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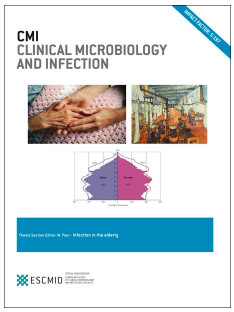

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Weili Sheng, M.D., Lixue Huang, M.D., Xiaoying Gu, Ph.D., Yeming Wang, M.D., Mingyan Jiang, M.D., Chao Hu, M.D., Jingya Li, M.D., Chunxue Ran, M.D., Hongxu Zhang, M.D., Na Wang, M.D., Yuling Wang, M.D., Xiaowei Qi, M.D., Lijun Suo, M.D., Bo Liu, M.D., Guangsheng Pei, M.D., Zhiyi He, M.D., Jinxiang Wang, M.D., Bin Cao, M.D.

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Procalcitonin-guided use of antibiotic in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease: a randomized clinical trial

Authors:

Weili Sheng M.D.[1]*, Lixue Huang M.D.[2]*, Xiaoying Gu Ph.D.[3]*, Yeming Wang M.D.[4]*, Mingyan Jiang M.D.[5]*, Chao Hu M.D.[5], Jingya Li M.D.[6],Chunxue Ran M.D.[7], Hongxu Zhang M.D.[7], Na Wang M.D.[7], Yuling Wang M.D.[8], Xiaowei Qi M.D.[9], Lijun Suo M.D.[9], Bo Liu M.D.[9], Guangsheng Pei M.D.[10], Zhiyi He M.D.[10], Jinxiang Wang M.D.[7]†, Bin Cao M.D. [11]†

Author affiliations:

1 Department of Pulmonary and Critical Care Medicine, Capital Medical University, Beijing, China; Department of Pulmonary and Critical Care Medicine, National Center for Respiratory Medicine, Center of Respiratory Medicine, National Clinical Research Center for Respiratory Diseases, China–Japan Friendship Hospital, Beijing, China; Department of Pulmonary and Critical Care Medicine, Daxing teaching hospital of Capital Medical University, Beijing, China.

2 Department of Pulmonary and Critical Care Medicine, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Science, Beijing, China.

3 National Center for Respiratory Medicine; State Key Laboratory of Respiratory Health and Multimorbidity; National Clinical Research Center for Respiratory Diseases; Institute of Respiratory Medicine, Chinese Academy of Medical Sciences; Department of Clinical Research and Data Management, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China.

4 National Center for Respiratory Medicine; State Key Laboratory of Respiratory Health and Multimorbidity; National Clinical Research Center for Respiratory Diseases; Institute of Respiratory Medicine, Chinese Academy of Medical Sciences; Department of Pulmonary and Critical Care

Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China.

5 Department of Pulmonary and Critical Care Medicine, Xiangtan Central Hospital, Hunan, China.

6 School of Medicine, Tsinghua Medicine, Tsinghua University, Beijing, China.

7 Department of Pulmonary and Critical Care Medicine, Beijing Luhe Hospital, Capital Medical University, Beijing, China.

8 Department of Pulmonary and Critical Care Medicine, Daxing teaching hospital of Capital Medical University, Beijing, China.

9 Department of Pulmonary and Critical Care Medicine, Zibo Central Hospital, Shandong, China.

10 Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Guangxi Medical University, Guangxi, China.

11 Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship hospital, Capital Medical University, Beijing, China; National Center for Respiratory Medicine, State Key Laboratory of Respiratory Health and Multimorbidity, National Clinical Research Center for Respiratory Diseases, Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China; Tsinghua University-Peking University Joint Center for Life Sciences, Beijing, China; Tsinghua University-Peking University Joint Center for Life Sciences, Beijing, China.

* These authors are first author and contributed equally.

† These authors are corresponding author and contributed equally.

Corresponding author:

Professor Bin Cao, E-mail: caobin_ben@163.com

Professor Jinxiang Wang, E-mail: jinxiangwang@ccmu.edu.cn

Abstract

Objectives: To analyze the effect and safety of PCT-guided antibiotic therapy in patients with AECOPD.

Methods: We conducted a multicenter, open-label, randomized controlled trial among patients hospitalized for AECOPD in six hospitals in China. Enrolled patients were randomly assigned to either the PCT-guided group or the Global Initiative for Chronic Obstructive Lung Disease（GOLD）strategy -guided group. The co-primary endpoints were antibiotic prescription rate for AECOPD within 30 days after randomization (to demonstrate superiority) and treatment success rate at day 30 after randomization (to demonstrate noninferiority). For primary outcomes, $\chi 2$ test, corrected $\chi 2$ test, or Fisher's exact test was used to evaluate the differences between the intervention and control groups. 95% confidence intervals (95% CIs) were calculated for all the outcomes. secondary outcomes, including days of antibiotic use during hospitalization, length of hospital stay, and change in mMRC and CAT score, were compared using the Student's *t*-test, with corresponding differences and 95% CIs calculated. Intention to treat (ITT)population were those who received randomization, and Per-Protocol population were those who strictly adhere to the treatment plan.

Results: A total of 455 patients underwent randomization, with 229 in the PCT-guided group and 226 in the GOLD-guided group. The rate of antibiotic prescription for AECOPD by day 30 was significantly lower in the PCT-guided group than that in the GOLD-guided group (38% [88/229] vs 59% [134/226]; difference -21%; 95% confidence interval [CI], -30% to -12%; p<0.0001) in the ITT analysis. There was no significant difference in the clinical treatment success rate by day 30 between the two groups (97% [223/229] vs 94% [212/229]; difference 4%, 95% CI, 0 to 7%; p=0.06). Compared with the GOLD strategy, PCT-guided antibiotic therapy was significantly associated with

lower antibiotic prescription rate during hospitalization (37% vs 59%, difference -22%, 95% CI, -31 to -13; p<0.0001), and fewer days of antibiotic use during hospitalization (2.63 ± 4.66 vs 4.86 ± 4.83, difference -2.23 days, 95%CI, -1.35 to -3.11; p<0.0001). There were no significant differences between the two groups in length of hospital stay, subsequent exacerbation rate, hospital readmission rate, ICU admission, and 30-day mortality in the ITT analysis. The results in the PP analysis were consistent with that in the ITT analysis.

Conclusions: Compared with the GOLD strategy, PCT-guided antibiotic therapy significantly reduced the rate of antibiotic prescription for patients with AECOPD, without negatively affecting the treatment success rate.

Keywords: procalcitonin; chronic obstructive pulmonary disease; acute exacerbation; antibiotic therapy; infection.

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide. In 2012, more than 3 million people died of COPD, accounting for 6% of all deaths globally [1]. Acute exacerbation of COPD (AECOPD) is the primary reason for hospitalization and death in COPD patients. Although bacterial infections and environmental factors could trigger AECOPD, respiratory viral infections are acknowledged as one of the predominant predisposing factors [2]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy traditionally recommends antibiotic prescription in AECOPD patients with Anthonisen I [3] and II with sputum purulence [4,5], as well as in patients requiring mechanical ventilation. According to previous research, purulence refers to sputum that is dark yellow or dark green in color [6]. Actually, more than 85% of inpatients with AECOPD received antibiotic prescription in the USA, Europe and China [7-9], probably suggesting the potential risk of antibiotic overuse as per the GOLD strategy. The high antibiotic prescription rate for AECOPD in clinical practice is attributed to the difficulty in accurately identifying those triggered by bacterial infections. Procalcitonin (PCT), a reliable biomarker of bacterial infections, has been investigated to determine the use of antibiotics in lower respiratory tract infection [10-12] and COPD exacerbation [13,14]. Our previous research indicated that antibiotic treatment did not provide benefits for AECOPD patients with PCT levels below 0.1 ng/ml [15]. The efficacy and safety of PCT-guided antibiotic therapy for AECOPD remain uncertain.

Consequently, we aimed to conduct a randomized controlled trial (RCT) to determine the effect of PCT-guided antibiotic therapy in patients with AECOPD. Our hypothesis was that compared with the GOLD strategy, the PCT-guided antibiotic therapy could reduce the antibiotic prescription rate for AECOPD without negative impact on the treatment success rate.

Methods

Study design and oversight

The multicenter, open-label RCT was planned to be conducted in the Department of Pulmonary and Critical Care Medicine of 10 tertiary care hospitals in China from January 2020 to April 2023, with a bed capacity totally exceeding 500. Details of the trial design have been published previously [16], and it was registered at Clinicaltrials.gov (NCT04682899). The trial was approved by the research ethic committees of all centers. An independent trial steering committee provided data monitoring. Written informed consent was required from eligible patients or their legal representative if the patients were unable to provide consent. To ensure the veracity and reliability of results, each center may adopt any one of the following validated assays to measure the value of PCT: B·R·A·H·M·S PCT sensitive KRYPTOR assay (Thermo Fisher Scientific, Hennigsdorf, Germany), Roche Elecsys B·R·A·H·M·S PCT assay, or the BioMérieux's Vidas B·R·A·H·M·S PCT assay.

Patients

We enrolled hospitalised patients aged ≥ 40 years with AECOPD. Patients with AECOPD were included in the study regardless of whether they had received antibiotics prior to randomization. We excluded patients with fever (axillary temperature ≥38°C), pneumonia, need for invasive mechanical ventilation or ICU admission, immunocompromised due to chemotherapy, AIDS or malignant tumour of the blood system, comorbidities requiring corticosteroids (at least prednisone 30 mg/day or equivalent for more than 30 days) and need for antibiotics for other infectious diseases. A full list of inclusion and exclusion criteria was present in the published protocol [16] and Supplementary

Appendix. Eligible participants were randomly assigned to either the PCT group or the GOLD group within 24 hours after hospitalization at a ratio of 1:1. The random sequence was generated by a statistician using SAS software, version 9.4. The Department of Clinical Research and Data Management of China-Japan Friendship Hospital is responsible for generating random numbers, grouping and informing each center of the random number by telephone, but not participating in the recruitment of patients and clinical treatment. The Department of Pulmonary and Critical Care Medicine of China-Japan Friendship Hospital is responsible for recruiting patients, requesting random number and clinical treatment. Once an eligible participant was recruited in each center, the site investigator contacted the manager via telephone to request a random number. The investigator received the group information based on the random number, and then conducted next step according to trial protocol.

Procedures

Hospitalized patients with AECOPD were prospectively screened on admission, with demographics, clinical symptoms, medical history, treatment before hospitalization, examination findings from clinicians, results of previous pulmonary function tests (PFTs), current medicine, a score of COPD Assessment Test (CAT) and modified Medical Research Council dyspnoea scale (mMRC) collected within 72 hours after randomization. The treatment strategy and the patients' response to the treatment during the period were recorded in paper version of case report form by the investigator that were blinded to the allocation at each participating center. Two experienced data managers ensured data accuracy and integrity throughout the study, including data collection, entry into clinical database according to paper version questionnaire, and data storage. They asked investigators to resolve any

queries identified, recorded the reasons for non-adherence and provided regular feedback to every center. We take GDPR compliance very seriously and have implemented a robust data protection framework throughout the study, with specific measures including but not limited to data minimization, anonymization, and data retention and access control. The follow-up lasted for 30 days after randomization. If participants were not able to attend the face-to-face interview on day 30, corresponding data were collected via telephone. The details were shown in our published protocol and Appendix.

Intervention

All participants were scheduled for a PCT test within 2 hours after randomization. For the PCT group, the attending clinician decided the antibiotic prescription mainly based on the initial PCT value. Antibiotics were strongly discouraged for patients with PCT levels below 0.1 ng/ml, discouraged for patients with PCT levels ranging from 0.1 to 0.25 ng/ml and without sputum purulence, but recommended for patients with PCT levels ranging from 0.1 to 0.25 ng/ml and sputum purulence, and strongly recommended for patients with PCT levels exceeding 0.25 ng/ml (Supplementary Appendix Figure S1). In GOLD-guided group, antibiotics were prescribed for those with three cardinal symptoms (increase in dyspnea, sputum volume and sputum purulence), two of the cardinal symptoms with increased purulence of sputum; or requiring mechanical ventilation (invasive or noninvasive). All patients were treated according to the 2020 report in GOLD-guided group, including standard care, inhaled corticosteroid and bronchodilator treatments. On the first treatment response assessment conducted on day 3, the attending physician evaluated whether to initiate antibiotic therapy for patients who did not initially receive antibiotics according to the patients' general condition, particularly their

response to therapy and microbiology etiology information. The adherence to the study protocol was guaranteed monthly by online meeting. Primary outcomes and secondary outcomes were assessed on day 30.

Endpoints

Referring to the design of C-Reactive Protein (CRP) Testing to Guide Antibiotic Prescribing for AECOPD [17], we used two primary outcomes: antibiotic prescription rate for AECOPD by day 30 after randomization and treatment success rate by day 30 post randomization. An independent clinician from each centre assessed treatment effect. The definition of treatment success was the resolution or relief of acute symptoms (dyspnea, cough and sputum production) to a baseline level of, and a return of the temperature to normal (axillary temperature <37.3°C) for patient with fever at enrollment. The definition of treatment failure included death, symptoms worsening or the lack of any resolution of acute symptoms (dyspnea, cough, sputum production or fever if present) [18]. Patients measured temperature by themselves. The details were demonstrated in the published protocol and Appendix. Secondary outcomes included antibiotic prescription rate for AECOPD by day 1 post randomization, the duration of antibiotic administration for AECOPD, the proportion of patients receiving antibiotics for AECOPD during hospitalization, intensive care unit (ICU) admission, length of hospital stay, rate of exacerbation after discharge, hospital readmission and mortality by day 30 post randomization, change in PFTs, CAT and mMRC.

Safety

Adverse events were collected and reported as part of routine follow-up. All events fulfilling the

definition of a serious adverse event, including death, that occurred during the research period were reported to the research center expert committee within 24 hours post event occurrence.

Statistical analysis

For the primary outcome, antibiotic prescription rate within 30 days after randomization, we hypothesized that the PCT-guided antibiotic prescription strategy would be superior to the GOLD strategy. Based on preliminary data, the 30-day prescription rates of guideline group and PCT group were 69.9% and 48.7%, respectively [19]. This study is designed to have adequate statistical power to detect 20% reduction from an estimated 70% within the 30 days following randomization. To detect a difference in proportions between 70% and 50% at the 5% significance level with 90% power required a total of 242 participants. Assuming a drop-out rate of 20%, we needed to enroll 302 participants.

For the primary outcome, treatment success rate at day 30, we hypothesized that the PCT-guided antibiotic prescription would be similar to the GOLD strategy. The estimated treatment success rate by day 30 after randomization was 80%, with the non-inferior margin of 0.1 [20]. Based on a one-sided significance level of 0.05% and 80% power, 396 participants were required. Again, with a drop-out rate of 20%, 495 participants were supposed to be included. Finally, considering these two primary endpoints, we aimed to recruit 500 participants in the study.

Baseline characteristics were demonstrated as numbers (proportion) for categorical variables, and mean ± standard deviation (SD) for continuous variables. Appropriate statistical tests were employed for comparisons, including the χ^2 test, corrected χ^2 test, Fisher's exact test, and Student's *t*-test. For primary outcomes, and secondary outcomes including proportion of antibiotics prescription at day 1 and during hospitalization, subsequent exacerbation by day 30, ICU admission, hospital readmission

by day 30, and 30-day mortality, χ^2 test, corrected χ^2 test, or Fisher's exact test was used to evaluate the differences between the intervention and control groups. For antibiotic prescription by day 30, subgroup analyses according to Anthonisen type were performed. Additionally, the comparison of treatments during hospitalization between the intervention and control groups were also performed. The differences and 95% confidence intervals (95% CIs) between the intervention and control groups were calculated for all the outcomes. The means and SDs of the other secondary outcomes, including days of antibiotic use during hospitalization, length of hospital stay, and change in mMRC and CAT score, were compared using the Student's *t*-test, with corresponding differences and 95% CIs calculated. To account for the confounding effect of Anthonisen type, multivariable adjusted logistic regression models were used to estimate the adjusted odds ratios (ORs) for primary outcomes.

Both intention-to-treat (ITT) and per-protocol (PP) analyses were performed. The definitions of Intention-to-Treat (ITT) and Per-Protocol (PP) analyses were explained in Appendix. For the participant with missing data for treatment success by day 30, we imputed the data according to the treatment success status observed during the hospitalization period. No other data imputation was performed. Data analyses were performed using SAS version 9.4 (SAS Institute Inc.).

Results

The multicenter, open-label RCT was conducted in 10 tertiary care hospitals in China. Unfortunately, our hospitals can't cooperate to continue the established research work because of the busy work rhythm and lack of staff under the COVID-19 epidemic, only 6 hospitals were included in our trial. A total of 3,791 hospitalized patients were screened in the participating centers from January 2020 to April 2023. Of these, 3,336 patients did not have AECOPD. 455 patients met the eligibility criteria

and underwent randomization, with 229 assigned to the PCT-guided group and 226 to the GOLD-guided group (Figure 1). In the PCT-guided group, 196 were included in the PP analysis after excluding 8 patients without a COPD diagnosis after hospitalization, 24 patients who did not strictly follow the PCT-guided strategy, and 1 patient who did not complete the 30-day follow-up. In the GOLD-guided group, 211 patients were included in the PP analysis after excluding 4 patients without a COPD diagnosis after hospitalization and 11 patients who did not strictly adhere to the GOLD-guided strategy. Treatment response was assessed on day 3, 24 patients began antibiotic therapy in PCT group and 7 patients began antibiotic therapy in GOLD group. Baseline characteristics of participants are present (Table 1), indicating that the groups were generally well-matched. Notably, the distribution of PCT levels was similar between the two groups, with nearly two-thirds having a PCT level below 0.1 ng/ml. The proportion of patients with Anthonisen type I and type II with sputum purulence was numerically higher in GOLD-guided group. Potential bacterial pathogens cultured from sputum samples at baseline were shown in Appendix (eTable 1). There were no significant differences in treatment during hospitalization between two groups (eTable 2).

Primary outcomes

In the ITT analysis, compared with the GOLD-guided group, the antibiotic prescription rate for AECOPD within 30 days of randomization was statistically lower in the PCT-guided group (38% [88/229] vs 59% [124/226]; difference -21%, 95% CI [-30 to -12]; p<0.0001) (Table 2). The trend towards a significantly lower antibiotic prescription rate in the PCT-guided group was also observed in the PP analysis (33% [64/196] vs 60% [126/226]; difference -27%, 95% CI [-36 to -18]; p<0.0001) (eTable 3).

In the ITT analysis, the PCT-guided group and the GOLD-guided group had similar treatment success rates by day 30 (97% [223/229] vs 94% [212/226]; difference 4%, 95% CI [0 to 7]; p=0.06), meeting the specified non-inferior margin of - 0.1, and consistent with the results in the PP analysis (97% of the PCT-guided group [191/196] vs 93% of the GOLD-guided group [197/211]; difference 4%, 95% CI [0 to 8]; p=0.05).

According to the classification of Anthonisen, the antibiotic prescription rate in patients with type I (61% [28/46] vs 96% [69/72]; difference -35%, 95% CI [-50 to -20]; p<0.0001), type II (29% [31/107] vs 46% [46/99]; difference -17%, 95% CI [-31 to -4]; p=0.0095), and type III (38% [28/73] vs 36% [18/50]; difference 2%, 95% CI [-15 to 20]; p=0.79) (eTable 4). The result for antibiotics prescription by day 30 remained significant with the adjustment for Anthonisen type, (OR, 0.46; 95% CI, 0.30-0.69). The OR for treatment success after adjustment for Anthonisen type was 2.64 (95% CI, 0.99-7.06). According to the procalcitonin levels, the antibiotic prescription rate in patients with a PCT level <0.1 ng/ml was statistically lower in the PCT-guided group (41% [61/149] vs 68% [101/148]; difference -27%, 95% CI [-38 to -16]; p<0.0001), however, the antibiotic prescription rate in patients with a PCT level of 0.1 to 0.25 ng/ml did not differ (p=0.81), the antibiotic prescription rate in patients with a PCT level >0.25 ng/ml was similar between two groups (p>0.99) (eTable 5).

Secondary outcomes

In the ITT analysis, the PCT-guided strategy significantly decreased antibiotic exposure compared with the GOLD-guided strategy, evidenced by a lower antibiotic prescription rate on day 1 (16% vs 51%, difference -35%, 95%CI [-43 to -27]; p<0.0001), a lower antibiotic prescription rate during hospitalization (37% vs 59%, difference -22%, 95% CI [-31 to -13]; p <0.0001), and fewer days of

antibiotic use during hospitalization (2.63 ± 4.66 vs 4.86 ± 4.83, difference -2.23 days, 95%CI [-1.35 to -3.11]; <0.0001) (Table 2). Additionally, the PCT-guided strategy was associated with a statistically smaller change in CAT score compared with the GOLD-guided group (4.62 ± 3.66 vs 5.51 ± 4.70; difference -0.89, 95%CI [-0.11 to -1.66]; p=0.025). There were no significant differences between the two groups in other outcomes, including length of hospital stay, subsequent exacerbation rate, hospital readmission rate, ICU admission, and 30-day mortality. The results of secondary outcomes in the PP analysis were consistent with that in the ITT analysis (eTable 3).

Safety

None of the patients in both groups died during hospitalization. After discharge, no patients died in the PCT-guided group, while 2 patients in the GOLD-guided group died due to coronary heart disease and severe acute pancreatitis, respectively. There was no difference in 30-day mortality between the two groups. More details are shown in eTable 6.

Discussion

In this multi-center RCT, our specified PCT-guided antibiotic prescription therapy resulted in a 21% absolute reduction in antibiotic prescription rates within 30 days of randomization compared with the GOLD strategy-recommended antibiotic prescription, without negatively affecting the treatment success rate by day 30. We also found that compared with the GOLD strategy, PCT-guided antibiotic prescription therapy was associated with lower antibiotic prescription rate on day 1 and during hospitalization, and fewer days of antibiotic use during hospitalization. The PCT-guided group had a statistically smaller change in CAT score.

The recommendations for AECOPD in the GOLD strategy are mainly based on the Anthonisen type proposed in 1987, assuming that sputum purulence could be a sign of bacterial infections in these patients. However, several studies have indicated that reported or witnessed sputum purulence was not a reliable marker for the presence of bacteria in AECOPD patients [21,22]. Current studies support the use of serum biomarkers to guide antibiotic prescription in infectious diseases, including AECOPD. CRP and PCT are most commonly used in these studies. However, neither is recommended to guide antibiotic prescription in the GOLD strategy. Two meta-analyses with small sample size on whether PCT-guided antibiotic prescription therapy could reduce antibiotic exposure have come to completely different conclusions [23,24]. Our study revealed that PCT-guided antibiotic treatment was associated with a 21% reduction in antibiotic use within 30 days, with no effects on treatment success rate. This large reduction may be explained by the findings that about two-thirds of AECOPD patients had a PCT level below 0.1ng/ml on admission, and antibiotics were not administered according to the PCT-guided strategy. Previous study also found that patients with PCT less than 0.1ng/ml accounted for a large proportion of hospitalized patients with AECOPD [15], which may partly reflect that bacterial infection was not the main cause of those AECOPD. In our previous study, the benefits of antibiotics for those AECOPD patients with a PCT level <0.1 ng/ml were not observed as well [15].

For patients with a PCT level of 0.1 to 0.25 ng/ml, the antibiotic prescription rate for AECOPD within 30 days of randomization was the same as GOLD-guided group in our study. This finding is consistent with previous studies. The treatment effect (clinical success rate at day 10 and day 30) in the doxycycline group was no better than placebo in AECOPD patients with a PCT level between 0.1 and 0.25 ng/ml [25]. Huang et al [10] also showed that the rates of antibiotic exposure within 30 days among patients with a PCT level of 0.1 to 0.25 ng/ml were similar in the PCT group and the usual-care

group. However, the results should be interpreted with caution as the sample size in all trails was too small to draw a solid conclusion. Whether these patients with a PCT value between 0.1 and 0.25 ng/ml could benefit from antibiotic treatment needs to be studied further.

Our study has several limitations. Firstly, patients and attending physicians were aware of group allocation. Nonetheless, an open-label design better reflects real-world situations, and additionally, the outcome assessment was blinded to the grouping to reduce bias. Secondly, patients who received invasive mechanical ventilation and ICU admission were excluded, which limits the generalizability of the results and was associated with a slightly lower mortality rate, consistent with previous studies [26]. Thirdly, due to the hospital management and control policy during the COVID-19 pandemic, not all patients completed the face-to-face interview on day 30, and a telephone visit was used as an alternative. The telephone follow-up was carried out by the experienced clinical staff that were blinded to the grouping at each center. Fourthly, the distribution of Anthonisen type was imbalanced in the two groups, stratification analysis was not planned, but we performed a multivariable logistic regression for primary outcomes with adjustment for Anthonisen type. Finally, it would be better to use a validated score to evaluate symptom.

Conclusion

The evidence from this trial suggests that compared with the GOLD strategy, the PCT-guided antibiotic prescription strategy reduces the antibiotic prescription rate in AECOPD patients, without negatively affecting the treatment success rate.

Author contributors: CB, JW and LH conceived and designed the study. YW and WS provided

suggestions for the study design. XG contributed to the statistical analysis.WS, HL, and BC contributed to writing of the report. BC contributed to critical revision of the report. All authors have contributed to the revision of the draft and have read and approved the final version.

Transparency declaration: All authors declare no competing interests.

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Tabe1.Baseline characteristics of the patients.

Characteristics	PCT group (n=229)	GOLD group (n=226)
Age, years	70.20 ± 8.30	70.50 ± 9.34
Male sex -No.(%)	195 (85%)	188 (83%)
BMI, (kg/m^2)	23.19 ± 3.89	23.61 ± 3.76
Cigarette smoking -no./total no.(%)		
Never-smoker	47/227 (21%)	42/224 (19%)
Current smoker	76/227 (33%)	68/224 (30%)
Former smoker	104/227 (46%)	114/224 (51%)
Duration of COPD, years	9.95 ± 9.39	10.53 ± 10.60
Comorbidities -no./total no.(%)		
Hypertension	115 (50%)	121 (54%)
Chronic cor pulmonale	37 (16%)	26 (12%)
Diabetes mellitus	29 (13%)	30 (13%)
Bronchiectasis	30 (13%)	21 (9%)
Cerebrovascular diseases	24/211 (11%)	23/208 (11%)
Chronic renal insufficiency	5 (2%)	5 (2%)
FEV_1 on admission [a]	1.46 ± 0.69	1.56 ± 1.93
FEV_1 (pre%) on admission [a]	50.66 ± 18.34	48.32 ± 18.75
FEV_1/FVC ratio on admission [a]	54.57 ± 10.46	54.71 ± 10.48
Maintenance therapy prior to hospitalization -no./total no.(%)		
Inhaled β2-bronchodilators	123 (54%)	112 (50%)
Inhaled anticholinergics	64 (28%)	67 (30%)
Inhaled corticosteroids	108 (47%)	104 (46%)
Oral corticosteroids	1 (<1%)	1 (<1%)
Theophylline	22 (10%)	32 (14%)
Long-term oxygen therapy	50 (22%)	53 (23%)
Antibiotic use for exacerbation prior to hospitalization -no./total no.(%)	87 (38%)	100 (44%)
Symptoms -no./total no.(%)		
Dyspnea	224 (98%)	218 (96%)
Cough	209 (91%)	217 (96%)
Sputum production	144 (63%)	150 (66%)
Sputum purulence	57 (25%)	96 (42%)
Anthonisen type-no./total no.(%) [b]		
Type I	46/226 (20%)	72/221 (33%)
Type II	107/226 (47%)	99/221 (45%)
Type III	73/226 (32%)	50/221 (23%)
Type I and Type II with sputum purulence	57/226 (25%)	96/221 (43%)
Vital signs		
Temperature -℃	36.45 ± 0.29	36.43 ± 0.31

Heart rate -beats/min	88.05 ± 13.63	87.42 ± 13.35
Respiratory rate -breaths/min	20.51 ± 2.61	20.97 ± 2.88
Oxygen saturation -% [c]	94.53 ± 6.98	94.39 ± 5.24
Systolic blood pressure -mmHg	133.03 ± 18.49	133.53 ± 18.27
Diastolic blood pressure -mmHg	79.29 ± 11.75	79.04 ± 11.00
White cell count, 10^9/L	7.07 ± 2.50	6.90 ± 2.56
Neutrophil count, 10^9/L	4.91 ± 2.20	4.86 ± 2.39
Procalcitonin level -no./total no.(%)		
<0.1 ng/ml	149 (65%)	148 (65%)
0.1-0.25 ng/ml	59 (26%)	55 (24%)
0.25-0.5 ng/ml	4 (2%)	1 (0%)
>0.5 ng/ml	17 (7%)	22 (10%)
mMRC score at enrollment	2.82 ± 0.92	2.92 ± 0.90
CAT score at enrollment	22.64 ± 5.81	24.10 ± 6.30
Hospitalizations prior to 1-year	0 (0-1)	0 (0-1)

All data are represented as mean (SD) and No. (%), as appropriate. All data were analyzed in accordance with the intention-to-treat principle.

Abbreviations: PCT, procalcitonin; BMI, body mass index (kg/m^2）; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume 1 second; FVC, forced vital capacity.

a Data on pulmonary function tests were missing for 112 patients in the PCT-guided group and for 129 patients in the GOLD-guided group.

b The Anthonisen criteria include increased dyspnea, increased sputum volume, and increased sputum purulence. Type I (aggravated dyspnea, purulent sputum, and increased sputum volume simultaneously); Type II (two of three symptoms); Type III(one of three symptoms).

c It was measured while patient was receiving oxygen therapy.

Table 2 Primary and secondary outcomes

	PCT group	GOLD group	Difference 95%*CI*	*P* value
Primary outcomes				
Intention-to-treat population,	(n=229)	(n=226)		
Antibiotic prescription by day 30	88 (38%)	134 (59%)	-21 (-30 to -12)	<0.0001
Treatment success rate at day 30	223 (97%)	212 (94%)	4 (0 to 7)	0.06
Secondary outcomes				
Intention-to-treat population	(n=229)	(n=226)		
Antibiotic prescription at day 1	37 (16%)	116 (51%)	-35 (-43 to -27)	<0.0001
Antibiotic prescription during hospitalization	85 (37%)	133 (59%)	-22 (-31 to -13)	<0.0001
Days of antibiotic use during hospitalization	2.63 ± 4.66	4.86 ± 4.83	-2.23 (-1.35 to -3.11)	<0.0001
Length of hospital stay	8.46 ± 3.94	8.08 ± 3.33	0.37 (1.05 to -0.30)	0.27
Subsequent exacerbation by day 30	6/228 (3%)	14/226 (6%)	-4 (-7 to 0)	0.06
Hospital readmission by day 30	5/228 (2%)	11/226 (5%)	-3 (-6 to 1)	0.12
30-day mortality	0	2/226 (1%)	-1 (-2 to 0)	0.25
Change in mMRC score	0.62 ± 0.68	0.74 ± 0.72	-0.12 (0.01 to -0.25)	0.07
Change in CAT score	4.62 ± 3.66	5.51 ± 4.70	-0.89 (-0.11 to -1.66)	0.025
ICU admission	1 (0%)	0	0 (0 to 1)	1.00

All data are represented as mean (SD) and No. (%), as appropriate.

Abbreviations: mMRC, modified Medical Research Council dyspnoea scale; CAT, COPD assessment test; ICU, intensive care unit.

Figure1. Screening, Randomization, and Follow-up