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Original article

Procalcitonin to guide taking blood cultures in the intensive care unit; a cluster-randomized controlled trial

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ABSTRACT

Objectives: We aimed to study the safety and efficacy of procalcitonin in guiding blood cultures taking in critically ill patients with suspected infection.
Methods: We performed a cluster-randomized, multi-centre, single-blinded, cross-over trial. Patients suspected of infection in whom taking blood for culture was indicated were included. The participating intensive care units were stratified and randomized by treatment regimen into a control group and a procalcitonin-guided group. All patients included in this trial followed the regimen that was allocated to the intensive care unit for that period. In both groups, blood was drawn at the same moment for a procalcitonin measurement and blood cultures. In the procalcitonin-guided group, blood cultures were sent to the department of medical microbiology when the procalcitonin was >0.25 ng/mL. The main outcome was safety, expressed as mortality at day 28 and day 90.
Results: The control group included 288 patients and the procalcitonin-guided group included 276 patients. The 28- and 90-day mortality rates in the procalcitonin-guided group were 29% (80/276) and 38% (105/276), respectively. The mortality rates in the control group were 32% (92/288) at day 28 and 40% (115/288) at day 90. The intention-to-treat analysis showed hazard ratios of 0.85 (95% CI 0.62–1.17) and 0.89 (95% CI 0.67–1.17) for 28-day and 90-day mortality, respectively. The results were deemed non-inferior because the upper limit of the 95% CI was below the margin of 1.20.
Conclusion: Applying procalcitonin to guide blood cultures in critically ill patients with suspected infection seems to be safe, but the benefits may be limited.
Trial registration: ClinicalTrials.gov identifier: ID NCT01847079. Registered on 24 April 2013, retrospectively registered. **P.J. van der Geest, CMI 2016;▪:1**

Introduction

Critical illness predisposes to bacteraemia, thereby increasing morbidity and mortality [1,2], particularly when diagnosis and administration of antibiotics are delayed [3,4]. Indeed, culturing costs time, and only 15%–25% of blood cultures taken in critically ill patients suspected of infection prove positive, which suggests a waste of resources [5]. The use of biomarkers, including procalcitonin, has been studied to improve a fast and accurate diagnosis of sepsis and bacteraemia with varying results [4,6–8]. However, we recently performed a meta-analysis of studies suggesting that a normal procalcitonin has 96% negative predictive value for bacteraemia [9]. Based on nine studies, the area under the receiver operating characteristic curve of procalcitonin for bacteraemia in critically ill patients was 0.88 [6,9–17]. The studies included, however, were relatively small [10–12,15–17] and not primarily designed to rule out or detect bacteraemia [6,10,12–14]. Nevertheless, a rapidly available and normal procalcitonin might allow early prediction of negative blood cultures when blood sampling is clinically indicated for suspicion of infection, and might thereby avoid unnecessary blood culturing.

In the hypothesis that a normal procalcitonin can be used to predict absence of bacteraemia in critically ill patients, we aimed to

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study the usefulness of a rapidly determined procalcitonin, in saving blood cultures in critically ill patients in whom taking blood for culture is clinically indicated because of a suspicion of infection. We hypothesized that such a strategy can be safely applied in critically ill patients without increasing morbidity and mortality.

Materials and methods

Patients and study design

We performed a prospective, single-blinded, cluster-randomized, cross-over trial, involving the intensive care unit (ICU) of the Erasmus Medical Centre Rotterdam and the Maasstad hospital Rotterdam. We conducted this trial between January 2013 and September 2014. The ICU of the Erasmus Medical Centre is a tertiary-care mixed medical–surgery ICU with 2000 admissions per year. The ICU of the Maasstad Hospital is a secondary-care mixed medical–surgical ICU with 1200 annual admissions. The trial was conducted in accordance with the ethical principles decreed by the Declaration of Helsinki and in compliance with the International Conference on Harmonization of Good Clinical Practice Guidelines. The final protocol, amendments and informed consent document were reviewed and approved by the institutional review board (IRB) or the independent medical ethics committee at each of the investigational centres. This study was finally approved by the medical ethics committee of the Erasmus Medical Centre (MEC 2011-505) and registered with ClinicalTrial.gov (protocol ID NCT 01847079). We used the CONSORT guideline to construct our cluster-randomized trial (see Supplementary material, Tables S1 and S2). All patients or their proxy provided written informed consent before study inclusion, as a presumed consent at ICU admission.

Patients on the ICU ≥18 years in whom a suspicion of infection was raised and for whom taking blood for culture was clinically indicated by the attending intensivist were enrolled in the study. Suspicion of infection could be increasing body (tympanic) temperature >38.3°C, chills, progressive leucocytosis or increased C-reactive protein, increasing consolidations on chest radiography or other imaging of potential infection sources. Patients could be included more than once; every time that blood for culture is taken counts as a suspicion-of-infection episode (SIE). Patients were excluded if they had one of the following exclusion criteria: pregnancy, neutropenia (defined as leucocyte count $<0.5 \times 10^9$/L) and pre-terminal illness with an expected death within 24 hours. Patients were not included if blood cultures were performed as part of a standard protocol (such as patients with veno-venous or veno-arterial extracorporeal membrane oxygenation) or were performed to check the effectiveness of treatment (such as in endocarditis), unless the blood culture was performed because of an SIE. A flow chart of the included patients is given in the Supplementary material (Fig. S1). Patients were otherwise taken care of by board-certified intensivists, according to local and national guidelines. In case of a microbial infection source control was performed when possible and antibiotic treatments were given in close collaboration with a medical microbiologist.

Study protocol

The participating ICUs (two per medical centre) were stratified and randomized by treatment regimen into a control group (standard of care) and a procalcitonin-guided group. Randomization was performed per cluster allocation, being an assigned ICU. The stratified randomization and enrolment of patients was performed by one of the investigators. All patients included into this trial followed the regimen that was allocated to the ICU for that period. The participating units switched the allocated regimen every 3 months. We used a wash-out period between the cross-over period, to minimize the risk for a patient to follow two different regimens. The wash-out period was set for 1 month, in which >99% of the patients in the previous period have left the ICU. None of the patients included in this study followed two regimens. The participating ICUs were matched for a 1:1 ratio of allocation (see Supplementary material, Fig. S2). No changes to methods or trial outcomes have been made after trial commencement. The study was stopped after achieving at least 550 inclusions based on the power calculation.

In both the control and procalcitonin-guided groups blood was taken at the same moment for the procalcitonin measurement and blood cultures. In the control group, two sets of blood cultures were sent directly to the medical microbiology department. The procalcitonin measurement in the control group was determined by the department of clinical chemistry, and results were blinded for the investigators and only available before analysis. In the procalcitonin-guided group the procalcitonin measurement was determined as a stat determination, rendering results within 1 hour. Blood samples for the procalcitonin measurement were immediately centrifuged at 3000 rpm for 10 minutes at room temperature (Hettich Rotina 420R, Tuttlingen, Germany). The procalcitonin measurement was performed on the automated Kryptor platform (Brahms AG, Hennigsdorf, Germany), using the Roche Elecsys Brahms procalcitonin assay. Upon receiving results, the attending intensivists determined whether to send the blood cultures to the medical microbiology department. We used a cut-off of 0.25 ng/mL in the procalcitonin-guided group. Values below this cut-off were regarded as normal, and so not worth culturing (and blood cultures taken were destroyed). It was possible for the attending intensivists to overrule the procalcitonin-guided strategy and still send in blood cultures at normal procalcitonin. For values higher than the cut-off of 0.25 ng/mL, patients' blood cultures were sent to the medical microbiology department for further analysis. Each set of blood cultures consists of one aerobic and one anaerobic bottle (BD Bactec, Franklin Lakes, NJ, USA) containing resin to enhance the recovery of organisms. The blood cultures were incubated for 7 days in an automatic analyser (BD Bactec) that automatically demonstrates the time to positive blood culture in the case of positive bacterial or fungal growth. Gram strains were performed, and the organisms were cultured on agar plates and after growth identification was performed, using the VITEK® 2 (Biomérieux, Marcy l'Etoile, France) for bacteria and the Auxacolor (Sanofi Diagnostics Pasteur, Lyon, France) for fungal growth. The PCR technique was carried out using a LightCycler480 PCR system (Roche Diagnostics, Almere, the Netherlands) to detect viral growth in blood samples. Bacteraemia was defined as having a positive blood culture with a recognized pathogen except skin contaminants [18,19]. In the case of skin contaminants, bacteraemia was only considered if at least two blood cultures drawn on separate occasions were positive for the same microorganism [18,19]. We otherwise determined inflammatory parameters such as C-reactive protein (turbidimetric assay) and white blood cell counts (XN 9000, Sysmex, Kobe, Japan).

Data collection

At the day of inclusion, baseline demographic data and clinical variables, including age, sex, pre-morbidity, reasons of admission, use of antibiotics excluding selective decontamination of the digestive tract, antifungal treatment, steroids, immunosuppressive medication, immune status (active malignancy or other causes of an immunocompromised state), recent surgery, mechanical ventilation, renal replacement therapy, total parenteral nutrition, central

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venous catheters and vital parameters were recorded. The acute physiology and chronic health evaluation IV (APACHE IV) and the sequential organ failure assessment (SOFA) scores were recorded at admission. Patients were followed until day 28 and day 90 after inclusion and length of ICU stay and vital outcomes were recorded.

Statistical analysis

The primary outcome measurement of this study is safety, expressed as mortality at day 28 and day 90. We calculated that 550 patients were needed to determine non-inferiority in a parallel group design with a power of 90%, a one-sided α error of 5% and a non-inferiority limit of 10% [20]. The sample size calculation was based on an assumed risk of death of 20% in both the control and intervention groups in procalcitonin-guided antibiotic studies [21–24]. A hierarchical Poisson regression model, using the logarithm of the survival time as an offset variable, was used to estimate the relative risk of mortality and associated 95% CI between control and procalcitonin-guided groups. The ward and ward-period interaction were used as random effects to account for systematic effects of ward and period on the outcome [25]. The results were deemed non-inferior when the 95% CI was <1.20 (non-inferiority limit 20%) as our design was more complicated than a parallel group design and had precluded a power analysis based on Poisson regression. We performed an intention-to-treat analysis (all procalcitonin-guided versus control patients), per-protocol analysis (procalcitonin-guided patients without blood cultures versus controls), and an as-treated analysis (procalcitonin-guided patients without blood cultures versus procalcitonin-guided patients with blood cultures and controls). All analyses were performed using R version 3.2.1 and the hierarchical Poisson models were fitted using the *lme4* package. Data are expressed as median (interquartile range) or as number of patients (percentage) where appropriate. Indeed, data were distributed non-normally (Kolmogorov–Smirnov test, $p < 0.05$). The Mann–Whitney *U* test and Fisher exact test were used to compare two groups. Analysis of variance was used to compare repeated measurements between two groups. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Exact p values >0.001 are given.

Results

Descriptives

In total, 1448 patients were possibly eligible for inclusion, of whom 564 were included and remained for analysis (Fig. S1). The control group consisted of 288 patients and the procalcitonin-guided group comprised 276 patients (Table 1). No difference was observed between the groups, except for more neurological premorbidity in the control group (Table 1).

Suspected infection episodes

Table 2 shows that the control group represented 554 SIE against 576 SIE in the procalcitonin-guided group, with a somewhat higher C-reactive protein in the latter. In the control group there were 118 episodes of bacteraemia in 58 patients, against 156 episodes in 63 patients in the procalcitonin-guided group (Table 3). In only six episodes of bacteraemia the procalcitonin value was >0.25 ng/mL (three *Enterococcus faecalis*, one *Enterococcus faecium*, one *Staphylococcus aureus* and one *Staphylococcus epidermidis*). The genus of the micro-organism cultures in the other 268 episodes were: 99 staphylococci, 39 streptococci, 88 *Enterobacteriaceae*, seven *Bacteroides*, five *Bacillus*, two *Burkholderia*, six *Pseudomonas* and 24 fungi and four viruses.

Table 1
Baseline demographic and clinical characteristics

	Control group ($n = 288$)	Procalcitonin-guided group ($n = 276$)	p value
Age (years)	59 (21)	61 (22)	0.36
Gender (male)	200 (69)	177 (64)	0.21
APACHE IV score	62 (36)	67 (45)	0.27
SOFA score	8 (6)	8 (6)	0.79
Pre-morbidity			
Neurological	75 (26)	47 (17)	0.02
Cardiac	95 (33)	91 (33)	0.99
Pulmonary	66 (23)	50 (18)	0.11
Gastrointestinal	89 (31)	91 (33)	0.60
Renal	37 (13)	28 (10)	0.26
Diabetes mellitus type 2	55 (19)	47 (17)	0.45
Cancer	63 (22)	77 (28)	0.08
Autoimmune	14 (5)	14 (5)	0.93
Steroids	46 (16)	50 (18)	0.57
Immune suppression	20 (7)	22 (8)	0.64
Reasons of ICU admission			0.70
Suspected sepsis	86 (30)	83 (30)	
Respiratory failure	54 (19)	61 (22)	
Renal failure	1 (1)	2 (1)	
Liver failure	0	2 (1)	
Neurology	35 (12)	26 (9)	
Cardiopulmonary resuscitation	14 (5)	14 (5)	
Shock	12 (4)	7 (3)	
Trauma	17 (6)	14 (5)	
Postoperative	55 (19)	58 (21)	
Miscellaneous	14 (5)	9 (3)	
Treatment in ICU			
Mechanical ventilation	245 (85)	246 (89)	0.15
Renal replacement therapy	63 (22)	69 (25)	0.44
Extra corporeal membrane oxygenation	9 (3)	3 (1)	0.09
Central venous catheter	210 (73)	179 (65)	0.04
Norepinephrine	225 (78)	232 (84)	0.07
Antibiotics	279 (97)	270 (98)	0.32
Total parenteral nutrition	86 (30)	99 (36)	0.13
Length of ICU stay (days)	10 (17)	12 (20)	0.21
Length of hospital stay (days)	23 (35)	31 (39)	0.005

Numbers (percentage) or median (interquartile range), where appropriate.
Abbreviations: APACHE IV, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; PCT, procalcitonin; SOFA, sequential organ failure assessment score.

Primary outcome

No difference was seen in 28-day or 90-day mortality between the groups (Table 3). The 28-day and 90-day mortality rate in the procalcitonin-guided group was 29% (80/276) and 38% (105/276), respectively. The mortality rate in the control group was 32% (92/288) at day 28 and 40% (115/288) at day 90. The intention-to-treat analysis showed hazard ratios of 0.85 (95% CI 0.62–1.17) and 0.89 (95% CI 0.67–1.17) for 28-day and 90-day mortality, respectively, favouring the procalcitonin-guided group. The per-protocol

Table 2
Infection markers of all 1130 suspected infection episodes

	Control group ($n = 554$)	Procalcitonin-guided group ($n = 576$)	p value
Temperature (°C)	38.1 (1.6)	38.0 (1.6)	0.14
Heart rate (beats/min)	109 (32)	111 (32)	0.11
Respiratory rate (breaths/ min)	30 (16)	28 (18)	0.97
White blood cell count (10^9/L)	12.6 (9.7)	12.5 (9.9)	0.40
C-reactive protein (mg/L)	111 (147)	148 (178)	<0.001
Procalcitonin (μg/L)	1.1 (5.2)	1.4 (6.1)	0.18

Median (interquartile range).

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Table 3
Primary outcome measures for suspicion-of-infection episode I

	Control group	Procalcitonin-guided group	p value
	($n = 288$)	($n = 276$)	
Mortality day 28	92 (32)	80 (29)	0.36
Mortality day 90	115 (40)	105 (38)	0.53
PCT <0.25 and no BC sent in	($n = 0$)	($n = 17$)	
Mortality day 28	—	5 (29)	—
Mortality day 90	—	6 (35)	—
PCT <0.25 and BC sent in	($n = 57$)	($n = 20$)	
Mortality day 28	11 (19)	4 (19)	0.57
Mortality day 90	15 (26)	6 (29)	0.65
PCT >0.25 and BC sent in	($n = 231$)	($n = 239$)	
Mortality day 28	81 (35)	71 (30)	0.20
Mortality day 90	100 (43)	93 (39)	0.27

Abbreviations: BC, blood culture; PCT, procalcitonin.

analysis showed hazard ratios of 0.89 (95% CI 0.67–1.17) and 0.89 (95% CI 0.67–1.17) for 28-day and 90-day mortality, respectively. The as-treated analysis showed hazard ratios of 0.89 (95% CI 0.67–1.17) and 0.89 (95% CI 0.67–1.17) for 28-day and 90-day mortality, respectively. The results were deemed non-inferior because the upper limit of the 95% CI was below the margin of 1.20. The length of ICU stay was comparable between groups, but the length of hospital stay was longer in the procalcitonin-guided group (Table 1).

Predictive values

Procalcitonin <0.25 ng/mL occurred in 121 and 76 SIEs in the control and procalcitonin-guided groups, respectively (Table 4). The sensitivity of a low procalcitonin for predicting bacteraemia was 98% with a specificity of 20%, negative predictive value 96% and positive predictive value 29%. Most patients were treated with antibiotics already at SIE I, without differences between procalcitonin-guidance and control groups.

Discussion

This study evaluated the predictive value of procalcitonin for bacteraemia and the safety of withholding blood cultures in critically ill patients with an SIE but a normal procalcitonin. Based on the high negative predictive value and the regression analyses, without exceeding a 20% group difference for mortality, a low procalcitonin can be safely used to rule out bacteraemia, but the benefits may be limited.

This study suggests that a procalcitonin-guided algorithm for performing blood cultures can be safely applied. The overall ICU mortality rate was 27% (30% control group versus 24% procalcitonin-guided group) and the overall in hospital mortality rate was 35% (38% control group and 33% procalcitonin-guided group), which agrees with an international study of the prevalence and outcomes of infection in ICUs [5] and a large systematic review and meta-analysis on procalcitonin-guided antibiotic therapy in critically ill patients with bacteraemia [22]. The longer length of hospital stay in the procalcitonin-guided group could be explained by a transfer delay from the regular ward.

The observed occurrence of bacteraemia in this study varies between 20% and 23%, which is comparable with a recently performed meta-analysis on the diagnostic accuracy of procalcitonin for bacteraemia [9]. In the current study we have chosen to use a cut-off value of 0.25 ng/mL for procalcitonin, which was based on two previous studies that looked at the predictive value of procalcitonin for bacteraemia in patients in the emergency department [26,27]. With the used cut-off of 0.25 ng/ml we found a sensitivity of 98% and a specificity of 20% for the prediction of bacteraemia. Other studies performed on the diagnostic accuracy of procalcitonin for bacteraemia in the critically ill used a cut-off value of 0.5 ng/ml [6,10–17]. By using a cut-off of 0.5 ng/ml we found a sensitivity of 86% and specificity of 32% for the prediction of bacteraemia. The results are comparable with other studies on the diagnostic accuracy of procalcitonin for bacteraemia [6,10–17]. The corresponding negative and positive predictive values at a cut-off value of 0.25 ng/ml are 96% and 29%, respectively, and are comparable with the observed negative predictive value of 98% and positive predictive value of 28% in a large meta-analysis [9].

A total of 1130 blood cultures were taken in this study, of which 197 (17%) could have been saved by using procalcitonin as a pre-test. The value is much lower compared with two other studies, which predicted a possible reduction of 37%–40% of blood cultures [26,27]. Both studies, only designed to evaluate predictive values, used a cut-off of 0.25 ng/mL and described sensitivities of 96% and 94%, respectively, which are comparable with our study [26,27]. The observed difference could be explained by the fact that both studies were performed on the emergency department or primary-

Table 4
Procalcitonin measurements and blood culture results for the different suspicion-of-infection episodes

	SIE I		SIE II		SIE III and IV	
	Control group	Procalcitonin-group	Control group	Procalcitonin-group	Control group	Procalcitonin-group
	($n = 288$)	($n = 276$)	($n = 149$)	($n = 127$)	($n = 117$)	($n = 173$)
Number (percentage) of blood cultures taken	288 (100)	259 (94)	149 (100)	126 (99)	117 (100)	173 (100)
Positive blood cultures	71 (25)	70 (25)	43 (29)	37 (29)	37 (32)	62 (36)
PCT <0.25 ng/mL and BC negative	47 (16)	15 (5)	24 (16)	15 (12)	25 (21)	17 (10)
PCT <0.25 ng/mL and BC contamination	8 (3)	4 (1)	6 (4)	2 (2)	7 (6)	3 (2)
PCT <0.25 ng/mL and BC positive	2 (1)	1 (1)	1 (1)	1 (1)	1 (1)	0
PCT ≥0.25 ng/mL and BC negative	170 (59)	174 (63)	82 (55)	74 (58)	55 (47)	94 (54)
PCT ≥0.25 ng/mL and BC contamination	4 (1)	3 (1)	1 (1)	0	7 (6)	1 (1)
PCT ≥0.25 ng/mL and BC positive	57 (20)	62 (22)	35 (23)	34 (27)	22 (19)	58 (33)
On antibiotics						
PCT <0.25 ng/mL and BC negative	43 (91)	30 (94)	24 (100)	16 (100)	25 (100)	17 (100)
PCT <0.25 ng/mL and BC contamination	8 (100)	4 (100)	6 (100)	2 (100)	7 (100)	3 (100)
PCT <0.25 ng/mL and BC positive	2 (100)	1 (100)	1 (100)	1 (100)	1 (100)	0
PCT ≥0.25 ng/mL and BC negative	167 (98)	171 (98)	81 (99)	74 (100)	55 (100)	94 (100)
PCT ≥0.25 ng/mL and BC contamination	4 (100)	3 (100)	1 (100)	0	7 (100)	1 (100)
PCT ≥0.25 ng/mL and BC positive	57 (100)	62 (100)	35 (100)	34 (1000)	22 (100)	58 (100)

Abbreviations: BC, blood culture; PCT, procalcitonin; SIE, suspicion of infection episode.

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care unit, including patients with a clinical suspicion of urinary tract infection or pneumonia. This contrasts with our study, which was performed in critically ill patients, in which a suspected infection can be proven in only 50% or less.

With the used cut-off, procalcitonin classified 143 SIEs correctly for not having bacteraemia (true negative) and classified six SIEs false for not having bacteraemia (false negative). In the latter cases, the cultured microorganisms were susceptible to antibiotics and patients were treated with vancomycin or flucloxacillin in the case of cultured staphylococci and enterococci. Arterial and central venous catheters were replaced. The question remains if we would have missed cases of severe bacteraemia by using the procalcitonin strategy and destruction of all blood cultures at low procalcitonin and whether this would have harmed patients. Many experts favour deferring antimicrobial therapy for a bacteraemia caused by *Enterococcus* spp. in the setting of a single positive blood culture, because catheter removal alone may be sufficient to cure the infection in patient where the intravascular catheter is the likely source of bacteraemia [8,28,29]. In the four cases of enterococcal bacteraemia in this study only a single blood culture was positive and the four cases could be regarded as low-grade infection in which removal of indwelling catheters could have been sufficient treatment. The other two cases of staphylococcal bacteraemia should be regarded as true bacteraemia, which would have been falsely classified as having no bacteraemia if cultures had been destroyed. In the case of *Staphylococcus epidermidis*, three sets of blood cultures were even positive. Anyway, clinical judgement should always predominate over procalcitonin determinations, including reasons for catheter removal and culture.

This study has several limitations. First of all, in only 17 (46%) patients with low procalcitonin levels, blood cultures were saved in the procalcitonin-guided group. When the protocol had been strictly followed, blood cultures could have been saved in 76 SIEs, for which a classic intention-to-treat analysis could be performed. However, we used a hierarchical approach as described by Christiansen and Morris, having several advantages such as removal of regression to the mean bias and the use of smaller sample sizes in the analysis [25]. In case of non-compliance a per-protocol analysis is as important as an intention-to-treat analysis. Therefore we provided a per-protocol and an as-treated analysis next to the intention-to-treat analysis. The different analyses showed no differences in hazard ratios, thereby suggesting that a procalcitonin-guided strategy could be safely performed in clinical practices. However, the mortality rates could have been higher in the procalcitonin-guided group in case the protocol was strictly followed, which suggests that a procalcitonin-guided strategy cannot be safely performed. Second, the intensity and standard of clinical care could have been affected, as this study was single-blinded and the attending intensivists were aware that the intervention was taking place. Third, for the primary sample size calculation of this study we used a non-inferiority limit of 10% by parallel group design, as an a priori power analysis based on Poisson regression appeared hardly possible, we decided to use a non-inferiority limit of 20% for final analysis by Poisson regression. A non-inferiority limit is usually set at 10%–20%, but choosing a non-inferiority limit remains difficult and debatable [30].

In the current study we demonstrated that PCT could be used to save blood cultures in critically ill patients suspected of infection. Using this strategy does not affect the prompt start of antibiotics in a patient suspected of a serious infection, neither does this strategy influence the time for a blood culture to become positive, as there is only a maximum delay of 1 hour. It may not limit overtreatment with antibiotics, however, unless it is decided upon to limit antibiotics at a low procalcitonin, which was not the purpose of the study. Nevertheless, most procalcitonin results in this study were obtained within 30 minutes, allowing in any case a timely administration of antibiotics if deemed necessary on clinical grounds. For de-escalation of antibiotics, local cultures should remain available when blood cultures are (presumably) negative.

Conclusion

In conclusion, this prospective multicentre randomized trial showed that using a procalcitonin-guided strategy to obtain blood cultures in critically ill patients with a suspicion of infection seems to be safe, though the benefits may be limited.

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Transparency declaration

The authors declare that they have no conflict of interests.

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Authors' contributions

PJG and ABJG designed the study and drafted the manuscript. PJG, DN and ABJG performed the analyses. PJG, MM and SD collected the data. All authors reviewed the manuscript. All authors read and approved the final version of this manuscript. PJG, ABG and DN had full access to the data. MM was the guarantor for the data.

Appendix A. Supplementary data

Additional Supporting Information may be found in the online version of this article at http://dx.doi.org/10.1016/j.cmi.2016.10.004.

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