Copeptin, C-Reactive Protein, and Procalcitonin as Prognostic Biomarkers in Acute Exacerbation of COPD*

Daiana Stolz, MD; Mirjam Christ-Crain, MD; Nils G. Morgenthaler, MD; Jörg Leuppi, MD; David Miedinger, MD; Roland Bingisser, MD; Christian Müller, MD; Joachim Struck, MD; Beat Müller, MD; and Michael Tamm, MD

Background: **A novel approach to estimate the severity of COPD exacerbation and predict its outcome is the use of biomarkers. We assessed circulating levels of copeptin, the precursor of vasopressin, C-reactive protein (CRP), and procalcitonin as potential prognostic parameters for in-hospital and long-term outcomes in patients with acute exacerbation of COPD (AECOPD) requiring hospitalization.**
Methods: **Data of 167 patients (mean age, 70 years; mean FEV_1, 39.9 ± 16.9 of predicted [± SD]) presenting to the emergency department due to AECOPD were analyzed. Patients were evaluated based on clinical, laboratory, and lung function parameters on hospital admission, at 14 days, and at 6 months.**
Results: **Plasma levels of all three biomarkers were elevated during the acute exacerbation ($p < 0.001$), but levels at 14 days and 6 months were similar (p = not significant). CRP was significantly higher in patients presenting with Anthonisen type I exacerbation ($p = 0.003$). In contrast to CRP and procalcitonin, copeptin on hospital admission was associated with a prolonged hospital stay ($p = 0.002$) and long-term clinical failure ($p < 0.0001$). Only copeptin was predictive for long-term clinical failure independent of age, comorbidity, hypoxemia, and lung functional impairment in multivariate analysis ($p = 0.005$). The combination of copeptin and previous hospitalization for COPD increased the risk of poor outcome ($p < 0.0001$). Long-term clinical failure was observed in 11% of cases with copeptin < 40 pmol/L and no history of hospitalization, as compared to 73% of patients with copeptin ≥ 40 pmol/L and a history of hospitalization ($p < 0.0001$).**
Conclusions: **We suggest copeptin as a prognostic marker for short-term and long-term prognoses in patients with AECOPD requiring hospitalization.** ***(CHEST 2007; 131:1058–1067)***

Key words: chronic bronchitis; hospitalization; marker; prognosis

Abbreviations: AECOPD = acute exacerbations of COPD; CRP = C-reactive protein; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IQR = interquartile range

Several clinical characteristics have been extensively validated as prognostic factors for mortality in acute exacerbations of COPD (AECOPD).[1–9] Although of epidemiologic interest, the predictive value of clinical parameters vary in the different studies,[2,7,9] and the majority of them do not allow precise individual risk assessment. Therefore, there has been increasing interest in using pulmonary

*From the Clinic of Pneumology and Pulmonary Cell Research (Drs. Stolz, Leuppi, Miedinger, and Tamm), Clinic of Endocrinology, Diabetes and Clinical Nutrition (Drs. Christ-Crain and B. Müller), and Department of Internal Medicine (Drs. Bingisser and C. Müller), University Hospital Basel, Basel, Switzerland; and Research Department (Drs. Morgenthaler and Struck), BRAHMS AG, Biotechnology Centre, Hennigsdorf, Germany.
Dr. B. Müller has served as consultant and received payments from BRAHMS (the manufacturer of procalcitonin and copeptin assays) to attend advisory board meetings and speaker engagements, or research. Dr. Morgenthaler and Dr. Struck are employees of BRAHMS. The other authors have no conflicts of interest to disclose.
Manuscript received September 22, 2006; revision accepted December 6, 2006.

Correspondence to: Daiana Stolz, MD, Clinic of Pneumology and Pulmonary Cell Research, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland; e-mail: dstolz@uhbs.ch
DOI: 10.1378/chest.06-2336

biomarkers to monitor disease severity in patients with AECOPD.[10] However, there is little information about how current biomarkers relate to significant clinical outcomes such as length of hospital stay, need for ICU treatment, and mortality.[10–14]

Arginine vasopressin, also termed *antidiuretic hormone*, is a nonapeptide produced by the hypothalamus.[15] Hypotensive, hypoxic, hyperosmolar, or acidotic stimuli, together with infectious conditions, are known to increase circulating vasopressin concentrations.[16–20] Vasopressin has gained additional interest as a prognostic biomarker and vasopressor agent in septic shock.[17,21,22] However, its instability makes reliable measurements difficult to achieve and precludes routine use.[23,24] Copeptin is the more stable C-terminal part of the vasopressin precursor and a 39-amino-acid–long glycosylated peptide. Copeptin remains stable *ex vivo* for several days at room temperature in serum or plasma and, thus, directly reflects levels of vasopressin.[25] Hence, copeptin might be of interest as a biomarker in AECOPD.

C-reactive protein (CRP) is an acute-phase reactant with well-documented sensitivity that is commonly used to diagnose infectious and inflammatory conditions, including exacerbations of COPD.[26–28] Procalcitonin, a hormokine ubiquitously released during bacterial infection, has been shown to allow antibiotic guidance in AECOPD.[29] In addition, persistently elevated procalcitonin levels have been shown to have prognostic implications in severe bacterial infections.[30–32]

The aim of our study was threefold: first, to investigated the correlation of copeptin, CRP, and procalcitonin with clinical characteristics thought to define condition severity in patients with AECOPD requiring hospitalization. Second, we analyzed the usefulness of the biomarkers to assess in-hospital prognosis in this population. And finally, we examined whether copeptin, CRP, or procalcitonin were able to predict clinical failure within 6 months after exacerbation.

Materials and Methods

Setting and Study Population

Data from 167 patients admitted for AECOPD to the emergency department of the University Hospital Basel, Switzerland from November 2003 to March 2005 and included in a randomized study was analyzed. A complete description has been reported elsewhere.[29] In brief, the primary end point of the study was to evaluate the prescription and duration of antibiotic use in patients randomly assigned to procalcitonin guidance as compared to usual care. To be eligible for the study, patients had to be admitted on the basis of clinical history, physical examination, and chest radiography, and to meet postbronchodilator spirometric criteria for COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[33] within 48 h after inclusion. Patients were excluded from the study if they were severely immunocompromised, had asthma or cystic fibrosis, or if infiltrates on chest radiography were present at hospital admission.

Baseline assessment included clinical data and routine blood tests. Spontaneously expectorated sputum samples were obtained and examined using standard techniques.[34]

Spirometry was performed by trained lung function technicians according to American Thoracic Guidelines.[35] Respiratory symptoms were quantified using a questionnaire for patients with respiratory illnesses (range, 0 to 95, with higher scores indicating greater discomfort).[36]

This trial was approved by the Basel Ethics Committee and was registered as with the Current Controlled Trials Database.[37] All participants gave written informed consent.

Outcome Measurements

The short-term and long-term follow-up visits performed 14 to 18 days and 6 months after hospital admission comprised clinical, laboratory, and lung function assessments. Medical records from hospital admission and family physicians were analyzed. Thereby, patients were classified as clinical success or clinical failure. Clinical failure was defined by the occurrence of an exacerbation of COPD requiring hospitalization or death of any cause up to 6 months after inclusion in the study.

Determination of Biomarkers Plasma Concentrations

Copeptin was measured using 50 μL of ethylenediamine tetra-acetic acid plasma by a new sandwich immunoluminometric assay employing two polyclonal antibodies to amino acids 132–164 of preprovasopressin (CT-proAVP LIA; BRAHMS AG; Hennigsdorf/Berlin, Germany).[25] The lower detection limit of the assay is 1.7 pmol/L, and the functional assay sensitivity is 2.25 pmol/L.[25] CRP was measured in ethylenediamine tetra-acetic acid plasma on a Hitachi Instrument 917 (Roche Diagnostics; Rotkreuz, Switzerland). Procalcitonin was measured using 20 to 50 μL of plasma or serum by a time-resolved amplified cryptate emission technology assay (PCT Kryptor; BRAHMS).[36] The assay has a functional assay sensitivity of 0.06 μg/L, threefold to tenfold above normal mean values.

Statistical Analysis

Discrete variables are expressed as counts (percentages) and continuous variables as mean ± SD or median (interquartile range [IQR]). Comparability of groups was analyzed by χ^2 test, two-sampled *t* test, Mann-Whitney *U* test, Kruskal-Wallis analysis of variance, or Wilcoxon matched-pair test, as appropriate. To analyze the relationship among different variables and copeptin levels on hospital admission, a multiple linear regression model including age, cardiopathy, Pa_{O_2}, leukocyte counts, CRP, procalcitonin, and FEV_1 percentage of predicted was used. To analyze the relationship among different clinical parameters and duration of hospital stay, a multiple linear regression model including age, cardiopathy, arterial hypertension, renal failure, diabetes mellitus, Pa_{O_2}, Pa_{CO_2}, and FEV_1 percentage of predicted was used. To assess the influence of age, hospitalization due to AECOPD in the previous year, cardiopathy, Pa_{O_2}, leukocyte counts, CRP, procalcitonin, and FEV_1 percentage of predicted and antimicrobial therapy during the index exacerbation on clinical failure, a Cox regression univariate and multivariate analysis were performed. Correlation analyses were performed using Spearman rank. The time to clinical failure was analyzed by Kaplan-Meier survival curves and compared by the log-rank test. All test were