest procalcitonin-based guidelines can reduce antibiotic use for respiratory infections. However, the accuracy of procalcitonin to discriminate between viral and bacterial pneumonia requires further dissection.

Methods. We evaluated the association between serum procalcitonin concentration at hospital admission with pathogens detected in a multicenter prospective surveillance study of adults hospitalized with community-acquired pneumonia. Systematic pathogen testing included cultures, serology, urine antigen tests, and molecular detection. Accuracy of procalcitonin to discriminate between viral and bacterial pathogens was calculated.

Results. Among 1735 patients, pathogens were identified in 645 (37%), including 169 (10%) with typical bacteria, 67 (4%) with atypical bacteria, and 409 (24%) with viruses only. Median procalcitonin concentration was lower with viral pathogens (0.09 ng/mL; interquartile range [IQR], <0.05–0.54 ng/mL) than atypical bacteria (0.20 ng/mL; IQR, <0.05–0.87 ng/mL; $P = .05$), and typical bacteria (2.5 ng/mL; IQR, 0.29–12.2 ng/mL; $P < .01$). Procalcitonin discriminated bacterial pathogens, including typical and atypical bacteria, from viral pathogens with an area under the receiver operating characteristic (ROC) curve of 0.73 (95% confidence interval [CI], .69–.77). A procalcitonin threshold of 0.1 ng/mL resulted in 80.9% (95% CI, 75.3%–85.7%) sensitivity and 51.6% (95% CI, 46.6%–56.5%) specificity for identification of any bacterial pathogen. Procalcitonin discriminated between typical bacteria and the combined group of viruses and atypical bacteria with an area under the ROC curve of 0.79 (95% CI, .75–.82).

Conclusions. No procalcitonin threshold perfectly discriminated between viral and bacterial pathogens, but higher procalcitonin strongly correlated with increased probability of bacterial pathogens, particularly typical bacteria.

Keywords. pneumonia; procalcitonin; etiology; antibiotic stewardship.

Pneumonia is a major source of morbidity and mortality in the United States, accounting for an estimated 63 000 deaths, 1.2 million hospitalizations, and 2.3 million emergency department visits annually [1–3]. A cornerstone of community-acquired pneumonia (CAP) management has been empiric treatment with antibiotics targeting the most likely bacterial pathogens [4, 5]. However, overuse of antibiotics is linked to the development of antibiotic resistance, antibiotic-associated complications, increased costs, and drug toxicities [6].

While viral respiratory infections can predispose patients to secondary bacterial pneumonia, recent etiology studies suggest that viruses alone account for a large proportion of CAP cases in both adults and children [7, 8]. Antibiotic therapy could be safely avoided in patients with isolated viral pneumonia if viral etiology could be reliably distinguished from bacterial and mixed viral/bacterial infections [9]. However, the lack of rapid, accurate tests to differentiate between viral and bacterial respiratory infections has been a major barrier to optimizing antibiotic use [10].

Procalcitonin (PCT) is a serum biomarker that has shown promise in discriminating between viral and bacterial infections [11]. PCT, a precursor to the hormone calcitonin and component of the innate proinflammatory response, is released into the systemic circulation within 4 hours of inoculation with bacteria or bacterial endotoxin [11, 12]. Cytokines typically associated with bacterial infection, including tumor necrosis factor and interleukin 6, enhance PCT release, while interferons, which are more often associated with viral infections, inhibit PCT release [11, 13]. Prior clinical studies have demonstrated that PCT levels tend to be higher in bacterial than viral respiratory infections, and several trials suggest that PCT-based guidelines for antibiotic prescribing can reduce antibiotic use [14–17]. However, additional study in patients with

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comprehensive pathogen testing is needed to further understand the accuracy of PCT for distinguishing between bacterial and viral infections [18]. Therefore, we evaluated the association of serum PCT concentration with pneumonia etiology in a large cohort of hospitalized adults with CAP who underwent systematic testing for viruses and bacteria.

METHODS

This diagnostic accuracy study was nested within the Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC) Study, a prospective, multicenter, active surveillance study conducted in the United States with patient recruitment from January 2010 through June 2012 [7]. Ethics review boards at each enrolling institution and the CDC approved the protocol. Written informed consent was obtained from each participant or representative.

Study Population

The adult EPIC study population has been previously described [7]. In brief, adults (≥18 years old) hospitalized with CAP were enrolled at 3 hospitals in Chicago, Illinois, and 2 hospitals in Nashville, Tennessee. Three hospitals were academic medical centers, 1 was a publicly funded county hospital, and 1 was a community hospital. All enrolled patients had clinical signs of CAP, including ≥1 sign of acute infection (fever, chills, hypothermia, leukocytosis, leukopenia, altered mental status) and ≥1 sign of acute respiratory illness (cough, sputum production, chest pain, dyspnea, tachypnea, abnormal lung examination, respiratory failure). Enrollment also required radiographic evidence of pneumonia as interpreted by a study-dedicated thoracic radiologist blinded to clinical data. Sera were collected from enrolled patients and stored at −80°C. The study population for the current analysis included patients enrolled in the adult EPIC study with comprehensive pathogen testing (defined below) and sufficient banked sera to measure PCT (200 μL).

Procalcitonin Measurement

PCT concentrations were measured in research laboratories at the enrolling centers using a VIDAS BRAHMS PCT immunoassay kit (bioMérieux, Marcy l'Etoile, France) [19]. The lower limit of PCT detection was 0.05 ng/mL. Study personnel performing PCT measurements were blinded to clinical information, and treating clinicians were blinded to PCT results.

Pathogen Testing

Each enrolled patient underwent systematic pathogen testing per study protocol [7]. Bacterial testing included blood culture; sputum culture (limited to high-quality specimens, defined as ≤10 epithelial cells and ≥25 white blood cells per low-power field [20]); urinary antigen test for *Streptococcus pneumoniae* and *Legionella pneumophila* (BinaxNOW, Alere) [21, 22]; and reverse transcriptase polymerase chain reaction (RT-PCR) of nasopharyngeal/oropharyngeal (NP/OP) swabs for *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* and of sputum for *Legionella* [23]. Bacterial cultures were performed on high-quality [20] endotracheal aspirates and bronchoalveolar lavage samples obtained for routine clinical care. Bacterial cultures and RT-PCR for Enterobacteriaceae, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus anginosus*, *Streptococcus mitis*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* were also completed on pleural fluid samples obtained for clinical care.

Viral testing included RT-PCR of NP/OP swabs with CDC-developed methods for adenovirus, coronaviruses, human metapneumovirus, human rhinovirus, influenza viruses, parainfluenza viruses, and respiratory syncytial virus [24, 25]. Acute and convalescent (3–10 weeks later) serology were tested for adenovirus, human metapneumovirus, influenza viruses, parainfluenza viruses, and respiratory syncytial virus [26, 27]. Other pathogen testing completed for routine clinical care, including mycobacterial and fungal testing, were also incorporated into the etiology determination.

Only patients who underwent at least 1 bacterial test and at least 1 viral test described above were considered to have adequate pathogen testing and included in the final study population.

Analysis

PCT Among Pathogen Groups

We classified patients into the following pathogen groups based on test results outlined above: (1) typical bacteria (detection of any bacteria other than atypicals); (2) atypical bacteria (*M. pneumoniae*, *C. pneumoniae*, or *Legionella*); (3) viral (detection of a virus without co-detection of bacteria); (4) mycobacterial/fungal; and (5) unknown (detection of no pathogen). Patients with co-detection of pathogens from multiple groups were classified according to the following rules: co-detection of typical bacteria with an atypical and/or virus classified as typical bacteria; and co-detection of atypical bacteria with a virus classified as an atypical.

We compared PCT distribution between patients in the viral group to those in the atypical and typical bacterial groups with the Wilcoxon rank-sum test. Using PCT cut-points described in the literature as thresholds for identifying bacterial infections and guiding antibiotic therapy [15, 28, 29], we categorized PCT values into 4 strata: <0.1 ng/mL; 0.1–0.24 ng/mL; 0.25–0.49 ng/mL; ≥0.5 ng/mL. The prevalence of each pathogen group within these PCT strata was calculated. These calculations were further stratified by initial location of hospitalization: general medical floor and intensive care unit (ICU).

Among patients with typical bacterial detection, we also categorized patients according to the type of test positive for bacteria: (1) blood culture; (2) respiratory sample; and (3) urinary antigen test. We then compared serum PCT concentration in patients positive for typical bacteria across these 3 different categories of positive tests.

Accuracy of PCT for Identifying Bacterial CAP

We evaluated the accuracy of PCT to identify bacterial CAP in 3 separate analyses. First, we compared patients with any bacterial pathogen, including both typical and atypical bacteria, with patients who had a viral pathogen detected to demonstrate the accuracy of PCT for discriminating between patients with microbiologically confirmed bacterial and viral CAP. Patients without any pathogens detected (unknown etiology) and those with fungal and mycobacterial pathogens were excluded from this analysis to focus on those who could be confidently categorized into bacterial and viral groups.

Second, we compared the typical bacteria group to the combined group of viruses and atypical bacteria. Because routine coverage of atypical bacteria in empiric antibiotic regimens for CAP is controversial [30, 31], we evaluated PCT accuracy specifically for typical bacterial CAP, for which antibiotics are universally recommended [4, 30, 31].

Third, we compared patients with any bacterial pathogen detected, including both typical and atypical bacteria, with all patients who did not have bacteria detected, which included patients with viral, fungal, and mycobacterial detections and those with no pathogen detected. This was an analysis of PCT accuracy for bacterial CAP assuming no patients with unknown etiology had undiagnosed bacterial disease.

For each of these 3 dichotomous analyses, we constructed a nonparametric receiver operating characteristic (ROC) curve to evaluate the diagnostic accuracy of PCT to discriminate between bacterial CAP and the comparator group. Area under the curve (AUC) was calculated. Sensitivity, specificity, and positive and negative predictive values were calculated using PCT cut-points of 0.1 ng/mL, 0.25 ng/mL, and 0.5 ng/mL [15, 28, 29]. We also assessed the association of PCT concentration on a continuous scale with the probability of bacterial CAP. PCT values were highly skewed; thus, we modeled PCT values with a restricted cubic spline function with 4 knots located at the 5th, 35th, 65th, and 95th percentiles [32]. Using the predicted probabilities from a logistic regression model with spline-transformed PCT concentration as the independent variable and CAP pathogen group (bacterial vs comparator) as the dependent variable, we estimated the probability of bacterial CAP according to PCT concentration [32].

Statistical analyses were performed with Stata software version 12 (StataCorp, College Station, Texas).

RESULTS

Study Population

During the 2.5-year study period, 2259 patients with radiographic pneumonia and specimens available for bacterial and viral tests were enrolled and 1735 patients (77%) with PCT measurements were included in the current analysis (Figure 1). Median age was 57 years (interquartile range [IQR], 47–70). The most common comorbidities were asthma (26%) and chronic obstructive pulmonary disease (21%); 22% were admitted to an ICU, 5% were mechanically ventilated, and 2% died during hospitalization (Supplementary Table 1).

No pathogen was detected in 1075 (62%) patients, while 409 (24%) were classified into the viral group, 67 (4%) into the atypical bacterial group, 169 (10%) into the typical bacterial group, and 15 (1%) into the mycobacterial/fungal group.

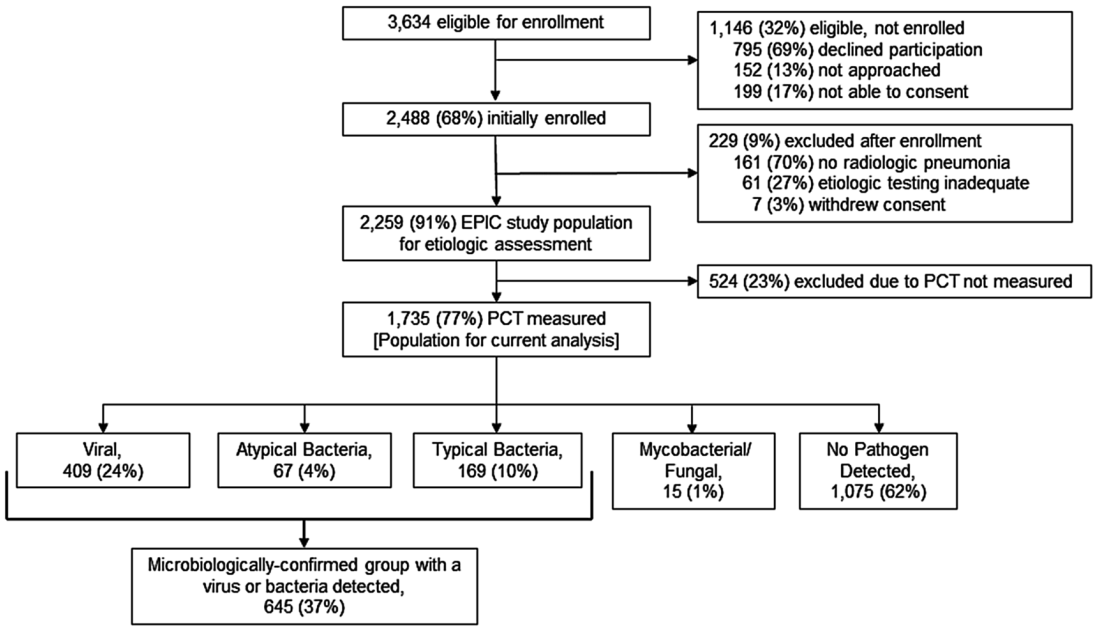

Figure 1. Flow diagram of patient participation. Abbreviations: EPIC, Etiology of Pneumonia in the Community; PCT, procalcitonin.

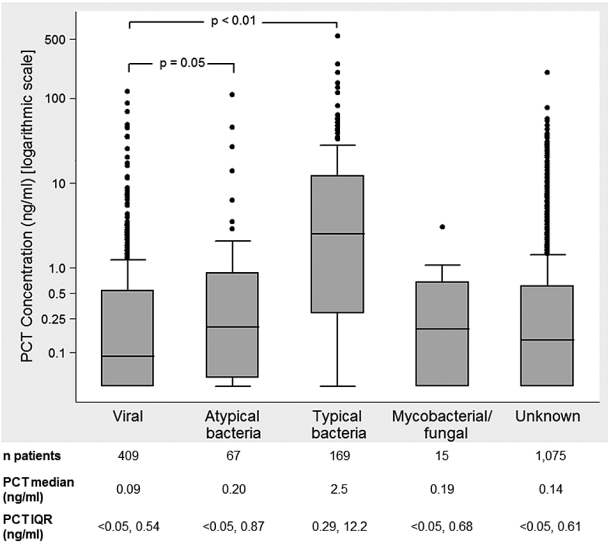

Figure 2. Box plot of serum procalcitonin (PCT) concentration by pathogen group. The center of each box plot represents the median, with the box denoting the interquartile range (IQR), the whiskers representing 1.5 times the IQR, and dots showing outliers beyond the whiskers. Displayed *P* values were calculated with the rank-sum test.

The most common pathogen in the viral, atypical bacterial, and typical bacterial groups were rhinovirus (n = 114), *M. pneumoniae* (n = 36), and *S. pneumoniae* (n = 93), respectively (Supplementary Table 2). Eight (12%) patients in the atypical group had concomitant viral detection; 44 (26%) patients in the typical bacterial group had concomitant viral (n = 43) or atypical (n = 1) detection.

Clinical characteristics and pathogens detected were similar between the 1735 patients who were included in the current analysis and the 524 patients in the EPIC study who were excluded because serum for PCT measurement was not available (Supplementary Table 3).

PCT Among Pathogen Groups

Median PCT was lower in the viral group (0.09 ng/mL; IQR, <0.05–0.54 ng/mL) compared with the atypical bacterial group (0.20 ng/mL; IQR, <0.05–0.87 ng/mL; $P = .05$) and the typical bacterial group (2.5 ng/mL; IQR, 0.29–12.2 ng/mL; $P < .01$) (Figure 2). Typical bacteria were more prevalent at higher PCT concentrations, from 3% among patients with PCT <0.1 ng/mL to 21% among patients with PCT ≥0.5 ng/mL (Table 1). Typical bacteria were more prevalent in the higher PCT strata among patients both in the ICU and general medical floor (Supplementary Table 4).

Among the 169 patients with typical bacteria detected, 39 (23.1%) had PCT <0.25 ng/mL and 21 (12.4%) had PCT <0.1 ng/mL. Median PCT was higher in patients with typical bacteria only (2.7 ng/mL; IQR, 0.41–15.9 ng/mL) compared to those with typical bacterial and viral co-detections (0.95 ng/mL; IQR, 0.15–5.6 ng/mL; $P = .05$) (Supplementary Figure 1). Median PCT was also higher in patients with typical bacteria detected by blood culture (6.7 ng/mL; IQR, 0.9–25.8 ng/mL) than by respiratory sample (0.8 ng/mL; IQR, 0.2–5.4 ng/mL; $P < .01$) or urinary antigen test (0.7 ng/mL; IQR, 0.06–3.4 ng/mL; $P < .01$) (Supplementary Figure 2).

Accuracy of PCT for Identifying Bacterial CAP

Any Bacterial CAP Versus Viral CAP

Using PCT to discriminate between any bacterial pathogens (n = 236) and viral pathogens (n = 409) resulted in an area under the ROC curve of 0.73 (95% CI, .69–.77) (Figure 3A). Using a PCT threshold ≥0.1 ng/mL to identify any bacterial pathogen resulted in sensitivity of 80.9% (95% CI, 75.3%–85.7%) and specificity of 51.6% (46.6%–56.5%) (Table 2). When considering PCT on a continuous scale using the logistic regression model, the probability of detecting bacterial pathogens increased substantially with increasing PCT in a nonlinear fashion (Figure 4A). Undetectable PCT (<0.05 ng/mL) was associated with a 0.25 (95% CI, .22–.29) probability of bacterial detection, while PCT of 10 ng/mL was associated with a 0.78 (95% CI, .69–.86) probability of bacterial detection.

Typical Bacterial CAP Versus Viral and Atypical CAP

Using PCT to discriminate typical bacterial pathogens (n = 169) from the combined group of viral and atypical pathogens (n = 467) resulted in an area under the ROC curve of 0.79 (95% CI, .75–.82) (Figure 3B). A PCT threshold of ≥0.1 ng/mL identified typical bacterial pathogens with a sensitivity of 87.6% (95% CI, 81.1%–92.1%) and specificity of 49.3% (95% CI, 44.8%–54.0%) (Table 2). In patients with an undetectable

Table 1. Prevalence of Pathogen Groups by Procalcitonin Strata

		Prevalence of Pathogen Group Detected, Row %				
Procalcitonin Stratum, ng/mL	Patients, No.	Virus	Atypical Bacteria	Typical Bacteria	Mycobacteria/Fungus	No Pathogen Detected
<0.1	738	29%	3%	3%	1%	64%
0.1–0.24	284	21%	5%	6%	0%	67%
0.25–0.49	157	18%	5%	8%	2%	68%
≥0.5	556	20%	4%	21%	1%	55%
All	1735	24%	4%	10%	1%	62%

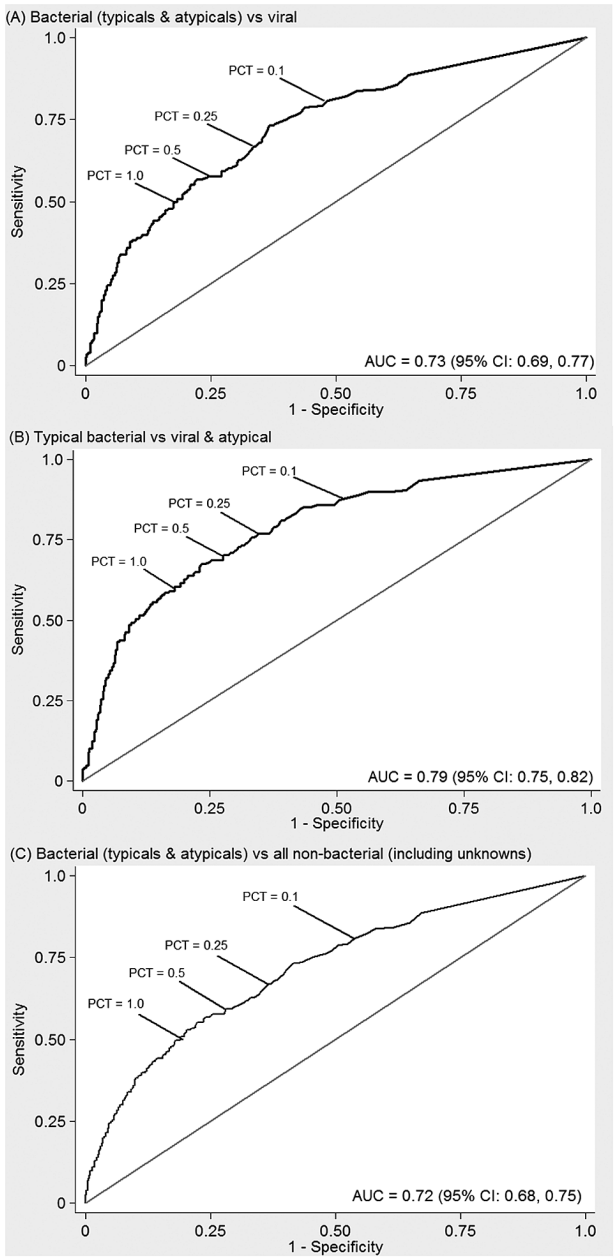

Figure 3. Receiver operating characteristic curves for procalcitonin (PCT) to discriminate bacterial (including typical and atypical bacteria) from viral pneumonia (*A*), typical bacterial from viral and atypical pneumonia (*B*), and bacterial (including typical and atypical bacteria) from nonbacterial pneumonia (*C*). Selected PCT cut-points (0.1 ng/mL, 0.25 ng/mL, 0.5 ng/mL, 1.0 ng/mL) are displayed. Abbreviations: AUC, area under the curve; CI, confidence interval.

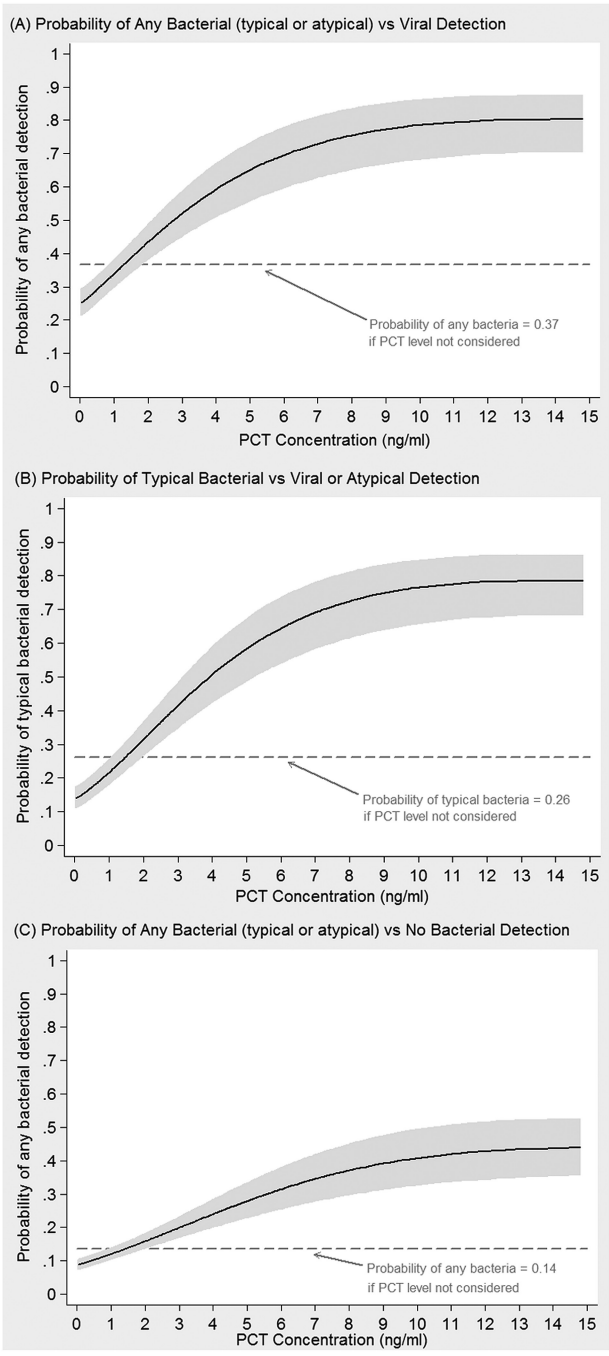

Figure 4. Probability of bacterial (atypical or typical) vs viral detection (*A*), typical bacterial vs viral or atypical detection (*B*), and bacterial (typical or atypical) vs no bacterial (including unknown etiology) (*C*) detection according to serum procalcitonin (PCT) concentration. Shaded areas represent 95% confidence intervals. Dashed lines show the overall prevalence of any bacteria (*A* and *C*) or typical bacteria (*B*) without considering PCT level. The x-axes were truncated at a PCT of 15 ng/mL due to the small number of patients with concentrations above this level.

PCT (<0.05 ng/mL), the probability of a typical bacterial pathogen detection was 0.14 (95% CI, .11–.17), while in patients with a PCT of 10 ng/mL, the probability of a typical bacterial pathogen increased to 0.77 (95% CI, .66–.85) (Figure 4B). Interestingly, PCT was higher with *Legionella* detection (median, 1.1 ng/mL) than other atypical bacteria, including *Mycoplasma* (median, 0.06 ng/mL) and *Chlamydophila* (median, 0.24 ng/mL) (Supplementary Table 2).

Bacterial CAP Versus Nonbacterial CAP

Within the full population, including patients with unknown etiology, using PCT to discriminate between patients with any bacterial pathogen (n = 236) and those without a detected

Table 2. Diagnostic Test Characteristics of Procalcitonin at Selected Cut-points

Procalcitonin Cut-point	Test Characteristic	Discrimination of Bacterial (Typicals and Atypicals) From Viral CAP, % (95% CI)	Discrimination of Typical Bacterial From Viral and Atypical CAP, % (95% CI)	Discrimination of Bacterial (Typicals and Atypicals) From All Nonbacterial CAP (Including Unknowns), % (95% CI)
≥0.1 ng/mL	Sensitivity	80.9 (75.3–85.7)	87.6 (81.6–92.1)	80.9 (75.3–85.7)
	Specificity	51.6 (46.6–56.5)	49.3 (44.8–54.0)	46.2 (43.7–48.8)
	PPV	49.1 (44.0–54.2)	38.3 (33.5–43.4)	19.2 (16.8–21.7)
	NPV	82.4 (71.2–86.9)	91.7 (87.7–94.9)	93.9 (91.9–95.5)
≥0.25 ng/mL	Sensitivity	66.9 (60.6–72.9)	76.9 (69.8–83.0)	66.9 (60.6–72.9)
	Specificity	66.5 (61.7–71.1)	64.9 (60.4–69.2)	63.0 (60.5–65.4)
	PPV	53.2 (47.4–58.9)	43.8 (38.0–49.6)	22.2 (19.2–25.4)
	NPV	77.6 (72.8–81.9)	88.7 (85.0–91.9)	92.4 (90.6–93.9)
≥0.5 ng/mL	Sensitivity	58.5 (51.9–64.8)	69.8 (62.3–76.6)	58.5 (51.9–64.8)
	Specificity	72.9 (68.3–77.1)	72.5 (68.2–76.4)	72.1 (69.8–74.4)
	PPV	55.4 (49.0–61.7)	47.4 (41.0–53.8)	24.8 (21.3–28.6)
	NPV	75.3 (70.7–79.4)	87.1 (83.4–90.3)	91.7 (90.0–93.2)

Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

bacterial pathogen (n = 1499) resulted in an area under the ROC curve of 0.72 (95% CI, .68–.75) (Figure 3C). A PCT threshold of ≥0.1 ng/mL resulted in sensitivity of 80.9% (95% CI, 75.3%–85.7%) and specificity of 46.2% (95% CI, 43.7%–48.8%) for identification of patients with any bacterial pathogen (Table 2).

DISCUSSION

In this multicenter study of 1735 adults hospitalized with CAP, including 645 with a viral or bacterial pathogen detected, higher levels of serum PCT at hospital admission were strongly associated with increased probability of bacterial pathogen detection. Patients with a PCT of 10 ng/mL were 4 times more likely to have a bacterial pathogen detected than those with an undetectable PCT <0.05 ng/mL. No PCT threshold allowed for perfect discrimination between viral and bacterial detection, as demonstrated by 23% of patients with typical bacterial pathogens having PCT <0.25 ng/mL and 12% having PCT <0.1 ng/mL. However, these data suggest that serum PCT concentration, which can be available to clinicians within 60 minutes after a simple blood draw [19], could be a useful adjunct in the etiologic assessment of patients hospitalized with CAP.

Several recent trials suggest that instituting antibiotic prescribing guidelines based on PCT levels can safely curtail the use of antibiotics for respiratory infections both in the inpatient and outpatient settings [15, 17, 28, 29]. Guidelines used in these trials discouraged antibiotics for patients with PCT <0.25 ng/mL and strongly discouraged antibiotics for PCT <0.1 ng/mL [15, 28, 29]. Our study, which, to our knowledge, is the largest to date evaluating the association of PCT with pneumonia etiology, provides important data to complement these trials. Among the 738 patients with a PCT <0.1 ng/mL in our study, 3% had a typical bacterial pathogen detected and 3% had an atypical bacterial pathogen detected; among the 1022 patients with a PCT <0.25 ng/mL, 4% had typical bacteria and 4% had atypical bacteria detected. While these results demonstrate lower frequency of bacterial pathogens in patient populations with PCT below both the 0.1 ng/mL and 0.25 ng/mL thresholds, some individual patients with bacterial pathogens did present to the hospital with low PCT levels, highlighting that clinicians cannot rely on PCT alone to guide antibiotic treatment decisions.

Interestingly, PCT values for patients with atypical bacteria were more similar to those with viruses than typical bacteria. This was particularly true for *Mycoplasma* and *Chlamydophila*, but not *Legionella*. Routine coverage for atypical bacteria in empiric antibiotic CAP regimens is controversial because *Mycoplasma* and *Chlamydophila* infections are often self-limited with low mortality risk, and clinical trial data have failed to consistently demonstrate improvement in patient outcomes when atypical coverage is added to β-lactam monotherapy [31]. Proponents of empiric atypical coverage note that antibiotics improve outcomes for patients with *Legionella* pneumonia and may shorten the duration of symptoms for *Mycoplasma* pneumonia [30]. Because of this controversy, we analyzed our data with the atypical bacteria grouped with typical bacteria, and then with atypical bacteria grouped with viruses. Our results suggest that PCT is a better marker for typical bacteria than for the combined group of typical and atypical bacteria. Although the small sample size of patients with *Legionella* pneumonia (n = 21) prevented robust evaluation of PCT specifically in *Legionella* in this study, relatively high PCT in these patients suggests that the PCT response to *Legionella* pneumonia may be more similar to that of typical bacterial pneumonia than *Mycoplasma* or *Chlamydophila* pneumonia. If this is confirmed with future studies, elevated PCT indicating increased probability of a pathogen necessitating prompt antibiotics (typical bacteria or *Legionella*) and low PCT indicating increased probability of a pathogen

not requiring prompt antibiotics (viruses, *Mycoplasma* or *Chlamydophila*) could be a useful paradigm.

A strength of our study was systematic, protocol-driven pathogen testing, which included both traditional culture-based and serology testing, as well as PCR-based techniques [7]. Despite this thorough testing, 62% of patients had no pathogen detected. This high proportion of patients with unknown etiology is similar to other contemporary CAP studies [14, 33], and presents a challenge for evaluating the accuracy of PCT for identifying bacterial pneumonia. Ideally, PCT would have been evaluated in a population of CAP patients who all had identified pathogens, enabling complete and precise classification of bacterial and nonbacterial disease. Unfortunately, identification of pathogens in all patients was not possible with currently available tests. Therefore, our approach included calculating PCT accuracy within both a microbiologically confirmed population (n = 645) of patients with identified bacterial and viral pathogens and the full population (n = 1735) including patients without any pathogens detected. Both of these populations have limitations. The microbiologically confirmed population is not directly generalizable into clinical practice because clinicians do not know which patients will test positive for pathogens when making initial decisions about antibiotics. Meanwhile, the full population likely included some patients who were misclassified into the nonbacterial group due to failure of pathogen testing to detect some of the relevant bacteria. Together, these complementary analyses provide an estimated range for the accuracy of PCT to identify bacterial CAP. It will be important to reassess PCT accuracy as pathogen testing for CAP improves and more patients can be classified into bacterial and viral groups [10].

In prior work, Kruger et al [14] studied PCT in a population of 1337 inpatients and outpatients with CAP, including 472 patients with an identified pathogen. Compared with Kruger et al, we found similar patterns of PCT across etiology groups, but identified a higher prevalence of viruses and found higher PCT in the bacterial groups, possibly due to a PCR testing for more viruses and inclusion of a more severely ill patient population limited to hospitalized patients in our study.

Our study had limitations. First, 23% of patients enrolled in the EPIC study were not included in this analysis because serum specimens for PCT measurement were not available; this had the potential to introduce a selection bias, but measured clinical characteristics and detected pathogens were similar between the included and excluded patients. Second, while some protocols recommend serial PCT measurements to guide antibiotic prescribing [34], we only measured PCT at the time of hospital admission. Third, invasive diagnostic testing (eg, thoracentesis, bronchoscopy) was only utilized when deemed medically necessary by the treating physicians; study-dictated invasive tests may have resulted in more patients with an identified pathogen. Fourth, all detected pathogens may not have represented causative agents for pneumonia; for example, viruses detected in NP/OP swabs may have represented infection limited to the upper airways or asymptomatic shedding [35]. Fifth, we sampled patients for pathogens at the time of hospital admission only; delayed bacterial pneumonias that developed after an initial viral infection would not have been detected with this sampling method. Finally, all enrolled patients were hospitalized and we are unable to comment on PCT in outpatients with pneumonia.

In conclusion, although no PCT threshold perfectly discriminated between bacteria and viruses, higher serum PCT strongly correlated with increased probability of a bacterial pathogen. These data suggest that PCT could assist clinicians in evaluating for potential pathogens, but highlight that basing antibiotic prescribing decisions exclusively on PCT would result in a proportion of patients with bacterial pneumonia not receiving antibiotics.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Study concept and design: W. H. S., C. G. G., R. A. B., S. J., K. M. E., R. G. W. Acquisition of data: W. H. S., D. J. W., R. A. B., D. M. C., E. J. A., A. M. B., C. T., S. F., K. M. E., R. G. W. Statistical analysis: W. H. S., C. G. G., Y. Z. Interpretation of data: W. H. S., C. G. G., R. A. B., D. J. W., E. J. A., G. W. W., A. J. B., S. J., K. M. E., R. G. W. Drafting of the initial manuscript: W. H. S. Critical revision of manuscript: All authors. Obtained funding: W. H. S., K. M. E., R. G. W. Study supervision: W. H. S., S. J., K. M. E., R. G. W. In addition, W. H. S. takes responsibility for the manuscript as a whole, including the data and analysis.

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