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Procalcitonin in critically ill patients: time to change guidelines and antibiotic use in practice


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Antibiotic overuse coupled with the emergence of multiresistant bacteria threatens public health. To address this issue, we must focus on implementation of antibiotic stewardship programmes to restrict use of antibiotics to only patients who would truly benefit from these drugs and to avoid long treatment courses. In addition to clinical parameters, monitoring of the blood marker procalcitonin allows individual tailoring of antibiotic therapy to the presence and resolution of systemic bacterial infection.[1,2] Procalcitonin is upregulated by microbial toxins and pro-inflammatory mediators, and is downregulated as these substances subside during recovery from infection.[3] Procalcitonin concentrations measured at hospital admission are strongly associated with detection of bacteraemia[4] and severity of infection.[5] Procalcitonin kinetics have prognostic implications with maintenance at specific concentrations pointing towards treatment being unsuccessful.[6]

Randomised trials[7,8] that enrolled more than 6000 patients assessed clinical effects of using procalcitonin stewardship protocols, mainly, for assessing the success of antibiotic treatment in respiratory infections. In the settings of primary care, emergency room, and hospital wards this approach resulted in large reductions in antibiotic consumption of 30–75%.[8] Additionally, use of these protocols reduced the risk for treatment failure for patients with community-acquired pneumonia.[9] Yet in the critical care setting, safety has been questioned by some, mainly for two reasons. First, the PRORATA trial[10] investigating procalcitonin-guided antibiotic stewardship in critical care reported a 25% reduction in antibiotic exposure and non-inferiority for mortality

at 28 days. Yet at day 60, a non-significant absolute increase in the risk of death of 3·8% (95% CI −2·1 to 9·7) was noted, and thus adverse effects after hospital discharge were possible. Second, in the Danish PASS-trial[11] diagnostic and therapeutic measures (including but not limited to antibiotics) were escalated based on increasing procalcitonin concentrations greater than 1 µg/L in patients. The Danish PASS-trial[11] documented a similar survival but—in the protocol-driven group—they reported more investigational procedures, increased side-effects, and organ-related harm due to the intensified antibiotic efforts, resulting in longer stays in the intensive care unit (ICU) than those not in the procalcitonin-protocol group. This trial[11] was criticised by many because the escalation algorithm was counter-intuitive in this setting. Additionally, surgical patients in the ICU enrolled in the PASS study[11] might initially show an unspecific procalcitonin increase, which does not necessarily point toward post-operative infection. Finally, communication of procalcitonin results was often delayed as samples had to be shipped to a central study laboratory.[2]

As a result for the critical care setting, the latest Surviving Sepsis Campaign (SSC) guidelines provide a weak recommendation (Grade 2C) for the use of procalcitonin testing and only "suggest the use of low procalcitonin to assist the clinician in the discontinuation of empiric antibiotics when no evidence of infection is found".[12] Thus a large and well done trial is needed to provide ultimate proof that procalcitonin-guided antibiotic stewardship does change clinicians' behaviour and indeed reduces mortality and morbidity when used adequately in patients who are critically ill.

In *The Lancet Infectious Diseases*, the Stop Antibiotics on Procalcitonin guidance Study (SAPS)[13] is the largest for procalcitonin guidance by enrolling 1546 critical care patients with assumed or proven infection, from three university medical centres and 12 teaching hospitals in the Netherlands. In this landmark trial by Evelin de Jong and colleagues,[13] all patients with suspected infection were started on antibiotics on admission to the ICU. In the procalcitonin-guided group (761 patients) the study protocol required the discontinuation of antibiotics if procalcitonin had decreased by 80% or more of its peak value or to 0·5 µg/L or more (stopping rules). In the second group (785 patients), treatment was based on standard care (standard-of-care group). Of note, in the Netherlands usual care means a very prudent use of antimicrobial therapy compared with other high-income countries. In the procalcitonin-guided group, physicians stopped administering antibiotics to patients within 48 h after reaching the procalcitonin-guided stopping rule in more than half of patients (297). The early stopping rule was highly efficient and resulted in a 25% reduction in antibiotic duration from 7 days (in the standard-of-care group) to 5 days (in the procalcitonin-guided group).

More importantly, de Jong and colleauges[13] also noted a 7% survival benefit using the procalcitonin guidance at 28-days follow-up, with only 107 deaths (20%) of 538 patients in the procalcitonin-guided group compared with 121 deaths (27%) of 457 patients in the standard-of-care group, according to per-protocol analysis (between-group absolute difference 6·6%, 95% CI 1·3–11·9, p=0·0154). This mortality benefit remained robust in the long-term follow-up after 1 year, with 191 deaths (36%) in the procalcitonin-guided group versus 196 deaths (43%) in the standard-of-care group, in the per-protocol analysis (between-group absolute difference 7·4%, 95% CI 1·3–13·8, p=0·0188). Length of stay and use of a second course of antibiotics were similar in both groups, but more second-course antibiotics were given for re-infection regarded to be possible relapses in the procalcitonin-guided group than the standard-of-care group (5% *vs* 3%).

The SAPS trial[13] has important implications for future patient care. First, the trial substantiates previous work in critically ill patients and shows that the strategy to initially start antibiotics in all patients with possible infection but then to de-escalate and stop treatment early if procalcitonin concentrations remain low or decrease to lower than normal values is highly efficicacious in reducing long antibiotic treatment courses. Importantly, their results[13] were reported in the Netherlands where physicians' prescribing of antibiotics is quite low and where parsimonious use of antibiotics has been a priority for many years, as evidenced by the short antibiotic course in the standard-of-care group. Second, the study[13] expands results from respiratory infection[8] to a broader patient population, namely general critically ill patients with assumed or proven infection. Although

initial use of antibiotics in these patients is justifiable due to the high risk associated with their condition, early stopping still resulted in important reductions in the overall exposure. Third, this high-powered study recorded a decrease in mortality associated with the use of the procalcitonin protocol compared with the standard of care, supporting data from patients with community-acquired pneumonia outside ICUs.[9] Apparently, to think about alternative diagnoses in allegedly infected patients with low procalcitonin concentrations might improve the diagnostic work-up, leading to more effective therapeutic decisions. Reduction of antibiotic side-effects could have also contributed to this finding.[13]

Despite the convincing results of SAPS[13] for critically ill patients, future research is needed. Similar to other critical care trials, adherence to the stopping rule was only moderate, particularly in patients who did not reach clinical stability. Confidence in use of procalcitonin measurements might increase once it is established in clinical routine. De Jong and colleagues[13] did not include immunosuppressed patients and those requiring long-term antibiotic treatments. Furthermore, future studies should assess combination of new, fast turn-around detection techniques for pathogens with a host-response marker such as procalcitonin.[14]

The accuracy of procalcitonin monitoring is far from perfect and sepsis is a heterogeneous and complex syndrome.[15] Hence, clinical judgement and common sense must always be an integral part of any antibiotic stewardship algorithm. Results of the SAPS trial[13] should now convince even critics about the benefits of procalcitonin monitoring for early stopping of antibiotics. No other biomarker or clinical algorithm has been evaluated in a similar number of well done, prospective, randomised trials in different settings. The SAPS trial[13] closes an important gap of evidence for critically ill patients. Additionally, in the ICU, a protocol to stop antibiotics early by monitoring of procalcitonin concentrations leads to an increasingly tailored antibiotic strategy with ultimate benefit for the patient; it may even save their life. We should begin widespread use of these protocols in clinical practice as an evidence-based first step to slow emergence of bacterial resistance and the collapse of antibiotic research, while waiting for more sophisticated diagnostic approaches in the long run.

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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.

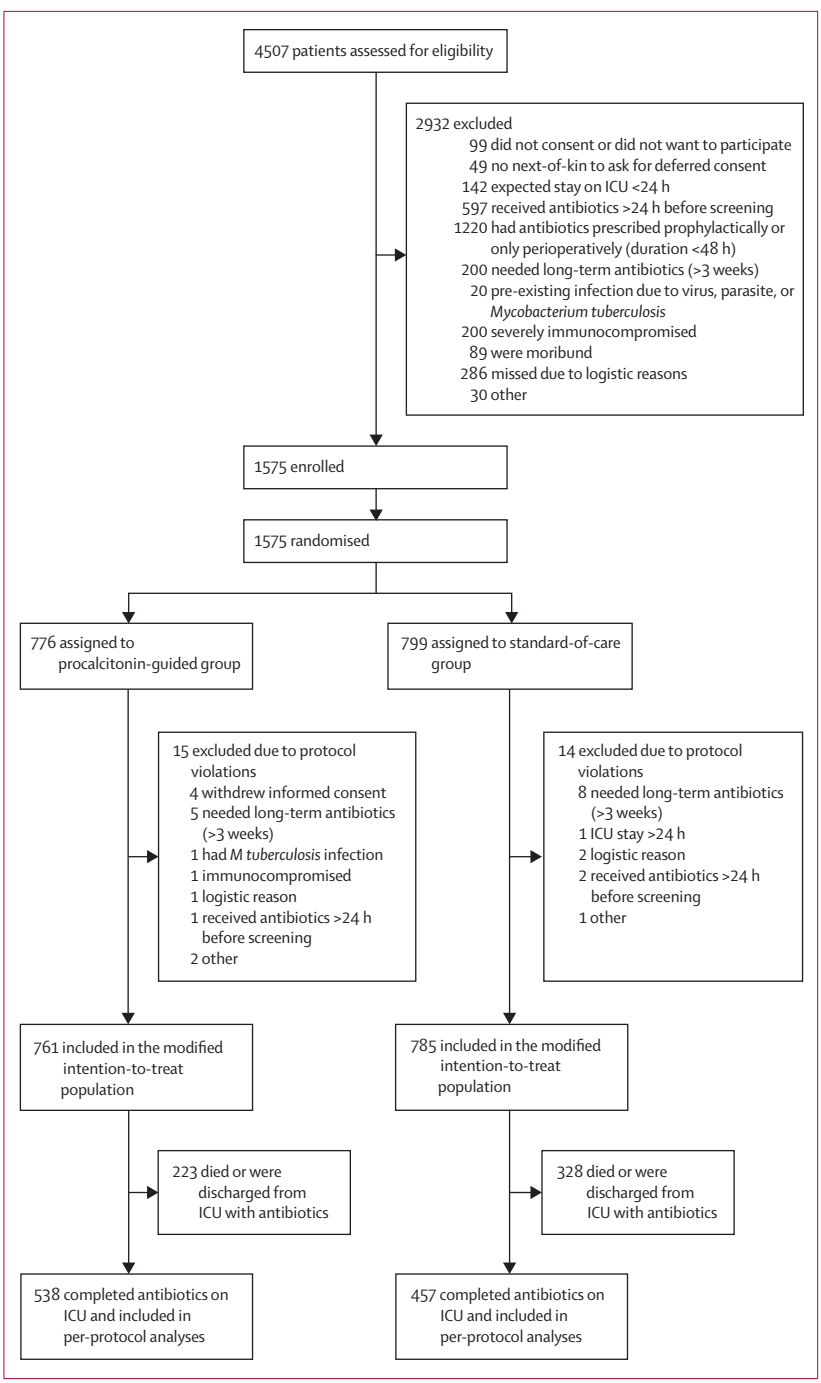

Figure 1: **Trial profile**
ICU=intensive care unit

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**

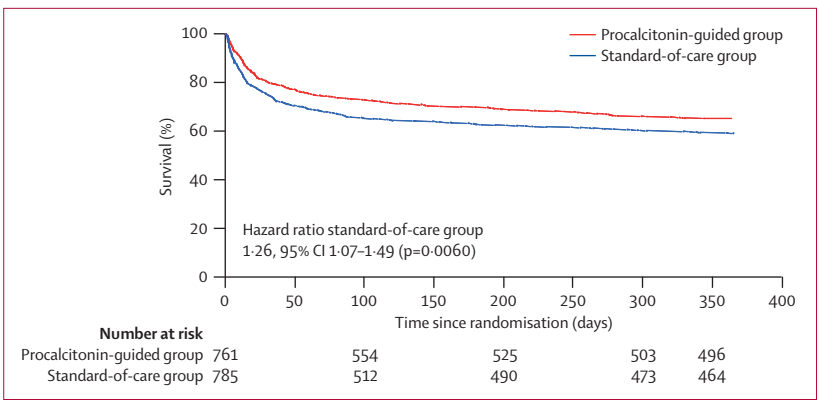

Figure 2: **Kaplan-Meier plot for probability of survival from random assignment to day 365, in the modified intention-to-treat population**

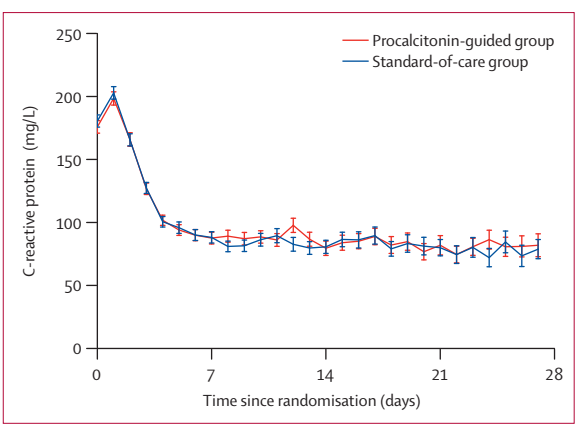

Figure 3: **Serial measurements of C-reactive protein concentrations in both study groups**
The mean values and SEs during the first 28 days after random assignment are shown. Patients discharged from the intensive care unit before day 28 were included as long as they were still admitted to the hospital.

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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antifungals in first-line treatment. With an estimated mortality rate of 39%, the sample size for a randomised trial would be 374 per treatment group, with a non-inferiority margin of 10% and 80% power.

The DEFEAT Mucor trial allowed 14 or more days of previous treatment and waived combination treatment active against *Mucor* spp. Six centres enrolled 20 patients over 22 months (0·15 patients per centre per month).[3] For comparison, monthly enrolment rates were 0·14 and 0·08 patients per centre in recent trials for invasive aspergillosis, which is a more frequent and easier to diagnose disease.[4,5] In mucormycosis, diagnosis is often delayed and patients are likely to receive empirical treatment, further limiting enrolment in a trial of true first-line treatment. Even under very optimistic assumptions, such trials would last more than 10 years. In the meantime, patients continue to await optimised treatments for this devastating disease.

Spellberg and Brass take interest in two patients treated with isavuconazole who experienced non-serious acute liver injury. Although triazoles can cause hepatotoxicity, isavuconazole was associated with fewer hepatobiliary events compared with voriconazole (9% *vs* 16%).[4]

Given all the data presented, the US Food and Drug Administration approved isavuconazole for first-line mucormycosis treatment and the European Medicines Agency approved this treatment for when amphotericin B is considered clinically inappropriate.

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Procalcitonin to guide antibiotic stewardship in intensive care

We read with interest the Stop Antibiotics on Procalcitonin guidance Study reported by Evelien de Jong and colleagues.[1] They ascertained that procalcitonin guidance of antibiotic therapy stimulates the reduction of treatment duration and daily defined doses in critically ill patients with a presumed bacterial infection. This reduction was associated with a significant decrease in both 28 day and 1 year mortality. Findings from a meta-analysis reported by Tang and colleagues[2] suggest procalcitonin alone is unlikely to be helpful in influencing the decision to start antibiotics, because it is associated with a pretest probability of 40% and might only raise the post-test probability of 66%. Conversely, with a negative likelihood ratio of 0·43, the application of a procalcitonin test would reduce the post-test probability to only 0·23, which is not quite enough to rule out an infection.

However, findings from a meta-analysis by Uzzan and colleagues[3] showed that procalcitonin performed significantly better than C-reactive protein (CRP; Q value for procalcitonin 0·78 [95% CI 0·71–0·84] *vs* Q value for CRP 0·71 [95% CI 0·64–0·76], corrected p=0·02) in the diagnostic identification process for sepsis; further, results from the PRORATA trial[4] suggested that a procalcitonin-guided strategy to treat suspected bacterial infections in non-surgical critically ill patients could reduce antibiotic exposure and selective pressure with no apparent adverse outcomes. Finally, a meta-analysis by Kopterides and colleagues[5] demonstrated how implementation of a procalcitonin-based algorithm might reduce antibiotic exposure in septic, critically ill patients without compromising clinical outcomes.[5]

Following on these premises, we ask de Jong and colleagues if it is still worth comparing these two markers, in view of the evidence that C-reactive protein has a lower sensitivity and specificity in guidance to antibiotic suspension. Furthermore, do the investigators agree the final, significantly higher mortality rate recorded in the control group would have suggested an earlier suspension of the trial if already found through an interim analysis, neither planned nor mentioned in the methods?

We declare no competing interests.

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We read with great interest the Article by Evelien de Jong and colleagues,[1] showing that procalcitonin guidance reduces treatment duration and daily defined doses in critically ill patients with a presumed bacterial infection. Although de Jong and colleagues's data do not immediately allow a cost-effectiveness analysis, they can, however, be used to inform a health economic model. Moreover, such a model has already been published,[2] and can thus be updated to immediately assess cost-effectiveness.

We used the reported difference in mean duration of intensive care unit and hospital stay, and in duration and costs of antibiotic treatment, between the procalcitonin group and the control group as input for the cost-effectiveness analysis (table). The corresponding means were estimated from the reported median values[3] (control group) and then combined with the reported difference in means (procalcitonin group). The mean number of procalcitonin measurements was set to seven[1]. Other laboratory analyses were assumed to be performed at intensive care admission, and once daily until hospital discharge or death. All other parameters were assumed equal in both groups. To reflect the combined uncertainty in model input parameters, probabilistic sensitivity analysis was performed using Monte Carlo simulation (10 000 samples). Previously, length of intensive care unit stay was found to have the biggest effect on costs.[2] Therefore, we performed a threshold analysis to determine the decrease in intensive care unit days required to make procalcitonin cost saving. Costs were expressed in euro (2015 value) and based on the recent Dutch costing manual.[4]

The procalcitonin strategy costs on average €27 777 per patient, compared with €27 556 per patient in the control group (ie, an increase of 0·80%; difference €221, 95% CI −1724 to 2164), and has a probability of 41% to be cost saving. However, the threshold analysis revealed that if the procalcitonin strategy would (for example) decrease intensive care unit stay from 10·0 to 9·0 days, the difference becomes a decrease of €2231 (95% CI −4152 to −293), with a 99% probability to be cost saving. The table shows the input parameters and model outcomes.

Our preliminary analysis does not conclusively demonstrate that the procalcitonin assay is cost saving. Because length of intensive care stay is the main cost driver, further research should focus on estimating this parameter more accurately. Finally, a formal cost-effectiveness analysis would also require incorporating evidence on health outcomes such as the effect of procalcitonin on decreasing mortality rates. Iteratively updating a health economic model with new evidence to update cost-effectiveness estimates is straightforward.

We declare no competing interests.

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	Resource use		Total costs		
	Control group	Procalcitonin group	Control group mean (95% CI)	Procalcitonin group mean (95% CI)	Difference mean (95% CI)
Antibiotic treatment, days	7·33	6·11	€156 (148 to 164)	€122 (116 to 129)	−€34 (−44 to −24)
Intensive care unit stay, days	10·00	10·21	€19 841 (18 509 to 21 203)	€20 285 (19 050 to 21 546)	€444 (−1361 to 2273)
Regular ward stay, days	14·67	14·07	€7028 (6668 to 7395)	€6740 (6254 to 7239)	−€288 (−898 to 331)
Procalcitonin measurements	0	7	..	€105 (86 to 126)	€105 (86 to 126)
Other laboratory tests, number of days	24·67	24·28	€531 (445 to 622)	€525 (449 to 613)	−€7 (−125 to 113)
Overall costs per patient	..	..	€27 556 (26 182 to 28 969)	€27 777 (26 457 to 29 154)	€221 (−1724 to 2164)
Overall yearly cost in the Netherlands	..	..	€358 000 000 (340 000 000 to 377 000 000)	€361 000 000 (344 000 000 to 379 000 000)	€3 000 000 (−22 000 000 to 28 000 000)

***Table*: Overview of input parameters and outcomes of the health economic model, in both the control group and the procalcitonin group.**

As veterans in procalcitonin research,[1] we read with interest the Stop Antibiotics on Procalcitonin guidance Study (SAPS) reported by Evelien de Jong and colleagues[2] (and the linked Comment by Philipp Scheutz and Beat Müeller[3]) investigating procalcitonin-guided antibiotic treatment in intensive care, but in our opinion the findings of this study are far from conclusive.

SAPS did not take into account some points affecting procalcitonin concentrations. Both the aetiology (Gram positive and negative rods, fungi, parasites) and drugs prescribed for septic episodes (cidal *vs* static) were not specified, the surgical source control of septic episode (eg, intra-abdominal infections) was not mentioned, and although about 10% of enrolled patients received renal replacement treatment in first 24 h, kidney function was not subsequently reported.

The investigators suggest that their findings will inform practical aspects for the introduction of procalcitonin testing, but the Article does not indicate reporting time for procalcitonin results—only that it was measured once a day. Laboratory testing on a routine or urgent basis is complex and expensive; the cost of procalcitonin reagents in Italy is at least three times higher than the €4 reported by the investigators as the highest price. Further, the treatment algorithm used in SAPS advises stopping of antibiotics if procalcitonin concentration decreases by at least 80% of its peak, but can this be accurately assessed if procalcitonin is measured only once a day? Although 60 day mortality was increased within the procalcitonin group of the PRORATA study, de Jong and colleagues reported a mortality reduction both at 28 days and at 1 year, but did not report mortality data at 60 days.

We disagree with the authors of the linked Comment that the SAPS findings should "convince even critics" about procalcitonin monitoring; a quarter of patients in both treatment groups received a second course of antibiotics after a mean of 5 days of first-course antibiotics, given after a median interval of 4 days, suggesting that the first treatment course was insufficient. We agree with the recent guidance from the UK National Institute for Health and Care Excellence that the National Health Service should not cover the expense for procalcitonin.[4]

The debate about the role of procalcitonin reminds us of the drotrecogin saga, aggressively promoted 10 years ago by the manufacturer and some intensivists, and an editorial discussing that case: "The challenges involved in producing first-rate guidelines and performance standards are only exacerbated by the intrusion of marketing strategies masquerading as evidence-based medicine".[5]

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Authors' reply

Procalcitonin is less suited for the management of non-bacterial infections, as correctly pointed out by Romolo Dorizzi and colleagues. However, non-bacterial infections were excluded, because the Stop Antibiotics on Procalcitonin guidance Study (SAPS) addressed the reduction of antibacterial therapy.[1] Additional information about site of infection, pathogens, and antibiotics is provided in the in the appendix.[1] We also agree that procalcitonin measurements are still much too expensive. The actual costs per measurement markedly exceeds €15 in many countries. For the SAPS trial, we estimated that the procalcitonin costs might only be offset by lowered antibiotic costs if procalcitonin would cost less than €4.

Kip and colleagues[2] previously modelled the cost-effectiveness of procalcitonin guidance in reducing antibiotic duration, with hospital length of stay being a main cause of their result. In a preliminary cost-effectiveness analysis based upon our published results they find that the procalcitonin arm was associated with higher costs. They speculate that inclusion of health outcome might make procalcitonin guidance cost effective.[1] We did not perform cost-effectiveness analysis, but observed no differences in intensive care unit length of stay (mean 14·5 days for procalcitonin *vs* 14·3 days for control) or hospital length of stay (31·4 days *vs* 31·8 days).[1] We agree with these investigators that their preliminary calculations are not conclusive. More formal and real-life based cost-effectiveness analysis may allow more definite conclusions.

Vincenzo De Santis and Alberto Corona are correct in stating that a single procalcitonin measurement cannot rule out bacterial infection.[4] The principle of the SAPS trial was

to use serial procalcitonin measurement,[1] which provides substantially more information than a single measurement. Daily procalcitonin is a valuable additional laboratory measurement that helps improve the quality of the decision whether to continue or discontinue antibiotics, but no more than that. Therefore, when a stopping criterion was reached, the algorithm explicitly provided advice—but not an order—to stop. The freedom of the attending physician to take other factors into account is underscored by the large number of patients for whom antibiotics were continued after advice to discontinue was provided by the algorithm.[1]

We believe that the potential in reducing inappropriate antibiotic use in the intensive care unit is large. With its limitations, the SAPS trial showed that daily procalcitonin measurements facilitated a safe reduction in antibiotic duration. In many patients, 5 days of antibiotic treatment are sufficient. In view of the global health threats posed by increasing antibiotic resistance, this is a fact that should not be ignored.

University Medical Centre Utrecht, as part of the steering group of the SAPS study, received financial compensation for the online case record forms from Thermo Fisher.

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Tenofovir resistance and first-line antiretroviral therapy

Since 2013, WHO guidelines have recommended a single regimen of tenofovir combined with efavirenz and either lamivudine or emtricitabine for treatment of HIV in adults and adolescents. This recommended regimen has been widely adopted by countries and is maintained in WHO's updated 2016 guidelines.[1]

The TeNoRes study group showed that a high proportion of patients who failed a tenofovir-containing antiretroviral therapy (ART) regimen carry an HIV virus that is resistant to this drug, which is concerning.[2] These findings raise questions around the suitability of the recommended first-line regimen and the need for affordable drug resistance testing for patient care in low-income and middle-income countries.[3]

Although this study is important in providing data for the nature of acquired drug resistance, the choice of first-line regimens should be based on levels of drug resistance among individuals who have yet to start ART, known as pre-treatment drug resistance. Although updated data are needed, available data up to 2013 suggest that rates of transmitted tenofovir resistance remain low, at 0·4% in sub-Saharan Africa.[4]

In the TeNoRes study, risk of acquired tenofovir resistance was associated with late presentation at start of ART and the use of nevirapine compared with efavirenz, and lamivudine compared with emtricitabine, as partner drugs. Although baseline CD4 cell count at start of ART is increasing over time, late presentation-to-care persists.[5] WHO recommends that ART should be started at any CD4 cell count as this approach will help reduce the proportion of people starting ART late.[1] Since 2013, WHO guidelines have given preference to efavirenz over nevirapine in recognition of the inferior efficacy of the tenofivir and nevirapine combination, and although 30% of patients in low-income and middle-income countries in the TeNoRes study received nevirapine, most countries no longer recommend nevirapine in first-line ART. The association between lamivudine use and increased risk of resistance is less compelling. In the TeNoRes study, only four of 30 studies found a statistically significant association between lamivudine and tenofovir resistance, while the remainder found no difference, which is consistent with data from randomised trials.[6]

Although the TeNoRes study provides important data for resistance patterns among ART failures, and therefore informs optimal selection of subsequent regimens, we do not think that these data warrant reconsideration of tenofovir as a preferred first-line agent, the interchangeability of lamivudine and emtricitabine, or the need for resistance testing for patient monitoring. WHO's recommended surveillance of HIV resistance to drugs used in first line regimens, including tenofovir, is intended to gain a better understanding of the extent of pre-treatment drug resistance.[7] Present rates do not justify a move away from current policy and practice, but WHO will continue to assess the latest data and incorporate these data into future ART guideline revisions.

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