PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Procalcitonin-guided initiation of antibiotics in AECOPD inpatients: study protocol for a multicenter randomized controlled trial
AUTHORS	Huang, Lixue; Wang, Jinxiang; Gu, Xiaoying; Sheng, Weili; Wang, Yeming; Bin, Cao

VERSION 1 – REVIEW

REVIEWER	Peng, Fei Zhongda Hospital, School of Medicine, Southeast University, Department of critical care medicine
REVIEW RETURNED	16-Mar-2021

GENERAL COMMENTS	1) The antibiotic prescription rate of AECOPD in China wasn't described in the manuscript. 2) The study lacks a good summary of the problems of previous research. The logic of the introduction is not clear enough. 3) The study did not describe the number of AECOPD patients admitted to each center per year and how long it is expected to take to complete the study. 4) What are the diagnostic criteria for AECOPD in the study? 5) What was the basis for the inclusion of the age range of the subjects? Were results after age stratification considered for analysis? 6) The study did not provide the range of PCT results for the healthy population at each study center, the range of PCT reagents tested, the rationale for selecting the range of 0.1-0.25 ng/mL for the protocol were not detailed, and why was the percentage of elevated or decreased PCT not included in the criteria for guiding antibiotic use? 7) The preamble mentions that purulent sputum cannot be used as a diagnostic indicator of bacterial infection, so why is it necessary to include it in the criteria for PCT to guide antibiotic use? 8) Should antibiotic adjustments (escalation/descending steps) be considered as prescribing? Or should they be simply ignored? 9) Clinical adherence to protocols with antibiotics in previous studies is generally low; how is this problem planned to be avoided in this study? How can clinicians' compliance with the study protocol be improved? 10) What is the rationale for not planning an interim summary for the study? 11) Is there a contradiction between the "Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences" in the protocol and the "GCP" in the informed consent form? 12) Is there a lack of detail about the benefits and risks to the subjects, e.g., is there a financial subsidy for subjects' follow-up?

REVIEWER	Pantzaris, Nikolaos-Dimitrios

	University Hospital of Patras
REVIEW RETURNED	21-Apr-2021

GENERAL COMMENTS	Well designed RCT. Numerous publications suggest that PCT is a helpful tool in the assessment of COPD exacerbations and the role of antibiotic use but a large well designed RCT would potentially validate this. Clear primary and secondary endpoints, and well defined markers of assessment.

REVIEWER	Ulrich, Robert NYU School of Medicine
REVIEW RETURNED	26-Apr-2021

GENERAL COMMENTS	**Comments to Author:** This study protocol aims to definitely answer the question if procalcitonin (PCT) use in AECOPD is superior to current standard of care in decreasing unnecessary antibiotic use and non-inferior in regards to clinical outcomes. The authors acknowledge there is a prior RCT addressing this question in AECOPD (by Stolz *et al.*), but point out that study was limited by a small sample size and unclear guidance for PCT between 0.1 and 0.25. They also note the success of PCT-guided therapy in RCTs of other LRTIs. Therefore, there is a precedent and knowledge gap for a rigorously designed RCT to assess the use of PCT to guide AECOPD antibiotic therapy. The proposed study design spans across ten hospitals in China, which increases feasibility of enrolling the proposed 500 subjects. The randomization is 1:1, PCT to standard of care, which is appropriate for a situation in which the intervention is thought to have equipoise at the start of the trial. Figure 1 shows the trial flow is simple and straightforward. The trial design is open-label to participants, healthcare providers, and laboratory staff but blinded to outcomes assessors and statisticians. Primary outcomes are clinically relevant and include antibiotic prescription (excluding non-AECOPD indications) within 30 days of randomization, and clinical cure or improvement at in person visit on D30. Secondary endpoints are also clinically relevant, including length of stay, amount of hospitalization antibiotics, mortality and ICU rates, and even objective measures of change in lung function. Sample size was calculated thoughtfully, taking into account that a non-inferior design will require increased participant numbers and using literature to cite the expected amount of antibiotic use and treatment success. The data collection plan is appropriate, although the planned interval (monthly) of checking CRFs and initiating queries could be shortened. The discussion reiterates the importance of this trial in the context of the current literature and correctly states that, if PCT-guided therapy is shown to decrease antibiotics without affecting clinical outcomes, the findings could change current guidelines for

	AECOPD. Therefore, this trial could be impactful on the field, and I commend the authors in taking on this important clinical question. SPIRIT checklist is supplied in supplementary materials. The trial has been appropriately registered on CT.gov prior to recruitment, and is currently listed as “Not yet recruiting.” All IRB approvals are documented. **MINOR COMMENTS** 1. Methods (line 190): Primary endpoint of clinical cure maybe slightly subjective and determined by a provider at D30. If these physicians are the blinded outcomes assessors, that is a good design. However, if these providers are unblinded, that could introduce bias. 2. Methods (line 257): Consider increasing the frequency of data tracking. With a follow-up period of 30 days and a common condition like AECOPD, would recommend the data managers track adherence to the protocol biweekly (rather than monthly). 3. Inclusion/Exclusion Criteria (Table 1): • The exclusion criteria of “fever” and “pneumonia identified by X-ray or CT of the lungs” you may find is too restrictive. As you mentioned in the introduction, the majority of AECOPD are caused by viral LRTI (e.g. influenza) which could present with fever and change in CXR appearance that would be called pneumonia by radiology. Consider removing these criteria before starting enrollment, or remove with an amendment in the future if they prove to be too restrictive. • Is the steroid exclusion criteria inclusive of any administration within the last 30 days, or steroid administration for at least 30 consecutive days? May want to clarify that language, as AECOPD patients receive bursts of steroids frequently.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
1. The antibiotic prescription rate of AECOPD in China wasn’t described in the manuscript.
Response: Thank you for your comments. After literature research, we found one study in China reported the antibiotic prescription rate for hospitalized patients with AECOPD was 86.2% (1434/1663).[1] Now, the corresponding description in our new manuscript is : “The prescription rate of antibiotics for inpatients with AECOPD in the United States, Europe, and China all exceeds 85%”. Please see Page 1, line 72-73.

[1] Ma Y, Huang K, Liang C, et al. Real-world antibiotic use in treating acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in China: Evidence from the ACURE study. Front Pharmacol. 2021;12:649884.

2. The study lacks a good summary of the problems of previous research. The logic of the introduction is not clear enough.
Response: Thank you for your comments. We are sorry for the unclear description and have rewritten the Introduction. Please see Page 1-2.

3. The study did not describe the number of AECOPD patients admitted to each center per year and how long it is expected to take to complete the study.
Response: Thank you for your comments. We added the estimated recruitment duration in the manuscript. “In the context of preventing and controlling COVID-19 pandemic, wearing a mask in whole people in China increase the difficulty of recruitment of eligible patients with AECOPD. According to the current recruitment speed, approximately 30 patients were enrolled into the study every month in 10 centers. We estimate that recruitment duration will last until April 2022. ” Please see Page 3, line 135-139.

4. What are the diagnostic criteria for AECOPD in the study?
Response: Thank you for your comments. The diagnostic criteria for AECOPD was based on the definition of AECOPD in GOLD 2020. An exacerbation of COPD is defined as an acute worsening of respiratory symptoms that results in additional therapy. The common worsening respiratory symptoms include increased dyspnea, sputum purulence and volume, cough and wheeze. The diagnosis of an AECOPD need to rule out other differential diagnoses, e.g. pneumonia, pleural effusion, pulmonary embolism and cardiac related disease. We added the criteria for AECOPD in Table 1. Please see Page 15.

5. What was the basis for the inclusion of the age range of the subjects? Were results after age stratification considered for analysis?
Response: Thank you for your comments. According to the China Pulmonary Health study, the estimated prevalence of COPD in people aged 40 years or older was 13.7% (95% CI 12·1–15·5), however, estimated prevalence in people aged 20-39 years was rather low (2·1%, 1·4–3·2).[1] Hence, we aimed to recruit those patients aged 40 years or older and conduct an analysis.

[1] Wang C, Xu J, Yang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. Lancet. 2018;391(10131):1706-1717.

6. The study did not provide the range of PCT results for the healthy population at each study center, the range of PCT reagents tested, the rationale for selecting the range of 0.1-0.25 ng/mL for the protocol were not detailed, and why was the percentage of elevated or decreased PCT not included in the criteria for guiding antibiotic use?
Response: Thank you for your comments. In our original manuscript, we noted that to ensure the veracity and reliability of results, each center may adopt any one of the following three 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. We now added the measuring range of these three assays and the mean values of healthy person. Now the section reads: “The direct measuring range of B·R·A·H·M·S PCT sensitive KRYPTOR assay is from 0.02-50 ng/ml, and the Functional Assay Sensitivity (FAS) is 0.06 ng/ml, which is 3-fold to 10-fold above normal mean values. The direct measuring range of Roche Elecsys B·R·A·H·M·S PCT assay is from 0.02-100 ng/ml, and the FAS is 0.06 ng/ml. The direct of measuring range of BioMérieux’s Vidas B·R·A·H·M·S PCT assay is 0.05-200 ng/ml, and the FAS is 0.09 ng/ml.” Please see Page 4-5, line 174-179.
As for the threshold value of PCT (0.1-0.25 ng/mL) in our protocol, we refer the previous research RCT design [1,2], which also explored the effect of PCT on antibiotic therapy in patients with AECOPD.
Thank you for your valuable suggestion about the percentage of elevated or decreased PCT could be a criteria. This criteria has also be applied in previous research to explore the effect of PCT on initiating or stopping antibiotic prescription during hospitalization in patients with LTRI [3]. In this study, PCT tests were received at multiple timepoints. However, in our study, we aimed to explore the

effect of PCT on initiating antibiotic prescription at hospital admission among patients with AECOPD. The PCT test was measured only once at the time of hospital admission. It is hard to determine the percentage of elevated or decreased PCT. According to threshold value of PCT to guide antibiotic prescription, it is simple and easy to conduct in daily clinical practice, and it has been used in previous studies.[1,2] Hence, we choose the threshold value of PCT to design the study.

[1] Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest. 2007;131(1):9-19.
[2] Daubin C , Valette X , F Thiollière, et al. Procalcitonin algorithm to guide initial antibiotic therapy in acute exacerbations of COPD admitted to the ICU: a randomized multicenter study[J]. Intensive Care Medicine, 2018.
[3] Schuetz P, Christ-Crain M, Thomann R, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA. 2009;302(10):1059-1066.

7. The preamble mentions that purulent sputum cannot be used as a diagnostic indicator of bacterial infection, so why is it necessary to include it in the criteria for PCT to guide antibiotic use?
Response: Thank you for your comments. According to the PCT-based protocol in a critical RCT about AECOPD [1], antibiotics were strongly recommended for PCT levels >0.25 ng/ml and strongly discouraged for levels <0.1 ng/ml. However, for those patients with a PCT level of 0.1 to 0.25 ng/ml, the decision of antibiotic prescription was up to the clinician's experience. This may bring subjective bias due to clinicians with different experience. Hence, we considered a uniform and objective criteria for these patients with a PCT level of 0.1 to 0.25 ng/ml. The purulent sputum was a common symptom during exacerbation of COPD and was always listed an indicator to consider the antibiotic prescription in GOLD guideline. So, the combination of PCT and purulent sputum was considered in our study, and we aimed to explore the effectivity and safety of this new protocol.

[1] Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest. 2007;131(1):9-19.

8. Should antibiotic adjustments (escalation/descending steps) be considered as prescribing? Or should they be simply ignored?
Response: Thank you for your comments. According to the RCTs about COPD mentioned in our manuscript, the common primary outcome was prescribing rate of antibiotics during hospitalization or a specified time period (expressed as the proportion of patients receiving antibiotics for AECOPD), the antibiotic adjustments was not reported as an primary or secondary endpoints. So we are more concerned about the antibiotic prescription rate within 30 days post randomization and antibiotic exposure during hospitalization in our study, rather than antibiotic adjustments.

9. Clinical adherence to protocols with antibiotics in previous studies is generally low; how is this problem planned to be avoided in this study? How can clinicians' compliance with the study protocol be improved?
Response: Thank you for your comments. As you mentioned, good clinical adherence to protocols is critical to a trial. In our original manuscript, we have described some measures. "All centers in our study are qualified by the 'Good Clinical Practice (GCP) training' of the State Food and Drug Administration for compliance in the training. To increase study awareness and protocol adherence, we will convene principle investigator in each center and organize a face-to-face meeting to discuss the study protocol before study initiation. Two experienced data managers from the China-Japan hospital biweekly check the CRF of each center, track clinicians' antibiotic prescription decisions in both groups and assess adherence to the protocol. They will ask investigators to resolve any queries identified, record the reasons for non-adherence and provide regular feedback to every center. To

solve the potential problems and grantee the quality of research, principle investigator at each center will gather and conduct an online meeting every month." Please see Page 7, Line 253-264.

10. What is the rationale for not planning an interim summary for the study?
Response: Thank you for your valuable comments. Interim analysis are commonly used in sizable trials while considering cost, resources, and meaningfulness of the project. Whenever necessary, such interim analysis can also call for potential termination or an early declaration of success. However, interim analysis increased the risk of type I error, there is a need to adjust the nominal P value, which was difficult to handle. Our trial has been registered on CT.gov prior to recruitment, and we have been recruiting eligible patients. After referring to the design of previous RCTs of PCT and considering our study significance, sample size and current recruitment speed, we do not intend to add an interim analysis, but intend to conduct a final analysis when the study is completed.

11. Is there a contradiction between the "Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences" in the protocol and the "GCP" in the informed consent form?
Response: China-Japan Friendship hospital is the leading center of the multicenter study, and the ethic committee of China-Japan Friendship Hospital has approved the study. Dr Bin Cao, professor of department of pulmonary and critical care medicine, China-Japan Friendship hospital, was the principle investigator of this study. Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS 2018-I2M-1–003 and 2020-I2M-CoV19–005) is a fund to Dr Cao and support the study. There was no contradiction.

12. Is there a lack of detail about the benefits and risks to the subjects, e.g., is there a financial subsidy for subjects' follow-up?
Response: Thank you for your comments. The benefits and risks to the subjects have been described in the informed consent form. There was no financial subsidy for subjects' follow-up.

Reviewer #2:
Well designed RCT. Numerous publications suggest that PCT is a helpful tool in the assessment of COPD exacerbations and the role of antibiotic use but a large well designed RCT would potentially validate this. Clear primary and secondary endpoints, and well defined markers of assessment.

Response：Thank you for your acknowledgement on our study significance and design .

Reviewer #3:
This study protocol aims to definitely answer the question if procalcitonin (PCT) use in AECOPD is superior to current standard of care in decreasing unnecessary antibiotic use and non-inferior in regards to clinical outcomes. The authors acknowledge there is a prior RCT addressing this question in AECOPD (by Stolz et al.), but point out that study was limited by a small sample size and unclear guidance for PCT between 0.1 and 0.25. They also note the success of PCT- guided therapy in RCTs of other LRTIs. Therefore, there is a precedent and knowledge gap for a rigorously designed RCT to assess the use of PCT to guide AECOPD antibiotic therapy.
The proposed study design spans across ten hospitals in China, which increases feasibility of enrolling the proposed 500 subjects. The randomization is 1:1, PCT to standard of care, which is appropriate for a situation in which the intervention is thought to have equipoise at the start of the trial. Figure 1 shows the trial flow is simple and straightforward. The trial design is open- label to participants, healthcare providers, and laboratory staff but blinded to outcomes assessors and statisticians. Primary outcomes are clinically relevant and include antibiotic prescription (excluding non-AECOPD indications) within 30 days of randomization, and clinical cure or improvement at in person visit on D30. Secondary endpoints are also clinically relevant, including length of stay, amount of hospitalization antibiotics, mortality and ICU rates, and even objective measures of change in lung

function. Sample size was calculated thoughtfully, taking into account that a non-inferior design will require increased participant numbers and using literature to cite the expected amount of antibiotic use and treatment success. The data collection plan is appropriate, although the planned interval (monthly) of checking CRFs and initiating queries could be shortened.
The discussion reiterates the importance of this trial in the context of the current literature and correctly states that, if PCT-guided therapy is shown to decrease antibiotics without affecting clinical outcomes, the findings could change current guidelines for AECOPD. Therefore, this trial could be impactful on the field, and I commend the authors in taking on this important clinical question.
SPIRIT checklist is supplied in supplementary materials. The trial has been appropriately registered on CT.gov prior to recruitment, and is currently listed as “Not yet recruiting.” All IRB approvals are documented.
Response: Thank you for your comments and acknowledgment of our study design.
MINOR COMMENTS
1. Methods (line 190): Primary endpoint of clinical cure maybe slightly subjective and determined by a provider at D30. If these physicians are the blinded outcomes assessors, that is a good design. However, if these providers are unblinded, that could introduce bias.
Response: Thank you for your comments. We agree with you that bias will occur if outcomes assessors were unblinded to the randomization. In our study design, physicians who are blinded to the randomization underwent outcome evaluation. Hence, the concern could be ignored.
2. Methods (line 257): Consider increasing the frequency of data tracking. With a follow-up period of 30 days and a common condition like AECOPD, would recommend the data managers track adherence to the protocol biweekly (rather than monthly).
Response: Thank you for your insightful comments. We have revised the frequency of data tracking according to your valuable suggestion. Now the sentence reads: “Two experienced data managers from the China-Japan hospital biweekly check the CRF of each center, track clinicians’ antibiotic prescription decisions in both groups and assess adherence to the protocol.” Please see Page 7, line 257-260.
3. Inclusion/Exclusion Criteria (Table 1):
• The exclusion criteria of “fever” and “pneumonia identified by X-ray or CT of the lungs”
you may find is too restrictive. As you mentioned in the introduction, the majority of AECOPD are caused by viral LRTI (e.g. influenza) which could present with fever and change in CXR appearance that would be called pneumonia by radiology. Consider removing these criteria before starting enrollment, or remove with an amendment in the future if they prove to be too restrictive.
Response: Thank you for your comments. Same to the inclusion and exclusion criteria of previous study design[1], we aimed to enrolled a cohort of patients with AECOPD and without pneumonia. Because if patients presented with AECOPD and pneumonia simultaneously, the occurrence of pneumonia may affect the disease process of COPD and the outcome evaluation. Now, our study was recruiting, and the above two exclusion criteria did not impede the recruitment speed. Hence, these two exclusion criteria remained in our protocol.
[1] Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy.
• Is the steroid exclusion criteria inclusive of any administration within the last 30 days, or steroid administration for at least 30 consecutive days? May want to clarify that language, as AECOPD patients receive bursts of steroids frequently.
Response: Thank you for your comments. We excluded those individuals who received corticosteroids therapy (at least prednisone 30mg/d or equivalent) more than 30 consecutive days.

VERSION 2 – REVIEW

REVIEWER	Peng, Fei Zhongda Hospital, School of Medicine, Southeast University, Department of critical care medicine
REVIEW RETURNED	06-Jul-2021

GENERAL COMMENTS	Well designed RCT. No other comments.

REVIEWER	Ulrich, Robert NYU School of Medicine
REVIEW RETURNED	16-Jul-2021

GENERAL COMMENTS	The authors adequately addressed all previously raised concerns, and the study protocol is much improved. I have no additional comments on the revised manuscript, wish the authors luck in recruitment, and look forward to reading their results.