Intensive Care Med (2012) 38:940–949
DOI 10.1007/s00134-012-2563-7

SYSTEMATIC REVIEW

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An ESICM systematic review and meta-analysis of procalcitonin-guided antibiotic therapy algorithms in adult critically ill patients

Received: 13 July 2011
Accepted: 17 March 2012
Published online: 27 April 2012

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Abstract *Purpose:* We sought to perform a systematic review and meta-analysis of procalcitonin(PCT)-guided antibiotic therapy algorithms for critically ill adult patients. *Methods:* We performed a search in PubMed and in the Cochrane Central Register of Controlled Trials. Seven evaluable randomised clinical trials (RCTs) were identified and analysed. Primary outcomes included the duration of antibiotic therapy for the first episode of infection and 28-day mortality. Secondary outcomes included length of ICU stay, length of hospitalisation, antibiotic-free days within the first 28 days of hospitalisation, recurrences, and superinfections. *Results:* Data on the duration of antibiotic therapy for the first episode of infection were provided in five out of seven included RCTs, while data on 28-day mortality were provided in all of the included RCTs. Duration of antibiotic therapy for the first episode of infection was reduced in favour of PCT-guided treatment [pooled weighted mean difference (WMD) = −3.15 days, random effects model, 95 % confidence interval (CI) −4.36 to −1.95, $P < 0.001$]. There was no difference in 28-day mortality between the compared arms [fixed effect model (FEM), odds ratio = 0.96, 95 % CI 0.79–1.15, $P = 0.63$). Antibiotic-free days were increased within the first 28 days of hospitalisation in favour of the PCT-guided treatment arm (pooled WMD = 3.08 days, FEM, 95 % CI 2.06–4.10, $P < 0.001$). No difference was found regarding the remaining outcomes. Sensitivity analyses including studies of higher quality and studies using the TRACE method to measure PCT yielded similar results. *Conclusions:* Procalcitonin-guided antibiotic therapy algorithms could help in reducing the duration of antimicrobial administration without having a negative impact on survival.

Keywords Intensive care · Gram-negative · Procalcitonin · Duration · Cost

Introduction

Procalcitonin (PCT) is a precursor of calcitonin and consists of the N-terminal end, calcitonin, and catacalcin, including 116 amino acids in total. In healthy subjects, it is produced by thyroid C cells. However, in cases of infection it is mainly produced by extrathyroid cells, such as neuroendocrine lung cells and monocytes. In healthy adults, PCT's plasma concentration is less than 0.1 ng/ml. It is normally elevated in full-term neonates, attaining its peak value in the first 24 h of life. Otherwise, PCT elevations are pathological and may occur as a result of

infectious and non-infectious causes including neoplasias and acute myocardial infarction [1]. PCT production is induced by exotoxins, TNF-α, and other cytokines, and is rapid after the onset of infection. Its concentration depends mainly on its production rate.

Consequently, PCT can be used in the diagnosis of sepsis. However, a recent meta-analysis estimates the accuracy of PCT as being relatively low when used alone for sepsis diagnosis in critically ill adult patients, namely 71 % for both sensitivity and specificity [2]. Nevertheless, it could be a useful biomarker to monitor the course of infection and sepsis if it is used in combination with clinical signs and laboratory findings [3, 4].

Timely antibiotic administration is crucial, as each hour of delay during the first 6 h after sepsis occurs results in an increase in mortality of 7.9 % [5]. Furthermore, the duration of antibiotic treatment for critically ill patients with infection and sepsis has been a controversial issue. While longer course regimens increase the risk of superinfections, adverse events, and emergence of resistant pathogens, short-course regimens increase the risk of recurrence of the infection. Given this, PCT has been used as a guide in order to shorten and optimise the duration of antibiotic treatment for community infections [6–10].

The ESICM working group on meta-analysis sought the available evidence to perform a systematic review and meta-analysis of randomised controlled trials (RCTs) so as to determine whether a similar approach could be applied to the critical care setting.

Methods

Data sources

Searches in databases including PubMed and the Cochrane Central Register of Controlled Trials generated the studies included in the meta-analysis. Bibliographies of evaluable studies were also hand searched. The search terms used were "procalcitonin", "intensive care", and "ICU". Two reviewers independently performed the literature search, evaluated the potentially eligible studies, and extracted the data. Any disagreement regarding the findings of the two reviewers was resolved in meetings including at least three of the authors.

Study selection criteria

A study was eligible for our meta-analysis if it was an RCT that compared PCT-guided antibiotic therapy with empirical or guideline-guided antibiotic therapy in critically ill adult patients with suspected or proven sepsis, and reported data regarding any of the following outcomes: duration of antibiotic therapy for the first episode of infection, mortality, recurrences, superinfections, antibiotic exposure, length of stay, and duration of mechanical ventilation. No studies were excluded because of language restrictions.

Quality assessment

The quality of the included studies was assessed by examining whether the included studies were randomised, blinded, and provided patient withdrawal data. Moreover, the appropriateness of randomisation and blinding was reviewed. One point was given for the presence of each of the first three criteria. A study could receive a maximum of 5 points. One point was either added or deducted if the last two criteria were appropriate or not, accordingly. A study was considered to be of good quality if it had a score of more than 2 points. Two reviewers calculated the quality score of each study independently [11, 12].

Data extraction

Data extracted from each eligible RCT included author name and year of publication, country and setting, size of the per protocol population, compared regimens, PCT measurement method, duration of antibiotic therapy for the first episode of infection, 28-day mortality, length of ICU stay, length of hospitalisation, antibiotic exposure per 1,000 days, antibiotic-free days within the first 28 days of hospitalisation, mechanical ventilation-free days, recurrences, and superinfections, as defined by the authors.

Outcomes

Duration of antibiotic therapy for the first episode of infection and 28-day mortality were the primary outcomes of this meta-analysis. If data on the antibiotic therapy of the first episode of infection were not provided, the available data regarding the duration of antibiotic treatment were used. Similarly, if data on 28-day mortality were not reported, the available data regarding mortality were used. The secondary outcomes were length of ICU stay, length of hospitalisation, antibiotic exposure per 1,000 days, antibiotic-free days within the first 28 days of hospitalisation, mechanical ventilation-free days, recurrences, and superinfections. To achieve results of adequate statistical quality, analyses were performed when data from at least two RCTs were available. Sensitivity analyses were performed including studies of higher quality (Jadad score >2) and studies using the TRACE method to measure PCT.

Statistical analysis

Statistical analysis was performed using STATA v.11 (StataCorp, Stata Statistical Software: release 11. College Station, TX: StataCorp LP 2009). Between-study statistical heterogeneity was assessed by χ^2 test and I^2 test; values of the I^2 index of 25, 50, and 75 % indicated the presence of low, moderate, and high between-trial heterogeneity, respectively, while a P value of < 0.10 was considered to denote statistical significance of heterogeneity [13]. Continuous variables were analysed using weighted mean differences (WMD) and 95 % confidence intervals (CIs). Where means and variances were not available, they were estimated from the medians, ranges, and size of the samples [14]. Pooled odds ratios (ORs) and 95 % CIs were calculated for dichotomous variables. For all analyses performed, if no significant heterogeneity was noted, fixed effect model (FEM) analysis using the Mantel-Haenszel method [15] was presented; otherwise, results of the random-effects model (REM) analysis using the DerSimonian-Laird method [16] were presented. The small number of the included RCTs did not allow the estimation of potential publication bias with the funnel plot method for any of the outcomes, either primary or secondary.

Results

Study selection process

The process of screening and selecting articles to be included in the meta-analysis is depicted in Fig. 1. We identified 436 and 34 potentially evaluable papers from PubMed and Cochrane Central Register of Controlled Trials, respectively. Finally, seven RCTs fulfilled the criteria to be included in the meta-analysis [17–22].

Study characteristics

In Table 1, we present the characteristics of the included RCTs. Four of the included trials were single centre [19, 20, 22, 23], while the remaining were multicentre

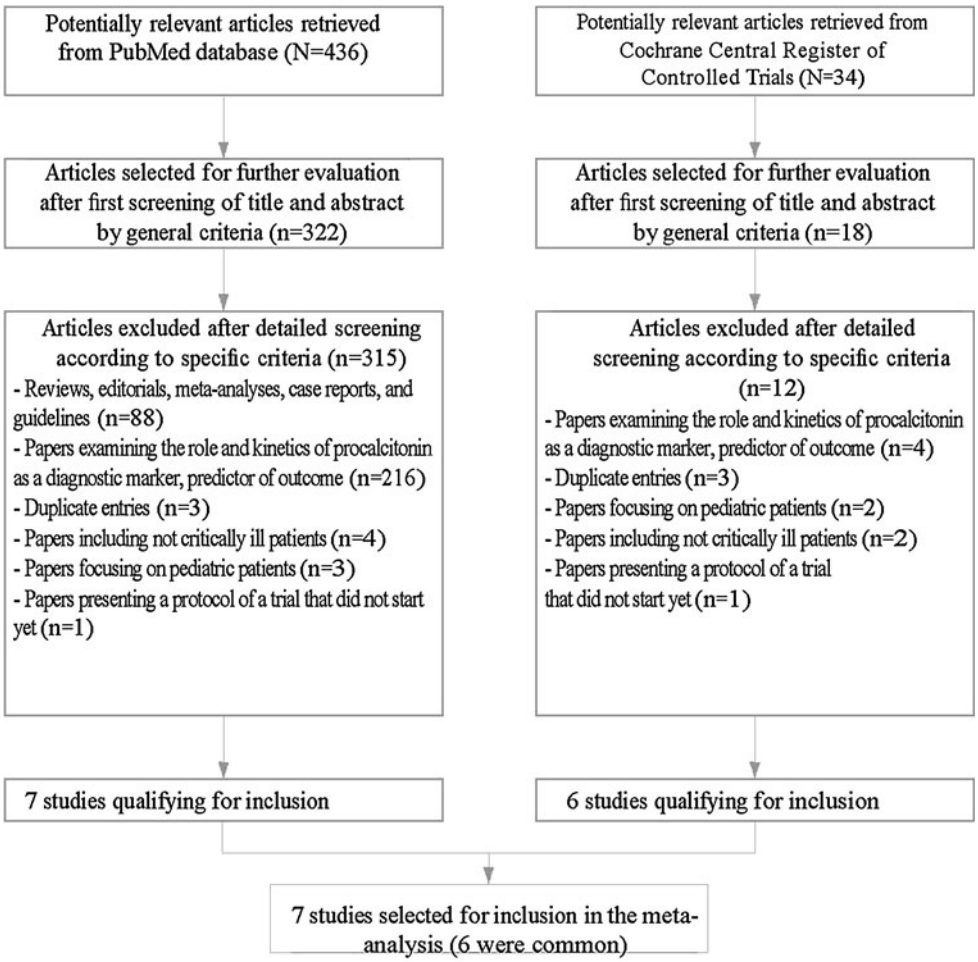

Fig. 1 Flow diagram of the article selection process for this meta-analysis

Table 1 Main characteristics of the included trials

Author [ref]	Country—setting	Included per protocol patients	PCT-guided arm protocol	Control arm protocol	PCT method	Jadad score
Jensen et al. [17]	Denmark—multicenter—mixed patients	1,200 total 604 PCT 596 control	If "alert PCT": increase of antimicrobial spectrum covered and intensification of diagnostic effort for uncontrolled infection sources "Alert PCT" ≥ 1.0 ng/ml that was not decreasing at least 10 % from the previous day At baseline, "alert PCT" = a single PCT ≥ 1.0 ng/ml	Antimicrobial therapy according to guidelines	TRACE	4
Bouadma et al. [18]	France—multicenter—mixed patients	621 total 307 PCT 314 control	Antibiotic discontinuation if PCT < 0.5 ng/ml or PCT < 80 % of the peak concentration	Regimens according to guidelines	TRACE	3
Hochreiter et al. [19]	Germany—single center—surgical patients	110 total 53 PCT 57 control	Antibiotic discontinuation if there was improvement of signs/symptoms and PCT < 1 ng/ml or 25-35 % of initial value over 3 days	Standard regimen over 8 days	LIA	1
Schröder et al. [20]	Germany—single center—abdominal surgery patients	27 total 14 PCT 13 control	Antibiotic discontinuation if there was improvement of signs/symptoms and PCT < 1 ng/ml or 25–35 % of initial value over 3 days	According to clinical signs and empiric rules	LIA	1
Stolz et al. [21]	USA/Switzerland—multicenter—VAP patients	101 total 51 PCT 50 control	Antibiotic discontinuation if PCT < 0.5 ng/ml or PCT < 80 % of initial value	According to clinical signs and empiric rules	TRACE	3
Nobre et al. [22]	Switzerland—single center—mixed septic patients	68 total 31 PCT 37 control	If baseline PCT > 1 ng/ml: antibiotic discontinuation if PCT < 0.25 ng/ml or PCT < 90 % of the baseline peak concentration If baseline PCT < 1 ng/ml: antibiotic discontinuation if PCT < 0.1 ng/ml and careful clinical evaluation	Regimens according to guidelines	TRACE	3
Svoboda et al. [23]	Czech Republic—single center—multiple trauma patients	72 total 38 PCT 34 control	If PCT > 2 ng/ml: change of antibiotics If PCT < 2 ng/ml: ultrasonography and/or CT followed by surgical treatment if infection was confirmed	Standard evaluation by consultant surgeon	LUMI	3

PCT procalcitonin, *VAP* ventilator-associated pneumonia, *CT* computed tomography, *TRACE* time resolved amplified cryptate emission, *LIA* immunoluminometric assay, *LUMI* immunoluminometric assay (older than LIA)

[17, 18, 21]. All of them were performed in Europe, specifically, two in Germany [19, 20], two in Switzerland (one of which was in collaboration with ICUs in the USA) [21, 22], one in Denmark [17], one in France [18], and one in the Czech Republic [23]. Three of the RCTs involved surgical patients [19, 20, 23], three involved mixed septic patients [17, 18, 22], and one patients with ventilator-associated pneumonia [21]. In total, 2,199 patients were included in the trials, of which 1,098 were assigned to the PCT-guided treatment arm and 1,101 were assigned to the control group. Five of the RCTs were considered to be of good quality [17, 18, 21–23]. In the PCT-guided treatment arm of all RCTs, antibiotics were discontinued when PCT was lower than a value that ranged from 0.5 to 1 ng/ml. In the control arm of all studies, regimens were based on routine practice and guidelines.

Primary outcomes

In Table 2, we present the extracted data regarding the primary and secondary outcomes of the meta-analysis.

Duration of antibiotic therapy for the first episode of infection

Data on the duration of antibiotic therapy for the first episode of infection were provided in five of seven of the included RCTs [18–22]. There was a reduction in the duration of antibiotic therapy for the first episode of infection in favour of PCT-guided treatment with a pooled WMD of −3.15 days ($P < 0.001$, $I^2 = 88.7$ %, REM: 95 % CI −4.36 to −1.95, $P < 0.001$) (Fig. 2).

Sensitivity analysis limited to studies of good quality [18, 21, 22] showed a reduction in the duration of antibiotic therapy for the first episode of infection in favour of the PCT-guided treatment arm with a pooled WMD of −4.32 days ($P = 0.30$, $I^2 = 17.2$ %, FEM: 95 % CI −5.17 to −3.48, $P < 0.001$). Sensitivity analysis excluding the study that provides data regarding the total duration of antibiotic treatment [21] showed a reduction in the duration of antibiotic therapy for the first episode of infection in favour of the PCT-guided treatment arm with a pooled WMD of −2.56 days ($P = 0.003$, $I^2 = 78.1$ %, REM: 95 % CI −3.51 to −1.61, $P < 0.001$). The findings of the sensitivity analysis including studies measuring PCT with the TRACE method correspond to those of the sensitivity analysis including studies of good quality.

Twenty-eight-day mortality

Data on 28-day mortality were provided in all RCTs included [17–23]. There was no difference in 28-day mortality between the compared arms ($P = 0.91$, $I^2 = 0$ %, FEM: OR = 0.96, 95 % CI 0.79–1.15, $P = 0.63$) (Fig. 3).

Sensitivity analysis including studies of good quality [17, 18, 20–22] showed no difference in 28-day mortality between the two arms ($P = 0.71$, $I^2 = 0$ %, FEM: OR = 0.95, 95 % CI 0.79–1.16, $P = 0.63$). Sensitivity analysis including studies measuring PCT with the TRACE method [17, 18, 20, 21] showed no difference in 28-day mortality between the two arms ($P = 0.77$, $I^2 = 0$ %, FEM, OR = 0.97, 95 % CI 0.80 to 1.19, $P = 0.79$). The sensitivity analysis excluding the studies that reported data regarding overall mortality [19, 20] yielded the same results as the analysis including studies of good quality.

Secondary outcomes

Length of ICU stay

Data regarding the length of ICU stay were provided in six out of seven of the included RCTs [17–20, 22, 23]. There was no difference in length of ICU stay between the compared arms ($P = 0.03$, $I^2 = 58.9$ %, FEM: WMD −0.36, 95 % CI −1.97–1.26, $P = 0.67$).

Sensitivity analysis including studies of good quality [17, 18, 22, 23] showed no difference in length of ICU stay between the compared arms ($P = 0.02$, $I^2 = 69.3$ %, REM: WMD = −0.18, 95 % CI −2.07–1.70, $P = 0.85$). The number of studies measuring PCT with the TRACE method yielded the same results as the analysis including studies of good quality.

Length of hospitalisation

Data regarding the length of hospitalisation were provided in three of seven of the included RCTs [18, 21, 22]. There was no difference in length of hospitalisation between the compared arms ($P = 0.28$, $I^2 = 22$ %, FEM: WMD = −0.12, 95 % CI −1.09–0.85, $P = 0.80$).

Sensitivity analysis including studies of good quality, as well as studies measuring PCT with the TRACE method yielded the same results as the main analysis.

Antibiotic-free days within the first 28 days of hospitalisation

Data on antibiotic-free days within the first 28 days of hospitalisation were provided in three out of seven of the included RCTs [18, 21, 22]. There was an increase in antibiotic-free days within the first 28 days of hospitalisation in favour of the PCT-guided treatment arm with a pooled WMD of 3.08 days ($P = 0.71$, $I^2 = 0$ %, FEM: 95 % CI 2.06–4.10, $P < 0.001$).

Table 2 Primary and secondary outcomes of the included trials

Outcome	Treatment arm	Jensen et al. [17]	Bouadma et al. [18]	Hochreiter et al. [19]	Schröder et al. [20]	Stolz et al. [21]	Nobre et al. [22]	Svoboda et al. [23]
Duration of antibiotic therapy for the first episode of infection (days)	PCT arm	NR	6.1 ± 6.0	5.9 ± 1.7	6.6 ± 1.1	10 (6–16)[#]	6 (4–16)	NR
	Control arm		9.9 ± 7.1	7.9 ± 0.5	8.3 ± 0.7	15 (10–23)[#]	10 (3–33)	
28-Day mortality [*n*/*N* (%)]	PCT arm	190/604 (31.5)	65/307 (21.2)	15/57 (26.3)*	3/14 (21.4)*	8/51 (15.7)	5/31 (16.1)	10/38 (26.3)
	Control arm	191/596 (32.0)	64/314 (20.4)	14/53 (26.4)*	3/13 (23.1)*	12/50 (24)	6/37 (16.2)	13/34 (38.2)
ICU length (days)	PCT arm	6 (3–12)	15.9 ± 16.1	15.5 ± 12.5	16.4 ± 8.3	NR	3 (1–18)	16.1 ± 6.9
	Control arm	5 (3–11)]	14.4 ± 14.1	17.7 ± 10.1	16.7 ± 5.6		5 (1–30)	19.4 ± 8.9
Hospitalisation length (days)	PCT arm	NR	26.1 ± 19.3	NR	NR	26 (7–21)	14 (5–64)	NR
	Control arm		26.4 ± 18.3			26 (16.8–22.3)	21 (5–89)	
Antibiotic exposure/1,000 days	PCT arm	NR	653	NR	NR	NR	504	NR
	Control arm		812				655	
Antibiotic-free days within the first 28 days (days)	PCT arm	NR	14.3 ± 9.1	NR	NR	13 (2–21)	17.4 ± 7.6	NR
	Control arm		11.6 ± 8.2			9.5 (1.5–17)	13.6 ± 7.6	
Mechanical ventilation-free days (days)	PCT arm	NR	16.2 ± 11.1	NR	NR	21 (2–24)	NR	NR
	Control arm		16.9 ± 10.9			19 (8.5–22.5)		
Recurrence [*n*/*N* (%)]	PCT arm	NR	20/307 (6.5)	NR	NR	6/51 (11.8)	1/31 (3.2)	NR
	Control arm		16/314 (5.1)			11/50 (22)	1/37 (2.7)	
Superinfection [*n*/*N* (%)]	PCT arm	NR	106/307 (34.5)	NR	NR	7/51 (13.7)	7/31 (22.5)	NR
	Control arm		97/314 (30.9)			6/50 (12)	11/37 (29.7)	

PCT procalcitonin, *ICU* intensive care unit, *NR* not reported

* Refers to total in-hospital mortality

[#] Refers to overall duration of antibiotic therapy

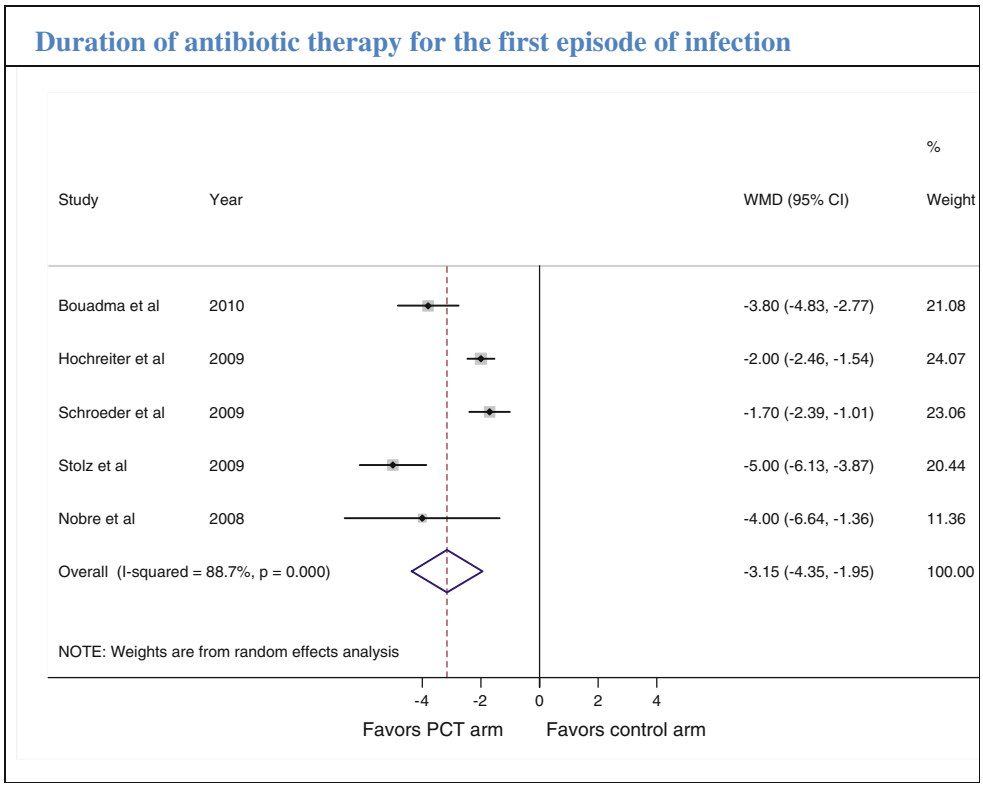

Fig. 2 Weighted mean difference of duration of antibiotic therapy for the first episode of infection. *Vertical line* "no difference" point in antibiotic duration between the two arms. *Horizontal lines* 95 % CI. *Square* odds ratio; the size of each square denotes the proportion of information provided by each trial. *Diamond* pooled odds ratio for all trials

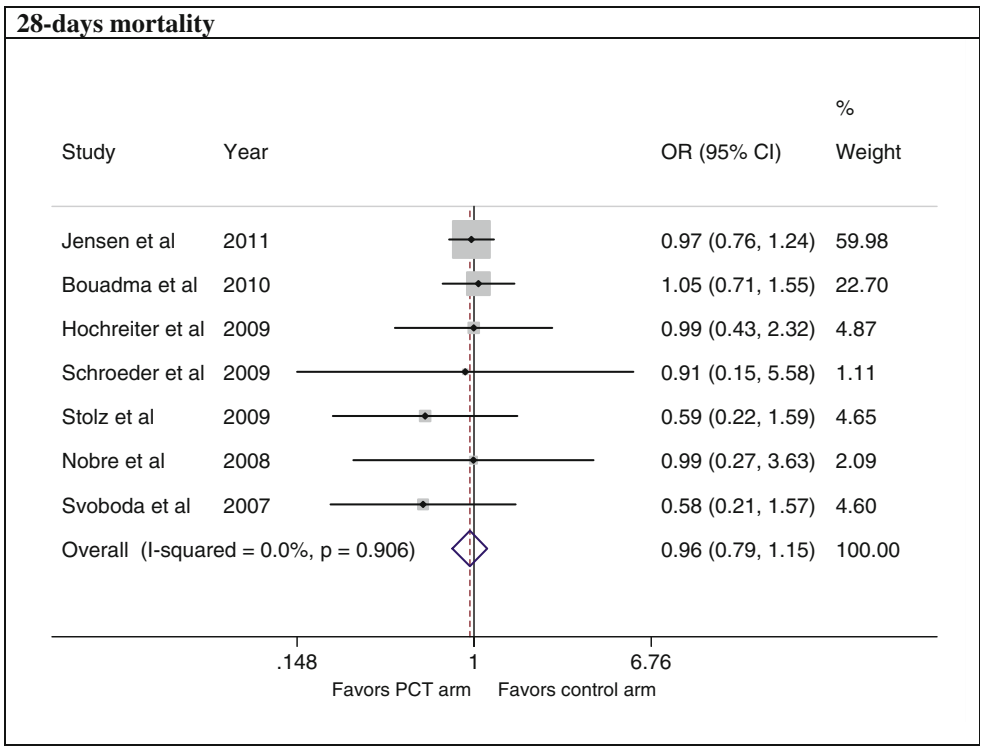

Fig. 3 Odds ratios of 28-day mortality. *Vertical line* "no difference" point in antibiotic duration between the two arms. *Horizontal lines* 95 % CI. *Square* odds ratio; the size of each square denotes the proportion of information provided by each trial. *Diamond* pooled odds ratio for all trials

Sensitivity analyses including studies of good quality as well as studies measuring PCT with the TRACE method were the same as the main analysis.

Recurrences

Data on recurrences were provided in three of seven of the included RCTs [18, 21, 22]. There was no difference in recurrences between the two arms ($P = 0.30$, $I^2 = 17.4$ %, FEM: OR = 0.98, 95 % CI 0.56–1.70, $P = 0.93$).

Sensitivity analyses including studies of good quality as well as studies measuring PCT with the TRACE method were the same as the main analysis.

Superinfections

Data on superinfections were provided in three out of seven of the included RCTs [18, 21, 22]. There was no difference in superinfections between the two arms ($P = 0.66$, $I^2 = 0$ %, FEM: OR = 1.13, 95 % CI 0.83–1.54, $P = 0.44$).

Sensitivity analyses including studies of good quality as well as studies measuring PCT with the TRACE method were the same as the main analysis.

Discussion

Our study suggests that PCT-guided treatment in comparison with standard practice may significantly shorten the duration of antibiotic administration in critically ill adult patients with sepsis by just over 3 days. However, there was no difference between PCT-guided treatment and standard treatment in terms of mortality. The findings of sensitivity analyses including studies of good quality and studies using the TRACE method for the measurement of PCT did not change these associations.

There was no difference between PCT-guided treatment and standard practice regarding any of the secondary outcomes, except antibiotic-free days within the first 28 days of hospitalisation, in which patients assigned to the PCT-guided treatment arm had an increase of about 3 days. This is roughly equal to the reduction in the duration of antibiotic administration.

The shortening of the duration of antimicrobial therapy may have a dual impact in the intensive care setting. First, less exposure to antibiotics may result in the reduction of emergence of resistance, which may consequently lead to multi-drug resistant or even pan-drug resistant pathogens [24]. In addition, adverse events may be reduced without compromising the effectiveness of the therapeutic regimen. Second, the reduction in antibiotic usage may also contribute to considerable savings with regard to antibiotic costs [25]. A relevant Canadian study estimated a mean daily reduction in antibiotic costs of Can$148.26 (ranging between Can$59.30 and Can$296.52) considering a scenario of 6-day procalcitonin measurement and a 2-day shortening of antibiotic administration [26]. These estimates might be even greater, depending on the antibiotic usage and the pricing policy in each country.

Three relevant meta-analyses have been published previously [27–29]. All studies had comparable findings, reporting a reduction in the duration of antibiotic therapy and in the total antibiotic exposure. Although varying, these reductions were consistent among the studies. However, two of the meta-analyses [28, 29] did not focus on critically ill patients. Additionally, other RCTs have been published since, which were not included in that analyses.

One may argue that the addition of the Danish study in the meta-analysis should be revisited because the protocol followed is the reverse of the ones in the rest of the included studies, namely escalation versus de-escalation strategies based on procalcitonin guidance. Furthermore, its findings are not supportive of PCT-based escalation therapeutic strategies, and this, given its sample size, is an important contribution to the field. We considered that the inclusion of studies with different PCT-based therapeutic strategies, either escalation or de-escalation, represents different approaches on the same topic, that is the use of PCT as a guide in implementing therapeutic protocols. Thus, the cumulative analysis of different protocols may further enlighten the use of this biomarker in the management of critically ill patients. With regards to the elimination of the findings of the Danish study, it is interesting to note that although it included more than half of the total sample, it did not have an impact on our findings on mortality and ICU length of stay in comparison with previous meta-analyses. On the contrary, our findings are comparable to those of other meta-analyses, but more robust because of the greater sample and, subsequently, the smaller confidence interval of the results. Whether a PCT-based escalation strategy leads to increased organ-related harm should be taken under consideration, but it is out of the scope of our analysis. It would be interesting if data on the duration of antibiotic therapy for the first episode of infection were provided, but the only relevant datum reported is the median length of an antibiotic course, which could not be included in our analyses.

Furthermore, an interesting debate developed regarding the 60-day mortality reported in the French study [18]. Although not significant, the reported mortality was 3.8 % higher in the procalcitonin arm. However, the confidence interval was wide, up to 9.8 % in the procalcitonin arm. Such a difference in mortality against procalcitonin-guided protocols, although a possibility, is not acceptable, and more studies with large numbers of participants are warranted to clarify the issue.

Thus, the question that arises is whether procalcitonin could be used as a sole biomarker determinant in optimising antibiotic therapy. Although procalcitonin seems to be a promising biomarker, caution is needed in its use. An algorithm combining gradually reducing procalcitonin values in consecutive measurements, strictly in combination with the assessment of the patient's clinical course and laboratory findings, could be a more effective guide in order to determine when it is suitable to stop antibiotics [30].

Further insights on the use of procalcitonin-guided antibiotic therapy algorithms will be provided in the future after four ongoing RCTs are completed [31–34]. Three of them are in the recruiting phase [31–33], while the last one is not yet open [34]. The German [31] and the Dutch [32] RCTs are estimated to have roughly 3,500 enrolled patients, which is more than one and a half times the study numbers included in our analysis. The remaining Brazilian [33] and the other Dutch trial [34], which is yet to open, will include smaller patient samples.

There are some limitations of our review that need to be considered. First, the number of studies was small, including 2,199 patients. However, overall quality was good with five out of seven RCTs attaining a Jadad score of 3 or more. Second, there was a considerable degree of statistical heterogeneity regarding some analyses. To cope with this heterogeneity, random effects models were used when appropriate. Furthermore, there was clinical heterogeneity regarding the type of ICU (medical/surgical) and the interventional protocol, while the included RCTs were conducted in different, although limited in number, countries. Thus, extrapolation of our findings in the ICU setting in general may be facilitated, since a variety of critically ill patients was included in our analyses. It should also be noted that all protocols required subsequent reductions in daily procalcitonin measurements until reaching normal values or lower than 10 % of the initial ones. Third, different measurement methods were used between the included RCTs, which may in turn cause bias in the results. Lastly, in some cases there was no consistency, especially regarding mortality, for which two of the studies report on total mortality [19, 20], whereas the rest report on 28-day mortality, in the reported outcomes between the studies. To overcome this limitation, sensitivity analyses were performed accordingly.

In conclusion, procalcitonin-guided antibiotic therapy algorithms could help in reducing the duration of antimicrobial administration without having a negative impact on survival. However, it should be emphasised that such algorithms are tools that should be used in conjunction with clinical signs and laboratory findings to ensure maximal efficacy.

Acknowledgments We would like to thank Prof. Hazel Inskip (MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, UK) for her kind suggestions during the preparation of the manuscript and Dr. Tannaze Tinati (MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK) for editing the manuscript in its final form.

Conflicts of interest None.

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