Antibiotic Treatment of Exacerbations of COPD*

A Randomized, Controlled Trial Comparing Procalcitonin-Guidance With Standard Therapy

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Background: Therapy with antibiotics influences recovery only in selected cases of COPD exacerbations. We evaluated the efficacy and safety of procalcitonin guidance compared to standard therapy with antibiotic prescriptions in patients experiencing exacerbations of COPD.

Methods: A total of 208 consecutive patients requiring hospitalization for COPD exacerbation were randomized at the index exacerbation to procalcitonin-guided or standard antibiotic therapy. Patients receiving procalcitonin-guided therapy were treated with antibiotics according to serum procalcitonin levels; standard-therapy patients received antibiotics according to the attending physician. The primary outcome was the antibiotic exposure at the index exacerbation and the subsequent antibiotic requirement for COPD exacerbation within 6 months. Secondary outcomes were clinical recovery, symptom scores, length of hospitalization, ICU stay, death, lung function, exacerbation rate, and time to next exacerbation.

Results: At the index exacerbation, procalcitonin guidance reduced antibiotic prescription (40% vs 72%, respectively; p < 0.0001) and antibiotic exposure (relative risk [RR], 0.56; 95% confidence interval [CI], 0.43 to 0.73; p < 0.0001) compared to standard therapy. Moreover, procalcitonin guidance at the index exacerbation allowed a significant sustained reduction in total antibiotic exposure for up to 6 months (RR, 0.76; 95% CI, 0.64 to 0.92; p = 0.004). Clinical outcome and improvement in FEV1 at 14 days and 6 months did not differ between groups. Within 6 months, the exacerbation rate (0.62 vs 0.64, respectively), the rehospitalization rate (0.21 vs 0.24, respectively), and mean (± SD) time to the next exacerbation (70.0 ± 46.1 vs 70.4 ± 51.9 days, respectively; p = 0.523) were similar in both groups.

Conclusions: Procalcitonin guidance for exacerbations of COPD offers a sustained advantage over standard therapy in reducing antibiotic use for up to 6 months with a number-needed-to-treat of 3.

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Key words: biomarker; chronic bronchitis; respiratory tract infection; spirometry

Abbreviations: CI = confidence interval; ECOPD = exacerbation of COPD; IQR = interquartile range; RR = relative risk

In the United States, COPD affects approximately 16 million adults, and is one of the fastest growing causes of morbidity and mortality.1,2 Exacerbations of COPD are responsible for > 2.4% of all acute medical hospital admissions and constitute the most important direct health-care costs associated with COPD.3,4 In the United States, the mean cost of hospital admission for COPD in a cohort of patients with severe COPD was estimated to be $7,100 (in US dollars).4,5

Exacerbations of COPD can be triggered by a variety of factors, such as viruses, bacteria, and common pollutants.6 Thus, corticosteroids,7,8 antioxidants,9,10 and antibiotics11,12 may all have beneficial effects in treating or preventing some episodes. Antibiotics have demonstrated a marginal efficacy in the treatment of exacerbations of COPD.11–24 Nevertheless, a recent survey25 including 69,820 patients who had been hospitalized for exacerbations of COPD in 360 hospitals throughout the United States showed that 85% of all patients were given...
antibiotics. Not all patients will equally experience benefit from antibiotics. Subgroups of patients selected by evidence of bacterial infection or by severity of illness are more likely to benefit than those patients who are less ill.11,14,21,24,26 Therefore, the definition of a biomarker, which potentially detects such episodes or is specific to one subtype of exacerbation would be of great interest.

Serum levels of procalcitonin increase rapidly in the presence of infection.27–29 The ubiquitous release of procalcitonin during infections is induced either directly by microbial toxins (eg, endotoxin) and/or indirectly by humoral factors or the cell-mediated host response.30,31 This induction is rather attenuated by cytokines released during viral infections.31 Therefore, circulating levels of procalcitonin are markedly elevated in patients with bacterial infections compared to those with viral infections or other inflammatory conditions.28,29

In previous studies,32,33 procalcitonin guidance markedly and safely reduced antibiotic prescriptions and the duration of antibiotic therapy in patients with lower respiratory tract infections. Therefore, we hypothesized that procalcitonin concentrations can serve as a marker for different antibiotic prescriptions and the duration of antibiotic therapy in patients with lower respiratory tract infections. To test this hypothesis, we conducted a study in which we prospectively randomized patients presenting with an exacerbation of COPD (ECOPD) to be treated according to internationally accepted guidelines (ie, the standard-therapy group) or to procalcitonin levels (ie, the procalcitonin group) on hospital admission.

**Materials and Methods**

**Patients**

From November 2003 to March 2005, consecutive patients ≥ 40 years of age who had been admitted to the emergency department of the University Hospital Basel (Basel, Switzerland) with an ECOPD and met post-bronchodilator therapy spirometric criteria, according to the Global Initiative for Chronic Obstructive Lung Disease guidelines,34 within 48 h of emergency department admission were included in this study. An ECOPD was defined as “a sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD.”35 Patients in whom there was found to be an alternative explanation for the presenting signs and symptoms other than a worsening of the underlying COPD were not included in the study. Patients who were considered to be vulnerable study participants (ie, those with psychiatric comorbidities) were excluded from the study. Other exclusion criteria were immunosuppression, asthma, cystic fibrosis, and the presence of infiltrates on chest radiographs on hospital admission.

**Study Design**

This single-center, randomized, controlled trial was approved by the institutional review board and was registered with the Current Controlled Trials Database.36 All participants gave written informed consent.

Baseline assessment included clinical data and routine blood tests. Procalcitonin levels were measured within 1 h after blood sampling using 20 to 50 μL of plasma or serum by a time-resolved amplified cryptate emission technology assay (Kryptor PCT; Brahms AG; Hennigsdorf, Germany).32 The assay has a functional assay sensitivity of 0.06 μg/L, which is 3-fold to 10-fold above normal mean values.

Spontaneously expectorated sputum samples were obtained for Gram staining and culture. Bacterial isolation and identification was performed with the use of standard techniques described by the American Society for Microbiology.37 Spirometry was performed by trained lung function technicians who were blinded to group assignment, according to American Thoracic Society guidelines.38 The patients’ functional status was assessed with the help of a visual analog scale, ranging from 0 (feeling extremely ill) to 100 (feeling completely healthy). Respiratory symptoms were quantified using a questionnaire for patients with respiratory illnesses (range, 0 to 95 [with higher scores indicating greater discomfort]).32

**Study Intervention**

Patients satisfying the entry criteria were randomly assigned to one of two groups at the time of admission to the emergency department. In the standard-therapy group, antibiotic therapy was started based on current guidelines, according to the decision of the attending physician, who was unaware of the patient’s procalcitonin levels. In the procalcitonin group, antibiotic use was based on the measurement of procalcitonin levels at hospital admission.32 A procalcitonin level of < 0.1 μg/L was considered...
to indicate the absence of bacterial infection, and the use of antibiotics was discouraged. A level of 0.1 to 0.25 µg/L indicated possible bacterial infection, and the use of antibiotics was discouraged or encouraged, respectively, based on the stability of the patient’s clinical condition. A procalcitonin level of > 0.25 was considered to suggest the presence of bacterial infection, and antibiotic treatment was encouraged.

Reevaluation of circulating procalcitonin levels and clinical status was recommended after 6 to 24 h if antibiotic therapy was withheld. Except for the prescription of antibiotics at the index exacerbation, the prescription of all other medications was left entirely to the discretion of the treating physicians throughout the study period in both groups.

**Short-term and Long-term Follow-up**

Patients were monitored daily until discharge from the hospital, and subsequent changes in clinical course and the prescription of new antibiotics were recorded. In all cases, the decision to initiate therapy with new antibiotics was left to the attending physician.

At the short-term follow-up visit (14 to 21 days), which was performed by a physician and a nurse on the study team, who were blinded to the group assignment, patients were evaluated based on clinical, laboratory, and lung functional criteria. Thereby, patients were classified into subgroups of “clinical success” (ie, improvement of symptoms compared to exacerbation status), and “clinical failure” (ie, the absence of the attenuation of symptom, the worsening of symptoms, or death).

The long-term follow-up visit (at 6 months), which was performed by a physician and a nurse on the study team, who were blinded to the group assignment, comprised a clinical, laboratory, and lung function assessment. Patients and family physicians were asked about the extent and the timing of health-care utilization due to exacerbations of COPD.

**Outcome Measures**

The primary end points of the study were total antibiotic use at the index exacerbation and up to 6 months, expressed as a percentage and relative risk (RR) of antibiotic exposure. Secondary end points included measures of clinical outcomes (eg, success, self-reported functional status, symptom scores, steroid dose, length of stay, need for ICU, or death), laboratory outcomes (eg, C-reactive protein and procalcitonin levels), and lung function outcomes on hospital admission, and at the short-term and long-term follow-ups. At 6 months, the exacerbation rate and time to the next ECOPD were assessed.

**Statistical Analysis**

Analyses were performed on an intention-to-treat basis by $\chi^2$ test, two-sampled t test, or Mann-Whitney U test. RR was calculated with 95% confidence intervals (CIs). All tests were two-tailed; $p < 0.05$ was defined as being significant.

The time to the occurrence of clinical events was analyzed by Kaplan-Meier survival curves and by the log-rank test. To describe the changes in parameters up to 6 months, a repeated-measures analysis of variance was performed.

The trial was designed to demonstrate the persistent superiority of procalcitonin guidance in decreasing antibiotic use up to 6 months after the index exacerbation. The sample size was calculated from the following assumptions: a 75% use of antibiotics to treat the index exacerbation; and an expected absolute reduction of this frequency from 75 to 45% with procalcitonin guidance. Considering an exacerbation rate of 70% within 6 months, and 75% antibiotic use in the following exacerbations, a sample size of 186 patients (93 patients per group) was necessary to detect a significant difference in antibiotic use between both groups with a power of 85% and an $\alpha$ error of 0.05. Considering a 20% dropout rate after assignment to the study, 223 inclusions were planned. Analyses were performed using a statistical software package (SPSS, version 13; SPSS Inc; Chicago IL).

**Results**

**Study Population**

From November 2003 to March 2005, 288 patients with suspected COPD exacerbations were admitted to the emergency department (Fig 1). Of the 226 randomly assigned patients, 18 were removed because they failed to meet spirometric criteria for the presence of COPD. No patient dropped out thereafter, and no patient was lost to follow-up.

Baseline characteristics of the patients in both groups were much the same (Table 1). Current use of antibiotic therapy for exacerbations of COPD was reported by 45 patients (22%), with equal distribution in both groups ($p = 0.753$).

Overall, cultures from sputum yielded pathogenic bacteria in 37 and 40 patients (36% and 38%, respectively; $p = 0.886$). Gram-negative bacteria accounted for 69% of all microorganisms recovered (53 organisms), and Gram-positive organisms accounted for 31% of all microorganisms recovered (24 organisms). The most frequently isolated organisms were Enterobacteriaceae spp (18 organisms) and *Streptococcus pneumoniae* (14 organisms).

The following medications were prescribed for the treatment of the exacerbation: enteral and/or parenteral steroids (88%; procalcitonin group, 89%; standard-therapy group, 93%; $p = 0.196$); inhaled steroids (91%; procalcitonin group, 93%; standard-therapy group, 89%; $p = 0.325$); $\beta_2$-agonist and/or anticholinergic agents (100%; procalcitonin group, 100%; standard-therapy group, 100%; $p = 1$); and theophylline (5%; procalcitonin group, 6%; standard-therapy group, 4%; $p = 0.437$).

On hospital admission, the median procalcitonin level was 0.096 ng/mL (interquartile range [IQR], 0.070 to 0.200). Figure 2 shows the procalcitonin values measured at admission to the emergency department. Procalcitonin values were $< 0.1$ ng/mL in 107 patients (51%), between 0.1 and 0.25 ng/mL in 60 patients (29%), and $> 0.25$ ng/mL in 41 patients (20%). Procalcitonin levels in patients pretreated with antibiotics were 0.097 ng/mL (IQR, 0.063 to 0.180) compared to 0.096 ng/mL (IQR, 0.070 to 0.21) in antibiotic-naive patients ($p = 0.601$).
Primary Outcome

At the index exacerbation, procalcitonin guidance significantly reduced antibiotic prescriptions (40% vs 72%, respectively; p < 0.0001) and antibiotic exposure (RR, 0.56; 95% CI, 0.43 to 0.73; p < 0.0001), compared to standard therapy (Fig 3). The reduction in RR of antibiotic exposure for patients in the procalcitonin group was 44% (95% CI, 0.27 to 0.57; p < 0.0001), and the absolute risk reduction was 31.5% (95% CI, 18.7 to 44.3%; p < 0.0001). Subsequent antibiotic use for the treatment of exacerbations of COPD within 6 months did not differ between the two groups (46 vs 43 courses, respectively; p = 0.290). Accordingly, procalcitonin-guided antibiotic therapy at the index exacerbation allowed a significant sustained reduction in total antibiotic exposure for up to 6 months (RR, 0.76; 95% CI, 0.64 to 0.92; p = 0.004). There was no difference in the mean (± SD) time to the next exacerbation treated with antibiotics in the procalcitonin and standard-therapy groups (76.7 ± 49.6 vs 76.1 ± 50.9 days, respectively; p = 0.819).

The antibiotics that were prescribed included aminopenicillins (62%), fluoroquinolones (16%), cephalosporins (11%), macrolides (8%), antipseudomonal penicillins (2%) and other agents (1%). A single antibiotic was used in 94 patients (80%; procalcitonin group, 83%; standard-therapy group, 68%; p = 0.124), two antibiotic agents were used in 20 patients (17%; procalcitonin group, 15%; standard-therapy group, 20%; p = 0.112), and three antibiotic agents were used in 3 patients (3%; procalcitonin group, 2%; standard-therapy group, 3%; p = 1).

Overall, pneumonia developed in 10 patients during the course of the index exacerbation: 5 patients had continued to receive antibiotic therapy since hospital admission (procalcitonin group, 2 patients; standard-therapy group, 3 patients; p = 1.0), and 5 patients had not received antibiotic therapy (procalcitonin group, 4 patients; standard-therapy group, 1 patient; p = 0.205). Two additional patients received antibiotic therapy due to clinical failure (procalcitonin group, one patient; standard-therapy group, one patient; p = 1.0). One patient in the standard-therapy group was treated with antibiotics by the family physician immediately after hospital discharge.

Secondary Outcome

In both groups, clinical and laboratory measures of outcome were similar at baseline, at short-term follow-up, and at long term follow-up (Table 2, 3).
Procalcitonin-guided therapy and standard therapy were equivalent in terms of clinical success rate (82.4% vs 83.9%, respectively; \( p = 0.853 \)). Compared to patients in the standard-therapy group, patients in the procalcitonin group had significantly lower FEV\(_1\) at baseline (\( p = 0.021 \)). How-
ever, this difference was no longer present at short-term and long-term follow-ups \( (p = 0.521 \text{ and } 0.366, \text{ respectively}) \).

Fourteen patients died during the study period (procalcitonin group, 5 patients [4.9%]; standard-therapy group, 9 patients [8.5%]; \( p = 0.409 \)). Overall, four patients died of COPD-related respiratory failure and eight patients died of a medical condition other than COPD (myocardial infarction, three patients; bronchial carcinoma, one patient; abdominal sepsis, one patient; gastric bleeding, one patient; aortic aneurysm rupture, one patient; aspiration pneumonia, one patient). In two patients, the cause of death remained unknown.

A total of 133 subsequent exacerbations occurred within 6 months of study inclusion (procalcitonin group, 63 exacerbations; standard-therapy group, 71 exacerbations; \( p = 0.755 \)). Hospitalization for ECOPD was required in 46 cases (21 vs 25 cases, respectively; \( p = 0.564 \)). There were no significant differences in the exacerbation rate (0.62 vs 0.64, respectively) and the hospitalization rate for exacerbations of COPD (0.21 vs 0.24, respectively) in both groups (Fig 4). The mean time to the next exacerbation was also similar in both groups (70.0 ± 46.1 vs 70.4 ± 51.9 days, respectively; \( p = 0.523 \)).

**Subgroup Analysis**

Sputum purulence was noted in 58% of patients (120 patients). In patients with and without sputum purulence, procalcitonin levels were similar \( (p = 0.287) \). Positive sputum bacteriology findings were not associated with elevated procalcitonin levels \( (p = 0.466) \). According to the classification of Anthonisen et al. \( ^{11} \), procalcitonin levels in patients with type I exacerbations (0.094 ng/mL; IQR, 0.073 to 0.171), type II exacerbations (0.098 ng/mL; IQR, 0.070 to 0.174), and type III exacerbations (0.110 ng/mL; IQR, 0.058 to 0.252) did not differ \( (p = 0.508) \). Antibiotic prescription was similar in all exacerbation types, as follows: 59% of patients with type I exacerbations (procalcitonin group, 41%; standard-therapy group, 78%), 54% of patients with type II exacerbations (procalcitonin group, 33%; standard-therapy group, 71%), and 54% of patients with type III exacerbations (procalcitonin group, 44%; standard-therapy group, 62%; procalcitonin group, \( p = 0.917 \); standard-therapy group, \( p = 0.395 \)). Procalcitonin levels on hospital admission correlated significantly with leukocyte counts \( (R = 0.224; p = 0.001) \) and C-reactive protein levels \( (R = 0.377; p < 0.001) \).

There was no correlation between FEV\(_1\) percent predicted and procalcitonin levels on hospital admission \( (p = 0.895) \). In patients who were treated without antibiotics, FEV\(_1\) improvement did not differ in both groups \( (p = 0.297) \) [Fig 5, top, A]. However, patients in the procalcitonin group, who were treated with antibiotics, had greater mean improvements in FEV\(_1\) (11.4 ± 23.8%) compared to antibiotic-treated patients in the standard-therapy group (0.72 ± 11.4%; \( p = 0.017 \)) [Fig 5, bottom, B].

**Discussion**

Our findings indicate that guidance with the measurement of procalcitonin levels reduces the exposure of patients to antibiotics after presentation to the emergency department for exacerbations of COPD. This initial difference in antibiotic exposure is not followed by increased antimicrobial usage after hospitalization for up to 6 months. Thereby, the clinical outcome, including exacerbation rate and time to the next exacerbation, was not compromised.
The absolute risk reduction of 31.5% in antibiotic exposure implies that for one in every four patients who were admitted to the hospital due to an ECOPD, one course of antibiotic therapy can be prevented (number-needed-to-treat, 3.2; 95% CI, 2.3 to 5.3).

Given the prevalence of COPD and the duration of illness, a reduction in antibiotic prescriptions for the treatment of exacerbations could have a tremendous impact on the overall economic burden of the disease under current budget constraints. In addition, the controlled prescription of antibiotics decreases selective pressure for the emergence of bacterial resistance.

A metaanalysis of placebo-controlled trials concluded that there was a small but significant benefit from the treatment of exacerbations of COPD with antibiotics in terms of overall recovery. A more recent extensive review of the literature suggested that antibiotic therapy significantly decreased mortality and lack of response to treatment in patients experiencing exacerbations of COPD. Moreover, it has been proposed that antibiotic therapy may reduce further antibiotic prescriptions following the presenting exacerbation and may increase the time until the next exacerbation in a selected population of patients. Several characteristics have been suggested to identify patients who are at a greater risk for severe exacerbation, including the presence or severity of underlying obstructive disease, comorbid conditions, frequency of exacerbation, and severity of symptoms at presentation. Most of these proposed criteria have been analyzed in different retrospective study designs. However, none has been validated by a prospective randomized trial.

Similarly, a wide variety of surrogate markers of the inflammatory process have been measured in patients in the stable state and during and

### Table 2—Clinical Outcome Parameters at Short-term Follow-up in Both Randomized Groups

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Procalcitonin Group (n = 102)</th>
<th>Standard Group (n = 106)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical success</td>
<td>84 (82.4)</td>
<td>89 (83.9)</td>
<td>0.853</td>
</tr>
<tr>
<td>Hospital stay &lt; 24 h</td>
<td>22 (21.6)</td>
<td>24 (22.6)</td>
<td>0.852</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>9 (1–15)</td>
<td>10 (1–15)</td>
<td>0.960</td>
</tr>
<tr>
<td>Need for ICU stay</td>
<td>8 (7.8)</td>
<td>11 (10.4)</td>
<td>0.526</td>
</tr>
<tr>
<td>Duration of ICU stay, d</td>
<td>3.3 ± 2.7</td>
<td>3.7 ± 2.1</td>
<td>0.351</td>
</tr>
<tr>
<td>Steroid use (%)</td>
<td>89 (87.3)</td>
<td>93 (87.7)</td>
<td>0.916</td>
</tr>
<tr>
<td>Steroid dose, mg</td>
<td>250 (119–400)</td>
<td>250 (183–421)</td>
<td>0.303</td>
</tr>
<tr>
<td>Hospitalization rate for ECOPD within 6 mo</td>
<td>18 (17.7)</td>
<td>22 (20.8)</td>
<td>0.507</td>
</tr>
<tr>
<td>Death of any cause within 6 mo</td>
<td>5 (4.9)</td>
<td>9 (8.5)</td>
<td>0.409</td>
</tr>
</tbody>
</table>

*Values are given as No. (%), median (IQR), or mean ± SD, unless otherwise indicated.

### Table 3—Clinical, Laboratory, and Lung Function Parameters on Hospital Admission, and at Short-term and Long-term Follow-up in Both Randomized Groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Procalcitonin Group (n = 102)</th>
<th>Standard-Therapy Group (n = 106)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom score</td>
<td>47 ± 14</td>
<td>40 ± 21</td>
<td>0.394</td>
</tr>
<tr>
<td>Functional status</td>
<td>40 ± 21</td>
<td>61 ± 20</td>
<td>0.852</td>
</tr>
<tr>
<td>FEV1/L</td>
<td>0.88 ± 0.41</td>
<td>1.04 ± 0.48</td>
<td>0.068</td>
</tr>
<tr>
<td>% predicted</td>
<td>38.7 ± 17.7</td>
<td>44.1 ± 19.7</td>
<td>0.176</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>43.8 ± 11.2</td>
<td>47.8 ± 14.7</td>
<td>0.215</td>
</tr>
<tr>
<td>Procalcitonin level μg/L</td>
<td>0.274 ± 1.049</td>
<td>0.207 ± 0.196</td>
<td>0.049 ± 0.056</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.087 (0.066–0.192)</td>
<td>0.022 (0.013–0.057)</td>
<td>0.017 (0.013–0.042)</td>
</tr>
<tr>
<td>CRP level mg/L</td>
<td>32 ± 42</td>
<td>13 ± 20</td>
<td>0.856</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>16 (5–53)</td>
<td>5 (2–16)</td>
<td>0.234</td>
</tr>
</tbody>
</table>

*Values are given as mean ± SD, unless otherwise indicated. CRP = C-reactive protein.
†Denote interaction between group and time.
Figure 4. Top, A: Kaplan-Meier estimates of the probability of remaining relapse-free and alive at 6 months in the procalcitonin-guided group (n = 102) and standard-therapy group (n = 106). Bottom, B: Kaplan-Meier estimates of the probability of remaining free of a relapse of COPD requiring hospitalization and alive at 6 months in the procalcitonin-guided group (n = 102) and standard-therapy group (n = 106).
Most of them provide laboratory confirmation supporting the diagnosis of exacerbation. Unfortunately, their role in patient management is far from certain, as prospective studies under long-term follow-up are not available.

In this prospective, interventional study, we randomized unselected, consecutive COPD patients to receive antibiotics based on serum procalcitonin levels at hospital admission. The vast majority of admitted patients took part in the study, assuring the applicability of the proposed approach under "real-life" conditions. The acquisition of data from family physicians provided unbiased long-term follow-up information.

Although procalcitonin guidance reduced antibiotic prescription by 44%, its use did not result in an increase in the relapse of COPD, a decrease in the length time before the next exacerbation, or a more rapid decline in lung function. Patients who were assigned to the procalcitonin group, who received antibiotics, indeed had greater improvement in FEV₁ compared to the patients who received antibiotics in the standard-therapy group. Thus, it is tempting to speculate that procalcitonin levels at hospital admission identifies patients who present with more severe or tissue-invasive bacterial infection and hence would most likely to benefit from antibiotic therapy.

Sputum microbiology is considered to be of limited value in investigating exacerbations of COPD. Conversely, the acquisition of new strains of microorganisms might indicate an impending bacterial exacerbation. In our study, there was no correlation between procalcitonin levels and sputum bacteriology. However, we could not analyze whether high procalcitonin levels at hospital admission were associated with the acquisition of new bacterial strains, as molecular genotyping has not been performed.

This study might have a potential limitation in regard to its generalizability. As previous experience with procalcitonin was available at the study site, physician adherence to the study protocol was facilitated. Furthermore, only patients with an ECOPD requiring hospitalization were included in the study. Thereby, procalcitonin measurement results were available within 1 h after hospital admission, allowing an immediate treatment decision. Thus, the applicability of these findings to mild exacerbations treated in the outpatient setting still has to be confirmed in multiinstitutional, international studies. Furthermore, we cannot exclude that some of the patients who were randomized to the procalcitonin group, who received antibiotics because of elevated circulating procalcitonin levels, would have recovered without antibiotic therapy. However, taking into account the well-established association between elevated procalcitonin levels and clinically relevant bacterial infection (ie, sepsis), we

Figure 5. Top, A: change in FEV₁ in patients who have not been treated with antibiotics during the index exacerbation in the procalcitonin-guided group (n = 61) and standard-therapy group (n = 30). p Values compare the change in FEV₁ over time between both groups. Bottom, B: change in FEV₁ in patients who have been treated with antibiotics during the index exacerbation in the procalcitonin-guided group (n = 41) and standard-therapy group (n = 76). p Values compare the change in FEV₁ over time between both groups.

ECOPD. Most of them provide laboratory confirmation supporting the diagnosis of exacerbation. Unfortunately, their role in patient management is far from certain, as prospective studies under long-term follow-up are not available.
considered the inclusion of a third study arm, which would withhold antibiotic treatment, to be in all cases unethical.

In conclusion, our results suggest that procalcitonin could be a suitable biomarker of exacerbations of COPD, which may be used to target management for each patient and episode more specifically, allowing a sustained reduction in antibiotic use for the treatment of COPD both at short-term and long-term follow-up.

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