Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial

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Summary

Background **In critically ill patients, antibiotic therapy is of great importance but long duration of treatment is associated with the development of antimicrobial resistance. Procalcitonin is a marker used to guide antibacterial therapy and reduce its duration, but data about safety of this reduction are scarce. We assessed the efficacy and safety of procalcitonin-guided antibiotic treatment in patients in intensive care units (ICUs) in a health-care system with a comparatively low use of antibiotics.**

Methods **We did a prospective, multicentre, randomised, controlled, open-label intervention trial in 15 hospitals in the Netherlands. Critically ill patients aged at least 18 years, admitted to the ICU, and who received their first dose of antibiotics no longer than 24 h before inclusion in the study for an assumed or proven infection were eligible to participate. Patients who received antibiotics for presumed infection were randomly assigned (1:1), using a computer-generated list, and stratified (according to treatment centre, whether infection was acquired before or during ICU stay, and dependent on severity of infection [ie, sepsis, severe sepsis, or septic shock]) to receive either procalcitonin-guided or standard-of-care antibiotic discontinuation. Both patients and investigators were aware of group assignment. In the procalcitonin-guided group, a non-binding advice to discontinue antibiotics was provided if procalcitonin concentration had decreased by 80% or more of its peak value or to 0·5 μg/L or lower. In the standard-of-care group, patients were treated according to local antibiotic protocols. Primary endpoints were antibiotic daily defined doses and duration of antibiotic treatment. All analyses were done by intention to treat. Mortality analyses were completed for all patients (intention to treat) and for patients in whom antibiotics were stopped while being on the ICU (per-protocol analysis). Safety endpoints were reinstitution of antibiotics and recurrent inflammation measured by C-reactive protein concentrations and they were measured in the population adhering to the stopping rules (per-protocol analysis). The study is registered with ClinicalTrials.gov, number NCT01139489, and was completed in August, 2014.**

Findings **Between Sept 18, 2009, and July 1, 2013, 1575 of the 4507 patients assessed for eligibility were randomly assigned to the procalcitonin-guided group (761) or to standard-of-care (785). In 538 patients (71%) in the procalcitonin-guided group antibiotics were discontinued in the ICU. Median consumption of antibiotics was 7·5 daily defined doses (IQR 4·0–12·7) in the procalcitonin-guided group versus 9·3 daily defined doses (5·0–16·6) in the standard-of-care group (between-group absolute difference 2·69, 95% CI 1·26–4·12, p<0·0001). Median duration of treatment was 5 days (3–9) in the procalcitonin-guided group and 7 days (4–11) in the standard-of-care group (between-group absolute difference 1·22, 0·65–1·78, p<0·0001). Mortality at 28 days was 149 (20%) of 761 patients in the procalcitonin-guided group and 196 (25%) of 785 patients in the standard-of-care group (between-group absolute difference 5·4%, 95% CI 1·2–9·5, p=0·0122) according to the intention-to-treat analysis, and 107 (20%) of 538 patients in the procalcitonin-guided group versus 121 (27%) of 457 patients in the standard-of-care group (between-group absolute difference 6·6%, 1·3–11·9, p=0·0154) in the per-protocol analysis. 1-year mortality in the per-protocol analysis was 191 (36%) of 538 patients in the procalcitonin-guided and 196 (43%) of 457 patients in the standard-of-care groups (between-group absolute difference 7·4, 1·3–13·8, p=0·0188).**

Interpretation **Procalcitonin guidance stimulates reduction of duration of treatment and daily defined doses in critically ill patients with a presumed bacterial infection. This reduction was associated with a significant decrease in mortality. Procalcitonin concentrations might help physicians in deciding whether or not the presumed infection is truly bacterial, leading to more adequate diagnosis and treatment, the cornerstones of antibiotic stewardship.**

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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 long antimicrobial treatment is undesirable because of increasing antibiotic resistance.[1] However, with

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Research in context

Evidence before this study

The decision to discontinue antibiotics in patients in intensive care units (ICUs) can be partly based on improvements offered by a biomarker such as C-reactive protein. The biomarker procalcitonin displays a stronger and faster modulation for severity of bacterial infection than does C-reactive protein. Thus a satisfactory drop in procalcitonin concentrations might help to discontinue antibiotic use in a more timely fashion. Despite its widespread availability, the procalcitonin assay is sparsely used in many countries. The reluctance for early discontinuation of antibiotics is based on doubts as to whether this practice is safe. We searched PubMed, Embase, and ClinicalTrials.gov for articles published between Jan 1, 1990, and Aug 31, 2015, using the search terms "procalcitonin", "infection", and "intensive care unit". Two trials with a stopping criterion based on procalcitonin each randomly assigned more than 100 patients. The largest of these two trials was the PRORATA trial, which randomly assigned 631 patients and used a stopping criterion of procalcitonin at 20% or lower of its peak value or procalcitonin at 0·5 μg/L or lower. This trial showed a significant reduction in antibiotic treatment duration, albeit in a context of relatively long duration of antibiotic treatment. However, since the PRORATA trial reported a non-significant, but higher, 60-day mortality in its procalcitonin arm, safety concerns were raised regarding the reliability of procalcitonin.

Added value of this study

The Stop Antibiotics on Procalcitonin guidance Study (SAPS) was conceived as a pragmatic trial with fewer exclusion criteria than previous trials, with mortality used as a safety endpoint. SAPS used the same procalcitonin criterion as PRORATA as non-binding advice. The SAPS trial showed that procalcitonin monitoring coupled with a non-binding advice to consider stopping using antibiotics reduced duration of antibiotic treatment. The procalcitonin-guided group had a lower mortality than the standard-of-care group.

Implications of all available evidence

The timecourse of procalcitonin provides information on the resolution of severe bacterial infection. All evidence indicates that procalcitonin-guided treatment can reduce antibiotic treatment duration. Even in the context of a comparatively short antibiotic treatment duration this is feasible.

Addition of procalcitonin measurements to the current diagnostic arsenal will help clinicians reduce antibiotic treatment duration. Whether the procalcitonin assay will also be cost-effective is not clear.

critically ill patients, physicians might be reluctant to shorten the duration of antimicrobial treatment.[2] Therefore, specific markers for resolution of infection might assist physicians in making antibiotic therapy decisions on an individual basis. Regularly used markers for this purpose are the leucocyte count and C-reactive protein (CRP). However, procalcitonin has been advocated as a marker with a better specificity and sensitivity than CRP for follow-up of severe bacterial infections.[3–10]

Findings from several studies[11–20] have shown that procalcitonin guidance can reduce the duration of antibiotic treatment for patients with bacterial infection, but the safety of such protocols has not been firmly established.[7,21,22] Additionally, most of these intensive care unit (ICU) trials were done in countries with a high baseline consumption of antibiotics. In the Netherlands the antibiotic consumption per person is quite low. By contrast, in terms of defined daily dosages per 1000 patient days, antibiotic consumption in France, Greece, the UK, and the USA is 1·5–3·3 times higher.[23]

The objective of this trial was to assess the efficacy and safety of procalcitonin-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 procalcitonin guidance to the standard of care could reduce the duration of antibiotic treatment and thus the amount of antibiotics given, without increasing mortality or recurrent infections.

Methods

Study design

The Stop Antibiotics on Procalcitonin guidance Study (SAPS)[24] was a prospective, multicentre, randomised, open-label intervention trial in patients admitted to the ICU of three university medical centres and 12 teaching hospitals in the Netherlands. This study was approved for all centres by the ethics committee of the VU University Medical Center (Amsterdam, Netherlands) and is in full compliance with the Helsinki Declaration. The study protocol is available online.[24]

Participants

Eligible patients had to be at least 18 years of age, be admitted to the ICU, and have received their first dose of antibiotics no longer than 24 h before inclusion to the trial for an assumed or proven infection. Patients were excluded in cases of systemic antibiotics as prophylaxis only, antibiotics solely as part of selective decontamination of the digestive tract, prolonged therapy (eg, endocarditis), expected ICU stay of less than 24 h, severe immunosuppression, severe infections (due to viruses, parasites, or *Mycobacterium tuberculosis*), and moribund patients. Patients who received corticosteroids were not excluded. Patients could only participate once in this trial. All patients or their legal representatives provided written informed consent.

Randomisation and masking

Patients were randomly assigned (in a 1:1 ratio) to receive either treatment according to procalcitonin guidance (procalcitonin-guided group) or standard of care (standard-of-care group). Randomisation was done centrally by use of a computer-generated list produced by an independent research organisation (the Julius Centre for Human Research, Utrecht, Netherlands). Randomisation was stratified according to treatment centre, whether the infection was acquired before or during ICU stay, and severity of infection (ie, sepsis, severe sepsis, or septic shock).[25] Patients and investigators were aware of treatment assignment.

Procedures

For patients randomly assigned to the procalcitonin-guided group, once a day measurements of procalcitonin concentrations were taken and made available to the attending physicians, including a baseline measurement as close to initiation of antibiotics as possible, at least within 24 h. Procalcitonin concentration was not measured in the standard-of-care group. Except for the procalcitonin measurements, all monitoring was similar between the procalcitonin-guided and the standard-of-care groups. Procalcitonin was measured on analysers available at the site (Kryptor machine [Thermo Fisher Scientific, Waltham, MA, USA] or a suitable Vidas [Marcy-l'Étoile, France] or Roche [Basel, Switzerland] immunoanalyser) that were maintained according to national quality standards. In the procalcitonin-guided group, procalcitonin concentration was measured until ICU discharge or until 3 days after systemic antibiotics were stopped. The study protocol advised to stop the prescribed antibiotics if procalcitonin concentration had decreased by 80% or more of its peak value (relative stopping threshold), or when it reached a value of 0·5 μg/L or lower (absolute stopping threshold). The attending physician was free to decide whether to continue antibiotic treatment in patients who had reached these thresholds. Reasons for non-adherence were recorded. Antibiotics in the standard-of-care group were stopped according to local or national guidelines and according to the discretion of attending physicians. The number of antibiotic-free days in the first 28 days after study inclusion were recorded (including antibiotic days on subsequent nursing wards). In both groups CRP concentrations were analysed once a day until 28 days after inclusion as an additional safety measure. Patients were followed up for 1 year after entering the study, allowing assessment of 28-day and 1-year mortality.

Outcomes

The primary outcome was the consumption of antibiotics (expressed as defined daily doses) and duration of antibiotic treatment (defined as the number of 24 h periods between start and end of antibiotic treatment) in in the two groups for all randomised patients who were not excluded (the modified intention-to-treat population). For every participant, the total amount of antibiotics given during the study period was assessed on the basis of individual drug administration records. Our definition of defined daily doses accords with the recommendations of WHO (appendix).[26] The route of administration was incorporated in the daily dose calculations. The primary safety outcome was mortality at 28 days and 1 year, assessed in the modified intention-to-treat population and the per-protocol population.

See **Online** for appendix

Secondary outcomes were the percentage of patients who had a recurrent infection, length of stay in hospital and ICU, costs of antibiotics, and costs of procalcitonin tests. 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 according to the Dutch National Health Care Institute, which reports the lowest and highest pharmacy purchase prices including 6% tax for all registered drugs.

For the **Dutch National Health Care Institute anitbiotic price list** see http://www.medicijnkosten.nl

The SAPS trial was supervised by an independent Data Safety Monitoring Board (consisting of an intensivist, statistician, and a pulmonologist), which was not involved in the study design, completion of the trial, or recruitment of patients. The Data Safety Monitoring Board concluded after the interim analysis (after the first 750 patients had been included; about 2 years after start of the study) that the trial could be continued.

Statistical analysis

The goal of this trial was to establish whether the procalcitonin-guided strategy was superior in terms of antibiotic use and duration, length of stay in the ICU, and cost-effectiveness and to show non-inferiority of the procalcitonin-guided antibiotic management regarding 28-day mortality and recurrent infections. For the superiority primary outcome, the power calculation was based on an estimated 15% reduction in duration of antibiotic treatment. We assumed a mean duration of antibiotic treatment of 8 days and an SD of 6 days.[17] With an α of 0·05 and a β of 0·1 we would need 526 patients in each group. However, some patients would be discharged from the ICU before reaching the stopping rules. These patients would not be stopped according to the procalcitonin guidelines. We assumed that 20% of patients were going to be discharged before the stopping rule was enacted. Hence, we needed 631 patients per study group.

For the **Netherlands national quality standards** see http://www.cckl.nl/index.php?pagina=35

We did not want the intervention to lead to excess mortality in the procalcitonin-guided group. In view of a 28% mortality in a previously published study,[17] for the procalcitonin-guided group to be non-inferior to standard of care in terms of safety, the non-inferiority margin for procalcitonin-guided treatment regarding 28-day mortality was set to 8%. This margin would lead to a mortality of 28% in the standard-of-care group versus

30% in the procalcitonin-guided group. On the basis of these assumptions and with an α of 0·025 and a β of 0·1 we would need 663 patients in each group for 90% power that the one-sided 97·5% CI excludes a difference in the standard-of-care group of more than 8%. On the basis of these two calculations the study needed at least 1326 patients.

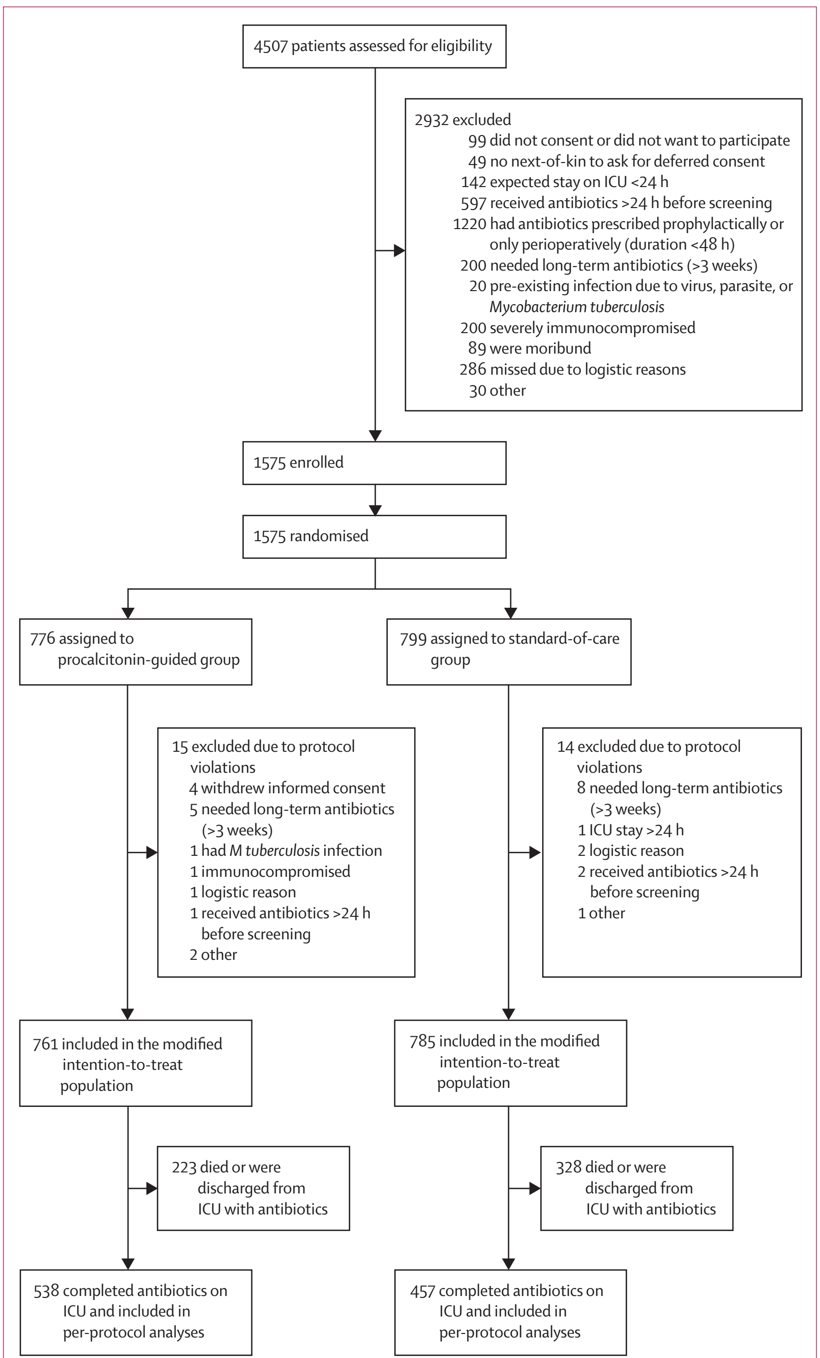

***Figure 1:* Trial profile**
ICU=intensive care unit

We compared baseline characteristics and outcomes with a *t* test or Mann-Whitney *U* test for continuous outcomes, χ^2 test for nominal outcomes, and a log-rank test to compare Kaplan-Meier survival curves. We calculated a cumulative event estimate by a hazard ratio (HR; 95% CI). All tests were two-sided, with p values of 0·05 deemed statistically significant. All analyses were completed using SPSS, version 20 (IBM software). The study is registered with ClinicalTrials.gov, NCT01139489.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
From Sept 18, 2009, to July 1, 2013, 4507 patients were screened in the 15 participating ICUs. Of these, 1575 patients (35%) were enrolled including 29 patients who (after being randomly assigned to a group) withdrew from the study or had major protocol violations, resulting in the modified intention-to-treat population of 1546 patients (761 in the procalcitonin-guided group and 785 in the standard-of-care group; figure 1). 223 (29%) of 761 patients in the procalcitonin-guided group had died or were discharged from the ICU before antibiotics were stopped. Although these patients did not discontinue their antibiotic treatment, they were included in the analyses as part of the procalcitonin-guided group (intention-to-treat principle). 761 patients in the procalcitonin-guided group and 785 patients in the standard-of-care group were included in the modified intention-to-treat analyses. Baseline characteristics of the 1546 patients were similar between the two groups (table 1).

In the study population of 1546 patients, median consumption of antibiotics was 7·5 defined daily doses (IQR 4·0–12·8) in the procalcitonin-guided group versus 9·3 defined daily doses (5·0–16·5) in the standard-of-care group (between-group absolute difference 2·69, 95% CI 1·26–4·12, p<0·0001). Median duration of treatment in the first 28 days was 5·0 days (IQR 3·0–9·0) in the procalcitonin-guided group versus 7·0 days (4·0–11·0) in the standard-of-care group (between-group absolute difference 1·22, 0·65–1·78, p<0·0001). Median antibiotic-free days within the first 28 days after being randomly assigned to a treatment group was 7·0 (IQR 0·0–14·5) in the procalcitonin-guided group versus 5·0 days (0·0–13·0) in the standard-of-care group (between-group absolute difference 1·31, 0·52–2·09, p=0·0016).

At 28 days after randomisation, 149 (20%) of 761 patients had died in the procalcitonin-guided group versus 196 (25%) of 785 patients in the standard-of-care group. The between-group absolute difference was 5·4% (95% CI 1·2–9·5, p=0·012). 1 year after randomisation this difference remained with 265 deaths (35%) of 761 patients in the procalcitonin-guided group versus 321 deaths (41%) of 785 patients in the standard-of-care group (log-rank test p=0·0070). The between-group absolute difference was 6·1% (1·2–10·9, p<0·0158; HR 1·26, 1·07–1·49, p=0·0060) in the intention-to-treat analysis. The Kaplan-Meier survival curves of both groups are shown in figure 2.

The remaining 538 (71%) of 761 patients in the procalcitonin-guided and 457 (58%) of 785 patients in the standard-of-care group completed their antibiotic treatment in the ICU; these two groups were compared as per-protocol analysis. 28-day mortality in this analysis was 107 (20%) of 538 patients in the procalcitonin-guided group versus 121 (27%) of 457 patients in the standard-of-care group (between-group absolute difference 6·6%, 95% CI 1·3–11·9, p=0·0154). 1-year mortality in the per-protocol analysis was 191 (36%) of 538 patients in the procalcitonin-guided group and 196 (43%) of 457 patients in the standard-of-care group (between-group absolute difference 7·4%, 1·3–13·8, p=0·0188). The differences in various other subgroups are shown in the appendix.

In the first 28 days after being assigned to a group, 175 (23%) of 761 patients in the procalcitonin-guided group received an additional course of systemic antibiotics versus 173 (22%) of 785 patients in the standard-of-care group (intention-to-treat p=0·67). These additional antibiotics were given after a median interval of 4·0 days (IQR 2·0–8·0) in both the procalcitonin-guided and standard-of-care groups (p=0·96). In 38 (5%) of 761 patients in the procalcitonin-guided group versus 23 (3%) of 785 patients in the standard-of-care group (p=0·0492), a second course of antibiotic treatment was given for a re-infection that was proven by culture to be the same pathogen and the same organ as the original infection. When asked if the re-infection was caused by an overly short initial course of antibiotics, physicians answered affirmatively for 16 (26%) of 61 patients with a recurrent infection. The non-inferiority analysis for the reinstitution of antibiotics in the per-protocol population was 151 (28%) of 538 in the procalcitonin-guided group versus 117 (26%) of 457 in the standard-of-care group (between-group absolute difference –2·5%, 95% CI –7·9 to 3·1, p=0·39).

A stopping criterion was reached in 557 patients in the procalcitonin-guided group during their ICU stay. Adherence to this stopping advice was for 243 patients (44%) who had their antibiotic treatments stopped within 24 h and 297 patients (53%) treatments were stopped within 48 h after reaching the stopping threshold. 17 patients (3%) did not have their antibiotics stopped. Of the reasons why intensivists decided to continue antibiotics in patients who reached the stopping rule, various non-specific concerns about stopping antibiotics were mentioned (appendix).

In 38 (7%) of 557 patients, antibiotics were already discontinued before reaching either stopping rule. Of the patients in whom physicians adhered to one of the stopping rules, 126 (42%) of 297 patients were stopped because of a decrease in procalcitonin concentrations to 20% or lower of the peak value, 154 (52%) of 297 patients were stopped as the procalcitonin concentration was 0·5 µg/L or lower, and 17 (6%) of 297 patients reached both these stopping rules simultaneously. Thus both

	Procalcitonin-guided group (n=761)	Standard-of-care group (n=785)
Age (years)	65 (54–75)	65 (57–75)
Men	464 (61%)	470 (60%)
Severity of illness		
APACHE IV score[27]	72·0 (52·0– 92·0)	71·0 (55·0–95·0)
Sepsis or severe sepsis	625 (82%)	634 (81%)
Septic shock	136 (18%)	151 (19%)
SOFA score*	6·0 (3·0–9·0)	6·0 (4·0–9·0)
Respiratory	3 (2–3)	3 (2–3)
Cardiovascular	3 (0–4)	3 (0–4)
Renal	0 (0–1)	0 (0–1)
Hepatic	0 (0–0)	0 (0–0)
Neurological	0 (0–2)	0 (0–1)
Coagulation	0 (0–0)	0 (0–1)
Acquisition of infection		
Community acquired	392 (52%)	400 (51%)
Hospital acquired	189 (25%)	186 (24%)
ICU acquired	180 (24%)	199 (25%)
Presumed infection site		
Pulmonary	491 (65%)	503 (64%)
CNS	29 (4%)	30 (4%)
Skin and soft tissue	13 (2%)	23 (3%)
Catheter-related infection	8 (1%)	11 (1%)
Intra-abdominal infection	108 (14%)	129 (16%)
Urinary tract infection	27 (4%)	24 (3%)
ENT	7 (1%)	7 (1%)
Bloodstream infection	4 (1%)	4 (1%)
Unknown focus	74 (10%)	54 (7%)
Infection and inflammation		
Procalcitonin (µg/L)	1·9 (0·40–14·1)	NA
C-reactive protein (mg/L)	202·0 (99·0–306·3)	204·0 (105·5–307·5)
Leucocytes (10^9 cells per L)	14·7 (10·6–21·3)	14·9 (10·4–21·0)
Temperature (°C)	38·0 (37·4–38·8)	38·0 (37·4–38·7)
Treatment in first 24 h		
Mechanical ventilation	617 (81%)	628 (80%)
Renal replacement in first 24 h	72 (9%)	86 (11%)
Inotropic or vasopressor support	729 (96%)	751 (96%)
Selective decontamination of the digestive tract	399 (52%)	421 (54%)
Corticosteroids	412 (54%)	420 (54%)

Data are median (IQR) or n (%). No substantial differences 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.

Table 1: **Baseline characteristics of the modified intention-to-treat population**

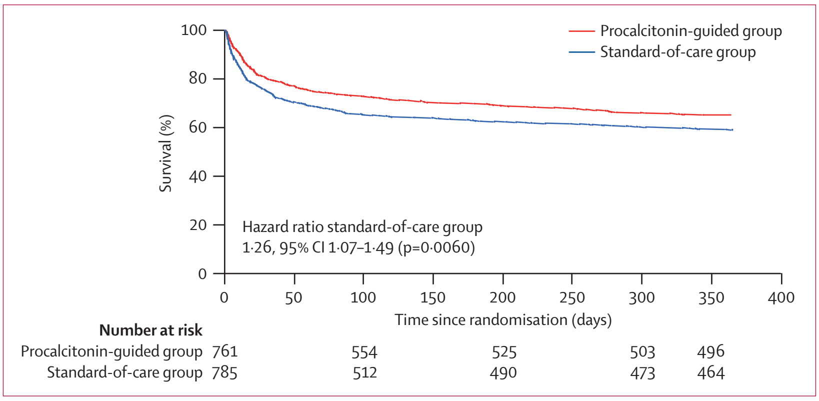

Figure 2: **Kaplan-Meier plot for probability of survival from random assignment to day 365, in the modified intention-to-treat population**

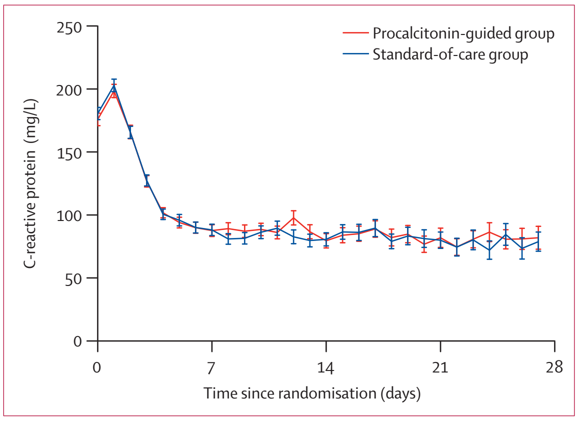

Figure 3: **Serial measurements of C-reactive protein concentrations in both study groups**
The mean values and SEs during the first 28 days after random assignment are shown. Patients discharged from the intensive care unit before day 28 were included as long as they were still admitted to the hospital.

components of the stopping rule seem to be of relevance. For both study groups the CRP concentrations showed no difference for day 1 to day 28 (figure 3), even without Bonferroni correction for multiple testing.[28] Median length of stay on the ICU was 8·5 days (IQR 5·0–17·0) in the procalcitonin-guided group versus 9·0 days (IQR 4·0–17·0) in the standard-of-care group (p=0·56; table 2). Median length of stay in the hospital was the same for both groups at 22 days (IQR 13·0–39·3 procalcitonin-guided *vs* 12·0–40·0 standard-of-care; p=0·77; table 2).

The median costs for the first course of antibiotics were €107 (IQR 51–229) in the procalcitonin-guided group versus €129 (66–273) in the standard-of-care group (p=0·0006; table 2). The cumulative estimated cost for the first course of antibiotics in the procalcitonin-guided group was €150 082 versus €181 263 in the standard-of-care group. These cost savings should be balanced against the costs of 5425 procalcitonin measurements taken in the intervention group.

Discussion

In the SAPS trial we noted a clear reduction of antibiotic treatment duration from 7 days in the standard-of-care group to 5 days in the procalcitonin-guided group. Early discontinuation of antibiotics was not associated with more subsequent antibiotic prescriptions or higher CRP concentrations in the procalcitonin-guided patients. Furthermore, this reduction was non-inferior in terms of 28-day mortality and was even accompanied by a lower mortality in the procalcitonin-guided group (19·6%) than in the standard-of-care group (25·0%).

Additionally, the reduction in antibiotic treatment duration achieved with procalcitonin guidance constitutes a relevant decrease in the volume of prescribed antibiotics on ICUs from 9·3 daily defined doses in the standard-of-care group to 7·5 daily defined doses in the procalcitonin-guided group. This decrease corresponded with a relative reduction in antibiotic consumption of 19%. The close similarity of the two CRP curves also suggests that the earlier discontinuation in the procalcitonin-guided group did not result in a higher rate of re-infection.

The total reduction in antibiotic costs using procalcitonin guidance was a mean of €34 per patient. In our study about a mean of seven procalcitonin measurements were taken per patient. Therefore, the reduction in antibiotic costs will only outweigh the costs of additional procalcitonin measurements if procalcitonin tests costs less than about €4 per measurement. In other settings this value might differ, but procalcitonin monitoring could offer many more important benefits than only reduction of antibiotic costs.

Reduction in 28-day mortality and 1-year mortality associated with the procalcitonin strategy was unexpected as this study was aiming for non-inferiority. If physicians suspect that a patient has a bacterial infection they will (pre-emptively) start antibiotics. If procalcitonin concentration is high, as expected, then these physicians are reassured about their initial diagnosis. However, if procalcitonin concentrations are low, it makes severe bacterial infection improbable and the initial diagnosis is questioned. Physicians then need to reconsider their diagnosis at an earlier stage. Therefore, knowledge of procalcitonin concentrations might lead to earlier and more adequate diagnoses and treatments, reducing mortality. Furthermore, antibiotics that are unnecessary might lead to adverse effects without benefits (eg, antibiotic resistance, selection of resilient pathogens such as clostridium, and drug reactions). Such adverse effects of antibiotic treatment have been previously noted.[29,30] In a de-escalation study[29] in ICU patients with severe sepsis and septic shock, the odds for mortality were reduced in patients in whom antibiotics were stopped or specifically aimed at the pathogens. The authors[29] proposed that the reduction of toxic effects of antibiotics might have contributed to the survival benefit—eg, low nephrotoxicity of some classes of antibiotics. The percentages of patients

	Procalcitonin-guided group (n=761)	Standard-of-care group (n=785)	Between-group absolute difference in means (95% CI)	p value
Antibiotic consumption (days)				
Daily defined doses in first 28 days	7·5 (4·0 to 12·8)	9·3 (5·0 to 16·5)	2·69 (1·26 to 4·12)	<0·0001
Duration of treatment	5·0 (3·0 to 9·0)	7·0 (4·0 to 11·0)	1·22 (0·65 to 1·78)	<0·0001
Antibiotic-free days in first 28 days	7·0 (0·0 to 14·5)	5·0 (0 to 13·0)	1·31 (0·52 to 2·09)	0·0016
Mortality (%)				
28-day mortality	149 (19·6%)	196 (25·0%)	5·4% (1·2 to 9·5)	0·0122
1-year mortality	265 (34·8%)	321 (40·9%)	6·1% (1·2 to 10·9)	0·0158
Adverse events				
Reinfection	38 (5·0)	23 (2·9)	–2·1% (–4·1 to -0·1)	0·0492
Repeated course of antibiotics	175 (23·0)	173 (22·0)	–1·0% (–5·1 to 3·2)	0·67
Time (days) between stop and reinstitution of antibiotics	4·0 (2·0 to 8·0)	4·0 (2·0 to 8·0)	–0·22 (–1·31 to 0·88)	0·96
Costs				
Total cumulative costs of antibiotics	€150 082	€181 263	NA	NA
Median cumulative costs antibiotics per patient	€107 (51 to 229)	€129 (66 to 273)	€33·6 (2·5 to 64·8)	0·0006
Length of stay (days)				
On the intensive care unit	8·5 (5·0 to 17·0)	9·0 (4·0 to 17·0)	–0·21 (–0·92 to 1·60)	0·56
In hospital	22·0 (13·0 to 39·3)	22·0 (12·0 to 40·0)	0·39 (–2·69 to 3·46)	0·77

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

Table 2: **Primary and secondary outcome measures**

who received a repeated course of antibiotics were similar between the groups (23% in the procalcitonin guided *vs* 22% in the standard of care; table 2). However, the cases considered to be re-infections by physicians were much lower in the standard-of-care group (3%) than in the procalcitonin-guided group (5%; table 2). Although the difference in re-infections was significant (table 2), the numbers suggest under-reporting, given the much higher reinstitution rate of antibiotics. Additionally, physicians might have been biased to considering re-infection earlier in patients in whom procalcitonin guidance contributed to the decision to discontinue antibiotics. The adequacy of the antibiotics, a more timely recognition of alternative diagnoses, and lower toxicity of antibiotics might all account for the lower mortality in our procalcitonin-guided study group than in the standard-of-care group.[30] However, this remains speculative and bias or a type I error might still play a part.

Previous studies[14–20] have addressed the possibility to stop antibiotic treatment based on a procalcitonin-guided strategy in critically ill patients. A small proof-of-principle study reported that a procalcitonin strategy was able to decrease antibiotic treatment for severe sepsis and septic shock.[14] This strategy was supported in two small ICU studies, but neither were powered for mortality.[16,18] The French PRORATA trial,[17] however, was larger and aimed to show efficacy and safety. In that study,[17] procalcitonin guidance led to a reduction of 23% in antibiotic exposure and 2·7 additional antibiotic-free days. Unfortunately, the 60-day mortality was 3·8% higher in the procalcitonin-guided group than in the control group.[17] Therefore, some debate remains whether procalcitonin guidance can safely reduce antibiotic duration in critically ill patients. This debate was fuelled by the 2014 ProGuard study,[20] which showed no significant reduction in duration of treatment, antibiotic-free days, or overall antibiotic exposure between a standard-of-care group versus a procalcitonin-guided group. However, this trial[20] used only an absolute stopping rule and a strict procalcitonin threshold of 0·1 μg/L. Our results show that both the absolute (ie, procalcitonin ≤0·5 μg/L) and the relative (ie, procalcitonin ≤20% of its peak value) stopping rules assisted in antibiotic discontinuation. Furthermore, the study[20] was designed with a size to detect—a rather ambitious—reduction of duration of treatment of at least 3·75 days. Although a reduction of 2 days was noted, it was not significant. Our study suggests that reduction in antibiotic exposure can be achieved without an increase in mortality, even in a context of low background use of antibiotics in critically ill patients. Lowering of the antibiotic exposure might have a beneficial effect on emergence of resistance. However, prophylactic use of antibiotics was not assessed in this study and such patients were not eligible, which is of importance because nine of the participating ICUs routinely used selective decontamination of the digestive tract. Antibiotics given as part of this decontamination strategy were only counted if the patient was considered to have an infection. Patients on selective decontamination of the digestive tract who had, or were suspected of having, an infection were not eligible for this study (appendix).

Several studies show that a well considered reduction of antibiotics, although not necessarily equal to early discontinuation, is associated with decreased mortality.[29] In patients with pulmonary infections a reduction in antibiotic use is associated with a reduction in mortality. In an individual patient meta-analysis,[30] studying 4211 patients, the mortality in the procalcitonin-guided group was 5·6% versus 6·3% in the control group. Although this difference was not significant, it corroborates our reduced mortality. Our study was conceived to include a heterogeneous ICU-patient population in a real-life setting, focusing only on the additional value of procalcitonin tests in responsible discontinuation of antibiotic treatment. To our knowledge, this is the largest procalcitonin study in the intensive-care setting so far, with more than 1500 patients included. To emphasise 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, a lower non-inferiority margin, such as 4%, would be desirable, but this margin would have required more than 5500 patients. An unexpected finding was the reduced mortality in the procalcitonin-guided group. We postulated that reduced mortality in the procalcitonin-guided group was the result of an earlier focus on an alternative diagnosis if procalcitonin concentrations were low. Alternatively, persistently high procalcitonin concentrations might suggest the need to critically review antimicrobial treatment.[31]

Several limitations of our study should be mentioned. First, about 30% of patients randomly assigned to the procalcitonin-guided strategy were discharged from the ICU before the algorithm recommended to stop antibiotic treatment. This figure was higher than the 20% we had anticipated when designing this study. Further reduction of antibiotics might have been achieved if procalcitonin guidance had 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 logistical reasons.

Second, physicians did not adhere to the stopping advice in more than half of the patients. The patients in whom antibiotic treatment was continued did differ in some baseline characteristics from those who actually stopped antibiotics (appendix). Apparently, physicians use procalcitonin concentrations to show that antibiotics can be safely stopped in stable patients. They are, however, hesitant to stop use if patients are not yet stable. Clearly, use of procalcitonin concentrations cannot convince them in such cases.[32] Whether discontinuation of antibiotics in these subjectively unstable patients would have led to increased mortality cannot be established by this study. Procalcitonin measurements can be used to support decision making in stable patients, but does not abolish proper clinical reasoning. Despite this limitation overall antibiotic consumption was reduced, indicating that especially inappropriate antibiotics were the first to be discontinued, which might turn out to be a major contributor to antibiotic stewardship.

Third, specific patients who were immunocompromised or treated for illnesses needing long durations of antibiotic treatment were excluded. These exclusions were chosen for safety and pragmatic reasons. Advice to stop antibiotic use in these patients was often ignored and therefore regarded as not useful. However, we are not aware of any reasons why measuring procalcitonin would not be useful in reducing duration of treatment in these infections too, albeit over longer timescales or with other thresholds. Particularly in these patient groups, early termination of antibiotic treatment might affect the overall consumption of antibiotics.

Fourth, clinicians were aware of the study group assignments and not all co-interventions that might have been affected by this knowledge could be assessed.

Fifth, we did not collect data for antibiotic resistance and, therefore, we are unaware of the appropriateness of the empirical antibiotic strategy. Additionally, in many patients cultures were negative or contained bacteria or fungi that were not thought of as true pathogens (eg, candida colonisation in sputum cultures). The patients who did not reach a stopping rule might be the patients for whom the initial therapy was inappropriate or inadequate. Such patients might be detected earlier in the procalcitonin-guided group than in the standard-of-care group, leading to an earlier antibiotic switch.

In conclusion, this large and pragmatic study shows that a reduction in antibiotic treatment duration and consumption can be achieved with the addition of a procalcitonin-guided algorithm to aid 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.

Contributors

EdJ, AB, JAvO, MWN, and DWdL were principal investigators of the Stop Antibiotics on Procalcitonin guidance Study (SAPS) and had full access to all of the study data and take responsibility for their integrity and the accuracy of the analysis. EdJ, JAvO, AB, MWN, and DWdL participated in the study design, supervised the study, analysed data, and drafted the manuscript. PV, LEH, BGL, TD, GCvM, YCK, HKe, MJvdE, JAS, JOS, HKr, HKi, GHK, VCvD, JvP, LB, MBO, ACR, HE, and JWT recruited patients in this study, collected data, and helped draft the manuscript. JWT and EMWvdG did data analyses. AMGAdS, JK, and ARG revised the manuscript for important intellectual content. All authors read and approved the manuscript.

Declaration of interests

EdJ has received a lecture fee from Thermo Fisher during the conduct of the study. JK has received personal fees from Becton Dickinson and QXV Communicating Limited, outside the submitted work.
DWdL reports that his institute has received financial support for an electronic database design for data collection and randomisation from Thermo Fisher Scientific (Waltham, MA, USA), and has received a personal fee for lecturing from Thermo Fisher. Thermo Fisher provided procalcitonin kits at reduced costs. Thermo Fisher had no involvement in data collection, data analysis, data interpretation, trial design, patient recruitment, or any aspect pertinent to the study. All other authors declare no competing interests.

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