Procalcitonin to Predict Bacterial Coinfection in Infants With Acute Bronchiolitis

A Preliminary Analysis

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Objective: The aim of this study was to conduct a preliminary analysis of serum procalcitonin (PCT) to predict bacterial coinfection in infants with acute bronchiolitis.

Methods: Retrospective cohort chart review of 40 infants admitted with acute bronchiolitis to the pediatric intensive care unit. Logistic regression models were used to determine the association of PCT and white blood count with presence of bacterial coinfection defined by either positive culture or chest radiograph result.

Results: Fifteen (38%) of 40 patients had a diagnosis of bacterial coinfection by positive culture (9/15) or chest radiograph (6/15). Procalcitonin ($P < 0.0001$) was significantly associated with bacterial coinfection. A cutoff value of 1.5 ng/mL had sensitivity of 0.80, specificity of 1.00, and area under the operating curve of 0.88. White blood count ($P = 0.06$) was borderline significant with sensitivity of 0.33, specificity of 0.96, and area under the operating curve of 0.67. Three of 15 patients were later found to have bacterial coinfection with initial PCT of less than 1.5 ng/mL. None had follow-up PCT measurements taken. Thirty-five of 40 were prescribed empiric antibiotic therapy, including 20 of 25 patients without evidence of bacterial coinfection. None had a PCT of greater than 1.5 ng/mL. If a PCT cutoff of greater than 1.5 ng/mL had been used, 57% fewer patients would have received antibiotics with a 45% reduction in antimicrobial charges.

Conclusions: An elevated PCT may assist clinicians in determining presence of bacterial coinfection at admission in infants with acute bronchiolitis. Implementation of a PCT cutoff of 1.5 ng/mL at admission may prevent unnecessary antibiotic use with associated cost savings. Serial PCT levels may increase sensitivity. Further validation is warranted.

Key Words: infants, bronchiolitis, procalcitonin, bacterial infections, antibiotics

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Bronchiolitis, a primary viral infection of the upper and/or lower respiratory tract, is the leading cause of infant hospitalization in the United States, with 90,000 to 120,000 annual admissions at an associated cost of approximately $700 million.[1–5] Of these, 3% to 10% develop respiratory distress or failure and are admitted to the pediatric intensive care unit (PICU).[6] Physicians responsible for these patients in the pediatric emergency department (ED) and PICU are then left with a diagnostic dilemma for which no clear guidelines exist, namely, the question of the need to exclude bacterial coinfection. The presence of concurrent bacterial coinfection has been reported as high as 44%.[7] This leads physicians to obtain cultures and initiate empiric antibiotic therapy at the risk of overuse of antimicrobials, which could lead to complications such as antibiotic resistance and unnecessary patient costs. As such, a tool to predict the presence of bacterial coinfection would be of benefit to the bedside clinician. Procalcitonin (PCT) may be such a tool having shown promise as a biomarker of bacterial infection in a variety of clinical settings and applications involving neonates, infants, and children.[8–20] As a result, we conducted a retrospective cohort analysis to test the hypothesis that a serum PCT may predict the presence of bacterial coinfection in infants with acute bronchiolitis at the time of admission to the PICU. If sufficiently accurate, the use of PCT testing may lead to a reduction in unnecessary use of antibiotics and associated patient charges.

METHODS

A retrospective cohort analysis of electronic medical records was conducted to evaluate the use of serum PCT to predict bacterial coinfection and potentially reduce antibiotic charges in infants with a primary diagnosis of acute bronchiolitis at the time of admission to the PICU. This study was approved by the institutional review board at the University of Kentucky. Inclusion criteria included infants admitted to the PICU with a primary diagnosis of acute bronchiolitis identified by *International Classification of Diseases, Ninth Revision* codes and a PCT assay obtained at admission from October 1, 2010, to April 30, 2012. Electronic medical records for these patients were then reviewed to confirm the diagnosis of acute bronchiolitis and to record white blood count (WBC), chest radiograph (CXR), and bacterial culture results. The diagnosis of bacterial coinfection was based on final bacterial culture results or official CXR interpretation and was then confirmed by its description in the discharge summary. Procalcitonin studies were performed by the BRAHMS VIDAS (bioMérieux, Inc, Hazelwood, Mo) quantitative assay technique. Antibiotic charges and cost of the PCT assay were provided by pharmacy services and clinical pathology, respectively. Logistic regression models were used to determine the association of PCT and WBC with presence of bacterial coinfection. Cutoff values were defined as the value of PCT or WBC at which a patient had a 50% chance of having a bacterial coinfection. Receiver operating characteristic curves were drawn to calculate the area under the curve.

RESULTS

Study Population

A total of 40 infants were admitted to the PICU from October 1, 2010, through April 30, 2012, with a PCT assay

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taken and an *International Classification of Diseases, Ninth Revision* code of acute bronchiolitis with confirmation of this diagnosis in the discharge summary. There were 25 boys (63%) and 15 girls (37%). The mean age was 2 months with a range of 0 to 9 months. All patients were tested for respiratory syncytial virus by polymerase chain reaction testing, and 75% (30/40) were found to be positive. Metapneumovirus and rhinovirus were found by viral culture in 2 others.

Bacterial Coinfection

On admission to the PICU, 38 (95%) of 40 patients had cultures of either blood, cerebrospinal fluid, tracheal aspirate (TA), or urine (UC) taken alone or in combination. All 40 patients had a CXR taken. Overall, bacterial coinfection was diagnosed in 15 (38%) of 40 study patients (Fig. 1). Nine patients were diagnosed with a bacterial coinfection based on 10 positive culture results (1 patient had both a positive TA and UC) and 6 nonintubated patients by positive CXR findings. Of the 9 patients diagnosed by positive culture results, bacterial pneumonia was diagnosed by TA in 8 (44%) of 18 patients tested and urinary tract infections (UC) in 2 (6%) of 33 patients tested. No cases of bacteremia (0/36 patients tested) or meningitis (0/12 patients tested) were detected.

Bacterial Organisms Detected

Nine (22%) of 40 patients had positive bacterial cultures. Five organisms were detected and were responsible for 10 bacterial coinfections (1 patient had simultaneous infections from TA and UC). They were *Streptococcus pneumoniae* (TA in 3 patients), *Haemophilus influenzae* (TA in 2 patients), *Moraxella catarrhalis* (TA in 2 patients), *Enterococcus faecalis* (UC in 1 patient), and group B β-hemolytic streptococci (TA and UC in 1 patient).

PCT and WBC Testing

Procalcitonin and WBC studies were performed in all 40 patients. The overall mean value for PCT was 3.9 ng/mL (<0.2–36.3 ng/mL). The mean value for those with positive bacterial cultures (n = 9) was 8.3 ng/mL, for patients diagnosed with pneumonia by CXR (n = 6) was 10.4 ng/mL, and for those without evidence of bacterial coinfection (n = 25) was 0.5 ng/mL. For WBC, the overall mean value was 10,900/μL (1200–27,800/μL). The mean value for those with positive bacterial cultures was 6640/μL, for patients diagnosed with pneumonia by CXR was 8753/μL, and for those without evidence of bacterial infection was 11,708/μL.

The raw PCT and WBC measurements are plotted in Figure 2. As Figure 2 illustrates, PCT is a far more reliable marker for bacterial coinfection than WBC. The statistical analysis presented in Table 1 confirms this observation. The association between PCT and bacterial coinfection is overwhelmingly significant ($P < 0.0001$), with PCT found to have a substantially higher sensitivity and specificity than WBC.

Antibiotic Usage and Charges

Antibiotic therapy was used empirically in 35 (88%) of 40 patients. Three (8%) of 35 patients received monotherapy, 22 (63%) of 35 received dual therapy, and 10 (29%) of 35 received triple therapy. No patient was pretreated with antibiotics before performance of bacterial cultures, CXR, or PCT assay. All 15 patients diagnosed with bacterial coinfection received empiric antibiotic therapy. The majority (12/15) of these patients had initial PCT levels of greater than 1.5 ng/mL; of concern, however, 3 did not and furthermore did not have any follow-up PCT studies. Of the other 25 patients who were without evidence of bacterial coinfection, 20 received empiric antimicrobial therapy. None of these 20 patients had a PCT level of greater than 1.5 ng/mL. Total empiric antibiotic charges for all 40 patients were $16,289. Antibiotic charges for those with bacterial coinfection were $8913 (55% of all antibiotic charges) and $7376 for those without bacterial coinfection (45% of all antibiotic charges). All patient charges for antibiotic therapy and cost of the admission PCT assay are summarized in Table 2.

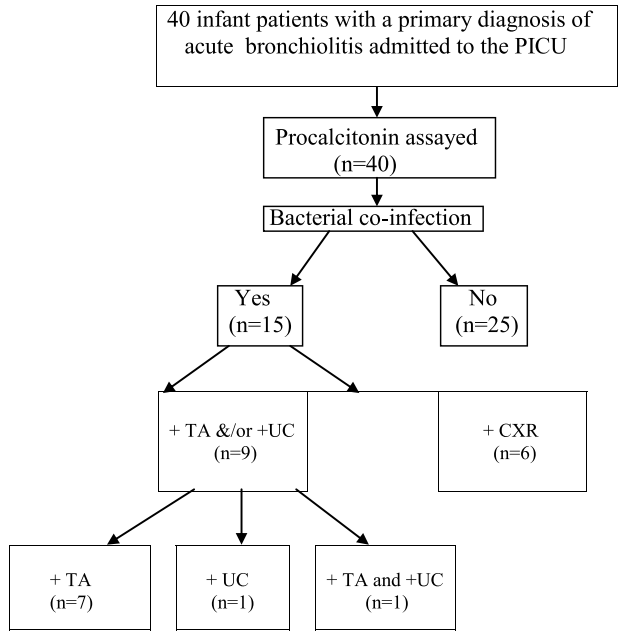

FIGURE 1. Flowchart of 40 infant patients with a primary diagnosis of acute bronchiolitis who had a PCT value drawn on admission to the PICU. + indicates positive.

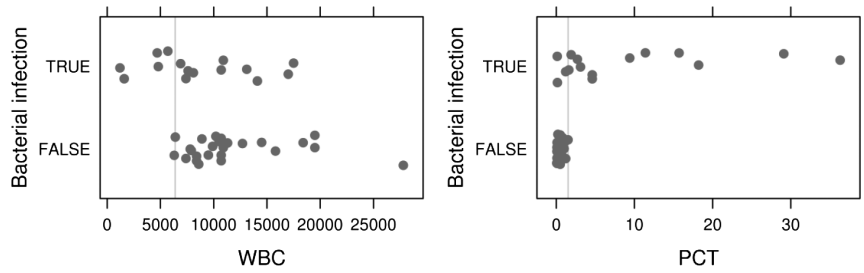

FIGURE 2. Strip plot of WBC and PCT test results for the 40 infant patients admitted to the PICU with a diagnosis of acute bronchiolitis. The light gray line denotes the cutoff presented in Table 1.

Savings in antibiotic charges remained following deduction for the cost of the PCT assay.

DISCUSSION

In this analysis of 40 infants admitted with a diagnosis of acute bronchiolitis to the PICU, we found PCT to be an accurate and highly specific marker for bacterial coinfection. A PCT value of greater than 1.5 ng/mL used at the time of admission would have led to a 45% reduction in unnecessary antibiotic use at a cost savings of $7376.

Of particular interest to admitting physicians is the presence of complications such as bacterial coinfection, which led to significantly prolonged length of stays and increased costs (PICU and hospital).[3,21] This complication has been noted to occur in 1.6% to 44% of patients admitted with acute bronchiolitis.[7,22–25] Unfortunately, the presence of community-acquired or nosocomial bacterial coinfection can be difficult to determine.[4,22] Prior studies are limited by confirmation of fever, absence of a control group, inclusion of patients with bronchiolitis of only respiratory syncytial virus origin, and pretreatment with antibiotics.[23] Furthermore, use of bacterial cultures of blood, urine, TA, and spinal fluid to diagnose bacterial (co)infection is hampered by a 2- to 3-day turnaround time before results are available.[26,27] Similarly, CXRs taken at the time of admission lack consistency in differentiating bacterial from viral pneumonia.[24] As a result, the absence of published evidence-based guidelines leads to continued wide practice variation.[23–25,28,29] As such, a biomarker to predict bacterial coinfection at the time of admission and therefore the necessity of empiric antimicrobial therapy would be of obvious value to admitting physicians who must weigh appropriate use against associated cost and threat of bacterial resistance. Procalcitonin may be suited as such a biomarker.

Procalcitonin, initially described in 1993 by Gendrel, has been found to be a highly sensitive and specific early marker of bacterial infections in infants and children.[7,8,30–32] It has shown promise in distinguishing bacterial from viral infections in a number of common medical scenarios: community-acquired pneumonia,[8,19] fever without a source of infection,[14,18] septic shock of bacterial origin,[8,13,17] occult bacteremia,[8] meningitis,[11,16] neonatal sepsis,[8,33] pyelonephritis complicated by renal scarring,[8,9,12,34,35] and ventriculitis.[10] The benefit of PCT to signal onset of new bacterial infection has also been demonstrated in postoperative, post–cardiopulmonary bypass, and trauma patients.[8,13,15,33] Undetectable in healthy individuals, PCT is secreted from multiple sites (liver, kidney, muscle, and fat) at the onset of acute bacterial infections leading to an early rise (2–4 hours), peak (at 6 hours), and plateau (at 6–24 hours) from the onset of bacterial infection.[8–15,32,36] This profile allows PCT to overcome disadvantages imposed by other biomarkers of bacterial infection such as absolute neutrophil count; C-reactive protein; erythrocyte sedimentation rate; interleukin α, 6, and 8; left shift; and tumor necrosis factor.[8,11,14,15,26,36,37] Other notable advantages of PCT include lack of age related changes,[36] declining values related to appropriate antibiotic therapy,[8,11,13] and correlation with outcome measures such as disease severity,[8,10–13,17,31,38] prognosis and disease progression,[8,13] PRISM score, and mortality.[11,17,38] As a result, PCT may be uniquely qualified to assist admitting physicians in the ED and PICU in their efforts to determine presence of bacterial infections and subsequently reduce unnecessary antibiotic use and lower associated costs in patients of both medical and surgical origin.

In this study, 88% (35/40) of infants admitted with a diagnosis of acute bronchiolitis to the PICU and in whom a serum PCT was obtained at admission were treated with antibiotics despite the fact that only 38% of those patients were later determined to have a bacterial coinfection. Procalcitonin was found to be an accurate and highly specific marker of bacterial coinfection. If a PCT cutoff of greater than 1.5 ng/mL had been used in this study, 45% of all antibiotic costs could have been avoided. These savings were greater than the cost of administering a PCT test to all study patients upon admission. In addition to the cost savings, a PCT test administered upon

TABLE 1. Performance of PCT Versus WBC to Predict Bacterial Coinfection for the 40 Patients Admitted With a Primary Diagnosis of Acute Bronchiolitis to the PICU

Variable	Cutoff Value	*P*	Sensitivity	Specificity	AUC
PCT	>1.5 ng/mL	<0.0001	0.80	1.00	0.88
WBC	<6400/μL	0.06	0.33	0.96	0.67

AUC indicates area under the curve.

TABLE 2. PCT Results, Presence of Bacterial Coinfection, Use of Empiric Antibiotics, Total Antibiotic Charges, and Cost of PCT Assay for the 40 Infant Patients Admitted With a Primary Diagnosis of Acute Bronchiolitis to the PICU

n	PCT	Bacterial Coinfection	Antibiotics	Antibiotic Charges (%)	Cost of PCT Assay
12	>1.5	Yes	Yes	$7950 (49)	$1800
3	<1.5	Yes	Yes	$963 (6)	$450
20	<1.5	No	Yes	$7376 (45)	$3000
5	<1.5	No	No	$0 (0)	$750
Total = 40				$16,289 (100)	$6000

admission would have reduced the number of patients treated with antibiotics by 57% and thereby assist efforts toward the reduction of the ongoing threat of bacterial resistance to antimicrobial therapy.

Limitations of the Study

The single-center focus, lack of uniform criteria for the diagnosis of bronchiolitis and bacterial pneumonia, and the sensitivity of the PCT assay technique are limitations of this preliminary analysis of serum PCT to predict bacterial coinfection in infants with acute bronchiolitis. However, the association of PCT and bacterial coinfection is overwhelmingly significant and supports further study to evaluate the use of PCT in an effort to limit unnecessary use of antibiotics, reduce costs, and assist efforts to lower the threat of bacterial resistance to antimicrobial therapy. Improvements in future study design would include use of multiple sites to improve generalizability to larger populations, the use of uniform criteria to diagnose bronchiolitis and bacterial pneumonia (as a coinfection), the uniform addition of PCT assays to all infants diagnosed with bronchiolitis, and the use of BRAHMS KRYPTOR assay technique with serial studies to improve the sensitivity of PCT to predict bacterial coinfection.

In conclusion, an elevated PCT may assist admitting physicians in the ED and the PICU in determining the presence of bacterial coinfection at the time of admission in infant patients admitted with a primary diagnosis of acute bronchiolitis. Implementation of a PCT cutoff of 1.5 ng/mL at admission may prevent unnecessary antibiotic use with an associated reduction in antibiotic charges in excess of its cost with the additional benefit of assisting efforts toward the reduction of the ongoing threat of bacterial resistance to antimicrobial therapy. Serial PCT levels and use of BRAHMS KRYPTOR assay technique may be useful to further increase PCT sensitivity. Validation in a large prospective, controlled trial utilizing explicit inclusion, diagnostic, and testing criteria is warranted before reliance on PCT to influence future clinical decision making is justified. The results of this preliminary analysis support such a study.

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