Risk Prediction With Procalcitonin and Clinical Rules in Community-Acquired Pneumonia

David T. Huang, MD, MPH
Lisa A. Weissfeld, PhD
John A. Kellum, MD
Donald M. Yealy, MD
Lan Kong, PhD
Michael Martino, MD
Derek C. Angus, MD, MPH
For the GenIMS Investigators

From the Clinical Research, Investigation, and Systems Modeling of Acute Illness Laboratory, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA (Huang, Weissfeld, Kellum, Kong, Angus); the Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, PA (Huang, Yealy); the Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA (Weissfeld, Kong); and the Department of Emergency Medicine, Jefferson Regional Medical Center, Pittsburgh, PA (Martino).

Study objective: The Pneumonia Severity Index and CURB-65 predict outcomes in community-acquired pneumonia but have limitations. Procalcitonin, a biomarker of bacterial infection, may provide prognostic information in community-acquired pneumonia. Our objective is to describe the pattern of procalcitonin in community-acquired pneumonia and determine whether procalcitonin provides prognostic information beyond the Pneumonia Severity Index and CURB-65.

Methods: We conducted a multicenter prospective cohort study in 28 community and teaching emergency departments. Patients presenting with a clinical and radiographic diagnosis of community-acquired pneumonia were enrolled. We stratified procalcitonin levels a priori into 4 tiers: I: less than 0.1; II: greater than 0.1 to less than 0.25; III: greater than 0.25 to less than 0.5; and IV: greater than 0.5 ng/mL. Primary outcome was 30-day mortality.

Results: One thousand six hundred fifty-one patients formed the study cohort. Procalcitonin levels were broadly spread across tiers: 32.8% (I), 21.6% (II), 10.2% (III), and 35.4% (IV). Used alone, procalcitonin had modest test characteristics: specificity (35%), sensitivity (92%), positive likelihood ratio (1.41), and negative likelihood ratio (0.22). Adding procalcitonin to the Pneumonia Severity Index in all subjects minimally improved performance. Adding procalcitonin to low-risk Pneumonia Severity Index subjects (classes I to III) provided no additional information. However, subjects in procalcitonin tier I had low 30-day mortality, regardless of clinical risk, including those in higher risk classes (1.5% versus 1.6% for those in Pneumonia Severity Index classes I to III versus classes IV/V). Among high-risk Pneumonia Severity Index subjects (classes IV/V), one quarter (126/546) were in procalcitonin tier I, and the negative likelihood ratio of procalcitonin tier I was 0.09. Procalcitonin tier I was also associated with lower burden of other adverse outcomes. Similar results were observed with CURB-65 stratification.

Conclusion: Selective use of procalcitonin as an adjunct to existing rules may offer additional prognostic information in high-risk patients. [Ann Emerg Med. 2008;52:48-58.]

0196-0644/$-see front matter

doi:10.1016/j.annemergmed.2008.01.003

SEE EDITORIAL, P. 61.

INTRODUCTION

Background

Community-acquired pneumonia accounts for 1.3 million hospitalizations in the United States each year[1] at a cost of $8.4 billion.[2] It is the most common cause of severe sepsis[3] and infection-related death.[4] Key to the safe and efficient management of community-acquired pneumonia is the ability to reliably predict who will fare well or poorly. The Pneumonia Severity Index[5] and CURB-65 (Confusion, Uremia, Respiratory rate, low blood pressure, age 65 years or older)[6] are clinical rules that identify a subset of individuals at low risk of death who are candidates for outpatient care.[7,8]

Editor's Capsule Summary

What is already known on this topic

Procalcitonin is a biomarker that appears to correlate with bacterial infection.

What question this study addressed

Does a procalcitonin level add prognostic information for pneumonia patients in conjunction with scoring systems such as the Pneumonia Severity Index or CURB-65?

What this study adds to our knowledge

Among 1,651 patients with community-acquired pneumonia in 28 US emergency departments, procalcitonin levels did not add prognostic information for most pneumonia patients. Among higher-risk groups by Pneumonia Severity Index score, low procalcitonin level predicted lower mortality.

How this might change clinical practice

Clinicians should continue using validated prognostic scoring systems for pneumonia. Low procalcitonin level could be considered as a factor for selected patients who would otherwise be considered high risk to be treated in a lower acuity setting.

However, all remaining patients are classified as high risk, usually prompting hospital admission and parenteral antibiotics, even though a large proportion may do well.[9] Thus, there has been considerable interest in the development of rapidly available biomarkers that might confer additional prognostic information.[10]

Importance

Procalcitonin is a calcitonin precursor that is generally increased in bacterial infections but low in viral infections.[11] Procalcitonin has good discrimination for bacterial infections and sepsis,[12-15] and 3 trials used low procalcitonin levels to withhold antibiotics in emergency department (ED) patients presenting with respiratory illnesses.[16-18] However, 2 recent meta-analyses concluded that procalcitonin could not reliably differentiate sepsis from noninfectious inflammation in critically ill patients[19] and had only moderate diagnostic performance for identifying bacteremia in ED patients.[20] Furthermore, the prognostic value of procalcitonin measurement beyond existing prediction rules is unclear. Masia et al[21] observed that patients with high Pneumonia Severity Index scores had higher procalcitonin levels and that higher concentrations were associated with mortality and complications,[21] but Beovic et al[23] found no association between procalcitonin and Pneumonia Severity Index score.[22] These single center studies were limited by small sample sizes and used older procalcitonin assays with low sensitivity.[23]

Goals of This Investigation

Our goal was to determine the prognostic utility of a newer, high-sensitivity procalcitonin assay for 30-day mortality and assess its value beyond established clinical prediction rules. We tested this assay within a multicenter, prospective cohort of patients presenting to the ED with a clinical and radiographic diagnosis of community-acquired pneumonia. We hypothesized that an early singular procalcitonin measurement would aid risk assessment beyond that available from the Pneumonia Severity Index and CURB-65.

MATERIALS AND METHODS

Study Design and Setting

We conducted a multicenter, prospective, cohort study of patients presenting to the EDs of 28 teaching and nonteaching hospitals in southwestern Pennsylvania, Connecticut, southern Michigan, and western Tennessee between November 2001 and November 2003 (Genetic and Inflammatory Markers of Sepsis study). A specific aim of the Genetic and Inflammatory Markers of Sepsis study was to develop and validate risk prediction tools according to information available early in the course of disease. As part of this aim, we sought to determine the prognostic utility of procalcitonin for 30-day mortality.

Selection of Participants

Eligible subjects were older than 18 years and had a clinical and radiologic diagnosis of pneumonia according to Fine et al.[5] We excluded those transferred from another hospital, discharged from a hospital within the previous 10 days, with an episode of pneumonia within the past 30 days, receiving chronic mechanical ventilation, with cystic fibrosis, with active pulmonary tuberculosis, with a known positive HIV antibody titer, having alcoholism with evidence of end-organ damage, admitted for palliative care, enrolled previously in the Genetic and Inflammatory Markers of Sepsis Study, incarcerated, and who were pregnant. We obtained informed consent from the subject or proxy. The institutional review boards of the University of Pittsburgh and all participating sites approved the study.

Data Collection and Processing

We gathered baseline and sequential clinical information by structured patient or proxy interviews, bedside assessment by study nurses, and structured medical record reviews. Median time from ED admission to day 1 blood sample collection was 1.3 hours. We did not obtain day 1 samples from patients presenting after 11 PM or on weekends and holidays for logistic reasons. Study personnel collected blood sample into pyrogen-free vials containing heparin and separated plasma by centrifugation within 1 hour. Plasma was frozen and shipped on dry ice to our central laboratory in Pittsburgh. We tracked clinical data and blood samples with unique anonymized identification numbers, merging data only after assay completion. We observed strict data confidentiality and audited