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Ineffectiveness of procalcitonin-guided antibiotic therapy in severely critically ill patients: A meta-analysis

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ABSTRACT

Background: Optimizing antibiotic therapy has an important impact on the management of critically ill patients. Procalcitonin (PCT) is considered to be of possible use in the guidance of antibiotic stewardship; however, its efficacy remains controversial. Thus, a meta-analysis was performed to determine the efficacy of PCT-guided antibiotic therapy in critically ill patients.

Methods: The relevant literature was searched in PubMed, Embase, Web of Science, and the Cochrane Library covering the period from 2004 to August 2018. Randomized controlled trials (RCTs) were included if critically ill patients were treated with PCT-guided antibiotic therapy or standard care. The primary outcome was short-term mortality; secondary endpoints were the duration of antibiotic treatment, intensive care unit (ICU) length of stay (LOS), and hospital LOS.

Results: Sixteen RCTs enrolling 6452 critically ill patients were included in this analysis. The pooled analysis demonstrated a comparable short-term mortality (rate ratio (RR) 0.90, 95% confidence interval (CI) 0.80–1.01; $p = 0.07$), ICU LOS (mean difference (MD) 0.38, 95% CI −0.05 to 0.81; $p = 0.09$), and hospital LOS (MD 0.19, 95% CI −1.56 to 1.95; $p = 0.83$) for PCT-guided antibiotic therapy and standard antibiotic therapy, and an antibiotic duration shorter by 0.99 days (95% CI −1.85 to −0.13 days; $p = 0.02$) for PCT-guided antibiotic therapy. In the subgroup analysis, patients with an average Sequential Organ Failure Assessment (SOFA) score of <8 in the PCT-guided cessation of antibiotics group had a lower short-term mortality compared with the standard care group (RR 0.81, 95% CI 0.66–0.99; $p = 0.04$), while no difference was found in the subgroup with an average SOFA score of >8 (RR 0.85, 95% CI 0.66–1.11; $p = 0.23$).

Conclusions: PCT-guided antibiotic therapy fails to decrease the mortality or LOS of critically ill patients with suspected or confirmed sepsis. PCT-guided cessation of antibiotic therapy could reduce the mortality in patients with an average SOFA score of <8, but not in those with an average SOFA score of >8.

Introduction

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer et al., 2016), remains a major contributor to death in critically ill patients. The initiation of broad-spectrum antibiotics within the first hour of triage in the emergency department or presenting from another care institution, is an essential aspect of high-quality sepsis management (Rhodes et al., 2017). However, the incorrect use or abuse of antibiotics is considered to lead to an increased risk of opportunistic infection, antimicrobial resistance, and mortality, and increased healthcare costs (Zilahi et al., 2016). Optimizing the management of antibiotic therapy has a very important impact on the treatment of sepsis and management of multidrug-resistant bacteria.

An organized and systematic approach to delivering interventions with proven efficacy and the prompt institution of appropriate therapy are the most effective means for improving the prognosis in the intensive care setting (Rhodes et al., 2017; Levy et al., 2018 Levy et al., 2018). The blood infection biomarker procalcitonin (PCT) has been approved and suggested for the guidance of antibiotic therapy in the context of acute infections and sepsis (Annane et al., 2013; Deliberato et al., 2013; Bloos et al., 2016; de Jong et al., 2016; Huang et al., 2017; Iankova et al., 2018; Lamping et al., 2018). PCT is a calcitonin precursor produced by the epithelial cell in response to bacterial infections, and levels reduce

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rapidly during recovery. Therefore, as a representative marker of the host response to acute infection, PCT has been proposed to assist physicians in determining individual infection status and making individualized antibiotic therapy decisions.

However, the efficacy of PCT-guided antibiotic therapy in suspected or confirmed infection and sepsis has proved controversial over recent decades (de Jong et al., 2016; Schuetz et al., 2017; Daubin et al., 2018; Huang et al., 2018; Iankova et al., 2018; Lamping et al., 2018). Several systematic reviews and meta-analyses have attempted to summarize the available literature and assess the value of PCT-guided strategies (Huang et al., 2017; Lamping et al., 2018). Previous meta-analyses have generally reported a marked decrease in antibiotic exposure with PCT-guided antibiotic therapy, but not in mortality or intensive care unit (ICU) and hospital length of stay (LOS) (Huang et al., 2017; Iankova et al., 2018; Lamping et al., 2018). Furthermore, a recent trial in France reported a comparable antibiotic exposure and mortality in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) admitted to the ICU in the PCT-guided antibiotic therapy group and standard care group (Daubin et al., 2018). Thus, its efficacy is ambiguous.

The present study was performed to address this prominent drawback of conflicting meta-analysis results and to provide an updated meta-analysis on the efficacy of PCT-guided antibiotic therapy. It was sought to expand on the previous analyses by including studies published more recently in a meta-analysis on the efficacy of PCT-guided antibiotic therapy in critically ill patients.

Materials and methods

This meta-analysis was performed and reported according to a pre-specified protocol registered in the International Prospective Register of Systematic Reviews (Moher et al., 2010) (PROSPERO registration number: CRD42018109721) and was prepared in accordance with the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses).

Literature search and data extraction

The PubMed, Embase, Web of Science, and Cochrane Central Register of Controlled Trials databases were searched for randomized controlled trials (RCTs) published between January 2004 and August 2018. The keywords ("Procalcitonin" OR "PCT") and ("Anti-Bacterial Agents" OR "Antibiotics" OR "Antibacterial") were searched to identify potentially relevant studies assessing PCT-guided antibiotic therapy among critically ill patients. No language restriction was imposed. (See **Supplementary Material** Table S1.)

Working in pairs, four reviewers screened citations and abstracts in duplicate and independently. The inclusion criteria encompassed PCT-guided antibiotic therapy compared with standard antibiotic therapy, critically ill adult patients, data reported for mortality, LOS, or duration of antibiotic use, and randomized controlled study design. Studies that did not use PCT to guide antibiotic clinical decision-making were excluded. Case reports, case series, observational or retrospective studies, systematic reviews, and meta-analyses were excluded. Research that was only available in abstract/poster format or that did not present original study data was also excluded. Trials performed before 2004 were not included in this review because the automated PCT immunoassay was only commercialized in that year. Discrepancies between the reviewers' decisions regarding inclusion and exclusion were resolved through discussion.

Two reviewers independently extracted variables from the identified studies including publication details, country of origin, setting, study design, patient characteristics, PCT algorithm used, interventions, methodological quality, compliance with the algorithm, and outcomes. The PCT algorithm was defined as the serum PCT result dictating the medical decision and guiding the initiation, cessation, or both (mixed) of antibiotic therapy. In brief, 'initiation of antibiotics' referred to the clinician's decision to start or not to start, or to escalate antibiotic therapy, and to intensify the diagnostic effort to identify uncontrolled sources of infection based on a PCT value. 'Cessation of antibiotics' referred to the clinician's decision to de-escalate or not to de-escalate, or to stop antibiotic therapy according to a lower baseline value or the drop in PCT concentration. Confirmed infection was defined in a patient with symptoms, signs, and positive laboratory examinations, or a definite diagnosis of sepsis or septic shock. Low adherence to PCT algorithms was defined as <70%, in accordance with Schuetz et al. (Schuetz et al., 2017). Ferreira et al. (Ferreira et al., 2001) showed that the initial Sequential Organ Failure Assessment (SOFA) score predicted the mortality of critically ill patients, with an area under the receiver operating characteristics curve (AUROC) of 0.79 (95% confidence interval (CI) 0.75–0.83) and optimal cut-off of 8 points. Thus, a SOFA score of 8 was chosen as the threshold to discriminate the more severely critically ill patients among the patients with sepsis. Discrepancies in data extraction were discussed with a senior researcher and finally resolved by consensus.

Risk of bias assessment

Two reviewers independently reviewed the included studies and evaluated the risk of bias using the Cochrane Collaboration tool (Higgins et al., 2011). A value of high risk, unclear risk, or low risk was assigned to random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. Discrepancies were resolved by discussion. A funnel plot was used to show the assessment of publication risk of bias.

Outcomes and analyses

The primary outcome was the short-term, all-cause mortality, which included mortality within approximately 28 days and ICU or hospital mortality. Secondary outcomes included the duration of antibiotics, hospital LOS, and ICU LOS. For each of the outcomes or subgroups, a meta-analysis was only performed if there were sufficient data and there were at least three studies in each subgroup, otherwise the studies were excluded from that analysis.

It was planned to assess four subgroups for short-term mortality based upon the following: the strategies of PCT-guided antibiotics, average SOFA score >8 or <8, suspected or confirmed sepsis, and adherence >70% or <70%.

Statistical analysis

For the primary endpoint, short-term mortality was expressed as a risk ratio (RR) and 95% CI; a weighted pooled RR was calculated among included studies using a fixed-effects model for data without heterogeneity and a random-effects model for data with significant heterogeneity. Duration of antibiotics, hospital LOS, and ICU LOS were summarized using the mean difference (MD). The median, interquartile range (IQR), and range in the studies were used to estimate the mean and standard deviation (SD) (Wan et al., 2014). Analyses were done following the intention-to-treat principle, analyzing patients according to the groups to which they were randomly assigned. Heterogeneity was tested by Cochran Q test and I^2. A p-value of <0.10 and I^2 > 50% was considered to indicate significant heterogeneity.

Further meta-regression that focused on strategies of PCT-guided antibiotics, suspected or confirmed infection, SOFA score, and adherence was performed if there was significant clinical heterogeneity. Covariate meta-regression analysis was used to identify the source of heterogeneity and the subgroups. A pre-specified sensitivity analysis was done for short-term mortality and antibiotic duration by influence analysis to evaluate the consistency of the results. A two-sided $p < 0.05$ was accepted to indicate statistical significance.

A trial sequential analysis (TSA) was conducted for the primary outcome to assess the risk of random errors and to calculate the required number of participants (required information size, RIS). The RIS of the TSA was based on 5% risk of a type 1 error and 20% risk of a type 2 error (power of 80%). Analyses were performed using Review Manager (RevMan version 5.3), Stata (version 15), and TSA (version 0.9.5.10).

Results

Study selection

A total of 838 records were identified in the literature databases according to the search strategy (285 in PubMed, 151 in Embase, 284 in Web of Science, and 118 in Cochrane). Of these, 737 potentially eligible articles were reviewed after excluding 101 duplicates. A further 639 were excluded after reading the title or abstract as they were not relevant to the theme. At the full-text stage, 46 were excluded for having no original data, 16 for not using PCT in the antibiotic decision, and 20 for enrolling patients who were not critically ill. Finally, 16 articles involving 6452 participants were included in this review (Nobre et al., 2008; Hochreiter et al., 2009; Schroeder et al., 2009; Stolz et al., 2009; Bouadma et al., 2010; Jensen et al., 2011; Layios et al., 2012; Annane et al., 2013; Oliveira et al., 2013; Shehabi et al., 2014; Najafi et al., 2015; Bloos et al., 2016; de Jong et al., 2016; Wang et al., 2016; Daubin et al., 2018; Deliberato et al., 2013). Decisions arising from the study selection process are presented in Figure 1.

All of the included studies were published in English between 2004 and 2018; 10 were multicenter studies and six were single-center studies. Oliveira et al. (2013) reported comparison arms of PCT- versus C-reactive protein (CRP)-guided antimicrobial therapy. Three RCTs reported PCT-guided initiation of antibiotic therapy, 10 reported the cessation of antibiotics, and three reported mixed initiation and cessation of antibiotic therapy. Nine trials included patients with an average SOFA score of <8 and five trials included patients with an average SOFA score of >8; Jensen et al. (2011) and Wang et al. (2016) did not report SOFA scores. Six studies included patients with confirmed infections, whereas the remaining 10 RCTs included patients with suspected infections. Adherence to PCT algorithms varied, ranging from 47% to 97%. A detailed description of the eligible studies is presented in Table 1.

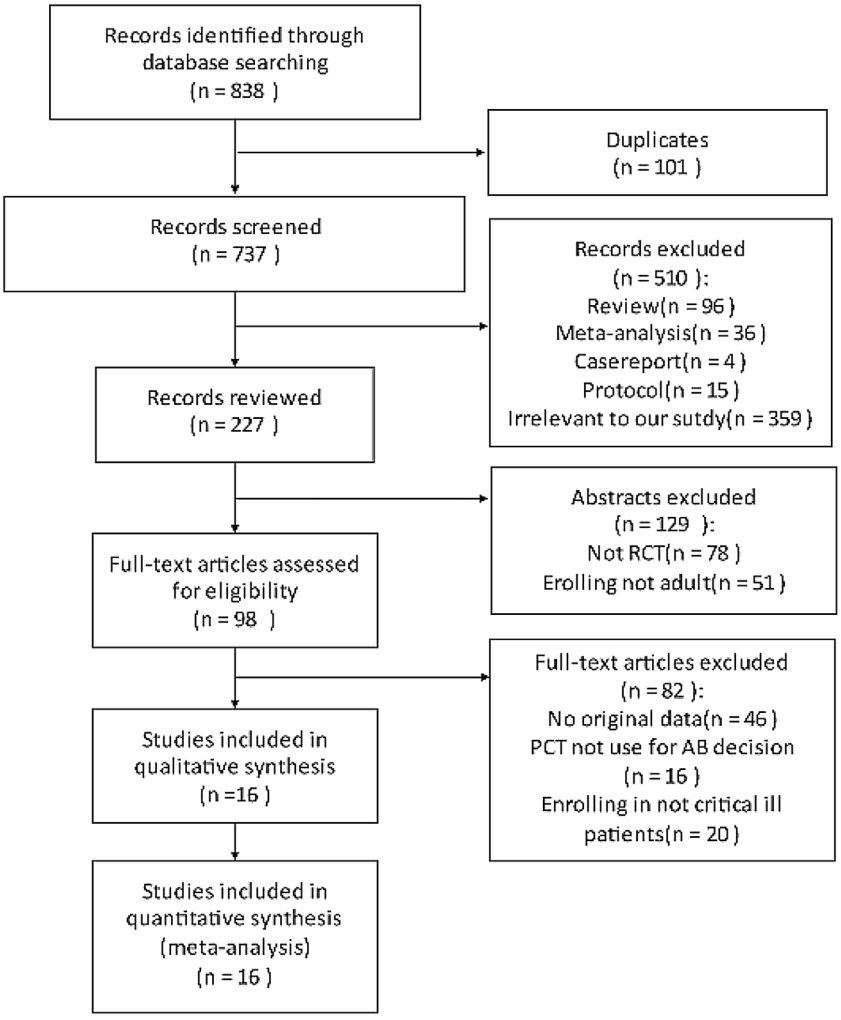

Figure 1. Study flow diagram.

Table 1
Main characteristics of the included RCTs.

First author Year	Study setting	SOFA score	Diagnosis(es) of interest	Cohort	PCT algorithm, ng/ml	Adherence	Short-term mortality	Antibiotics duration, days	Hospital LOS, days	ICU LOS, days
Annane et al. (2013),	8 ICUs in France	10 (8–11) PCT 9.5 (8.5–11) SC	Suspected sepsis	31 PCT 31 SC	0.25 μg/l Mixed	63%	7/31 (22.6%) PCT 10/30 (32.3%) SC[a,b]	5 (4–5) PCT 5 (2–5) SC	27 (9–49) PCT 33 (11–69) SC	22 (8–42) PCT 23 (10–60) SC
Bloos et al. (2016)	33 ICUs in Germany	10.0 (3.3) total	Severe sepsis or septic shock	552 PCT 537 SC	<1 ng/ml or drop by >50% Cessation	<50%	140/547 (25.6%) PCT 149/529 (28.2%) SC[c]	7 (3–12) PCT 7 (3–12) SC	29 (18–46) PCT 26 (16–44) SC	12 (6–24) PCT 11 (6–21) SC
Bouadma et al. (2010)	7 ICUs in France	8.0 (4.7) PCT 7.7 (4.6) SC	Suspected bacterial infections	307 PCT 314 SC	0.5 μg/l or less than 80% Mixed	47%	65/307 (21.2%) PCT 64/314 (20.4%) SC[c]	10.3 ± 7.7 PCT 13.3 ± 7.6 SC	26.1 ± 19.3 PCT 26.4 ± 18.3 SC	15.9 ± 16.1 PCT 14.4 ± 14.1 SC
Daubin et al. (2018)	11 ICUs in France	4 (2–5) PCT 3 (2–5.75) SC	Severe acute exacerbations of COPD	151 PCT 151 SC	0.1 μg/l or less than 90% Mixed	93%	19/151 (12.6%) PCT 17/151 (11.3%) SC[c]	7.9 ± 8 PCT 7.7 ± 5.7 SC	18.85 ± 18.29 PCT 14.82 ± 9.48 SC	9.67 ± 13.37 PCT 7.19 ± 5.98 SC
de Jong et al. (2016)	15 ICUs in the Netherlands	7 (4–10) PCT 7 (5–10) SC	Assumed or proven infection	761 PCT 785 SC	≤0.5 μg/l or drop to ≤20% Cessation	56.9%	149/761 (19.6%) PCT 196/785 (25.0%) SC[c]	5 (3–8) PCT 7 (4–10) SC	21 (12–40) PCT 21 (11–38) SC	8 (4–18) PCT 8 (4–17) SC
Deliberato et al. (2013)	ICU in São Paulo, Brazil	6.29 ± 2.85 PCT 5.38 ± 3.33 SC	Suspected sepsis, severe sepsis, or septic shock	42 PCT 39 SC	<0.5 ng/ml or drop >90% Cessation	20/42 31/39	2/42 (4.8%) PCT 4/39 (10.3%) SC[b]	10 (3–39) PCT 11 (2–45) SC	11 (3–547) PCT 11 (2–228) SC	3.5 (1–57) PCT 3 (1–28) SC
Hochreiter et al. (2009)	ICU at the West Coast Hospital Heide	<8	Confirmed or suspected bacterial infections	57 PCT 53 SC	<1 ng/ml or drop to 35% Cessation	NR	15/57 (26.3%) PCT 14/53 (26.4%) SC[b]	5.9 ± 1.7 PCT 7.9 ± 0.5 SC	NR	15 ± 12.5 PCT 17.7 ± 10.1 SC
Jensen et al. (2011)	9 ICUs across Denmark	NR	Critically ill patients	604 PCT 596 SC	≥1.0 ng/ml Initiation	47%	190/604 (31.5%) PCT 191/596 (32%) SC[c]	6 (3–11) PCT 4 (3–10) SC	NR	6 (3–12) PCT 5 (3–11) SC
Layios et al. (2012)	5 ICUs of the University Hospital of Liege, Belgium	9.3 ± 4.9 PCT 9.1 ± 5.4 SC	Critically ill patients	258 PCT 251 SC	>0.50 μg/l Initiation	46.3%	56/258 (21.7%) PCT 53/251 (21.1%) SC[a]	NR	NR	7 (4–16) PCT 7 (4–18) SC
Najafi et al. (2015)	ICU at Sina Hospital, Iran	5.4 ± 3.6 PCT 5.7 ± 2.8 SC	Critically ill patients with SIRS	30 PCT 30 SC	≥2 ng/ml Initiation	NR	5/30 (16.7%) PCT 4/30 (13.3%) SC[b]	NR	20 (8–44) PCT 22 (6–65) SC	4 (2–20) PCT 6 (2–28) SC
Nobre et al. (2008)	ICU at University Hospital of Geneva, Switzerland	6.6 ± 3.0 PCT 6.4 ± 3.3 SC	Severe sepsis or septic shock	39 PCT 40 SC	<0.25 μg/l or drop >90% Cessation	81%	8/39 (20.5%) PCT 8/40 (20.0%) SC[c]	6 (2–33) PCT 9.5 (3–34) SC	17 (3–96) PCT 23.5 (5–44) SC	4 (1–21) PCT 7 (1–91) SC
Oliveira et al. (2013)	2 ICUs in Brazil	7.5 (5–10) PCT 7 (4–10) CRP	Suspected severe sepsis or septic shock	49 PCT 45 CRP	<0.1 ng/ml or decrease ≥90% Cessation	87.8%	16/49 (32.7%) PCT 15/45 (33.3%) CRP[c]	8.1 ± 3.7 PCT 7.2 ± 3.5 CRP	36 (20–59) PCT 25 (13–52) CRP	14 (9–24) PCT 12 (7–18) CRP
Schroeder et al. (2009)	ICU of the Westküsten-klinikum Heide, Germany	7.3 ± 3.5 PCT 8.3 ± 4.2 SC	Severe sepsis	14 PCT 13 SC	<1 ng/ml or drop to 35% Cessation	NR	3/14 (21.4%) PCT 3/13 (23.0%) SC[b]	6.6 ± 1.1 PCT 8.3 ± 0.7 SC	NR	16.4 ± 8.3 PCT 16.7 ± 5.6 SC
Shehabi et al. (2014)	11 ICUs in Australia	6 (3–9) PCT 6 (3–8) SC	Suspected bacterial infection	196 PCT 198 SC	<0.1 ng/ml or decline >90% Cessation	97%	30/196 (16%) PCT 26/198 (13%) SC[b]	9 (6–21) PCT 11 (6–22) SC	15 (9–29) PCT 17 (10–32) SC	6 (3–9.5) PCT 6 (4–10) SC
Stolz et al. (2009)	7 ICUs in USA and Switzerland	8.2 ± 3.4 PCT 7.3 ± 3.4 SC	Ventilator-associated pneumonia	51 PCT 50 SC	<0.25 μg/l or decrease by ≥80% Cessation	NR	8/51 (16%) PCT 12/50 (24%) SC[c]	10 (6–16) SC 15 (10–23) PCT	26 (7–21) PCT 26 (16.8–22.3) SC	NR
Wang et al. (2016)	Department of Respiratory and CCM Beijing Luhe Hospital, China	NR	Acute exacerbations of COPD	95 PCT 96 SC	<0.1 ng/ml Cessation	NR	5/95 (5.6%) PCT 2/96 (2.1%) SC[b,d]	17 ± 17.9 PCT 12 ± 12.5 SC	10.9 ± 8.1 PCT 9.9 ± 5.1 SC	NR

CCM, critical care medicine; COPD, chronic obstructive lung disease; CRP, C-reactive protein; ICU, intensive care unit; LOS, length of stay; NR, not reported; PCT, procalcitonin-guided antibiotic therapy; RCT, randomized controlled trial; SC, standard care; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

[a] 28-day mortality.
[b] 30-day mortality.
[c] ICU mortality.
[d] Hospital mortality.

Risk of bias

The quality of the trials was appraised according to the Cochrane Collaboration tool: the risk of bias was in high in four trials, moderate in nine trials, and low in three trials (**Supplementary Material** Figure S1). The funnel plot did not show any obvious publication bias, with a relatively uniform distribution either side of the line of unity (**Supplementary Material** Figure S2).

Primary outcome

A total of 16 RCTs (6452 participants) were included in the primary analysis of short-term mortality. The combined estimate of the pooled RR for all studies based on the fixed-effects model for short-term mortality was 0.90 (95% CI 0.80–1.01; $p = 0.07$), with no statistically significant difference observed between PCT-guided antibiotic therapy and standard antibiotic therapy (Figure 2). The test for heterogeneity was not significant ($p = 0.88$; $I^2 = 0\%$), as shown in the sensitivity analysis (**Supplementary Material** Figure S3). On analysis of each PCT strategy subgroup, PCT-guided cessation of antibiotics decreased the short-term mortality of patients in the PCT-guided group compared with those in the standard care group (RR 0.82, 95% CI 0.70–0.96; $p = 0.01$), while no difference was found for the subgroups of initiation strategy (RR 0.99, 95% CI 0.81–1.22; $p = 0.96$) or mixed strategy (RR 1.02, 95% CI 0.73–1.41; $p = 0.92$). No significant subgroup heterogeneity was observed ($p > 0.50$; $I^2 = 0\%$).

With regard to the PCT cessation strategy, patients with an average SOFA score of <8 in the PCT-guided group had lower short-term mortality compared with the standard care group in the subgroup analysis (RR 0.81, 95% CI 0.66–0.99; $p = 0.04$; Table 2), while no difference was found in the subgroup with a SOFA score >8 (RR 0.85, 95% CI 0.66–1.11; $p = 0.23$). There was no indication of heterogeneity ($p > 0.50$; $I^2 = 0\%$). In the subgroup analysis, patients with suspected sepsis or lower algorithm adherence in the PCT-guided group had lower short-term mortality compared with those in the standard care group, while no difference was found in the subgroups of confirmed sepsis or higher algorithm adherence.

A post hoc TSA for mortality at short-term mortality with included trials showed a TSA-adjusted RR of 0.91 (95% CI 0.80–1.02; $p = 0.0988$; $I^2 = 0\%$; diversity (D^2) = 0%). The cumulative did not cross the *Z*-curve, the conventional boundary, or the trial sequential monitoring boundary (Figure 3; **Supplementary Material** Figure S4), indicating the urgent need for larger well-designed RCTs.

Eight trials assessed 28-day mortality and no statistically significant difference was observed between the two groups ($p = 0.05$). Furthermore, there was no statistically significant difference between the groups for ICU mortality (reported in five trials; $p = 0.86$) or hospital mortality (assessed in nine trials; $p = 0.52$) (Table 3).

Secondary outcomes

Antibiotic duration was assessed in 14 trials, with 10 in the cessation subgroup and three in the mixed subgroup, and one in the initiation subgroup. Two studies (Layios et al., 2012; Najafi et al., 2015) were excluded because their measurement of antibiotic duration differed from that in the other studies. The overall mean antibiotic duration was 0.99 days shorter (95% CI −1.85 to −0.13 days; $p = 0.02$; Figure 4) in the PCT-guided group compared with that in the standard care group using a random-effects model. Significant heterogeneity between the pooled trials was observed ($p < 0.001$; $I^2 = 90\%$; **Supplementary Material** Figures S5 and S6). On analysis of each PCT strategy subgroup, the duration was 1.34 days shorter (95% CI −2.08 to −0.60 days; $p = 0.02$) for the patients in the cessation subgroup of the PCT-guided group, while the duration was not significantly shorter in the mixed subgroup patients (95% CI −3.1 to 1.71; $p = 0.57$). The tests for subgroup heterogeneity were significant ($p < 0.001$, $I^2 = 76\%$ and $p < 0.001$, $I^2 = 92\%$, respectively).

Data on the ICU LOS were assessed in 14 trials. A significant reduction was demonstrated in the mixed PCT strategy subgroup. The ICU LOS in

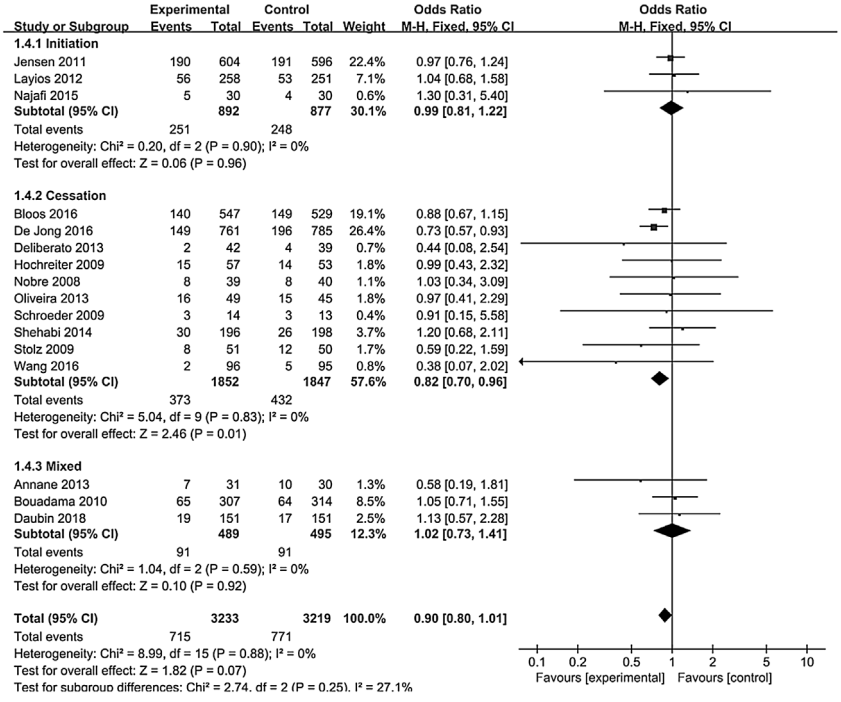

Figure 2. Forest plot of the effects of PCT-guided antibiotic strategies on short-term mortality.

Table 2
Subgroups of PCT-guided cessation of antibiotic therapy.

Subgroups	Number of trials	Mortality: PCT vs. SC	Pooled OR	95% CI	*p*-Value	Heterogeneity: I^2; *p*-value
Cessation	10	373/1852 vs. 432/1847	0.82	0.70–0.96	0.01	0%; 0.83
SOFA score	9	371/1756 vs. 427/1752	0.83	0.70–0.97	0.02	0%; 0.84
SOFA >8	3	151/612 vs. 164/592	0.85	0.66–1.11	0.23	0%; 0.75
SOFA <8	6	220/1144 vs. 263/1160	0.81	0.66–0.99	0.04	0%; 0.62
Diagnosis	10	373/1852 vs. 432/1847	0.82	0.70–0.96	0.01	0%; 0.83
Suspected	4	196/1110 vs. 241/1131	0.79	0.64–98	0.03	13%; 0.33
Confirmed	6	177/742 vs. 191/716	0.86	0.68–1.09	0.21	0%; 0.93
Adherence	10	373/1852 vs. 432/1847	0.95	0.85–1.07	0.01	0%; 0.83
Adherence >70%	4	56/380 vs. 54/378	1.03	0.68–1.56	0.90	0%; 0.65
Adherence <70%	6	317/1472 vs. 378/1469	0.79	0.67–0.94	0.007	0%; 0.84

CI, confidence interval; OR, odds ratio; PCT, procalcitonin-guided antibiotic therapy; SC, standard care; SOFA, Sequential Organ Failure Assessment.

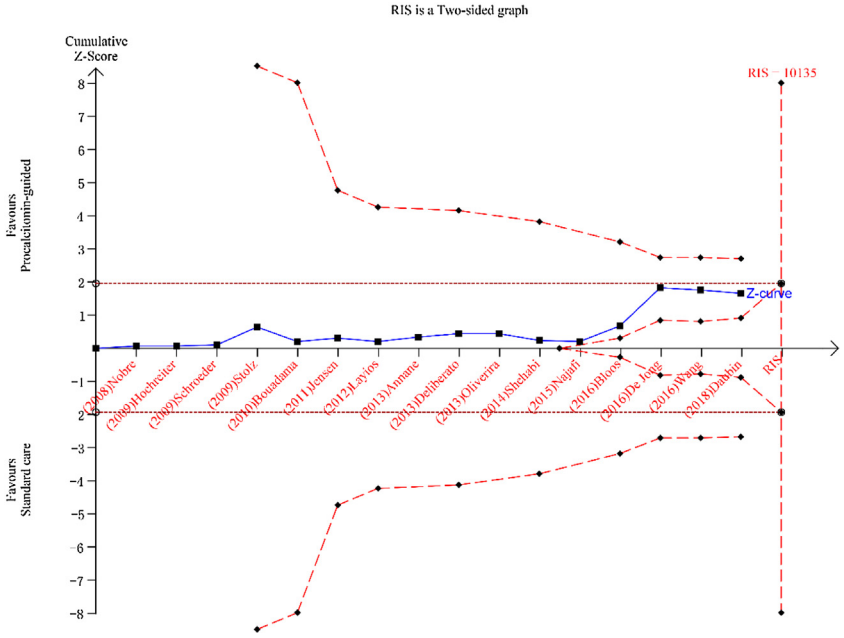

Figure 3. Post hoc trial sequential analysis (TSA) for mortality at short-term mortality with included trials with no events.
*A post hoc TSA for mortality at short-term mortality with included trials with no events, type 1 error of 5%, and power of 80%, revealed a TSA-adjusted RR of 0.91 (95% CI 0.80–1.02; $p = 0.0988$; $Q = 9.5$, $I^2 = 0\%$; diversity (D^2) = 0%; Figure 3 and **Supplementary Material** Figure S3). On the basis of a mortality incidence of 23.8% in the control arm and risk reduction of 10.00%, the required information size (RIS) is 10 135.

Table 3
Time horizon for mortality.

Term of mortality	Number of trials	Mortality: PCT vs. SC	Pooled OR	95% CI	*p*-Value	Heterogeneity: I^2; *p*-value
28-day mortality	8	595/2509 vs. 652/2510	0.88	0.77–1.00	0.05	0%; 0.66
ICU mortality	5	99/677 vs. 95/669	1.03	0.75–2.93	0.86	0%; 0.43
Hospital mortality	9	83/556 vs. 89/548	0.90	0.64–1.25	0.52	0%; 0.84
Other mortality	6[a]	844/2566 vs. 874/2573	0.95	0.85–1.07	0.40	57%; 0.04

CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PCT, procalcitonin-guided antibiotic therapy; SC, standard care.
[a] 60-day mortality was assessed in two trials, 90-day mortality in three trials, 1-year mortality in one trial.

the PCT-guided groups was reduced by 2.01 days (95% CI 0.18–3.85 days; $p = 0.03$; **Supplementary Material** Figure S7) compared with that in the standard care groups, without heterogeneity ($p = 0.50$; $I^2 = 0\%$). However, there was no statistically significant difference in the cessation PCT strategy subgroup analysis or the whole pooled meta-analysis (MD 0.13, 95% CI −0.47 to 0.73; $p = 0.67$ and MD 0.38, 95% CI −0.05 to 0.81; $p = 0.09$), with moderate heterogeneity ($p = 0.04$, $I^2 = 44\%$ and $p = 0.04$, $I^2 = 53\%$, respectively).

Among the 14 trials included in the meta-analysis for hospital LOS, both the random- and fixed-effects models could not demonstrate a significant reduction in the PCT-guided group compared with the standard care group (MD 0.19, 95% CI −1.56 to 1.95; $p = 0.83$; **Supplementary Material** Figure S8). Moderate heterogeneity was observed ($I^2 = 56\%$; $p = 0.009$). Furthermore, there was no statistically significant difference in the subgroup analysis of the PCT strategy subgroups or SOFA score subgroups (all $p > 0.10$), with moderate heterogeneity.

Discussion

The use of PCT-guided antibiotic therapy to optimize antibiotic treatment has been controversial over the past decades. This meta-

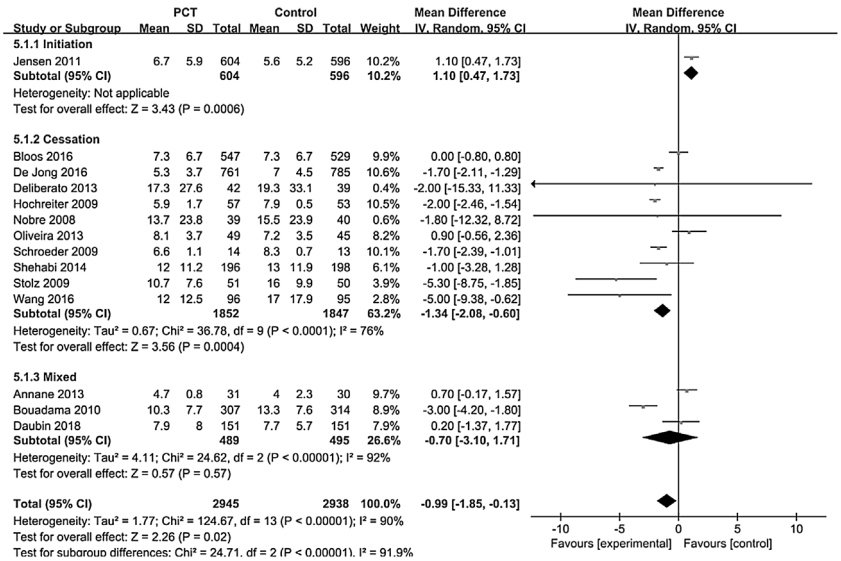

Figure 4. Forest plot of effects of PCT-guided antibiotic strategies on antibiotic duration.

analysis of 16 studies, including 6452 patients with infections treated in ICUs, revealed that PCT-guided antibiotic therapy did not lead to a decrease in mortality (a robust effect) and that PCT-guided initiation or mixed strategies of antibiotic therapy did not decrease the short-term mortality of critically ill patients with sepsis. Although the subgroup analysis of PCT-guided cessation of antibiotics revealed a lower short-term mortality in the PCT-guided groups and in those patients with a mean SOFA score of <8, the short-term mortality was comparable in the two groups in the SOFA score >8 subgroup and in those in the confirmed sepsis subgroup.

There are several possible explanations for this result. Firstly, sepsis is a heterogeneous syndrome developing from different possible infected organs and with different clinical presentations based on severity (Cecconi et al., 2018; Levy et al., 2018). Appropriate antibiotic therapy and close monitoring remain the cornerstone of sepsis care, but not all. Starting antibiotic treatment in the ambulance when the patient is suspected of suffering from an infection was found not to lead to improved survival (Alam et al., 2018). The severity of infection is often associated with the development of multidrug-resistant bacterial pathogens, which is detrimental to the patient outcome (Busani et al., 2019; Kollef et al., 2017). It is possible that PCT-guided antibiotic therapy is more suitable for patients without multiple organ failure in the emergency department or general ward setting.

Secondly, PCT levels have been shown to increase in the event of systemic inflammatory response syndrome (SIRS) or organ dysfunction attributable to the presence of various non-infectious causes, such as trauma or ischemic conditions (Wanner et al., 2000; Hoshino et al., 2017; Parli et al., 2018), and correlate with the severity of organ dysfunction and the number of affected organs (Sudhir et al., 2011). Furthermore, PCT levels and PCT guidance failed to identify the response to antibiotic therapy or prevent potential adverse events, such as a toxic effect or bacterial resistance (Bouadma et al., 2010). In addition, the stewardship and movement towards shorter courses of antibiotic treatment may contribute to a further reduction in antibiotic exposure (Chastre et al., 2003; Pugh et al., 2015; Spellberg, 2016; Rhodes et al., 2017), which is associated with lower mortality and treatment failure risk in sepsis patients (Chotiprasitsakul et al., 2018; Montravers et al., 2018). Further research is necessary to assess the effect of combined PCT testing with other management of sepsis.

Thirdly, compliance varied in the included trials, and lower compliance with PCT-guided antibiotic therapy was associated with a shorter antibiotic duration (Table 2). Finally, the interventions used in the control groups and the randomization in the included trials are debatable (Lisboa et al., 2018; van Oers et al., 2018). Clear initiation or cessation rules for antibiotic duration based on strict guidelines would make the control group more compatible with the PCT-guided group (Silverman and Miller, 2004) and could lead to a better evaluation of the effect of PCT guidance.

The strengths of this meta-analysis include the large number of subjects enrolled and the variety of study characteristics. Moreover, focus was placed on the severity of sequential organ failure and whether infection was confirmed in the critically ill patients. However, this meta-analysis has several limitations. Firstly, the average SOFA score, which indicates severity of the enrolled population, was not feasible to explicitly evaluate the severity of critically ill. We used average SOFA scores for grouping, so the two subgroups of patients may have over-lapping SOFA scores, which might bring heterogeneity to analysis. Secondly, the small number of trials in the subgroup of PCT-guided initiation or mixed strategies of antibiotic therapy may have led to an underestimation of the effect of PCT guidance. Thirdly, the diagnostic criteria of sepsis varied between the included studies.

In conclusion, this meta-analysis demonstrated that PCT-guided cessation of antibiotic therapy decreased the short-term mortality of sepsis patients, but that PCT-guided initiation of antibiotics or mixed cessation and initiation strategies did not decrease the short-term mortality and that PCT-guided antibiotics did not decrease other term mortality. PCT-guided antibiotic therapy decreased the duration of antibiotics in the overall meta-analysis and the cessation of antibiotics subgroup analysis; however, this was in contrast to the subgroup of the mixed strategies and a SOFA score >8. Furthermore, PCT-guided antibiotic therapy did not reveal any benefit in the length of ICU or hospital stay. Taken together, it is deemed that the study findings can be attributed to the fact that the PCT-based prescribing guidelines provide fewer opportunities to change antibiotic decisions.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Consent for publication

Not applicable.

Ethical approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions: FP and YY studied the design; FP, WC, JFX, and QS conducted the study; FP and WC analyzed the data; FP, WC, JFX, and YY were involved in the data interpretation; FP, WC, HBQ, and YY wrote and revised the paper. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.05.034.

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