Chapter 9

Effectiveness and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients.

de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, Loef 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.

Lancet Infect Dis. 2016 Jul;16(7):819-27

Abstract

Introduction

Procalcitonin (PCT) is increasingly used for guidance of antibacterial therapy to minimize systemic antibiotic exposure in critically ill patients.

Methods

In this trial, we assigned patients admitted to the intensive care unit and who received antibiotics for presumed infection to PCT-guided or standard-of-care antibiotic discontinuation. A non-binding advice to discontinue antibiotics was provided if PCT was ≤20% of its peak value or ≤0.5 ug/L. Primary efficacy endpoints were antibiotic daily defined dosages (DDDs) and duration of antibiotic treatment (DOT). Safety endpoints were reinstitution of antibiotics, recurrent inflammation as reflected by C-reactive protein (CRP) levels and mortality.

Results

In 15 ICUs 1546 patients were randomized for PCT-guidance (n=761) or standard-of-care (n=785). The PCT-threshold was reached in 539/761(71%) patients and followed by discontinuation of antibiotics in 271/539 (50%) of the patients. The median DDDs under PCT-guidance was 7.5 DDDs (IQR 4.0-12.7) versus 9.3 DDDs (IQR 5.0-16.6) in the standard-of-care group (P<0.001). The median DOT was 5 (3-8) and 7 days (4-10) respectively (P<0.001). We observed no difference in reinstitution of antibiotics or CRP-levels within 28 days after randomization. Mortality at 28 days was 149/761 (19.6%) and 196/785 (25.0%) in the PCT and standard-of-care group respectively (P=0.006). One-year mortality was 265/761 (34.8%) and 321/785 (40.9%) in the PCT and standard-of-care group respectively (log-rank test P=0.006).

Conclusion

PCT-guidance in the treatment of presumed bacterial infections in critically ill patients safely reduced antibiotic treatment duration and dosage in a setting of already short antibiotic treatment duration.

Introduction

Sepsis remains a major cause of death in critically ill patients. Rapid and adequate antibiotic therapy is of great importance in critically ill patients, but overly prolonged antimicrobial treatment is undesirable because of increasing resistance.[1] However, in critically ill patients physicians may be reluctant to shorten the duration of antimicrobial treatment.[2] Therefore, specific markers for resolution of infection might assist physicians in making individualized antibiotic therapy decisions. Regularly used markers for this purpose are the leukocyte count and C-reactive protein (CRP). However, procalcitonin (PCT) has been advocated as a marker with a better specificity and sensitivity than CRP for follow-up of severe bacterial infections.[3-10]

Several studies have shown that PCT guidance can reduce the duration of antibiotic treatment for patients with bacterial infection,[11-20] but the safety of such protocols has not been firmly established.[21-23] Additionally, most of these ICU trials were performed in countries that have a high baseline consumption of antibiotics.In contrast, in the Netherlands the antibiotic consumption per capita is relatively low: in terms of defined daily dosages (DDDs) per 1000 patient days, the consumption in the United Kingdom, the United States, France and Greece is 1.5 to 3.3 times higher.[24]

The objective of this trial was to evaluate the efficacy and safety of PCT-guided antibiotic treatment in a large heterogeneous set of ICU-patients in a health care system with a comparatively low use of antibiotics. Our hypothesis was that addition of PCT to the standard-of-care could reduce the duration of antibiotic treatment and thus the amount of antibiotics administered, without increasing mortality or recurrent infections.

Methods

Study participants

Eligible patients were at least 18 years of age, admitted to the ICU, receiving their first dose of antibiotics within 24 hours for an assumed or proven infection before inclusion. Patients were excluded in case of: systemic antibiotics as prophylaxis only, antibiotics as part of selective decontamination of the digestive tract (SDD) only, prolonged therapy (e.g. endocarditis), expected ICU stay <24h or severe immunosuppression. Patients who received corticosteroids were not excluded. Patients could only participate once in this trial.

Study design and oversight

The Stop Antibiotics on PCT guidance Study (SAPS) was a pragmatic, prospective, open-label, multi-center, randomized intervention study in patients admitted to the ICU of three university medical

centers and 12 teaching hospitals in the Netherlands. Patients were randomly assigned, in a 1:1 ratio, to either PCT-guidance or standard-of-care. Randomization was performed centrally with a computer-generated list that was produced by an independent research organization, the Julius Center for Human Research, Utrecht, the Netherlands.

Randomization was stratified according to treatment center, whether the infection was acquired before or during ICU stay and depending on severity of infection (i.e. sepsis, severe sepsis or septic shock).[25] When randomized for the PCT-group, daily PCT-measurements were performed, including a baseline measurement as close to initiation of antibiotics as possible, but at least within 24 hours. Except for the PCT measurements, all monitoring was similar between the PCT-guided and the conventional group. PCT was measured on analyzers that were maintained according to national quality standards. In the intervention group PCT was measured until ICU-discharge or until the third day after systemic antibiotics were stopped. The study protocol advised to stop the prescribed antibiotics if PCT had decreased to ≤20% of its peak value (relative stopping threshold) or when PCT reached a value of ≤0.5 ug/L (absolute stopping threshold). The attending physician was free to decide to continue antibiotics despite reaching these thresholds. Reasons for non-adherence were recorded.
All patients or their legal representatives provided written informed consent. This trial (ClinicalTrials.gov NCT01139489) was approved by the institutional review board of the VU University Medical Center Amsterdam and is in full compliance with the Helsinki declaration.[26] The PCT-kits were provided at reduced costs by the manufacturer, who was not involved in the design or conduct of the study, analysis or the drafting of the manuscript.

Follow-up and outcomes

The primary outcome was the amount of antibiotics (expressed as DDDs) and duration of antibiotic treatment (DOT) in the two arms. For each study participant, the total amount of antibiotics administered during the study period was assessed based on individual drug administration records. Our definition of DDDs is in accordance with the recommendations of the World Health Organization (see supplementary material).[27] The route of administration was incorporated in the calculations. The DOT was defined as the number of 24-hour periods between start and end of antibiotic treatment. The number of antibiotic-free days in the first 28 days after inclusion were recorded (including antibiotic days on subsequent nursing wards). Patients were followed for one year after entering the study, allowing assessment of 28-day and 1-year mortality.
Secondary outcomes included length of stay in hospital and ICU. In both groups CRP-levels were analyzed until 28 days after inclusion as an additional safety measure. Antibiotic costs were compared for both groups. The total direct costs of antibiotic treatment per patient were calculated by multiplying the total amounts of all antibiotics used with the lowest Dutch list price.[28] This Dutch

National Health Care Institute website reports the lowest and highest pharmacy purchase prices including 6% VAT for all registered drugs.

Patient safety

The SAPS-trial was supervised by an independent Data Safety Monitoring Board that was neither involved in the design and conduct of the trial, nor in the recruitment of patients. The DSMB concluded after the interim analysis (750 patients included) that the trial could be continued.

Statistical analysis

The power calculation based on an expected mortality of 28% and a non-inferiority margin of 8%. This was based on previous trials, such as the PRORATA-study, which had a crude mortality rate of 26.2% and a non-inferiority margin of 10%.[17] With a significance á-level of 5.0 % and a power of 90%, 1558 evaluable patients needed to be included.

Baseline characteristics and outcomes were compared with a t-test or Mann-Whitney test for continuous outcomes, chi-square for nominal outcomes and a log-rank test to compare Kaplan Meier survival curves. All tests were two-sided. All analyses were performed on SPSS 20 (IBM software).

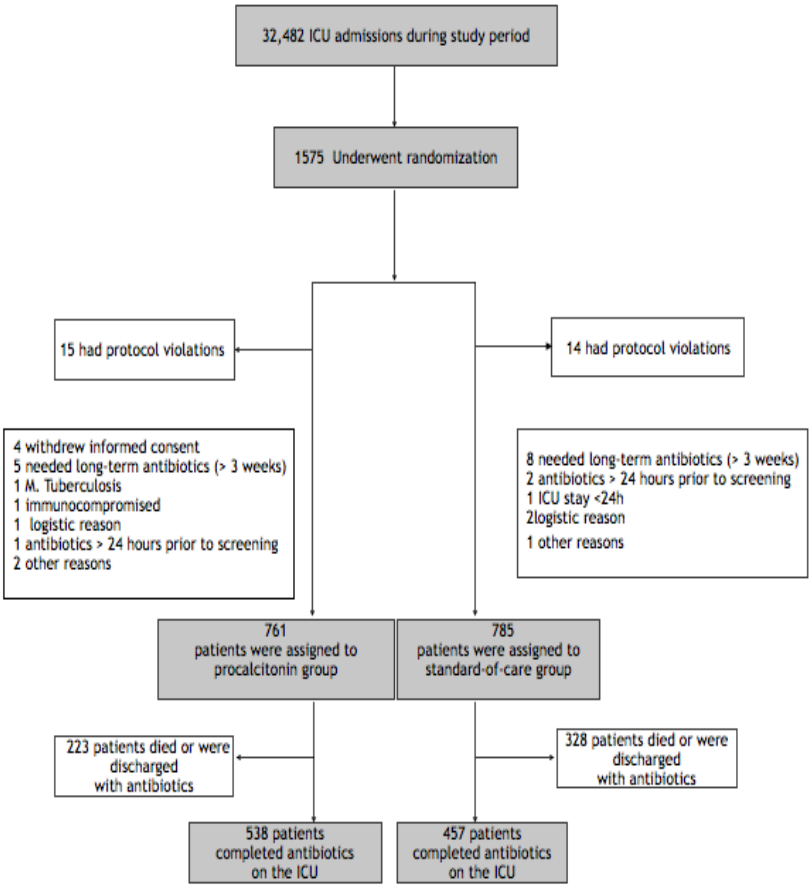

Figure 1: Trial profile

Results

Trial population

During the study period 32,482 patients were admitted to the 15 participating ICUs. Details are provided in supplementary material. Of these patients, 1575 were enrolled, including 29 patients who subsequently withdrew from the study or because of major protocol violations, which resulted in a study population of 1546 patients; 761 in the PCT assisted group and 785 in the standard-of-care group (Fig. 1). Baseline characteristics of the 1546 patients were similar between the two groups (Table 1).

Adherence to the PCT-guidance versus standard of care

A total of 223/761 patients in the PCT-group (29.3 %) had died or were discharged from the ICU before reaching one of the two stopping rules. Although these patients were not given the advice to discontinue their antibiotic treatment, they were analyzed as part of the PCT study arm (intention-to-treat principle). The remaining patients (n=538, 70.7%) reached the PCT-threshold. The adherence to these stopping advices was as follows: in 306/538 (56.9%) of the patients the antibiotics were stopped within 24 hours and in 380/538 (70.6%) within 48 hours after the stopping threshold was reached. Among the reasons why intensivists decided to continue antibiotics in patients who reached the stopping rule, concern about stopping antibiotics (6.9%) was most frequently encountered (table 3, supplementary material). In the standard-of-care group in only 457/785 (58.2%) of the patients the antibiotics were stopped before ICU discharge.

Primary Outcome

Duration of antibiotic treatment and defined daily doses of antibiotics

In the study population of 1546 patients the median DOT in the first 28 days was 5 days (IQR 3-8 days) in the PCT-guided patient group versus 7 days (IQR 4-10 days) in the standard-of-care group (P<0.001). The median antibiotic-free days within the first 28 days after randomization was 19 (IQR 10-23 days) in the PCT-guided group versus 16 days (IQR 6-16 days) in the standard-of-care group (P<0.001). The median consumption of antibiotics, expressed as DDDs, was 7.5 DDDs (IQR 4.0-12.7) in the PCT-guided group versus 9.3 DDDs (IQR 5.0-16.6) in the standard-of-care group (P<0.001).

Mortality

The Kaplan-Meier survival curves of both groups are shown in Fig. 2. At 28 days after randomization 149/761 (19.6%) patients had died in the PCT-guided group versus 196/785 (25.0%) in the standard-of-care group (P=0.006). One year after randomization this difference remained with 265/761 (34.8%) deaths in the PCT-guided group versus 321/785 (40.9%) in the standard-of-care group (log-rank test P=0.006)

Table 1 Characteristics of the Patients at Baseline		
Characteristic	**Procalcitonin group (N = 761)**	**Standard-of-care group (N = 785)**
Age —yr	65 (54 - 75)	65 (57 - 75)
Male sex—no. (%)	466 (61.2)	470 (59.8)
Severity of illness		
APACHE IV score	72 (51.5 - 92)	71 (54 - 95)
sepsis or severe sepsis —no. (%)	627 (82.4)	635 (80.9)
septic shock —no. (%)	137 (18.0)	151 (19.2)
SOFA-score ¶	7 (4-10)	7 (5 - 10)
respiratory	3 (2 - 3)	3 (2 - 3)
cardiovascular	3 (0 - 4)	3 (0 - 4)
renal	0 (0 - 1)	0 (0 - 2)
hepatic	0 (0 - 1)	0 (0 - 1)
neurologic	0 (0 - 2)	0 (0 - 2)
coagulation	0 (0 - 1)	0 (0 - 1)
Acquisition of infection		
Community-acquired —no. (%)	391 (51.4)	400 (51.0)
Hospital acquired —no. (%)	190 (25.0)	187 (23.8)
ICU-acquired —no. (%)	180 (23.7)	198 (25.2)
Presumed infection site		
pulmonary —no. (%)	486 (63.8)	492 (62.7)
CNS —no. (%)	27 (3.5)	29 (3.7)
Skin and soft tissue —no. (%)	12 (1.6)	23 (2.9)
Catheter-related infection —no. (%)	7 (1.0)	9 (1.1)
Intra-abdominal infection —no. (%)	96 (12.6)	122 (15.5)
Urinary tract infection —no. (%)	25 (3.3)	22 (2.8)
ENT —no. (%)	7 (1.0)	6 (0.8)
Blood stream infection —no. (%)	3 (0.4)	4 (0.5)
Unknown focus —no. (%)	98 (12.9)	78 (9.9)
Infection and inflammation		
Procalcitonin (µg/L)	2.0 (0.38 - 14.9)	-
C-reactive protein (mg/L)	197.5 (97 - 304)	204 (102 - 307)
Leukocytes (10E9/L)	14.9 (10.7 - 21.4)	15.0 (10.4 - 21.2)
Temperature (°Celsius)	38.0 (37.4 -38.8)	38.0 (37.3 - 38.7)

Treatment in first 24 hours		
Mechanical Ventilation —no. (%)	619 (81.3)	628 (80.0)
Renal replacement in first 24 hours —no. (%)	72 (9.5)	86 (11.0)
Inotropic/vasopressor support —no. (%)	731 (96.0)	751 (95.7)
SDD —no. (%)	399 (52.4)	421 (53.6)
corticosteroids —no. (%)	412 (54.1)	420 (53.5)

Data are median (IQR) or n (%). No substantial diff erences were noted between the two groups. APACHE IV=Acute and Chronic Health Evaluation IV score.27 SOFA=Sequential Organ Failure Assessment score. ICU=intensive care unit.
*ENT=an infectious focus in ear-nose-throat area. NA=not applicable. *SOFA contains six subscores (respiratory, cardiovascular, renal, hepatic [liver], neurological, and coagulation), each subscore can be attributed 0–4 points depending on the extent of organ dysfunction; the original SOFA score was used, including the mean arterial pressure of <70 mm Hg to obtain 1 point for cardiovascular failure.*

Secondary Outcomes

Recurrent infection

A total of 142/761 (18.2%) patients in the PCT-guided group received an additional course of systemic antibiotics within the first 28 days of randomization versus 113/785 (14.4%) in the standard-of-care group (P=0.10). These additional antibiotics were given after a median interval of 4 days (IQR 1-8 days) in the PCT-guided group versus 4 days (IQR 2-8) in the standard-of-care group (P=0.86). In the PCT-guided group in 38/761 (4.9%) of these instances a second course of antibiotic treatment was given for a reinfection that was considered to involve the same pathogen and the same organ, versus 23/785 (2.9%) in the standard-of-care group (P=0.05). When asked if the “reinfection" was caused by an overly short initial course of antibiotics, physicians answered this affirmatively for 16/1546 (1%) (See supplementary material Table 3).

For both study groups the CRP-levels showed no difference for day 1 through 28 (Fig. 3), even without Bonferroni correction for multiple testing.

Length of stay

The median length of stay on the ICU was 8 days in both groups (IQR for PCT 4-18 days and for the standard-of-care 4-17 days, P=0.63). The median length of stay in the hospital for both groups was 21 days (IQR for the PCT-guided group 12-40 days and 11-38 days for the standard-of-care, P = 0.53) (Table 2).

Antibiotic costs

The median costs for the first course of antibiotics were €107 in the PCT group (IQR €51-231) versus €128 in the standard-of-care group (IQR €66-274) (Table 2). The cumulative estimated cost for the first course of antibiotics in the PCT arm was €150,200 versus €181,700 in the standard-of-care group

(P <0.001). These cost savings should be balanced against the costs of 5425 PCT measurements that were performed in the intervention arm.

Table 2 Primary and secondary outcome measures

Variable	Procalcitonin group (N = 761)	Standard-of-care group (N = 785)	P-value
Antibiotic consumption			
DDDs in first 28 days	7.5 (4 - 12.7)	9.3 (5.0 - 16.6)	<0.001
DOT (days)	5 (3 - 8)	7 (4-10)	<0.001
Antibiotic free days in first 28 days	19 (10-23)	16 (6 - 21)	<0.001
Mortality			
28-day mortality (%)	149 (19.6)	196 (25.0)	0.006
1-year mortality (%)	265 (34.8)	321 (40.9)	0.006
Adverse events			
reinfection	38	23	0.43
repeated course of antibiotics	142	113	0.10
time (days) between stop and reinstitution of antibiotics	4 (1-8)	4 (2-8)	0.86
Costs			
Total Cumulative costs antibiotics (€)	€150235	€181731	<0.001
Median cumulative costs antibiotics per patient (€)	107 (51 - 231)	129 (66 - 274)	<0.001
Length of stay (LOS)			
LOS on the ICU	8 (4-18)	8 (4-17)	0.63
LOS in hospital	21 (12-40)	21 (11-38)	0.53

Data are median (IQR), n (%), or mean (95% CI). Between-group absolute diff erences were calculated using the mean values, percentage diff erences, and 95% CIs. NA=not applicable.

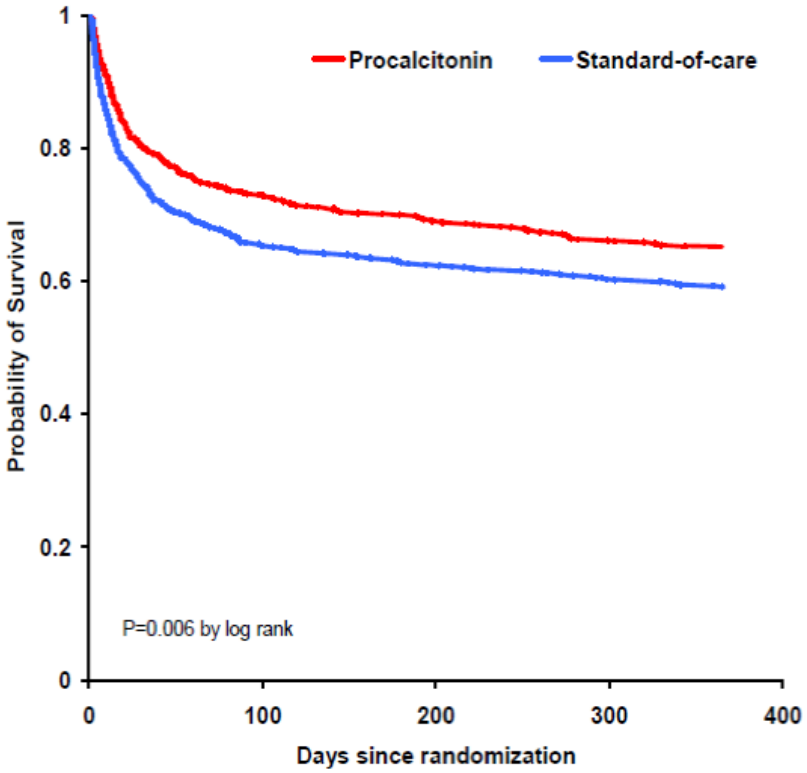

Figure 2: Probability of survival from randomization through day 365

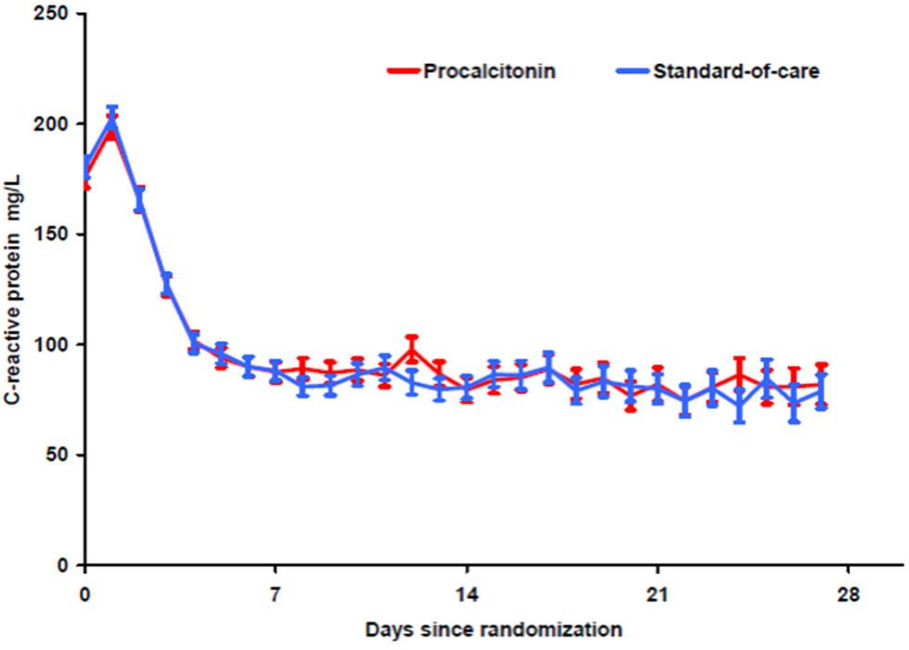

Figure 3: Serial measurements of CRP in both study groups.

Discussion

SAPS was a large prospective randomized trial which examined the addition of PCT-measurements to assist intensivists in the timely recognition of resolution of bacterial infection. We observed a clear reduction of antibiotic treatment from 7 days in the standard-of-care group to 5 days in the PCT-guided patient group. The earlier discontinuation of antibiotics was not associated with more subsequent antibiotic prescriptions or higher CRP-levels in the PCT-guided patients. Furthermore, this reduction proved to be non-inferior in terms of mortality and was even accompanied by a modest decrease in mortality in the PCT-group.

The reduction in antibiotic treatment duration which was achieved with PCT-guidance also constitutes a relevant decrease in the volume of prescribed antibiotics on ICUs from 9.3 DDDs in the standard-of-care group to 7.5 DDDs in the PCT-group. This corresponds to a relative reduction in antibiotic consumption of 19%. In the PCT-guided group 539/761 patients (70%) reached one of the PCT-stopping rules while still on the ICU and in 50% of these patients, antibiotics were discontinued within 24h. The close similarity of the two CRP-curves of also suggests that the earlier discontinuation in the PCT-guided group did not result in a higher rate of reinfection.

The total reduction in antibiotic costs using PCT-guidance was €31,500 or €33 (mean) per patient. In our study approximately 7 PCT-measurements were performed per patient. Therefore, the reduction in antibiotic costs will only outweigh the costs of additional PCT-measurements if PCT would cost less than approximately €5 per measurement. In other settings this might differ, but PCT may offer much more important benefits than only reduction of antibiotic costs.

Previous studies have addressed the possibility to stop antibiotic treatment based upon a PCT-guided strategy in the critically ill patient.[14-20] A small proof of principle study found that PCT was able to decrease antibiotic treatment in severe sepsis and septic shock.[14] This strategy was confirmed in two small ICU-studies, but none was powered for mortality.[16,18] The French PRORATA-trial, however, was larger and aimed to demonstrate efficacy as well as safety.[17] In this study, PCT-guidance led to a reduction of 23% in antibiotic exposure and 2.7 more antibiotic-free days. Unfortunately, the 60-day mortality was 3.8% higher in the PCT-guided group. Therefore, some debate remained whether PCT can safely reduce antibiotic duration in critically ill patients. This debate was fueled by the recent ProGuard study, which showed no significant reduction in DOT, antibiotic-free days and overall antibiotic exposure.[20] However this trial used only an absolute stopping rule also with a stricter PCT-threshold of 0.1 ug/L. Furthermore, they designed the study with a size to detect - a rather ambitious - reduction of DOT of at least 3.75 days. Although a reduction of two days was achieved, it was not statistically significant.Our study shows that reduction in antibiotic exposure can be achieved without

an increase in mortality, even in a context of low background usage of antibiotics in critically ill patients. Lowering the antibiotic exposure might have a beneficial impact on emergence of resistance. However, prophylactic use of antibiotics was not evaluated in this study and such patients were not considered eligible. This is of importance because some of the participating ICUs (n=9/15) routinely used SDD. Antibiotics given as part of the SDD strategy were only counted if the patient was considered having an infection. Patients on SDD not having an infection were not eligible.

Our study was conceived to include a heterogeneous ICU patient population in a real life setting, focusing only on the additional value of PCT in responsibly discontinuing antibiotic treatment. This study is the largest PCT-study in the intensive care setting so far, with over 1500 patients. To emphasize the importance of safety, our study set the non-inferiority margin at 8% and estimated the sample size with a power of 90% instead of 80%. Ideally, if a lower non-inferiority margin such as 4% would be desirable, this would have required over 5,500 patients. An unexpected finding was the observed lower mortality in the PCT-group. We hypothesized that the reduced mortality in the PCT-group was the result of an earlier focus on an alternative diagnosis if PCT-levels were low. Alternatively, persistently high levels of PCT might suggest the need to critically review antimicrobial treatment.[30]

Several limitations of our study should be mentioned. First, approximately 30% of the patients randomized to the PCT-guided strategy were discharged from the ICU before the algorithm recommended to stop the antibiotics. This was higher than the 20% we had anticipated when conceiving this study. Further reduction of antibiotics might have been achieved if PCT-guidance would have been continued on the wards. However, this study was designed for patients during ICU stay and continuation of the protocol on the ward was not deemed possible for logistic reasons.
Second, certain patients were excluded, e.g. immunocompromised patients or patients treated for illnesses requiring prolonged antibiotic treatment. These exclusions were chosen for safety and pragmatic reasons. Advising to stop antibiotics in these patients would often be ignored and therefore considered not useful. However, we are not aware of any principal reasons why measuring PCT would not be useful in reducing DOT in these infections as well, albeit on longer time scales or with other thresholds. Particularly in these patient groups earlier termination of antibiotic treatment might impact on the overall consumption of antibiotics.
Third, clinicians were aware of the study group assignments and not all cointerventions that might have been affected by this knowledge could be assessed.

In conclusion, this large and pragmatic study shows that a considerable reduction in antibiotic treatment duration and consumption can be achieved by the addition of a PCT-guided algorithm to

clinical judgment. This reduction of antibiotic duration was achieved in a setting with an already low background consumption of antibiotics without an increase in mortality.

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