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Effectiveness of procalcitonin-guided antibiotic therapy to shorten treatment duration in critically-ill patients with bloodstream infections: a systematic review and meta-analysis

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SUMMARY

Evaluation of serum procalcitonin (PCT) levels has been suggested for diagnosis of infection, precise medical decision making and guidance for prescribing antibiotics in critically-ill patients. The aim of this study was to assess the effectiveness of PCT to shorten antibiotic treatment in critically-ill patients with bloodstream infections. Furthermore, the mortality and ICU length of stay (LOS) in such patients were secondary outcomes. Medline/PubMed, EMBASE, Scopus and Cochrane Databases were searched from January 1, 2007 to September 1, 2018. Randomized controlled trials (RCTs) on using PCT to guide antibiotic therapy compared with routine treatments for administration of antibiotics in critically-ill adult patients published in English were included. Two reviewers assessed the methodology of the studies included and extracted their data using the CONSORT checklist. Inverse-variance weighting and fixed and random effects meta-analyses were performed using the length of antibiotic treatment, LOS in an intensive care unit (ICU) and all-cause mortality. No significant reduction was found in the length of antibiotic treatment: although the cut-off point of 0.25<PCT<0.5ng/mL resulted in the reduced length of antibiotic treatment, this effect was not significant. Moreover, there was no significant reduction in ICU LOS and mortality. The analysis showed the effectiveness of the PCT cut-off level of 0.25<PCT<0.5ng/mL in decreasing the length of antibiotic treatment and ICU LOS, although this effect was not significant. Further studies are required to evaluate the results of this study on patients with recurrent infections, super-infections and also multidrug-resistant infections.

Keywords: procalcitonin, critical care, anti-bacterial agents, antimicrobial stewardship, sepsis.

INTRODUCTION

Antibiotics are one of the most widely prescribed medications for treatment in critically-ill patients. Despite their numerous advantages, antibiotics are associated with several side effects including multidrug-resistance, antibiotic-related colitis, allergic reactions and several others, especially in prolonged antibiotic therapy [1-3]. Moreover, these complications have shown to be linked to the increased length of hospitalization and healthcare costs [4].

The evaluation of some biomarkers to improve the accuracy of early diagnosis of sepsis is an appropriate strategy, which may lead to more desirable

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clinical outcomes [5-7]. Among these biomarkers, procalcitonin (PCT), the peptide precursor of calcitonin, has been widely studied to guide antibiotic prescription in critically-ill patients [8-13].
PCT-guided treatment may play an important role in antibiotic-resistant reduction by shorten of antibiotic therapy duration, but the results are still controversial [14]. However, in a study by Jensen et al., PCT-guided therapy resulted to improve survival in the intensive care unit [15], but in another similar study, Annane et al. found that PCT-guided treatment is inappropriate in critically-ill patients [16].
The appropriate prescribing of antibiotics and timely discontinuation of antibiotics in severe infections, such as bloodstream infections (BSIs) are challenging clinical decision and shortening the length of stay (LOS) in intensive care unit (ICU) can reduce the health care costs. This review investigated the effectiveness of PCT-guided algorithm to guide antibiotic therapy for BSIs in adults in comparison with the routine care and also its efficacy on the length of antibiotic therapy, length of stay (LOS) in intensive care unit (ICU) and mortality.

MATERIALS AND METHODS

A systematic review and meta-analysis of randomized controlled trials (RCTs) published in peer-reviewed journals was performed to identify original articles on the use of PCT-guided treatment compared to the standard care for adult patients with BSIs, according to the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) for reporting in systematic reviews and meta-analyses.

Search strategy and study selection
The databases, including PubMed/Medline, EMBASE, Scopus and the Cochrane Database were

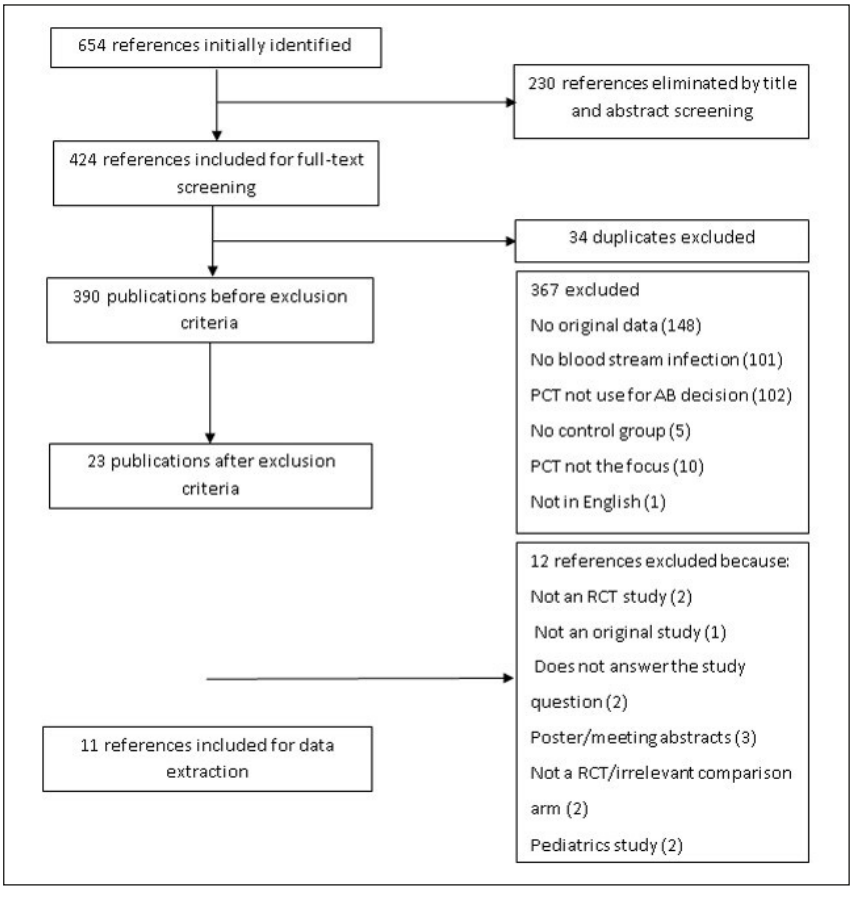

Figure 1 - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

searched using a prospectively defined algorithm from January 2007 to September 2018. The following keywords were used: "Procalcitonin" AND ("anti-infective agents" OR "anti-bacterial agents" OR "bacterial infections/drug therapy" OR "antibiotic") AND "bacteremia". Forward citation tracking was also included.

A flowchart for the literature search is shown in Figure 1. Inclusion criteria included all RCT's, quasi-randomized trials (allocation is not considered strictly random) and review articles published in English from January 2007 to September 2018 studying the considered subjects. Studies were screened by title and abstract and they were entered into the study following a review of their full texts. We included studies on adult hospitalized patients with suspected sepsis, in which bacteremia with a known pathogen was confirmed via blood culture and the evaluation of PCT levels was performed within 24 h of enrolment. In addition, a detailed description of patient groups and baseline demographic variables were also provided. All primary intervention studies, in which the PCT-guided therapy was compared with the standard care according to current guidelines and also met the following inclusion criteria were included:

1) Studies surveying the efficacy of PCT-based treatment;
2) Studies with a well-defined criteria for the studied condition (severe bacterial infection), using definitions according to the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) Consensus Conference [17] and the German Sepsis Society (DSG) [18];
3) Studies providing sufficient information to measure the hazard ratios (HRs) together with their 95% confidence interval (CI) and the relative risk (RR) together with their 95% CI.

The corresponding authors of the studies that met the inclusion criteria, in which sufficient data for review was not provided, were contacted to retrieve additional data. We excluded observational studies, case reports, editorials, commentaries, letters, meeting abstracts, poster presentations and studies on animals and in patients younger than 18 years old. Two investigators (SHAO and MRA) independently evaluated all approved studies for inclusion and extracted the data. Disagreements about choosing and inclusion of studies were resolved by iteration and consensus.

Data extraction was done using a structured data collection form consisting of the following items: authors, country and year of study, length of treatment, number of participants, intervention according to the PCT test, outcomes and key findings [9-12, 14, 16, 19-23] (Table 1). The primary outcome of this review was duration of antimicrobial therapy, whereas the 28-day mortality and ICU LOS in critically-ill patients were the secondary outcomes. The approved studies with insufficient data or those with no replies from the authors were excluded.

Cut-off points were different among the included studies. The values were specified to three cut-off categories and the effect of each cut-off point for discontinuation of antibiotic therapy on the three outcomes was analyzed.

Statistical analyses

The mean and standard deviation (SD) of length of antibiotic therapy, the ICU LOS and mortality rate in the intervention and control groups were extracted and where mid-quartile and interquartile ranges were reported, the mean and SD were estimated and a meta-analysis was used to analyze the results [24]. The I^2 and Cochrane's Q tests were used to estimate the fraction of variability between the studies' mean due to the heterogeneity rather than chance. Where I^2 was lower than 50, the fixed-effect model was chosen according to the Mantel-Haenszel method and where I^2 was greater than 50 or $P<0.05$, the random-effect model used to determine the overall effect size. Egger's regression test and Funnel Plot were used to assess the publication bias. Statistical analysis was done by Comprehensive Meta-Analysis (CMA, Biostat Inc., Englewood, USA) v. 2.0 software and the P values of less than 0.05 were considered significant.

RESULTS

Study selection

According to the search strategy, we found 654 unique records, including 156 records through PubMed, 180 records through EMBASE, 108 records through Cochrane Database, and 210 records through Google scholar. Twenty-three articles out of 654 abstracts were selected for full text review. Twelve articles were excluded and 11

Table 1 - Outcomes of randomized controlled trials included in meta-analysis.

First author, country and year	*Time of endpoint*	*PCT No.*	*Control No.*	*PCT Algorithm for ABx Cessation (ng/mL)*	*Mean(SD)ABx days of use in PCT and control*	*Mean(SD) LOS in ICU (days) in PCT and control*	*Mortality in PCT and control*	*Key finding*
Nobre Switzerland 2008 (9)	28 day	31	37	<0.25 if initial level ≥1.0; <0.1 if initial level <1.0; >90% change if initial PCT≥1.0	14.3 (23) 33 (23)	8.7 (14.8) 5.7 (66.7)	16% 16%	Reduction in ABx duration and ICU LOS without adverse events
Hochreiter Germany 2009 (10)	Time until ICU discharge	57	53	< 1.0; ≥65-75% change from initial level and current level >1.0	5.9 (1.7) 7.9 (.5)	15.5 (12.5) 17.7 (10.1)	26% 26%	Reduction in ABx duration and ICU LOS without adverse events
Schroeder Germany 2009 (17)	Length of hospital stay	14	13	≤1.0; ≥65-75% change from initial level	6.6 (1.1) 8.3 (0.7)	16.4 (8.3) 16.7 (5.6)	21% 23%	Shorter ABx duration
Bouadma France 2010 (11)	28 day	307	314	<0.5; >80% change from peak	10.3 (7.7) 13.3 (7.6)	15.9 (16.1) 14.4 (14.1)	21% 20%	Reduction in ABx use without increase in mortality rate
Layios Belgium 2012 (18)	Time until ICU discharge	258	251	<0.5	4.4 (2.4) 4 (2.4)	9.0 (8.9) 9.7 (10.4)	22% 21%	Significantly decrease the number of treatments when infection was considered as possible
Deliberato Brazil 2013 (8)	Time until ICU discharge	42	39	<0.5; >90% change from peak	12.7 (14.1) 20.3 (31.1)	20.5 (41.5) 11 (20)	2% 10%	Limiting antimicrobial therapy in ICU patients with documented bacterial infection
Annane France 2013 (14)	Time until ICU discharge	31	31	<0.5	4.7 4.0	24.0 31.0	23% 32%	PCT levels are unhelpful to in reducing ABx exposure in patients
Shehabi Australia 2014 (19)	28 day	196	198	<0.1; <0.1-0.25 if infection unlikely; >90% change from baseline level	11.7 (10.4) 13.0 (11.9)	6.2) (6.3) 6.7 (4.4)	15% 13%	Reduction in total ABx use without increase in mortality rate
Najafi Iran 2015 (20)	Length of hospital stay	30	30	<0.5	NA	8.7 (13.3) 12 (19.3)	17% 13%	Reduced antibiotics exposure and length of ICU stay without difference in mortality rate
De Jong Netherlands 2016 (12)	28 day	761	785	≤0.5; ≥80% change from peak	5.7 (4.4) 7.3 (5.2)	30.5 (8.9) 10.0 (9.6)	20% 25%	Reduction of duration of treatment and daily defined doses with decrease in mortality
Bloos Germany 2016 (21)	≤ 21 day	276	262	≤1; ≥50% change from previous level	7.3 (6.7) 7.3 (6.7)	14 (13.3) 12.7 (11.1)	28% 23%	Application of a PCT-guided algorithm needs further evaluation

Abx: Antibiotics, ICU; Intensive Care Unit, LOS, Length of Stay; PCT, Procalcitonin; NA, Non Accessible, Non Applicable.

trials that met the inclusion criteria done on 2003 patients in the PCT and 2013 patients in the control groups were remained (Figure 1). Thirteen recent published meta-analyses were identified and there was no RCT which were not included in the current study.

AGGREGATED RESULTS

Effect on the length of antibiotic therapy

We aggregated all trials and reported the means and SD of length of antibiotic therapy and no significant reduction was found in the length of

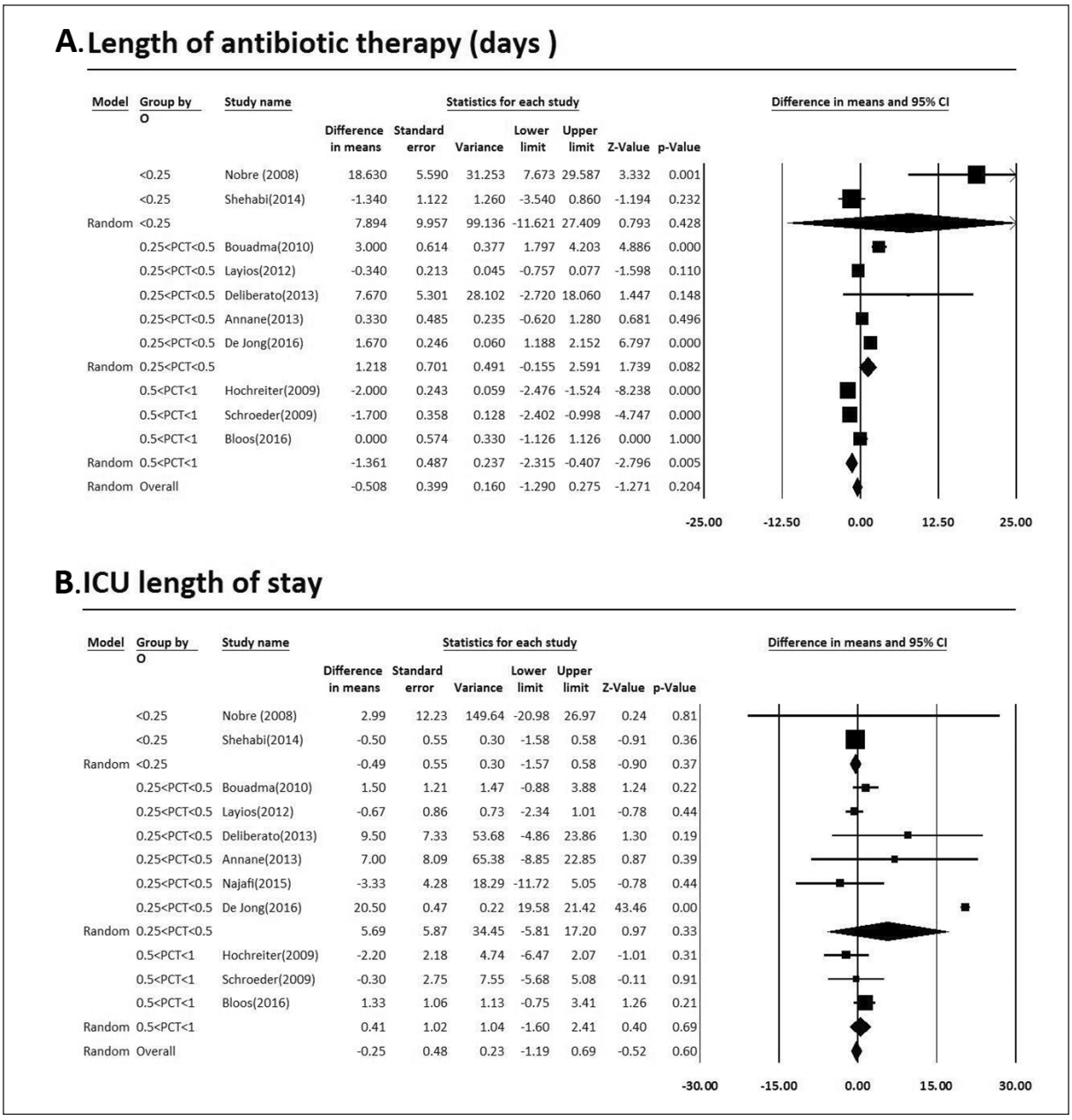

Figure 2 - Forest plot of difference in mean between PCT and control group; A, for length of antibiotic therapy in critically-ill patients; B, for ICU length of stay in critically-ill patients.

antibiotic treatment, nevertheless the cut-off point of 0.25<PCT<0.5 ng/mL resulted in the reduced length of antibiotic treatment, but this effect was not significant [weighted mean difference: 1.218 (95% CI: -0.155-2.591; P=0.082)] (Figure 2A.).

Effect on ICU LOS

There was not a significant difference in the total effect of antibiotic therapy according to the PCT measuring on ICU LOS. The weighted mean difference for cut-off of 0.25<PCT<0.5 ng/mL was 5.69 (95% CI: -5.81-17.20; P=0.33) (Figure 2B.).

Effect on mortality

The analysis of 11 studies indicated that there was no significant difference in hospital mortality [risk ratio: 0.95, 95% CI: 0.84-1.08; P=0.45] (Figure 3).

The funnel plot of standardized mean difference is shown in Figure 4. The following values were obtained from the Egger's regression test for primary outcome: t-value =0.43, df =8.0, and P-value =0.84.

Risk of bias

Cochrane Collaboration tool was employed for assessing risk of bias by judging the following seven items, which represented the sources of risk of bias: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessor, incomplete outcome data, selective reporting, and other biases [25]. The items were evaluated and the classification of each item, including low risk of bias, high risk of bias or uncertain risk of bias was determined (Table 2).

DISCUSSION

Several investigations have recently aimed at defining objective criteria for initiating and discontinuation of antibiotic treatment and to customize antibiotic treatments to fit each patient's requirement [2, 26]. The usefulness of serial measurements of serum PCT levels has been widely studied for this purpose in different clinical settings, including the ICU and it has found that PCT cut-

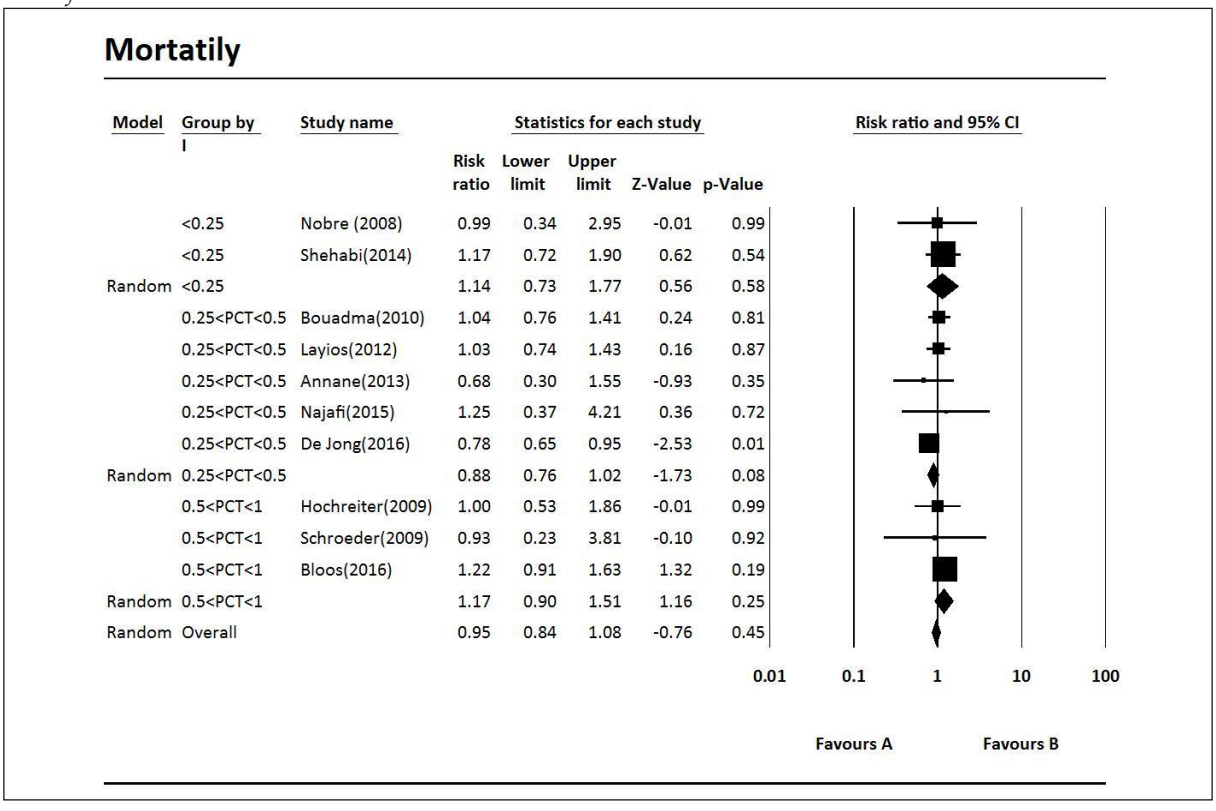

Figure 3 - Forest plot of risk ratio (RR) between PCT and control group for mortality in critically ill patients.

off level for discontinuation of antibiotic therapy is widely varied in all of the studies conducted in this setting [8, 10-12, 27-30].

The current systematic review and meta-analysis evaluated 11 randomized clinical trials on PCT-guided treatment in adults (≥18 years old) with severe bacterial infection. Data analysis did not show any significant effect by this approach on ICU LOS and mortality. However other included studies reported its significant effect on

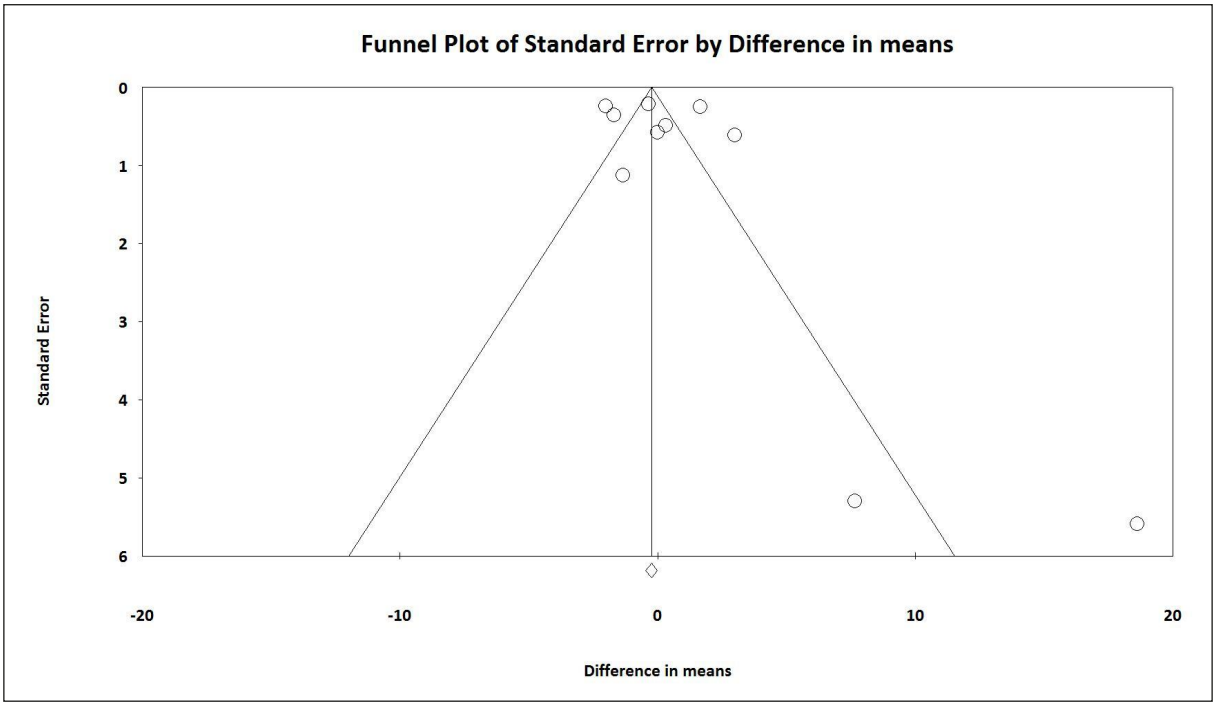

Figure 4 - Funnel plot of standard error by difference in means.

Table 2 - Review authors' judgments summary about each risk of bias item for included studies.

Author, Year	*Random sequence generation (selection bias)*	*Allocation concealment (selection bias)*	*Binding of participants and personnel (performance bias)*	*Binding of outcome assessment (detection bias)*	*Incomplete outcome data (alteration bias)*	*Selective reporting (reporting bias)*	*Other bias*
Nobre (9), 2008	Yes	Yes	No	No	Yes	Yes	Yes
Hochreiter (10), 2009	NR	No	No	No	Yes	Yes	Yes
Schroeder (17), 2009	NR	NR	NR	NR	Yes	Yes	Yes
Bouadma (11), 2010	Yes	NR	Yes	NR	Yes	Yes	Yes
Layios (18), 2012	Yes	Yes	NR	Yes	Yes	Yes	Yes
Deliberato (8), 2013	Yes	No	No	No	Yes	Yes	Yes
Annane (14), 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Shehabi (19), 2014	Yes	Yes	No	No	Yes	Yes	Yes
Najafi (20), 2015	Yes	Yes	No	NR	Yes	Yes	Yes
De Jong (12), 2016	Yes	Yes	No	NR	No	Yes	No
Bloos (21), 2016	Yes	Yes	No	No	Yes	Yes	Yes

NR, Not reported.

the reduced ICU LOS and mortality [9, 14, 16, 20]. The effectiveness of evaluation of PCT levels in decreasing the mortality rate has also reported in another study [31].

In fact, according to the results, no significant reduction was observed in the length of antibiotic treatment, despite the cut-off point of 0.25<PCT<0.5 ng/mL resulted in the reduced length of antibiotic treatment, but this effect was not significant. However, some of the RCT's included in analysis and also another RCT, most of them using the mentioned cut-off level, have shown a significant decrease in the length of antibiotic treatment, and also in a review, it has reported that antibiotic use should be dropped, when PCT is dropped to the less than 0.5 ng/mL [9, 14, 16, 20, 10, 23, 32, 33].

The meta-analysis of data for 4,211 patients confirmed that the implementation of PCT-guided algorithm reduces the average length of antibiotic treatment from 10 days to 7 days without an increase in the risk of mortality or treatment failure. In this meta-analysis, in 9 out of 13 included studies, antibiotic treatment discontinued as soon as PCT levels were less than 0.5 ng/mL [8]. PRORATA, a large multicenter randomized trial was conducted on 621 unselected patients hospitalized in ICU randomized to be treated according to the PCT-guided treatment, studied the initiation and discontinuation of antibiotic treatment and also used the conventional strategy based on clinical criteria and international and institutional guidelines [12]. The physicians decided to discontinue antibiotic treatment on the 3rd day, as soon as PCT level decreased more than 80% from its peak level or reduced to less than 0.5 ng/mL. The PCT group patients had significantly longer antibiotic-free days than those in the control group and also mortality rate on the days 28 and 60, infection relapse, superinfection and acquisition of multidrug-resistant bacteria in two groups were comparable.

According to previous studies, PCT-guided antibiotic therapy in critically-ill patient can reduce the health-care costs from 17 to 75% [9, 20]. An economic evaluation by Heyland et al. showed that PCT-guided therapy may reduce overall costs of health-care [29]. Bouadma et al. compared the cost of PCT-guided method (€ 10-15) with the cost of daily used antibiotics (€ 114) to treat nosocomial bloodstream infection in adult patients [12]. By multiplying the cost of daily used antibiotics in the needed days to treat the infection via conventional method in comparison with PCT-guided method, remarkable cost saving using PCT-guided strategy was found. It is noticeable that this therapeutic method can decrease the nosocomial bloodstream infection by shortening the ICU LOS, earlier rehabilitation, making patients able to return to work and saving hospital expenditures.

There were some limitations in the current study. The lack of perfect blinding of participants and personnel as well as blinding of outcome assessment in most of the used RCT's can be considered as one of our study limitations.

The difference between our considered endpoints and the surveyed studies and also the difference in duration of treatment in different studies were other limitations. In addition, in this analysis, infection relapse, superinfection and acquisition of multidrug-resistant bacteria were not addressed.

CONCLUSIONS

The analysis showed the effectiveness of PCT cut-off (0.25<PCT<0.5) in decreasing the length of antibiotic treatment and ICU LOS, however this effect was not statistically significant. Further studies are needed to examine the effect of other PCT cut-off levels on mortality, ICU LOS and the length of antibiotic treatment and also to investigate infection relapse, superinfection, and acquisition of multidrug-resistant in bacteria. Also, a systematic review regarding cost-effectiveness of PCT-guided therapy in critically-ill patient is recommended.

Conflicts of interests

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence this study.

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Conflicts of interest

none

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