



HAL
open science

Procalcitonin algorithm to guide initial antibiotic therapy in acute exacerbations of COPD admitted to the ICU: a randomized multicenter study

Cédric Daubin, Xavier Valette, Fabrice Thiolliere, Jean-Paul Mira, Pascal Hazera, Djillali Annane, Vincent Labbé, Bernard Floccard, François Fournel, Nicolas Terzi, et al.

► To cite this version:

Cédric Daubin, Xavier Valette, Fabrice Thiolliere, Jean-Paul Mira, Pascal Hazera, et al.. Procalcitonin algorithm to guide initial antibiotic therapy in acute exacerbations of COPD admitted to the ICU: a randomized multicenter study. *Intensive Care Medicine*, 2018, 44 (4), pp.428-437. 10.1007/s00134-018-5141-9. hal-02155549

HAL Id: hal-02155549

<https://normandie-univ.hal.science/hal-02155549>

Submitted on 9 Apr 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

SEVEN-DAY PROFILE PUBLICATION



Procalcitonin algorithm to guide initial antibiotic therapy in acute exacerbations of COPD admitted to the ICU: a randomized multicenter study

Cédric Daubin^{1*} , Xavier Valette¹, Fabrice Thiollière², Jean-Paul Mira³, Pascal Hazera⁴, Djillali Annane^{5,6}, Vincent Labbe⁷, Bernard Floccard⁸, François Fournel⁹, Nicolas Terzi^{10,11}, Damien Du Cheyron¹ and Jean-Jacques Parienti^{9,12} for the BPCTrea Study Group

© 2018 The Author(s)

Abstract

Purpose: To compare the efficacy of an antibiotic protocol guided by serum procalcitonin (PCT) with that of standard antibiotic therapy in severe acute exacerbations of COPD (AECOPDs) admitted to the intensive care unit (ICU).

Methods: We conducted a multicenter, randomized trial in France. Patients experiencing severe AECOPDs were assigned to groups whose antibiotic therapy was guided by (1) a 5-day PCT algorithm with predefined cutoff values for the initiation or stoppage of antibiotics (PCT group) or (2) standard guidelines (control group). The primary endpoint was 3-month mortality. The predefined noninferiority margin was 12%.

Results: A total of 302 patients were randomized into the PCT ($n = 151$) and control ($n = 151$) groups. Thirty patients (20%) in the PCT group and 21 patients (14%) in the control group died within 3 months of admission (adjusted difference, 6.6%; 90% CI -0.3 to 13.5%). Among patients without antibiotic therapy at baseline ($n = 119$), the use of PCT significantly increased 3-month mortality [19/61 (31%) vs. 7/58 (12%), $p = 0.015$]. The in-ICU and in-hospital antibiotic exposure durations, were similar between the PCT and control group (5.2 ± 6.5 days in the PCT group vs. 5.4 ± 4.4 days in the control group, $p = 0.85$ and 7.9 ± 8 days in the PCT group vs. 7.7 ± 5.7 days in the control group, $p = 0.75$, respectively).

Conclusion: The PCT group failed to demonstrate non-inferiority with respect to 3-month mortality and failed to reduce in-ICU and in-hospital antibiotic exposure in AECOPDs admitted to the ICU.

Keywords: Chronic obstructive pulmonary disease, Procalcitonin, Antibiotic stewardship, Respiratory tract infection, Community-acquired pneumonia, Viral infection

*Correspondence: daubin-c@chu-caen.fr

¹ Department of Medical Intensive Care, CHU de Caen, 14000 Caen, France

Full author information is available at the end of the article

The members of the BPCTrea Study Group are listed in the Acknowledgements and in the electronic supplementary material.

Introduction

Severe acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) are a leading cause of admission to medical intensive care units (ICUs). Prompt initiation of antibiotics is recommended in this setting despite the fact that bacteria are found to be the cause of disease in only approximately 50% of cases [1]. COPD exacerbations can be triggered by other factors, such as viruses, allergens and common pollutants [<http://www.goldcopd.org>]. However, in clinical practice, the signs and symptoms of bacterial and non-bacterial AECOPDs overlap [2, 3]. Therefore, identifying the patients with severe AECOPDs who are most likely to benefit from antibiotics remains a challenge for physicians focused on reducing the frequency and duration of antibiotic treatment to prevent the emergence of multidrug-resistant bacteria in the ICU. Procalcitonin (PCT) is considered useful for determining the likelihood that patients will develop bacterial infections in emergency settings. PCT-based strategies have been shown to substantially and safely reduce antibiotic use in patients without severe lower respiratory tract infections [4, 5], community-acquired pneumonia [6] or AECOPDs [7]. However, data on the efficacy and safety of PCT-based strategies in critically ill patients are scarce [8–11]. Previous studies regarding this issue showed that PCT-guided strategies reduced antibiotic exposure without causing adverse outcomes in heterogeneous groups of patients with suspected severe bacterial infections.

We hypothesized that the use of PCT reduces antibiotic exposure while not affecting or even lowering mortality. We compared 3-month mortality and in-ICU and in-hospital antibiotic use between groups of patients with severe AECOPDs who were admitted to the ICU whose antibiotic therapy was guided by a serum PCT protocol or current guidelines. The preliminary results of this study were presented at the Congrès REANIMATION 2017 (Submission reference 000533), Paris, France, January 2017.

Methods

Patients

We conducted a prospective, multicenter, parallel-group, randomized controlled trial in the ICUs of 11 hospitals, including 7 tertiary care hospitals, in France between October 2010 and March 2016. All consecutive adult patients experiencing severe AECOPDs with suspected lower respiratory tract infections with or without pneumonia who were admitted to the ICU were eligible for the study and were assigned 1:1 to groups whose antibiotic therapy was guided by (1) a PCT algorithm with predefined cutoff values for the initiation or stoppage of

Take-home message

The reduction of antibiotic use remains a major concern in ICU and procalcitonin is a promising biomarker in this field. This prospective randomized controlled trial of 302 severe acute exacerbation of COPD with or without pneumonia admitted in ICU failed to demonstrate the ability of a PCT-guided strategy to safely reduce antibiotic exposure, in particular among patients without antibiotics at inclusion. Prompt initiation of antibiotherapy in this population improves 3-month survival regardless of the level of PCT.

antibiotics (PCT group) or (2) standard guidelines (control group). The time interval between hospital admission and inclusion in the study was required to be less than 48 h.

This academic trial was registered at ClinicalTrials.gov, NCT02521636. The following patients were excluded from the study: those under 18 years, with known pregnancies, with clinical evidence of infection other than a lower respiratory tract infection, with severe acute asthma, who were moribund or suffering from a disease with an estimated survival time of less than 2 months, who were severely immunosuppressed (i.e., patients with HIV infection, with neutropenia, recipients of stem cell transplants, receiving immunosuppressive treatments, and receiving corticosteroid treatment at a dose greater than 0.5 mg/kg/day for more than 10 days), with nosocomial infections, refused to participate in the study, included in another biomedical research protocol that was in progress or lasted less than 30 days, and those with a known PCT level at the time of their ICU admission.

The study protocol was approved by the local research ethic committee (Comité de Protection des Personnes Nord Ouest III) for all participating centers, and written informed consent was obtained from the patients or their surrogates upon their enrolment in the study. An independent data and safety monitoring board reviewed the trial's progress and adverse event rates according to treatment assignments.

Randomization

Patients were randomly assigned (in a 1:1 ratio) to groups whose antibiotic therapy was guided by a PCT protocol (PCT group) or standard guidelines (control group). The randomization was stratified on the center and the presence or absence of pneumonia. Randomization was performed with an independent, centralized 24-h, web-based system (eol®Medsharing Système de randomisation: IWRS/IVRS essaionline.com) using permuted-block randomization. The block sizes varied.

Procedures

Circulating PCT levels were sequentially assessed at inclusion (PCT-H0), at 6 h after inclusion (PCT-H6), and

on days 1, 3 and 5 after inclusion. PCT levels were measured by Elecsys BRAHMS PCT immunoassay (Roche Diagnostics, Mannheim, Germany) using a cobas e411 analyzer, according to the manufacturer's instructions.

In the PCT group, the antibiotic treatment was guided by serum procalcitonin levels. The patients were classified into the following three groups based on the probability of bacterial infection, according to the PCT level, which was measured as described in previous reports [4–7] and our prospective pilot studies in the indicated setting [12, 13]: group 1, PCT < 0.1 µg/L, which indicated that no bacterial infection was present, and the initiation or continuation of antibiotics was strongly discouraged; group 2, PCT > 0.1 and < 0.25 µg/L, which indicated that bacterial infection was possible [12, 13], and the initiation or continuation of antibiotics was encouraged; and group 3, PCT > 0.25 µg/L, which indicated that bacterial infection was present, and the initiation or continuation of antibiotics was strongly encouraged. In addition, the investigators were encouraged to discontinue antibiotics when the PCT concentration was less than 90% of the peak concentration or an absolute concentration less than 0.1 µg/L was noted.

In the control group, PCT concentrations were measured in all blood samples; however, the results were not disclosed to the treating physicians. Thus, the physicians were unaware of the results throughout the entire study period. The data were used only for the final analysis. Both the control and PCT groups could use CRP as a serial biomarker. Antibiotics were started and stopped according to usual care in each center; however, all physicians were encouraged to comply with current guidelines [1, 14].

Except for the prescription of antibiotics during the PCT algorithm period, all other treatments were left to the discretion of the attending physicians throughout the study period in both groups.

All patients were followed until 3 months after randomization.

Outcomes

The primary endpoint was 3-month mortality from any cause, and the secondary endpoints were the in-ICU and in-hospital antibiotic exposure durations, which were defined as the cumulative numbers of 24-h periods in which the patients received antibiotics, and the number of patients who received antibiotics during the algorithm phase (i.e., the first 5 days after inclusion).

Data collection and definitions

Detailed information regarding recorded baseline characteristics and definitions (i.e., AECOPD with and without

pneumonia [15, 16] and severity status [17–19]) may be found in the Supplemental Appendix.

Sample size and statistical analysis

The hypotheses tested were that PCT-based antibiotic therapy was non-inferior to standard therapy with respect to 3-month mortality (primary endpoint) and that PCT-based therapy would significantly decrease in-ICU and in-hospital antibiotic exposure compared with standard therapy (secondary endpoint). The primary outcome was analyzed on an intention-to-treat basis.

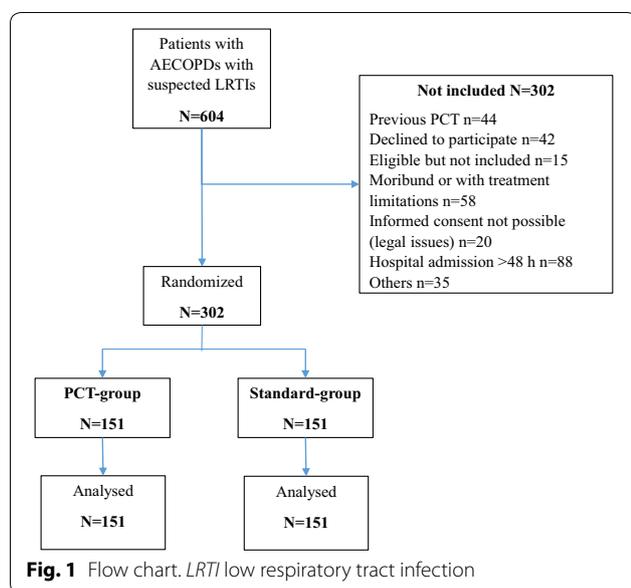
The expected overall 3-month mortality rate was 20% (i.e., 30% [12] and 10% [13] for patients with and without pneumonia, respectively; the distributions were equal), the expected non-inferiority margin was 12%, and the expected one-sided alpha risk was 5%. We estimated that 140 patients per group were needed to demonstrate that excess mortality was absent in the PCT group with 80% power. We concluded that 300 patients were needed. Given the size of the study population and based on the results of our previous reports [12, 13], we estimated that the PCT protocol would reduce the number of days of in-hospital antibiotic exposure by more than 24% compared with standard therapy [an average decrease of 1.9 days in the PCT group (24% of 8 days of antibiotic therapy in the non-PCT group), with a standard deviation of ± 5 days, a two-sided alpha risk of 5 and 90% power]. The difference in 3-month mortality (the primary endpoint) between the randomized groups was computed by a generalized linear model of risk difference adjusting for the presence or absence of pneumonia, as appropriate. The upper-limit of the 90% CI, which corresponded to a 5% risk, had to be lower than the 12% non-inferiority margin for a declaration of non-inferiority. The difference in antibiotic therapy exposure (the secondary endpoint) between the randomized groups was computed by the weighted inverse variance mean difference. No interim analysis was planned. We conducted predefined subgroup analysis based on the presence or absence of pneumonia and post hoc subgroup analyses based on the presence or absence of antibiotic therapy at baseline and the delay between admission and randomization, using the same approach as the overall analysis. The presence of interaction between subgroups was tested by the Breslow-day test.

SAS v.9.4 software (SAS Institute, Cary, NC, USA) was used for the data analysis. All tests were 2-sided, and a *p* value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 302 patients were randomized into the PCT (*n* = 151) and control (*n* = 151) groups. Three ICUs from



teaching hospitals consecutively included 81% of the sample size. The groups included 64 and 61 patients with AECOPDs with pneumonia, respectively (Fig. 1). The baseline characteristics of the randomized patients are shown in Table 1 (detailed information pertaining to each subgroup may be found in the Supplemental Appendix). A higher percentage of patients with home oxygen and home noninvasive ventilator support were randomized in the PCT group. Overall, 264 patients (87%) needed mechanical ventilation.

Antibiotic therapy during the first 48 h after inclusion included: cephalosporins (31%), macrolides (25%), antipseudomonal penicillins (19%), aminopenicillins (18%), and fluoroquinolones (5%). Patients with pneumonia received combination therapy in 88% of cases (52/64 in PCT group and 58/61 in control group, $p = 0.013$).

During the ICU stay, there were no differences between the PCT and control groups with respect to the following parameters (detailed information may be found in the Supplemental Appendix): the number of patients needing vasopressors and dialysis; the incidences of shock (i.e., septic and cardiogenic shock), ARDS, multi-organ failure, ICU-acquired pneumonia, other ICU-acquired infections, and ICU-acquired pneumothoraxes; mechanical ventilation durations; lengths of stay; and the decision to withhold or withdraw treatment; and mortality. In addition, at the 3-month follow-up, the two groups had experienced a similar number of relapses needing hospitalization.

Microbiological findings

No differences in microbiological findings were noted between the two study groups (Table 1). A total of 128 patients (42%) had AECOPDs with a confirmed microbiological cause (i.e., 53 (18%) patients had bacterial infections, 62 patients (20%) had viral infections, and 13 patients (4%) had bacterial and viral co-infections). (Detailed information pertaining to each subgroup may be found in the Supplemental Appendix.)

PCT levels

The two study groups were also similar with regards to the circulating PCT levels at inclusion (PCT-H0), at 6 h after inclusion (PCT-H6), and on days 1, 3 and 5 after inclusion. (Detailed information regarding the two study groups and each subgroup may be found in the Supplemental Appendix.)

Primary endpoint

At 3 months after inclusion, 51 (17%) patients had died [30 (20%) in the PCT group and 21 (14%) in the control group; adjusted difference, 6.6%; 90% CI -0.3 to 13.5%] (Fig. 2).

The results of the subgroup analyses are shown in Fig. 2. The effect size was not significantly different between patients with and without pneumonia (interaction test, $p = 0.2$). Among patients without antibiotic therapy at baseline ($n = 119$), the use of PCT significantly increased 3-month mortality [19/61 (31%) vs. 7/58 (12%); adjusted difference, 19.1%; 90% CI 7.2–31.1%, $p = 0.015$ by Fisher exact test]. Among patients with antibiotic therapy at baseline ($n = 182$), the use of PCT was non-inferior to the control group regarding 3-month mortality [10/89 (11%) vs. 14/93 (15%); adjusted difference, -3.0% ; 90% CI -10.6 to 4.6%]. The effect size was significantly different between patients with and without antibiotics at baseline (interaction test, $p = 0.019$).

Secondary endpoint

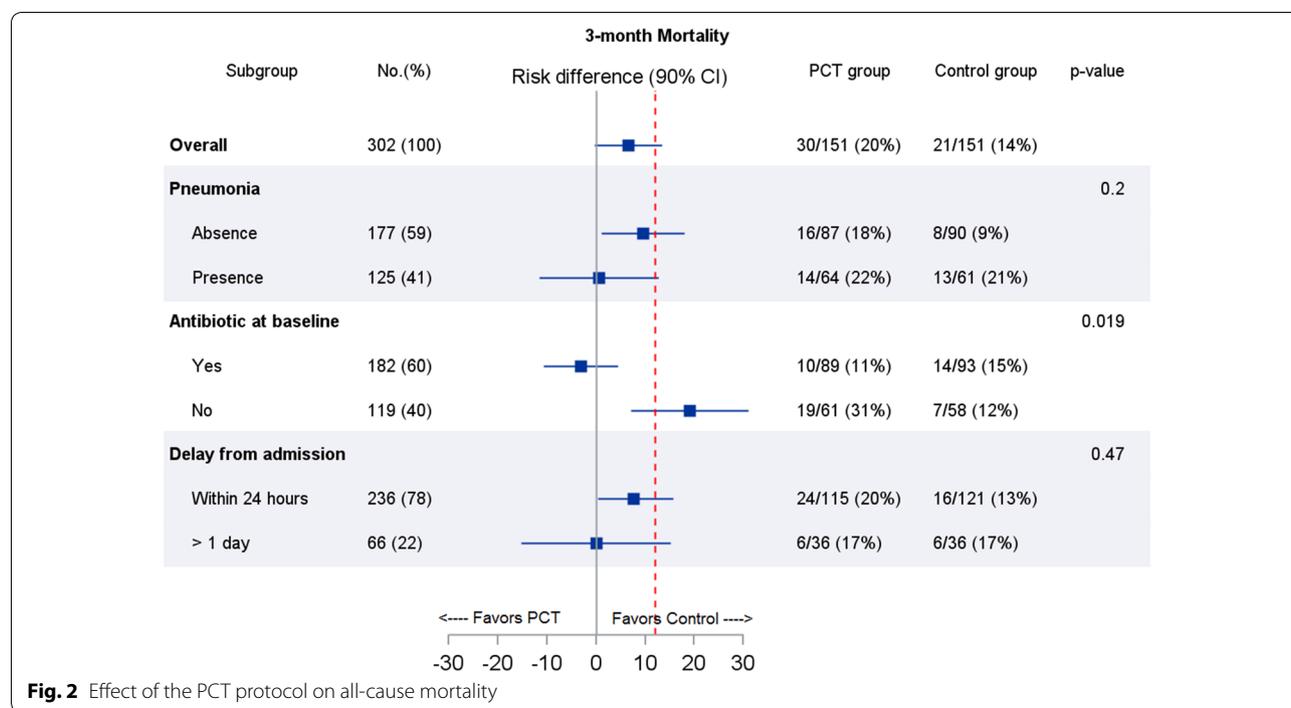
The number of patients in the PCT group who received antibiotics during the PCT algorithm phase was significantly lower than the number of patients in the control group who received antibiotics during the PCT algorithm phase (Fig. 3) (detailed information pertaining to each subgroup may be found in the Supplemental Appendix); however, the in-ICU and in-hospital antibiotic exposure durations, respectively, were similar between the PCT and control group (5.2 ± 6.5 days in the PCT group vs. 5.4 ± 4.4 days in the control group, $p = 0.85$, and 7.9 ± 8 days in the PCT group vs. 7.7 ± 5.7 days in

Table 1 Patient characteristics

	PCT group <i>n</i> = 151	Standard group <i>n</i> = 151
Age (years), median (Q1–Q3)	67 (61–76)	67 (61–75)
Men, <i>n</i> (%)	108 (71.5)	100 (66.2)
Body mass index, median (Q1–Q3)	26.0 (22.5–32.0)	24.5 (21.7–30.1)
Current smokers, <i>n</i> (%)	61 (40.4)	53 (35.1)
Comorbidities		
Arterial hypertension, <i>n</i> (%)	81 (53.6)	75 (49.7)
Cardiopathy, <i>n</i> (%)	57 (37.7)	48 (31.8)
Arteritis, <i>n</i> (%)	27 (17.9)	21 (13.9)
Diabetes mellitus, <i>n</i> (%)	32 (21.2)	27 (17.9)
Malignancy, <i>n</i> (%)	8 (5.3)	10 (6.6)
Chronic renal failure requiring dialysis, <i>n</i> (%)	4 (2.6)	1 (1.0)
Severity of COPD, <i>n</i> (%)		
GOLD stage 0	6 (4)	4 (3)
GOLD stage I (FEV ₁ ≥ 80% predicted)	6 (4.0)	8 (5.3)
GOLD stage II (FEV ₁ ≥ 50 to < 80% predicted)	25 (16.6)	22 (14.6)
GOLD stage III (FEV ₁ ≥ 30 to < 50% predicted)	41 (27.2)	50 (33.1)
GOLD stage IV (FEV ₁ ≤ 30% predicted)	58 (38.4)	53 (35.1)
GOLD stage unknown	15 (9.9)	14 (9.3)
Baseline FEV ₁ , mean (SD)	1050 (463)	1026 (522)
Baseline FEV ₁ % predicted, mean (SD)	41 (15.5)	39 (16.5)
FEV ₁ /FVC ratio, mean (SD)	48 (14)	47 (13.5)
Home oxygen, <i>n</i> (%)	63 (41.7)	51 (33.8)
Home noninvasive ventilatory support, <i>n</i> (%)	44 (29.1)	30 (19.9)
Number of hospitalizations for AECOPD in previous year		
Mean (SD)	0.93 (1.45)	0.87 (1.43)
Median (Q1–Q3)	0 (0–1)	0 (0–1)
Acute exacerbation of COPD		
With pneumonia, <i>n</i> (%)	64 (42.4)	61 (40.4)
Without pneumonia, <i>n</i> (%)	87 (57.6)	90 (59.6)
Severity of illness		
SAPS II, median (Q1–Q3)	35 (28–44)	34 (27–43)
SOFA score, median (Q1–Q3)	4 (2–5)	3 (2–5.75)
Pneumonia severity index, <i>n</i> (%)		
Score, median (Q1–Q3)	136 (109–155)	134 (108–156)
Score, mean (SD)	133.7 (33.13)	130.7 (36.2)
Pneumonia severity index class, <i>n</i> (%)		
I (predicted mortality 0.1%)	0 (0.0)	0 (0.0)
II (predicted mortality 0.6%)	1 (1.6)	5 (8.2)
III (predicted mortality 2.8%)	7 (10.9)	2 (3.3)
IV (predicted mortality 8.2%)	21 (32.8)	22 (36.1)
V (predicted mortality 29.2%)	35 (54.7)	32 (52.5)
Time between hospital admission and inclusion, <i>n</i> (%)		
< 24 h	115 (76.2)	121 (80.1)
≥ 24 h < 48 h	33 (21.9)	19 (12.6)
≥ 48 h < 72 h	2 (1.3)	11 (7.3)
Mechanical ventilation at the time of inclusion, <i>n</i> (%)		
Invasive, <i>n</i> (%)	42 (27.8)	40 (26.5)
Non-invasive, <i>n</i> (%)	95 (63)	87 (57.6)

Table 1 continued

	PCT group <i>n</i> = 151	Standard group <i>n</i> = 151
Antibiotics at the time of inclusion, <i>n</i> (%)	89 (58.9)	93 (61.6)
Steroids at the time of inclusion, <i>n</i> (%)	88 (58.3)	91 (60.3)
Oral	74 (49.0)	74 (49.0)
Intravenous	4 (2.6)	8 (5.3)
Oral and intravenous	10 (6.6)	8 (5.3)
Microbiologically documented cause of AECOPD, <i>n</i> (%)		
Bacterial	27 (17.9)	26 (17.2)
Viral	35 (23.2)	27 (17.9)
Co-infection	3 (2.0)	10 (6.6)
PCT H0 ($\mu\text{g/L}$)	0.28 (0.10–0.90)	0.19 (0.08–0.79)
PCT < 0.1 $\mu\text{g/L}$, <i>n</i> (%)	37 (25.0)	39 (25.8)
0.1 \leq PCT < 0.25 $\mu\text{g/L}$, <i>n</i> (%)	33 (22.3)	40 (28.2)
PCT \geq 0.25 $\mu\text{g/L}$, <i>n</i> (%)	78 (52.7)	63 (44.4)
Data unknown, <i>n</i> (%)	3 (2.0)	9 (6.3)
Leukocyte count ($\times 10^9/\text{L}$)		
Mean (SD)	15,003 (12,578)	14,825 (10,630)
Median (Q1–Q3)	12,040 (8865–16,775)	12,820 (9607–17,152)



the control group, $p=0.75$, respectively) (Fig. 4). Notably, the in-ICU antibiotic exposure duration was not significantly lower in AECOPDs without pneumonia in the PCT group than in AECOPDs without pneumonia in the control group (4 ± 4.6 days in the PCT group vs. 4.8 ± 4.6 days in the control group, $p=0.25$).

Discussion

In this multicenter, randomized, controlled clinical study, the use of PCT-guided antibiotic therapy failed to demonstrate non-inferiority with respect to 3-month mortality among patients with severe AECOPDs with suspected lower respiratory tract infections who were admitted to

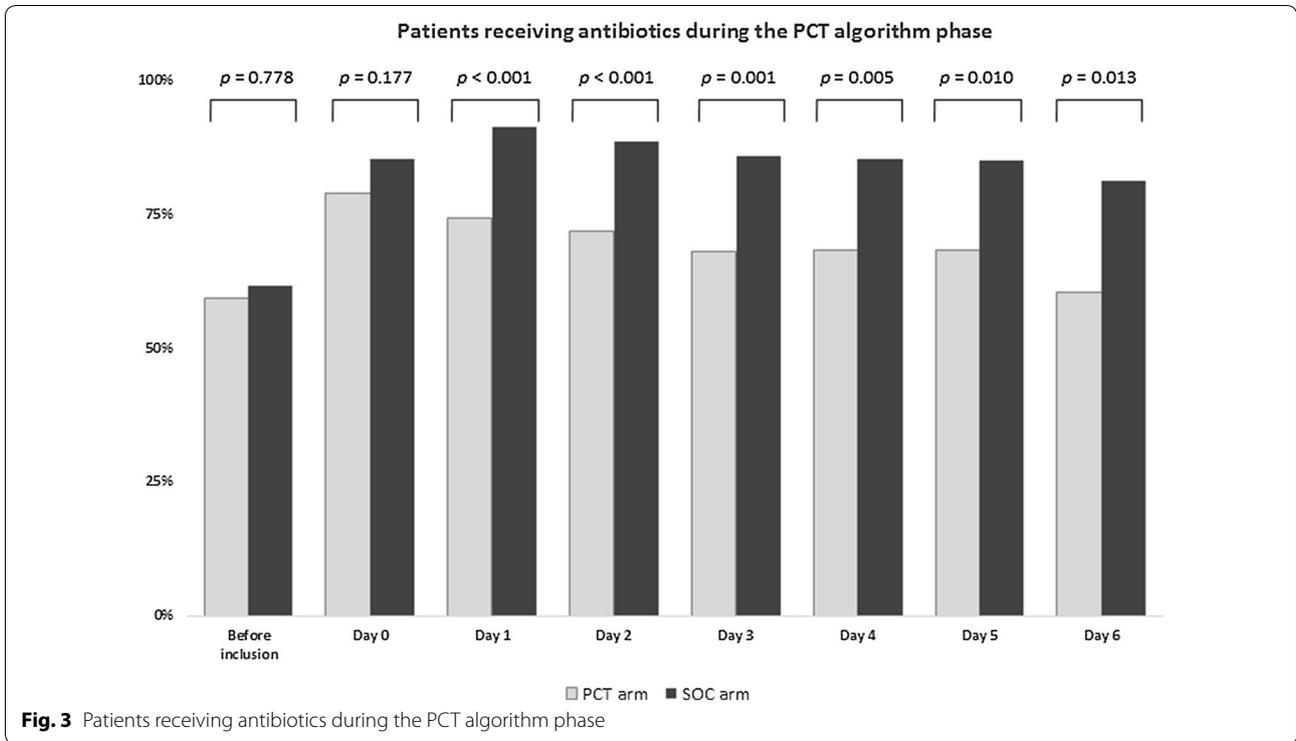
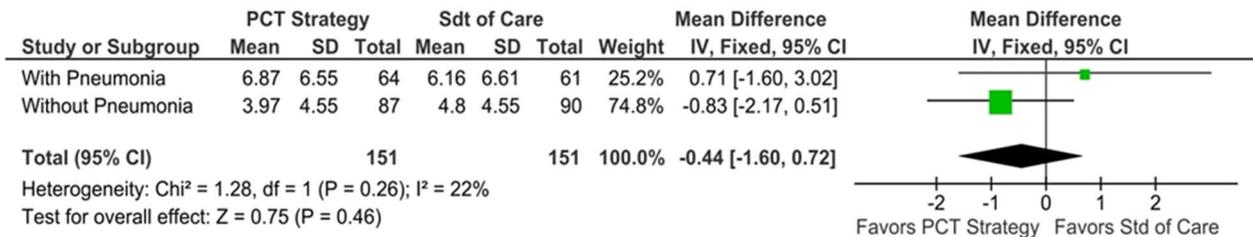


Fig. 3 Patients receiving antibiotics during the PCT algorithm phase

a In-ICU antibiotic treatment durations



b In-hospital antibiotic treatment durations

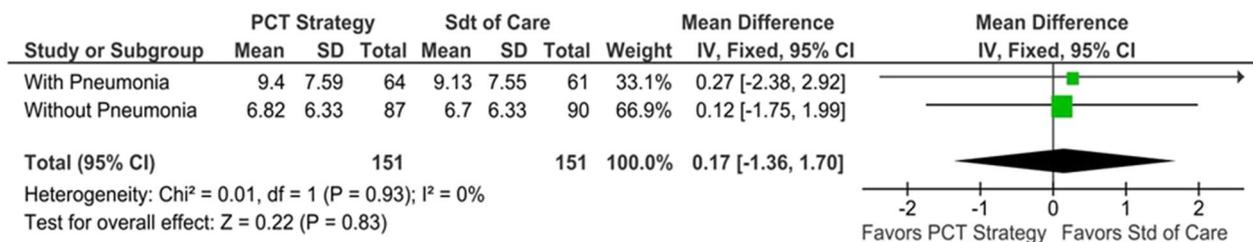


Fig. 4 Effect of the PCT protocol on in-ICU (a) and in-hospital (b) antibiotic treatment durations in the groups randomized according to the presence or absence of pneumonia

the ICU. The upper limit of the 90% CI was 13.5%, a percentage that exceeded the 12% predefined non-inferiority margin. This lack of non-inferiority is mainly due to the subgroup of patients without antibiotic therapy at baseline, who had a significant higher 3-month mortality in the PCT group used to initiate antibiotic therapy compared with the control group. Furthermore, the in-ICU and in-hospital antibiotic exposure durations were similar between the PCT and control groups.

This result contrasts with those of all previous large randomized trials assessing the effects of PCT-based protocols on antibiotic use and outcomes in lower respiratory tract infections [4, 5, 20], community-acquired pneumonia [6, 21] and moderate AECOPDs [7, 22]. In these studies, PCT-based therapeutic strategies substantially and safely reduced antibiotic use. However, in these studies, the mean duration of antibiotic therapy in the control group was rather long compared to the duration of treatment recommended by more recent guidelines [1, 14], contributing statistical relevance to comparisons. In addition, most of the patients included in the indicated trials [4–7, 20–22] were admitted to the emergency department for disease of low or moderate clinical severity. Only a minority of patients (range 0–14% [4–7, 20–22]) required hospitalization in the ICU.

Our results also contrast with those of previous randomized trials [8–11, 23–27] demonstrating that PCT-guided strategies reduce antibiotic exposure (with the exception of [24, 25]) without leading to adverse outcomes in critically ill patients with suspected severe bacterial infections. However, only two of the trials were also designed to demonstrate the non-inferiority of PCT-guided strategies with respect to mortality. Interestingly, these two large randomized trials reported contradictory results. In one study [9], 60-day mortality was higher in the PCT group than in the control group, and the non-inferiority margin of 10% was almost reached. In the other study [10], 28-day and 1-year mortality were significantly lower in the PCT group than in the control group, and the non-inferiority margin was 8%. Between-study differences in the PCT-guided antibiotic protocols may explain the above discrepancies. One protocol provided rules for the initiation, continuation and discontinuation of antibiotic treatment [9], while the other focused on the deescalation of antibiotic therapy [10]. One study [23], designed to demonstrate the superiority of PCT-guided therapy with respect to mortality, noted no improvements in 28-day mortality in the PCT group compared with the control group. The results of different meta-analyses were also inconsistent [28–31]. In addition, a large controlled clinical trial [32] failed to demonstrate the ability of PCT-guided antimicrobial escalation to improve survival of patients with severe sepsis or shock

in surgical ICUs. Therefore, the ability of PCT-based strategies to safely reduce antibiotic exposure in critically ill patients, especially patients with severe AECOPDs, remains unclear.

To our knowledge, this was the first randomized controlled clinical trial investigating the ability of a PCT-based strategy to safely reduce antibiotic exposure in a homogenous population of patients (i.e., patients with AECOPDs) with suspected lower respiratory tract infections who need noninvasive or invasive mechanical ventilation (a routine situation in an adult medical ICU). This study failed to achieve its primary objective (i.e., to demonstrate the non-inferiority of a PCT-based strategy with respect to 3-month mortality) and to achieve its secondary objective (i.e., to demonstrate that PCT-based strategies decrease, the in-ICU and in-hospital antibiotic exposure durations) in the overall cohort and the predefined subgroups (i.e., AECOPDs with and without pneumonia). From a theoretical point of view, two different explanations could explain the lack of non-inferiority of PCT-guided algorithms in this cohort with severe AECOPD. Firstly, PCT could fail to distinguish between infectious and non-infectious causes of AECOPD. Alternatively, patients with AECOPD benefit from antibiotic therapy regardless of the cause of AECOPD, and any delay in antibiotic prescription in such patients leads to poorer outcome. The subgroup analysis of patients without antibiotic therapy at baseline strongly support the latter hypothesis. Therefore, AECOPD patients admitted in the ICU should promptly initiate antibiotic therapy, regardless of the level of PCT. This point is also supported by a Cochrane meta-analysis [33] reporting that antibiotics reduced the risk of treatment failure in severe AECOPDs and reduced mortality in patients hospitalized in the ICU.

Several limitations of the study warrant discussion. First, this study was an open intervention trial in which the clinicians knew that their treatment decisions were observed. Second, the time frame required for reaching the preplanned sample size (i.e., 6 years) was long. Third, to reflect clinical practice, we chose to include pneumonic and non-pneumonic AECOPD patients with different prognoses; however, randomization was stratified according to whether pneumonia was present or absent allowing a similar distribution between groups. Fourth, antibiotic treatment before the randomization of specific subsets of patients may have affected PCT levels. However, previous reports showed that PCT levels were not different between patients pre-treated with antibiotics and antibiotic-naïve patients [6, 7, 12, 13]. Fifth, the algorithm proposed in the present study may have underestimated the probability that a patient could be infected at the lowest PCT threshold. However, our group has

prospectively evaluated the validity of the PCT algorithm previously in similar patients [12, 13]. In these studies, no bacteria judged responsible for infection exacerbations were detected by the systematic screening of the subgroup of patients with COPD with PCT levels $<0.1 \mu\text{g/L}$. Finally, this PCT algorithm was similar to those used in previous major studies in the field [4–7].

Conclusion

In this study, we failed to demonstrate non-inferiority with respect to 3-month mortality of a PCT-based strategy focusing both on initiation or discontinuation of antibiotics in patients with severe AECOPDs with suspected lower respiratory tract infections who needed mechanical ventilation. Furthermore, the PCT-based strategy failed to reduce in-ICU and in-hospital antibiotic exposure durations. This result may have substantial clinical implications for the management of critically ill patients with AECOPDs. Finally, our study indirectly supports the prompt initiation of antibiotic therapy among severe AECOPD admitted in ICU to contribute to reduce 3-month mortality.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-018-5141-9>) contains supplementary material, which is available to authorized users.

Author details

¹ Department of Medical Intensive Care, CHU de Caen, 14000 Caen, France. ² Intensive Care Unit, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France. ³ Department of Medial Intensive Care, Cochin University Hospital, Paris, France. ⁴ Department of Intensive Care Medicine, General Hospital, Saint Lô, France. ⁵ Service de Médecine Intensive et Réanimation, Hôpital Raymond Poincaré (APHP), Garches, France. ⁶ Laboratoire Infection and Inflammation, U1173 Université de Versailles SQY-Paris Saclay—INSERM, Paris, France. ⁷ Service de Réanimation et USC Médico-chirurgicale, AP-HP, Hôpitaux Universitaires de l'Est Parisien, Hôpital Tenon, Paris, France. ⁸ Department of Anesthesiology and Critical Care Medicine, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France. ⁹ Department of Biostatistics and Clinical Research, CHU de Caen, 14000 Caen, France. ¹⁰ Department of Medical Intensive Care, CHU de Grenoble Alpes, 38000 Grenoble, France. ¹¹ INSERM, U1042, University of Grenoble-Alpes, HP2, 38000 Grenoble, France. ¹² EA2656 Groupe de Recherche sur l'Adaptation Microbienne (GRAM 2.0), Université Caen Normandie, Caen, France.

Acknowledgements

We thank Marion Provent and Severine Fournel (Unité de Recherche Clinique, Intensive Care Unit, Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Pierre Bénite, France) and Nathalie Marin (Unité de Recherche Clinique, Department of Medical Intensive Care, Cochin University Hospital, Paris, France) for their outstanding efforts in the monitoring of the study.

BPCTrea Study Group members Cédric Daubin, Xavier Valette, Amélie Seguin, Jennifer Brunet, Pierre Charbonneau and Damien Du Cheyron (CHU de Caen, Department of Medical Intensive Care, Caen, 14000, France); Stephane Allouche (Department of Biochemistry, Caen, F-14032, France, and Normandie Univ, UNICAEN, CHU Caen, Signalisation, Electrophysiologie et Imagerie des Lésions d'Ischémie-reperfusion Myocardique, Caen, F-14032, France CHU de Caen); François Fournel and Jean-Jacques Parienti (CHU de Caen, Department of Biostatistics and Clinical Research, Caen, 14000, France, and EA4655 Risque Microbiens, Caen Normandie Université, Caen, France); Bertrand Sauneuf (Service de Réanimation Médicale Polyvalente, Centre Hospitalier Public du Cotentin, BP 208, 50102 Cherbourg-en-Cotentin, France); Fabrice Thiollière and Julien Bohe (Intensive Care Unit, Hospices Civils de Lyon,

Centre Hospitalier Lyon Sud, Pierre Bénite, France); Jean-Paul Mira and Fabrice Daviaud (Department of Medical Intensive Care, Cochin University Hospital, Paris, France); Nicolas Terzi (CHU de Grenoble Alpes, Department of Medical Intensive Care, F-38000 Grenoble, France and INSERM, U1042, University of Grenoble-Alpes, HP2, F-38000 Grenoble, France); Pascal Hazera and Michel Ramakers (Department of Intensive Care Medicine, General Hospital, Saint Lô, France); Djillali Annane and Andréa Polito (Service de Médecine Intensive et Réanimation, Hôpital Raymond Poincaré (APHP) and Laboratoire Infection & Inflammation, U1173 Université de Versailles SQY—Paris Saclay, INSERM General Intensive Care Unit, Raymond Poincaré Hospital, Garches, France U1173 Lab Inflammation & Infection, University of Versailles SQY-Paris Saclay—INSERM, Garches, France); Vincent Labbe and Muriel Fartoukh (Service de Réanimation et USC Médico-chirurgicale, AP-HP, Hôpitaux Universitaires de l'Est Parisien, Hôpital Tenon); Groupe de Recherche Clinique CARMAS, Collégium Galilée); Bernard Floccard (Department of Anesthesiology and Critical Care Medicine, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France); Gérard Alvado and Olivier Cabon (Department of Intensive Care Medicine, General Hospital, Bayeux, France); Mehdi Boustia (Department of Intensive Care Medicine, General Hospital, Havre, France); Jean-Philippe Rigaud (Department of Intensive Care Medicine, General Hospital, Dieppe, France Department of Intensive Care, Dieppe General Hospital, Dieppe, France); and Claire Andrejak (Respiratory and Intensive Care Unit, University Hospital Amiens, Amiens, 80054, France).

Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The study protocol was approved by the local research ethic committee (Comité de Protection des Personnes Nord Ouest III) for all participating centres.

Informed consent

Written informed consent was obtained from the patients or their surrogates upon their enrolment in the study.

Open Access

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

Received: 31 January 2018 Accepted: 16 March 2018

Published online: 16 April 2018

References

1. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, Orqvist A, Schaberg T, Torres A, van der Heijden G, Read R, Verheij TJ, Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases (2011) Guidelines for the management of adult lower respiratory tract infections—full version. *Clin Microbiol Infect* 17(Suppl 6):E1–E59
2. Soler N, Torres A, Ewig S, Gonzalez J, Celis R, El-Ebiary M, Hernandez C, Rodriguez-Roisin R (1998) Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 157:1498–1505
3. Cameron RJ, de Wit D, Welsh TN, Ferguson J, Grissell TV, Rye PJ (2006) Virus infection in exacerbations of chronic obstructive pulmonary disease requiring ventilation. *Intensive Care Med* 32:1022–1029
4. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, Müller B (2004) Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 363:600–607
5. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, Neidert S, Fricker T, Blum C, Schild U, Regez K, Schoenenberger R, Henzen

- C, Bregenzer T, Hoess C, Krause M, Bucher HC, Zimmerli W, Mueller B (2009) ProHOSP Study Group. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 302:1059–1066
6. Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, Müller B (2006) Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia. *Am J Respir Crit Care Med* 174:84–93
 7. Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Müller C, Huber P, Müller B, Tamm M (2007) Antibiotic treatment of exacerbations of COPD, a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest* 131:9–19
 8. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J (2008) Use of procalcitonin to shorten antibiotic treatment duration in septic patients. *Am J Respir Crit Care Med* 177:498–505
 9. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, Schortgen F, Lasocki S, Veber B, Dehoux M, Bernard M, Pasquet B, Régnier B, Brun-Buisson C, Chastre J, Wolff M, PRORATA trial group (2010) Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 375:463–474
 10. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, Loeff BG, Dormans T, van Melsen GC, Kluiters YC, Kemperman H, van den Elsen MJ, Schouten JA, Streefkerk JO, Krabbe HG, Kieft H, Kluge GH, van Dam VC, van Pelt J, Bormans L, Otten MB, Reidinga AC, Endeman H, Twisk JW, van de Garde EM, de Smet AM, Kesecioglu J, Girbes AR, Nijsten MW, de Lange DW (2016) Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis* 16:819–827
 11. Stolz D, Smyrniotis N, Eggimann P, Pargger H, Thakkar N, Siegemund M, Marsch S, Azzola A, Rakic J, Mueller B, Tamm M (2009) Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. *Eur Respir J* 34:1364–1375
 12. Daubin C, Parianti JJ, Fradin S, Vabret A, Ramakers M, Terzi N, Freymuth F, Charbonneau P, du Cheyron D (2009) Procalcitonin levels and bacterial aetiology among COPD patients admitted to the ICU with severe pneumonia: a prospective cohort study. *BMC Infect Dis* 21:157
 13. Daubin C, Parianti JJ, Vabret A, Ramakers M, Fradin S, Terzi N, Freymuth F, Charbonneau P, du Cheyron D (2008) Procalcitonin levels in acute exacerbation of COPD admitted in ICU: a prospective cohort study. *BMC Infect Dis* 8:145
 14. Conférence de consensus en thérapeutique anti-infectieuse (2006) Prise en charge des infections des voies respiratoires basses de l'adulte immunocompétent. *Med Malad infect* 36:235–244
 15. Rodriguez-Roisin R (2000) Toward a consensus definition for COPD exacerbations. *Chest* 117:3985–4015
 16. Lieberman D, Lieberman D, Gelfer Y, Varshavsky R, Dvoskin B, Leinonen M, Friedman MG (2002) Pneumonic vs nonpneumonic acute exacerbations of COPD. *Chest* 122:1264–1270
 17. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/ North American multicenter study. *J Am Med Assoc* 270:2957–2963
 18. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 22:707–710
 19. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN (1997) A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 336:243–250
 20. Kristoffersen KB, Sogaard OS, Wejse C, Black FT, Greve T, Tarp B, Storgaard M, Sodemann M (2009) Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission—a randomized trial. *Clin Microbiol Infect* 15:481–487
 21. Long W, Deng X, Zhang Y, Lu G, Xie J, Tang J (2011) Procalcitonin guidance for reduction of antibiotic use in low-risk outpatients with community-acquired pneumonia. *Respirology* 16:819–824
 22. Corti C, Fally M, Fabricius-Bjerre A, Mortensen K, Jensen BN, Andreassen HF, Porsbjerg C, Knudsen JD, Jensen JU (2016) Point-of-care procalcitonin test to reduce antibiotic exposure in patients hospitalized with acute exacerbation of COPD. *Int J Chron Obstruct Pulmon Dis* 22:1381–1389
 23. Bloos F, Trips E, Nierhaus A, Briegel J, Heyland DK, Jaschinski U, Moerer O, Weyland A, Marx G, Gründling M, Kluge S, Kaufmann I, Ott K, Quintel M, Jelschen F, Meybohm P, Rademacher S, Meier-Hellmann A, Utzolino S, Kaisers UX, Putensen C, Elke G, Ragaller M, Gerlach H, Ludwig K, Kiehntopf M, Bogatsch H, Engel C, Brunkhorst FM, Loeffler M, Reinhart K, for SepNet Critical Care Trials Group (2016) Effect of sodium selenite administration and procalcitonin-guided therapy on mortality in patients with severe sepsis or septic shock: a randomized clinical trial. *JAMA Intern Med* 176:1266–1276
 24. Layios N, Lambermont B, Canivet JL, Morimont P, Preiser JC, Garweg C, Ledoux D, Fripiat F, Piret S, Giot JB, Wiesen P, Meuris C, Massion P, Leonard P, Nys M, Lancellotti P, Chapelle JP, Damas P (2012) Procalcitonin usefulness for the initiation of antibiotic treatment in intensive care unit patients. *Crit Care Med* 40:2304–2309
 25. Shehabi Y, Sterba M, Garrett PM, Rachakonda KS, Stephens D, Harrigan P, Walker A, Bailey MJ, Johnson B, Millis D, Ding G, Peake S, Wong H, Thomas J, Smith K, Forbes L, Hardie M, Micallef S, Fraser JF, ProGUARD Study Investigators; ANZICS Clinical Trials Group (2014) Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. *Am J Respir Crit Care Med* 190:1102–1110
 26. Hochreiter M, Köhler T, Schweiger AM, Keck FS, Bein B, von Spiegel T, Schroeder S (2009) Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. *Crit Care* 13:R83
 27. Schroeder S, Hochreiter M, Koehler T, Schweiger AM, Bein B, Keck FS, von Spiegel T (2009) Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study. *Langenbecks Arch Surg* 394:221–226
 28. Heyland DK, Johnson AP, Reynolds SC, Muscedere J (2011) Procalcitonin for reduced antibiotic exposure in the critical care setting: a systematic review and an economic evaluation. *Crit Care Med* 39:1792–1799
 29. Prkno A, Wacker C, Brunkhorst FM, Schlattmann P (2013) Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock—a systematic review and meta-analysis. *Crit Care* 17:R291
 30. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Kristoffersen KB, Burkhardt O, Welte T, Schroeder S, Nobre V, Wei L, Bucher HC, Annane D, Reinhart K, Falsely AR, Branche A, Damas P, Nijsten M, de Lange DW, Deliberato RO, Oliveira CF, Maravić-Stojković V, Verduri A, Beghé B, Cao B, Shehabi Y, Jensen JS, Corti C, van Oers JAH, Beishuizen A, Girbes ARJ, de Jong E, Briel M, Mueller B (2018) Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. *Lancet Infect Dis* 18:95–107
 31. Huang HB, Peng JM, Weng L, Wang CY, Jiang W, Du B (2017) Procalcitonin-guided antibiotic therapy in intensive care unit patients: a systematic review and meta-analysis. *Ann Intensive Care* 7:114
 32. Jensen JU, Hein L, Lundgren B, Bestle MH, Mohr TT, Andersen MH, Thornberg KJ, Løken J, Steensen M, Fox Z, Tousei H, Sørensen P, Lauritsen AØ, Strange D, Petersen PL, Reiter N, Hestad S, Thormar K, Fjeldborg P, Larsen KM, Drenck NE, Ostergaard C, Kjær J, Grarup J, Lundgren JD, Procalcitonin And Survival Study (PASS) Group (2011) Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. *Crit Care Med* 39(9):2048–2058
 33. Vollenweider DJ, Jarrett H, Steurer-Stey CA, Garcia-Aymerich J, Puhon MA (2012) Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 12:CD010257