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Perspective

Acute exacerbations of chronic obstructive pulmonary disease with low serum procalcitonin values do not benefit from antibiotic treatment: a prospective randomized controlled trial

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SUMMARY

Objective: The majority of patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) have low serum procalcitonin (PCT) values. The aim of this study was to determine whether these patients may benefit from antibiotic treatment.
Methods: A total of 457 patients with AECOPD were screened; 194 patients with AECOPD and PCT <0.1 ng/ml were assigned randomly to an antibiotic group or a control group. In the per-protocol (PP) population, the antibiotic group subjects were required to have used antibiotics for at least 3 days, and the control group subjects were required not to have used antibiotics within the 10 days after admission. The intention-to-treat (ITT) population was defined as the patients who were randomized. The primary outcome was the treatment success rate on day 10 after admission. Secondary outcomes were symptoms assessed on a visual analog scale (VAS), length of hospitalization, mortality, exacerbation rate, and re-hospitalization within 30 days of follow-up (study registered at chictr.org.cn: ChiCTR-TRC-14004726).
Results: 95 patients in the antibiotic group and 96 patients in the control group completed the study. In the ITT population, the overall treatment success rate in the control group (95.8%) was similar to that in the antibiotic group (93.7%), with no significant difference ($p = 0.732$). Five patients in the antibiotic group died, either in hospital or within 30 days of discharge. In the control group, two died within 30 days of discharge. Antibiotic use in the control group was 17.7% (17/96), and age ≥75 years was a predictive risk factor for requiring antibiotic therapy in the control group (odds ratio 4.055, 95% confidence interval 1.297–12.678; $p = 0.012$). According to the PP analysis, the treatment success rate on day 10 after admission was 98.7% (78/79) in the control group and 93.7% (89/95) in the antibiotic group, also with no significant difference ($p = 0.193$). No secondary outcome was significantly different between the two groups.
Conclusion: Antibiotic treatment is no better than placebo in AECOPD with a PCT level <0.1 ng/ml.

1. Introduction

The prevalence of chronic obstructive pulmonary disease (COPD) in China is 8.2% in adults over the age of 40 years.[1] COPD has become an important economic burden for both urban and rural residents all over the world, and the management of acute exacerbations of COPD (AECOPD) increases healthcare costs significantly.[2–4] For patients with AECOPD in the USA and Europe, antibiotic prescription rates of 85%[5] and 86%,[6] respectively, have been reported. Moreover, two retrospective analyses showed that antibiotic treatment benefited patients with AECOPD.[7,8] However, not all patients with AECOPD will benefit from antibiotic therapy,[9,10] and the overuse of antibiotics may increase the risk of microbial resistance.

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In order to reduce antibiotic use in AECOPD patients, a few studies have focused on identifying clinical characteristics and inflammatory biomarkers to guide antibiotic treatment in these patients. Studies have shown that patients with type I Anthonisen exacerbation,[9] purulent sputum,[11,12] and those with very severe lung function impairment requiring invasive or non-invasive mechanical ventilation, are likely to benefit from antibiotic treatment.[13] Procalcitonin (PCT) is a specific biomarker of bacterial infection. It has been studied prospectively as a biomarker to guide antibiotic treatment in patients with AECOPD and lower respiratory tract infections.[14–16] Studies have shown that PCT-guided therapy leads to a reduction in antibiotic use in patients with AECOPD and lower respiratory tract infections.[14–16]

The aim of previous studies on PCT-guided antibiotic therapy in patients with AECOPD and lower respiratory tract infections has been to reduce antibiotic prescription. In these studies, patients with a PCT level of >0.25 ng/ml were considered to have bacterial infections, and antibiotic treatment was encouraged. A level of 0.1 to 0.25 ng/ml was considered to indicate a possible bacterial infection, and antibiotics were discouraged or encouraged according to the stability of the patient's clinical condition. A PCT level of 0.1 ng/ml or less was considered to indicate the absence of bacterial infection, and the use of antibiotics was discouraged.[14–16] However, a subgroup analysis showed that patients with AECOPD and a PCT level of <0.1 ng/ml benefited from treatment with doxycycline.[17] Therefore, the value of antibiotic treatment for hospitalized AECOPD patients with low serum PCT values is controversial.

It was hypothesized that antibiotic treatment would benefit AECOPD patients with a PCT level of <0.1 ng/ml. In order to confirm this hypothesis, a single-center, prospective randomized controlled trial was conducted. The study was registered at chictr.org.cn (ChiCTR-TRC-14004726).

2. Materials and methods

2.1. Study design and objectives

From June 10, 2014 to September 5, 2015, all patients with AECOPD admitted to the Department of Respiratory and Critical Care Medicine of Beijing Luhe Hospital were screened. A diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014 criteria was required. AECOPD was defined as an acute change in symptoms that were beyond normal day-to-day variation and that required a change in daily therapeutic drug regimen.[2] All patients included in this study were classified into Anthonisen type I to type III.[9] Patients with AECOPD who were ≥40 years of age, had sound understanding and language abilities, and who had a PCT level <0.1 ng/ml were included. Exclusion criteria were fever (≥38.0 °C), tracheal intubation within 24 h after hospital admission, a PCT level of ≥0.1 ng/ml on admission, pneumonia, chronic renal failure, history of malignant disease, immunosuppressive therapy, and refusal to participate. The study protocol was approved by the Ethics Committee of Luhe Hospital (Institutional Review Board approval number 2014-01), and all patients provided written informed consent.

A computer digital table method was used to generate randomization numbers. Researchers in this study had 24-h access to randomization numbers, allowing immediate and concealed allocation to the trial. Each patient was allocated a unique trial number. Persons responsible for allocation concealment were not allowed to be involved in the measurement of results. Eligible patients were assigned randomly to either the control group or the antibiotic group.

Antibiotics were withheld from patients in the control group. However, antibiotics could be administered later for patients whose clinical condition was unstable[16] or who had a worsening of symptoms and signs, and for those with positive evidence of bacteria as assessed by the attending physicians. In the antibiotic group, antibiotics were administered routinely. In order to cover the most common pathogenic bacteria, piperacillin–sulbactam (CR Double-Crane Pharmaceuticals Co., Ltd) was selected as the first choice of antibiotic; ceftazidime (Hainan Haiyao Pharmaceuticals Co., Ltd) or levofloxacin (CR Double-Crane Pharmaceuticals Co., Ltd) was substituted in the case of a penicillin allergy. Antibiotic agents could be adjusted according to microbial culture results and depending on the recommendations of the attending physicians. The duration of antibiotic treatment was also determined by the attending physicians. Other treatment methods in the two groups were instituted by the attending physicians in accordance with the GOLD guidelines.

2.2. Measurement

The baseline characteristics of the patients with AECOPD were collected on the day of hospital admission. PCT was measured using an immunoluminescence assay (VIDAS BRAHMS PCT) within 2 h after hospitalization. C-reactive protein (CRP) was measured by the immune turbidity method. Blood was collected for routine laboratory examinations, and chest computed tomography (CT) was performed within 48 h of hospitalization. Lung function tests were performed by trained technicians upon hospital admission and on the day of hospital discharge according to the guidelines of the American Thoracic Society.[18]

Symptoms were assessed by the patients themselves on a visual analog scale (VAS); the symptoms assessed included dyspnea, cough, fatigue, and sputum purulence.[19] The symptom VAS score was obtained upon hospital admission, at 3 days after hospitalization, and on the day of discharge. The assessment scale ranged from 0 (feeling completely healthy) to 10 (feeling extremely sick).

Treatment efficacy was evaluated by per-protocol (PP) and intention-to-treat (ITT) analysis on day 10 after hospitalization. In the PP population, the antibiotic group subjects were required to have used antibiotics for at least 3 days, and the control group subjects were required not to have used antibiotics within the 10 days after admission. The ITT population was defined as all patients who were randomized.

Treatment success was defined as cure (a complete resolution of signs and symptoms associated with the exacerbation) or improvement (a resolution or reduction of the symptoms and signs associated with the exacerbation, without new symptoms or signs). Treatment failure was defined as a worsening of symptoms and signs or death.[20] Telephone follow-up was performed on day 30 after hospital discharge. Follow-up assessments included exacerbations, re-admission, antibiotic use, and death.

The primary outcome was the treatment success rate on day 10 after admission. The secondary outcomes included symptoms assessed by VAS (at hospital admission, 3 days after hospitalization, and on the day of hospital discharge), the length of hospital stay, intubation rate, mortality during hospitalization and in the 30-day follow-up period, the rate of antibiotic use, and re-admission due to AECOPD within the 30-day follow-up period.

2.3. Statistical analysis

SPSS version 17.0 for Windows software (SPSS Inc., Chicago, IL, USA) was used for data management and the statistical analysis. Measurement data were expressed as the mean ± standard deviation, while categorical data were presented as a number or percentage. An independent samples *t*-test was applied to compare the difference in measurement data between groups; for comparisons of enumeration data, the Pearson Chi-square test or continuous correction Chi-square test was used. Binary logistic regression