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Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections (Review)

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ABSTRACT

Background

Acute respiratory infections (ARIs) comprise of a large and heterogeneous group of infections including bacterial, viral, and other aetiologies. In recent years, procalcitonin (PCT), a blood marker for bacterial infections, has emerged as a promising tool to improve decisions about antibiotic therapy (PCT-guided antibiotic therapy). Several randomised controlled trials (RCTs) have demonstrated the feasibility of using procalcitonin for starting and stopping antibiotics in different patient populations with ARIs and different settings ranging from primary care settings to emergency departments, hospital wards, and intensive care units. However, the effect of using procalcitonin on clinical outcomes is unclear. This is an update of a Cochrane review and individual participant data meta-analysis first published in 2012 designed to look at the safety of PCT-guided antibiotic stewardship.

Objectives

The aim of this systematic review based on individual participant data was to assess the safety and efficacy of using procalcitonin for starting or stopping antibiotics over a large range of patients with varying severity of ARIs and from different clinical settings.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE, and Embase, in February 2017, to identify suitable trials. We also searched ClinicalTrials.gov to identify ongoing trials in April 2017.

Selection criteria

We included RCTs of adult participants with ARIs who received an antibiotic treatment either based on a procalcitonin algorithm (PCT-guided antibiotic stewardship algorithm) or usual care. We excluded trials if they focused exclusively on children or used procalcitonin for a purpose other than to guide initiation and duration of antibiotic treatment.

Data collection and analysis

Two teams of review authors independently evaluated the methodology and extracted data from primary studies. The primary endpoints were all-cause mortality and treatment failure at 30 days, for which definitions were harmonised among trials. Secondary endpoints were antibiotic use, antibiotic-related side effects, and length of hospital stay. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using multivariable hierarchical logistic regression adjusted for age, gender, and clinical diagnosis using a fixed-effect model. The different trials were added as random-effects into the model. We conducted sensitivity analyses stratified by clinical setting and type of ARI. We also performed an aggregate data meta-analysis.

Main results

From 32 eligible RCTs including 18 new trials for this 2017 update, we obtained individual participant data from 26 trials including 6708 participants, which we included in the main individual participant data meta-analysis. We did not obtain individual participant data for four trials, and two trials did not include people with confirmed ARIs. According to GRADE, the quality of the evidence was high for the outcomes mortality and antibiotic exposure, and quality was moderate for the outcomes treatment failure and antibiotic-related side effects.

Primary endpoints: there were 286 deaths in 3336 procalcitonin-guided participants (8.6%) compared to 336 in 3372 controls (10.0%), resulting in a significantly lower mortality associated with procalcitonin-guided therapy (adjusted OR 0.83, 95% CI 0.70 to 0.99, P = 0.037). We could not estimate mortality in primary care trials because only one death was reported in a control group participant. Treatment failure was not significantly lower in procalcitonin-guided participants (23.0% versus 24.9% in the control group, adjusted OR 0.90, 95% CI 0.80 to 1.01, P = 0.068). Results were similar among subgroups by clinical setting and type of respiratory infection, with no evidence for effect modification (P for interaction > 0.05). Secondary endpoints: procalcitonin guidance was associated with a 2.4-day reduction in antibiotic exposure (5.7 versus 8.1 days, 95% CI -2.71 to -2.15, P < 0.001) and lower risk of antibiotic-related side effects (16.3% versus 22.1%, adjusted OR 0.68, 95% CI 0.57 to 0.82, P < 0.001). Length of hospital stay and intensive care unit stay were similar in both groups. A sensitivity aggregate-data analysis based on all 32 eligible trials showed similar results.

Authors' conclusions

This updated meta-analysis of individual participant data from 12 countries shows that the use of procalcitonin to guide initiation and duration of antibiotic treatment results in lower risks of mortality, lower antibiotic consumption, and lower risk for antibiotic-related side effects. Results were similar for different clinical settings and types of ARIs, thus supporting the use of procalcitonin in the context of antibiotic stewardship in people with ARIs. Future high-quality research is needed to confirm the results in immunosuppressed patients and patients with non-respiratory infections.

PLAIN LANGUAGE SUMMARY

Testing blood procalcitonin levels to decide when to start and stop antibiotics in adults with acute respiratory tract infections

Review question

What are the effects of using procalcitonin to start or discontinue antibiotics in people with acute respiratory infections compared to routine care on mortality and treatment failure?

Background

In people with acute respiratory infections, unnecessary antibiotic use significantly contributes to increasing bacterial resistance, medical costs, and the risk of drug-related adverse events. The blood marker procalcitonin increases in bacterial infections and decreases when patients recover from the infection. Procalcitonin can be measured in the blood of patients by different commercially available assays with a turnaround time of around one to two hours and support clinical decision making about initiation and discontinuation of antibiotic therapy.

Search date

We conducted electronic searches on 10 February 2017. We conducted searches for ongoing trials on 12 April 2017.

Study characteristics

All included trials randomised participants with acute respiratory infections to receive antibiotics based on procalcitonin levels ('procalcitonin-guided' group) or a control group. The trials were performed in primary care, the emergency department and medical wards, and the intensive care unit. Included participants had acute upper or lower respiratory infections, including pneumonia, bronchitis, exacerbation of chronic obstructive pulmonary disease, and others.

Study funding sources

All studies were investigator-initiated trials. Half of the trials were funded by national agencies or did not report funding, and half of the trials received funding from the biomarker industry (e.g. Thermo Fisher Scientific).

Key results

We studied 6708 participants from 26 trials in 12 countries. Mortality at 30 days was significantly lower in procalcitonin-guided participants compared to control participants (286 deaths in 3336 procalcitonin-guided participants (8.6%) versus 336 deaths in 3372 controls (10.0%)). There was no significant difference with regard to treatment failures. Results were similar for different clinical settings (primary care, emergency department, intensive care unit) and types of respiratory infection. Regarding antibiotic exposure, participants in the procalcitonin-guided group had a 2.4-day reduction in antibiotic exposure and a reduction in antibiotic-related side effects (16.3% versus 22.1%).

Quality of the evidence

The quality of the evidence was high for mortality and antibiotic exposure. Most of the trials did not use blinding, however we did not expect that mortality would be biased by this limitation. The quality of the evidence was moderate for treatment failure and antibiotic-related side effects because the definitions for these endpoints among trials were not identical.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Procalcitonin algorithm compared to standard care for guiding antibiotic therapy in acute respiratory tract infections

Procalcitonin algorithm compared to standard care for guiding antibiotic therapy in acute respiratory tract infections

Patient or population: people with acute respiratory tract infections
Settings: primary care, emergency department, intensive care unit
Intervention: PCT-guided care
Comparison: standard care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard care	PCTalgorithm				
Mortality Follow-up: 30 days	**Study population**		**OR 0.83** (0.70 to 0.99)	6708 (26 studies)	⊕⊕⊕⊕ **High**[1]	
	100 per 1000	**86 per 1000** (76 to 95)				
Treatment failure Clinical assessment[3] Follow-up: 30 days	**Study population**		**OR 0.90** (0.80 to 1.01)	6708 (26 studies)	⊕⊕⊕⊖ **Moderate**[2 3]	
	249 per 1000	**230 per 1000** (216 to 245)				
Antibiotic-related side effects Follow-up: 30 days	**Study population** **221 per 1000**	**163 per 1000** (145 to 182)	**OR 0.68** (0.57 to 0.82)	3034 (6 studies)	⊕⊕⊕⊖ **Moderate**[4]	
Antibiotic exposure Total days of antibiotic therapy in all randomised participants	The mean antibiotic exposure in the control groups was **8.1 days**.	The mean antibiotic exposure in the intervention groups was 2.43 days**lower** (2.15 to 2.71)	-	6708 (26 studies)	⊕⊕⊕⊕ **High**[1]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio: **PCT:** procalcitonin

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

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[1]No downgrading for serious concerns. Still, there is some concern about unconcealed allocation in several trials in the emergency department and intensive care settings. There is also some concern about low adherence with the PCT algorithm in the intervention group. We consider unblinded outcome assessment as not relevant for the outcome of death.
[2]Downgraded one level for serious inconsistency: trials used differing definition of treatment failure and some rare events were not systematically assessed among trials.
[3]For the primary care setting, treatment failure was defined as death, hospitalisation, acute respiratory infection (ARI)-specific complications (e.g. empyema for lower ARI, meningitis for upper ARI), recurrent or worsening infection, and participants reporting any symptoms of an ongoing respiratory infection (e.g. fever, cough, dyspnoea) at follow-up. For the emergency department setting, treatment failure was defined as death, intensive care unit (ICU) admission, rehospitalisation after index hospital discharge, ARI-associated complications (e.g. empyema or acute respiratory distress syndrome for lower ARI), and recurrent or worsening infection within 30 days of follow-up. For the ICU setting, treatment failure was defined as death within 30 days of follow-up.
[4]Downgraded one level for incomplete reporting: only 6 trials reported side effects from antibiotics, and none of these trials were conducted in the ICU setting.

BACKGROUND

Acute respiratory infections (ARIs) account for over 10% of global disease burden and are the most common reason for antibiotic therapy in primary care and hospital settings (Evans 2002; Gonzales 1997; Zaas 2014).

Description of the condition

Acute respiratory infections comprise a heterogeneous group of infections including bacterial, viral, and other aetiologies. As many as 75% of all antibiotic doses are prescribed for ARIs, despite their mainly viral cause (Doan 2014; Evans 2002). Early initiation of adequate antibiotic therapy is the cornerstone in the treatment of bacterial ARIs and is associated with improved clinical outcomes (Hoare 2006; Kumar 2006; Kumar 2009; Liberati 2009b; Spurling 2010). However, overuse of antibiotics by overprescription in outpatients with bronchitis (Arnold 2005), for instance, and prolonged duration of antibiotic therapy in people with bacterial ARIs in the hospital and intensive care unit (ICU) settings is associated with increased resistance to common bacteria, high costs, and adverse drug reactions (Gonzales 1997; Goossens 2005; Lawrence 2009; Zaas 2014).

Description of the intervention

The presence of a diagnostic 'gold standard' or reference standard represents the best available method for establishing the presence or absence of a disease. Optimally, a morphological verification such as histopathology or, in the case of ARIs, growth of typical pathogens in blood cultures or sputum cultures can be obtained to establish the 'correct' diagnosis. Regrettably, the use of blood cultures as the assumed gold standard in ARIs lacks sensitivity, specificity, or both, with only around 10% of people with pneumonia having positive cultures and some of them being false positives (Muller 2010). In this diagnostic uncertainty, surrogate biomarker to estimate the likelihood for the presence of a bacterial infection and to grade disease severity are of great interest (Schuetz 2015). In such a circumstance, two fundamentally different concepts are employed. One concept tends to ignore potential dilemmas in the accuracy of the alleged gold standard but assumes a well-defined illness, which is represented by the assumption drawn following a diagnostic test or a clinical diagnosis. The second concept discards alleged gold standards and focuses on patient outcomes. In the case of ARIs, the clinical benefit of a diagnostic biomarker, such as procalcitonin (PCT), can be measured by clinical outcomes of randomised intervention studies, assuming that if the person recovered without antibiotics then there was no relevant bacterial illness.

In recent years, PCT has emerged as a promising marker for the diagnosis of bacterial infections because higher levels are found in severe bacterial infections but remain fairly low in viral infections and non-specific inflammatory diseases (Muller 2000; Muller 2001; Muller 2010). Procalcitonin is released in multiple tissues in response to bacterial infections via a direct stimulation of cytokines, such as interleukin (IL)-1β, tumour necrosis factor (TNF)-α, and IL-6. Conversely, PCT production is blocked by interferon gamma, a cytokine released in response to viral infections (Muller 2000). Hence, PCT may be used to support clinical decision making for the initiation and discontinuation of antibiotic therapy in different types of infections and indications (Sager 2017; Schuetz 2016). Randomised controlled trials (RCTs) have demonstrated the feasibility of such a strategy in different ARI patient populations and different settings ranging from primary care to emergency departments and hospital wards to medical and surgical ICUs (Bloos 2016; Branche 2015; Corti 2016; De Jong 2016; Deliberato 2013; Layios 2012; Long 2014; Maravić-Stojković 2011; Oliveira 2013; Shehabi 2014; Verduri 2015; Wang 2016).

How the intervention might work

Procalcitonin levels correlate with the risk of relevant bacterial infections and decrease upon recovery. Procalcitonin testing may therefore help physicians decide in which patients antibiotics are needed and when it is safe to stop treatment (Kutz 2015). The use of PCT in clinical protocols may thus decrease antibiotic consumption in two ways: by preventing unnecessary antibiotic prescriptions and by limiting durations of antibiotic treatment (Sager 2017; Schuetz 2011a).

Why it is important to do this review

While several RCTs have evaluated PCT-guided antibiotic treatment, most individual trials included participants with different types of respiratory and non-respiratory infections and lacked the statistical power to assess the risk for mortality and severe infectious disease complications associated with PCT-guided decision making. Previous meta-analyses of RCTs investigating the effect of PCT algorithms on antibiotic use focused on the critical care setting, people with suspicion of bacterial infections, and people with sepsis and respiratory infections (Heyland 2011; Hoeboer 2015; Tang 2009; Wacker 2013). However, these meta-analyses used aggregated data and were not able to investigate the effects of PCT on different ARI diagnoses and on outcomes other than mortality. A previous meta-analysis based on individual participant data published in the Cochrane Library did not find a significant difference in clinical outcomes, but confidence intervals remained relatively wide (Schuetz 2012). Safety of using PCT for antibiotic decision making remained thus unproven.

OBJECTIVES

The aim of this systematic review based on individual participant data was to assess the safety and efficacy of using procalcitonin for starting or stopping antibiotics over a large range of patients with varying severity of ARIs and from different clinical settings.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective RCTs comparing a strategy to initiate or discontinue antibiotic therapy based on PCT levels with a control arm without PCT measurements were eligible for inclusion. Participants were randomised to receive antibiotics either based on PCT levels ('PCT-guided' group) or a control group without knowledge of PCT levels, including antibiotic management based on usual care or guidelines. We did not include non-randomised studies.

Types of participants

We included adult participants with clinical diagnoses of ARIs: either a lower ARI including community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), acute bronchitis, exacerbation of asthma, or

exacerbation of chronic obstructive pulmonary disease (COPD); or an upper ARI including common cold, rhino-sinusitis, pharyngitis, tonsillitis, or otitis media. We also included people with sepsis and suspected ARIs in the analyses. We excluded trials if they focused exclusively on children or used PCT to escalate antibiotic therapy. We made no exclusions based on language of reports or clinical setting. We included trials from primary care, emergency departments, and medical and surgical ICUs.

Types of interventions

Strategies to initiate or discontinue antibiotic therapy based on PCT levels compared with usual care were eligible.

Types of outcome measures

We defined primary and secondary outcomes to a follow-up time of 30 days. For trials with shorter follow-up periods, we used the available information (i.e. until hospital discharge). We excluded all trials with different follow-up times for mortality in a sensitivity analysis.

Primary outcomes

1. All-cause mortality following randomisation up to a follow-up time of 30 days.
2. Setting-specific treatment failure within 30 days of inclusion.

For the primary care setting, we defined treatment failure as death, hospitalisation, ARI-specific complications (e.g. empyema for lower ARIs, meningitis for upper ARIs), recurrent or worsening infection, and still having ARI-associated discomfort at 30 days. For the emergency department setting, we defined treatment failure as death, ICU admission, rehospitalisation after index hospital discharge, ARI-associated complications (e.g. empyema or acute respiratory distress syndrome for lower ARIs), and recurrent or worsening infection within 30 days of follow-up. For the medical and surgical ICU setting, we defined treatment failure as death within 30 days of follow-up and recurrent or worsening infection.

Secondary outcomes

1. Antibiotic use (initiation of antibiotics, duration of antibiotics, and total exposure to antibiotics (total amount of antibiotic days divided by total number of participants)).
2. Length of hospital stay for hospitalised participants.
3. Length of ICU stay for critically ill participants.
4. Number of days with restricted activities within 14 days after randomisation for primary care participants.
5. Antibiotic-related side effects.

Search methods for identification of studies

We updated the search strategy for this review in February 2017 in collaboration with the Cochrane Acute Respiratory Infections Group's Information Specialist. We performed data collection based on the protocol of a previous meta-analysis of individual participant data published in the Cochrane Library (Schuetz 2008).

Electronic searches

We updated the searches for this review in February 2017, running the search across all databases from the date of inception to 10 February 2017. We screened all new references identified by the search. We searched the following databases for published studies:

- The Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1), part of the Cochrane Library, which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, www.cochranelibrary.com/ (accessed 10 February 2017) (Appendix 1);
- MEDLINE Ovid (1966 to 10 February 2017) (Appendix 2);
- Embase.com (1980 to 10 February 2017) (Appendix 3).

We used the search strategy in Appendix 4 to conduct searches for the 2012 version of this review (Schuetz 2012).

We also searched for ongoing and completed trials in the following trial register:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/; searched 12 April 2017).

We did not apply any language or publication restrictions.

Searching other resources

We contacted experts for further eligible trials.

Data collection and analysis

We requested individual participant data from the investigators of all included trials. We checked all provided data against published reports, and if needed, corrected any discrepancies.

We prepared this review update according to PRISMA guidelines and the PRISMA-IPD guideline (Liberati 2009a; Stewart 2015).

Selection of studies

At least two review authors (RS, YW, PS) independently assessed trial eligibility based on titles, abstracts, full-text reports, and further information from investigators as needed.

Data extraction and management

We checked data from each trial against reported results and resolved any queries with the principal investigator, trial data manager, or statistician. The mortality and adverse outcome rates from trials included in this review may differ slightly from previous reports because we treated data in a consistent manner across all trials.

Assessment of risk of bias in included studies

Two review authors (RS, YW) assessed the methodological quality of each included study using the Cochrane 'Risk of bias' tool and resolved any disagreements by discussion (Higgins 2011). Methodological criteria included: adequate sequence generation and concealment of treatment allocation; blinding of participants, physicians and clinical outcome assessment; whether the study was free of selective reporting; and the proportion of participants lost to follow-up. We documented the proportion of participants in the PCT group that adhered to the PCT algorithm used in each study, defining adherence to the PCT algorithm of lower than 70% as high risk of bias, and, if not reported, as unclear risk. Due to the study design of the included studies, physicians were aware of the participants' study group because in the intervention group physicians used the PCT result for decision making about antibiotic treatment, while in the control group no PCT result was communicated to the physicians. Blinding of physicians was

therefore not feasible, resulting in an unclear risk for performance bias in all studies.

We assessed the quality of evidence at the outcome level using the GRADE approach (GRADEpro GDT 2014).

Measures of treatment effect

We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using multivariable hierarchical logistic regression for the co-primary endpoints of mortality from any cause and treatment failure (Thompson 2001; Turner 2000). We fitted corresponding linear and logistic regression models for continuous and binary secondary endpoints, respectively. We calculated Kaplan-Meier curves for time to death for graphical display.

We used Stata version 12.1 (College Station, TX) for statistical analyses (Stata 12.1).

Unit of analysis issues

The unit of our primary analysis was the individual study participant. We analysed all participants in the study group to which they were randomised. We calculated summary estimates using aggregated data from individual trials as a sensitivity analysis.

Dealing with missing data

We received the full data sets from all trials included in the individual participant data analysis (n = 26) with all available follow-up information (if recorded in the trials).

We assumed in our main analysis that participants lost to follow-up did not experience an event. We explored if a complete-case analysis (excluding participants lost to follow-up) or an analysis assuming that participants lost to follow-up experienced an event would change the results for the primary outcomes of mortality and treatment failure in sensitivity analyses. We checked all individual participant data against the published results but did not find significant differences that warranted further exploration.

Assessment of heterogeneity

We performed prespecified analyses stratified by clinical setting (i.e. primary care, emergency department, ICU) and ARI diagnosis (CAP, COPD, bronchitis, VAP) to investigate the consistency of results across our heterogeneous patient populations in terms of disease severity. We formally tested for potential subgroup effects by adding the clinical setting and ARI diagnosis in turn to the regression model together with the corresponding interaction term with the PCT group as a fixed-effect model. We assessed heterogeneity by estimating the I^2 statistic (the percentage of total variance across trials that is due to heterogeneity rather than chance) in meta-analyses using aggregated data and by testing for heterogeneity using the Cochran Q test (Higgins 2003).

Assessment of reporting biases

We assessed reporting bias by attempting to identify if the study was included in a trial registry, a protocol was available, and if the methods section provided a list of outcomes. We compared listed outcomes from those sources to outcomes reported in the published papers.

Data synthesis

We used multivariable hierarchical logistic regression to combine participant data from the trials (Thompson 2001; Turner 2000). Apart from the group variable indicating the use of a PCT algorithm, we included important prognostic factors such as participant age and ARI diagnosis as an additional fixed effect; to account for within- and between-trial variability, we added a categorical trial variable to the model as a random effect. In meta-analyses with aggregated trial data we calculated summary ORs using a random-effects model and the Mantel-Haenszel facility of Review Manager 5 (RevMan 2014).

GRADE and 'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes: all-cause mortality at 30 days, setting-specific treatment failure at 30 days, total exposure to antibiotics, and antibiotic-related side effects (Summary of findings for the main comparison). The results reported in this table correspond to the main IPD analysis and are slightly different from the aggregate data analysis. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used the methods and recommendations in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT 2014). We justified all decisions to down- or upgrade the quality of studies using footnotes, and we made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We performed prespecified analyses stratified by clinical setting and ARI diagnosis and formally tested for potential subgroup effects by adding an interaction term into the statistical model.

Sensitivity analysis

We performed prespecified sensitivity analyses based on the main quality indicators: allocation concealment, blinded outcome assessment, adherence to the PCT algorithm (we defined low adherence to PCT algorithms as < 70%), and follow-up time for mortality other than one month. We also performed an aggregate data meta-analysis using all trials with potentially eligible participants.

RESULTS

Description of studies

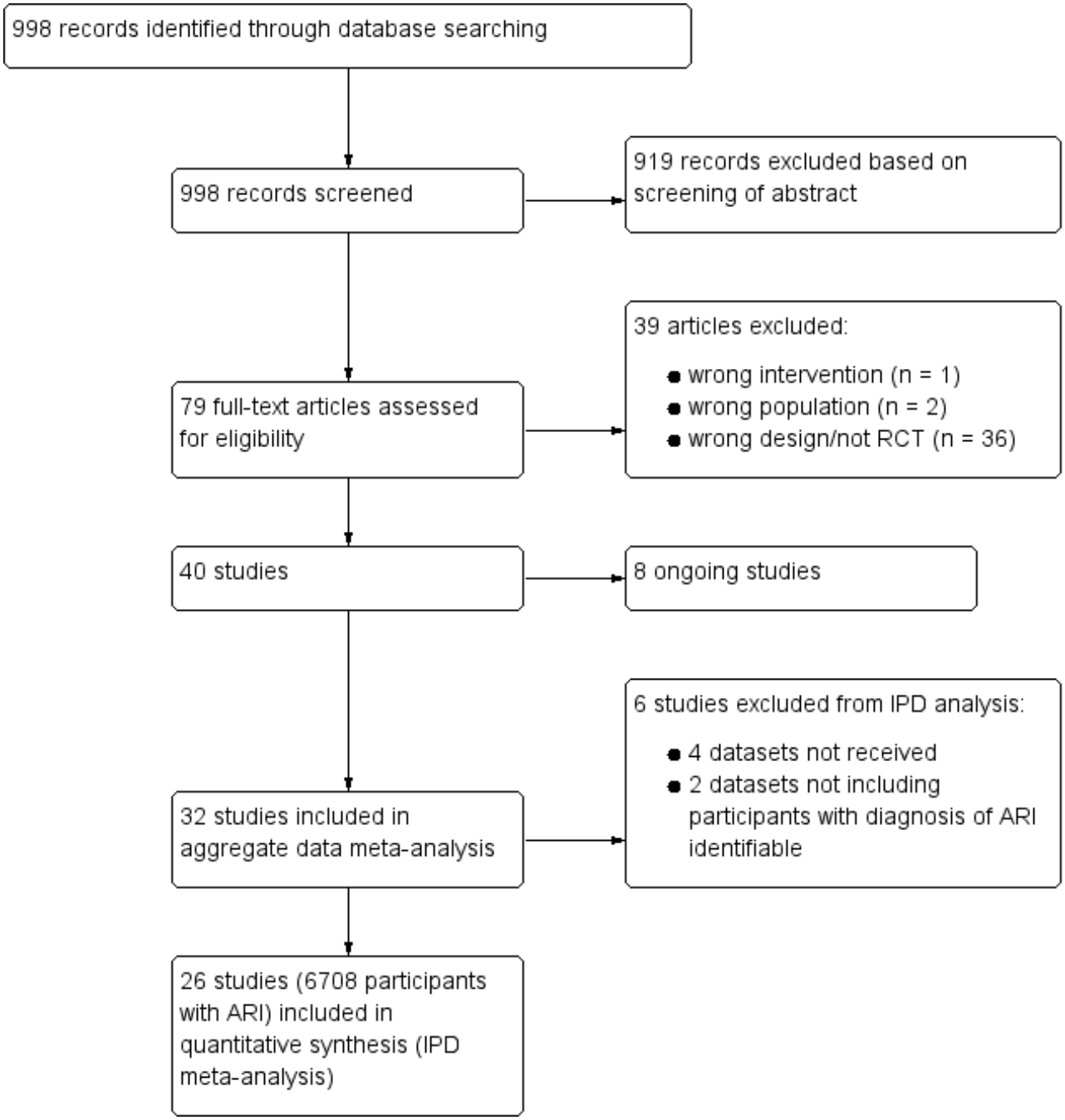
See: Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies tables.

Results of the search

After removal of duplicates, we identified 998 records that we further assessed based on title and abstracts, excluding 919 records. We obtained 79 full-text study reports, and following assessment excluded 39 that did not meet our inclusion criteria. Eight studies were ongoing trials. From 32 eligible RCTs (9909 participants) including 18 new trials for this 2017 update, we obtained individual participant data from 26 trials including 6708 participants, which were included in the main individual

participant data meta-analysis (see Figure 1). We did not obtain individual participant data for four trials, and two trials did not include participants with confirmed ARIs. The sensitivity aggregate analysis includes all 32 trials.

Figure 1. Study flow diagram. Abbreviations: ARI: acute respiratory infection; IPD: individual participant data; RCT: randomised controlled trial



Included studies

We included a total of 26 studies involving 6708 participants in the main individual participant data meta-analysis. Study characteristics are presented in Table 1.

Participants

Baseline characteristics of included participants were similar in the PCT and control groups with respect to important prognostic features (Table 2). Most participants were recruited either in the emergency department or ICU setting, and CAP was the most frequent ARI diagnosis, reported in more than 40% of participants.

Settings

Trials were conducted in 12 countries: Switzerland, Germany, France, Italy, USA, China, Denmark, Netherlands, Brazil, Belgium, Australia, and Serbia. Trials were conducted in different clinical settings including primary care, emergency departments and medical wards, and ICU. There were two primary care trials with upper and lower respiratory infection patients; 11 emergency department and medical ward trials with lower ARI patients; and 13 ICU trials with mostly septic patients due to infections of the lower respiratory tract.

Interventions

Procalcitonin algorithms used in the different trials were similar in concept and recommended initiation and/or continuation of antibiotic therapy based on similar PCT cut-off levels (reviewed in Schuetz 2011a). However, there were differences: some trials in primary care and the emergency department used only a single PCT measurement on admission to guide initiation of antibiotics, while the other trials (predominantly in hospitalised patients with severe infections) used repeated measurements for guiding the duration of treatment. One trial used a point-of-care device (Corti 2016). Adherence to algorithms varied, ranging from 44% to 100% (Table 3).

Comparators

In control group participants, PCT was not used to guide treatment decisions, but this decision was up to the treating physician team. In some trials, physicians were asked to follow antibiotic guidelines for control group participants (Briel 2008; Schuetz 2009). In one trial, the control group was guided with C-reactive protein levels (Oliveira 2013).

Funding sources

All studies were investigator-initiated trials. Half of the trials were funded by national agencies or did not report funding; the other half of the trials received funding from the biomarker industry (e.g. Thermo Fisher Scientific).

Excluded studies

We excluded a total of 39 studies due to wrong intervention (n = 1), wrong population (n = 2), and wrong design (not RCT) (n = 36). A total of nine studies reported as ongoing in the 2012 review were now available for assessment; we included four of these studies in this current update (Annane 2013; Bloos 2016; De Jong 2016; Lima 2016), and did not include five studies due to wrong population (paediatrics).

Ongoing studies

Our searches of the trial register identified seven ongoing studies that we will assess for inclusion for the next review update (Ongoing studies). These studies focus on the utility of PCT in people with pneumonitis (NCT02862314), pulmonary embolism (NCT02261610), lower respiratory infection (NCT02130986), heart failure (NCT02787603), and intraoperative positive-end expiratory pressure optimisation (NCT02931409). Two trials are antibiotic efficacy trials (NCT02332577; NCT02440828).

Risk of bias in included studies

The overall risk of bias is presented graphically in Figure 2 and Figure 3. The risk of bias was mostly low for random sequence generation, allocation concealment, incomplete outcome data, and selective reporting; unclear for blinding of personnel in all studies; and mostly high for blinding of outcome assessment.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

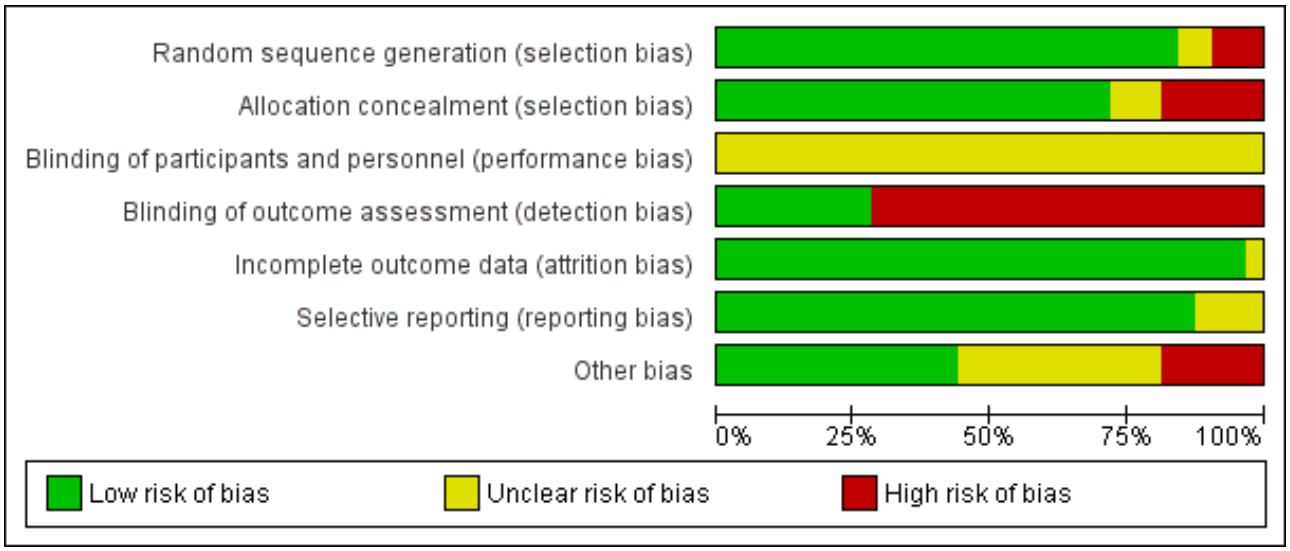


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

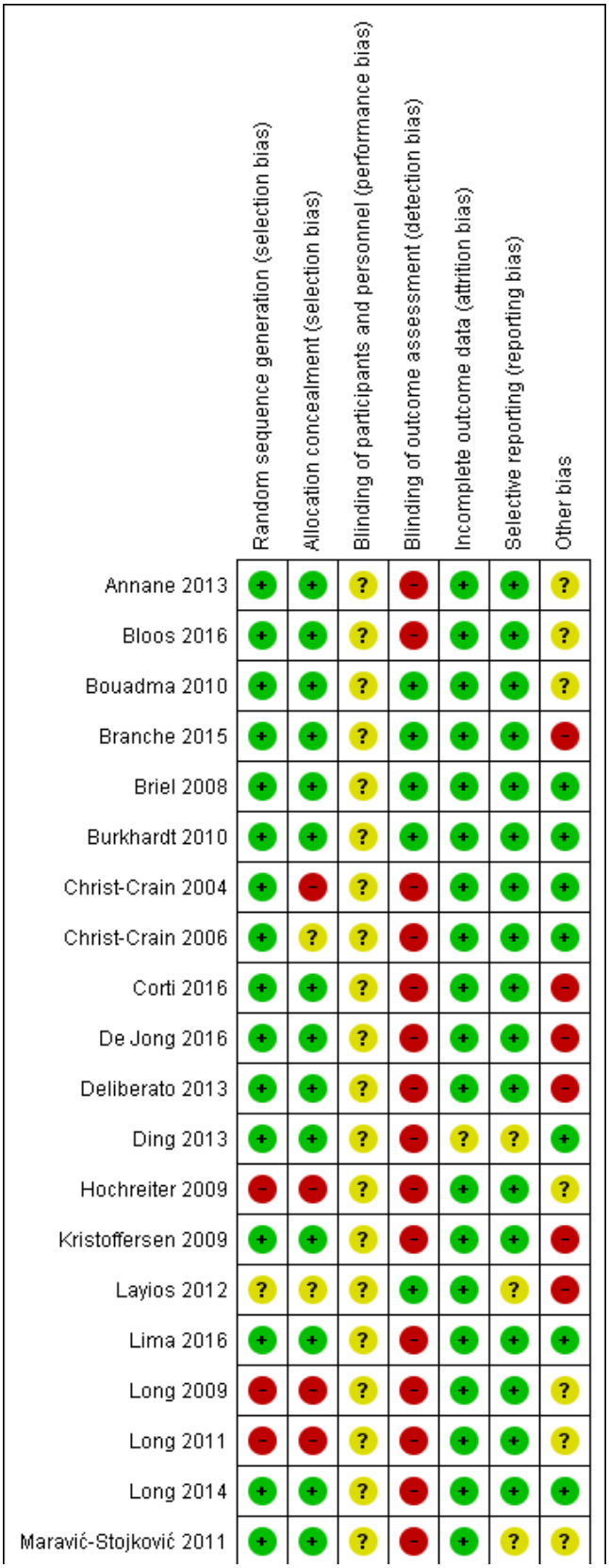
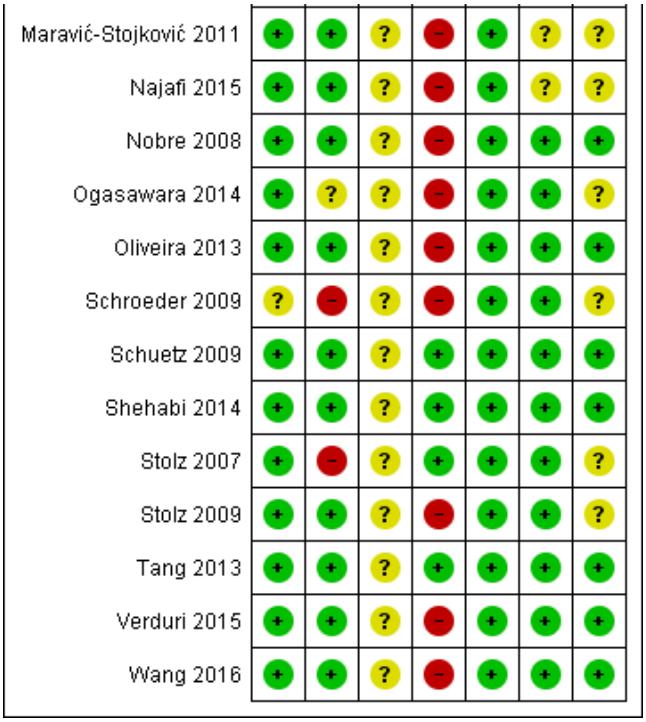


Figure 3. (Continued)



Allocation

All studies randomised participants to intervention (PCT testing) or control groups. A total of 25 trials with mainly computer-generated lists and centralised randomisation were at low risk of selection bias. Seven trials were at high or unclear risk of selection bias. Risk for selection bias with regard to random sequence generation was due to weekly allocation (Christ-Crain 2004), unnumbered envelopes (Christ-Crain 2006; Stolz 2007), use of odd and even patient identification numbers (Long 2009; Long 2011), and unconcealed drawing of lots (Hochreiter 2009; Schroeder 2009).

Blinding

None of the included trials blinded physicians to group allocation because PCT was used for decision making in the intervention group, thus all trials had unclear risk for blinding of participants and personnel.

All trials used blinded outcome assessment (Briel 2008; Bouadma 2010; Branche 2015; Layios 2012; Schuetz 2009; Shehabi 2014; Stolz 2007; Tang 2013), employing blinded telephone interviews to assess vital status and other outcomes.

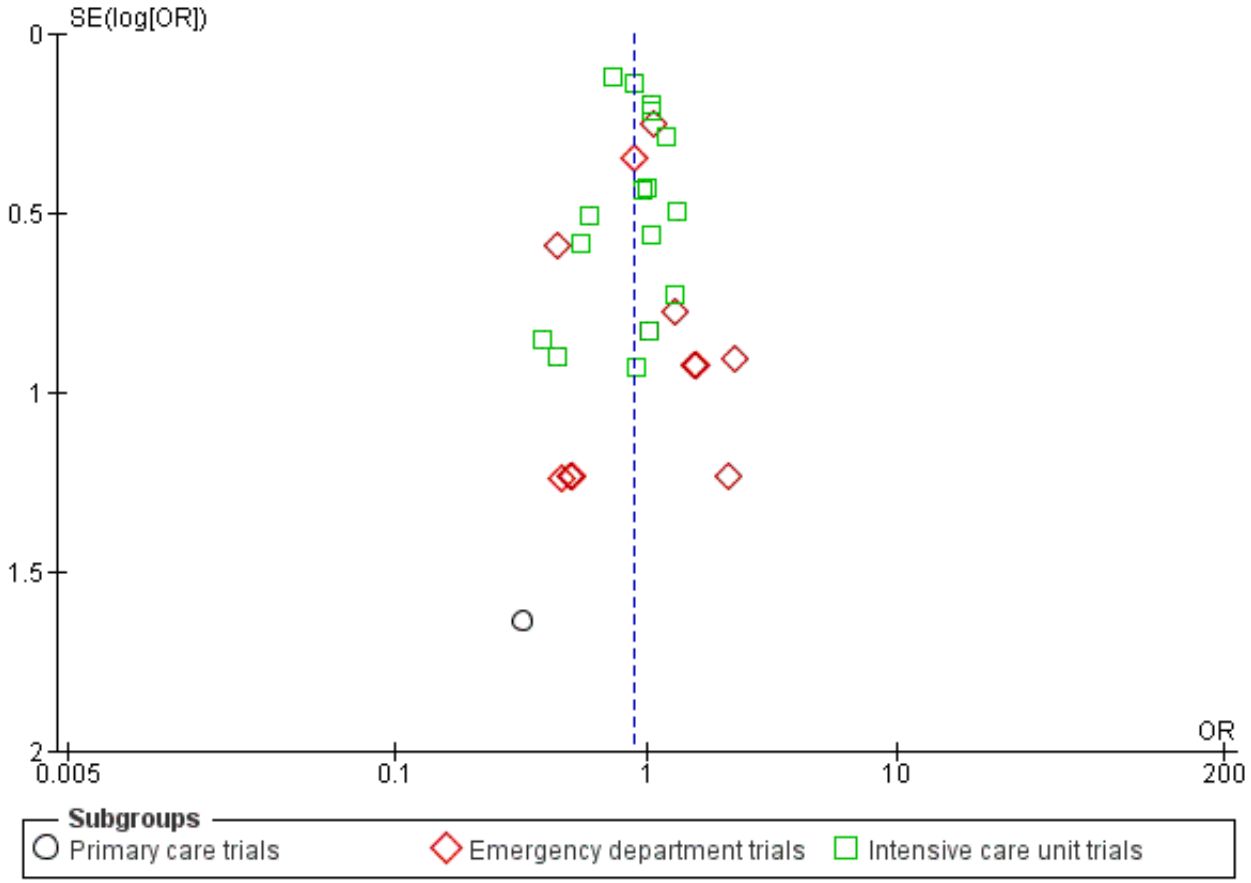
Incomplete outcome data

The included trials had a high follow-up for mortality with few participants lost to follow-up (Table 3). In seven trials, outcome assessment was done after hospital or ICU discharge (Deliberato 2013; Hochreiter 2009; Kristoffersen 2009; Layios 2012; Long 2009; Schroeder 2009; Shehabi 2014). One trial had a high number of post randomisation exclusions (six in the intervention arm versus four in the control group) and thus had an unclear risk of bias (Ding 2013).

Selective reporting

No reporting bias was found when study protocols and final results were compared. However, we did not find registration numbers for four trials (Ding 2013; Layios 2012; Maravić-Stojković 2011; Najafi 2015), which we considered to be at unclear risk of bias. We found no evidence of reporting bias by visual inspection of funnel plots (Figure 4).

Figure 4. Funnel plot of comparison: 1 Procalcitonin algorithm versus no procalcitonin algorithm stratified by clinical setting, outcome: 1.1 Mortality at 30 days.



Other potential sources of bias

Another potential source of bias relates to low adherence to the PCT algorithms, particularly for safety endpoints. Overall, adherence varied, ranging from 44% to 100% (Table 3).

With regard to funding, 16 trials reported no industry funding (six did not report any funding, 10 reported public funding), and in 16 trials Thermo Fisher, the producer of the PCT assay, funded or co funded the studies by providing free-of-charge PCT kits or additional research funds, or both.

Effects of interventions

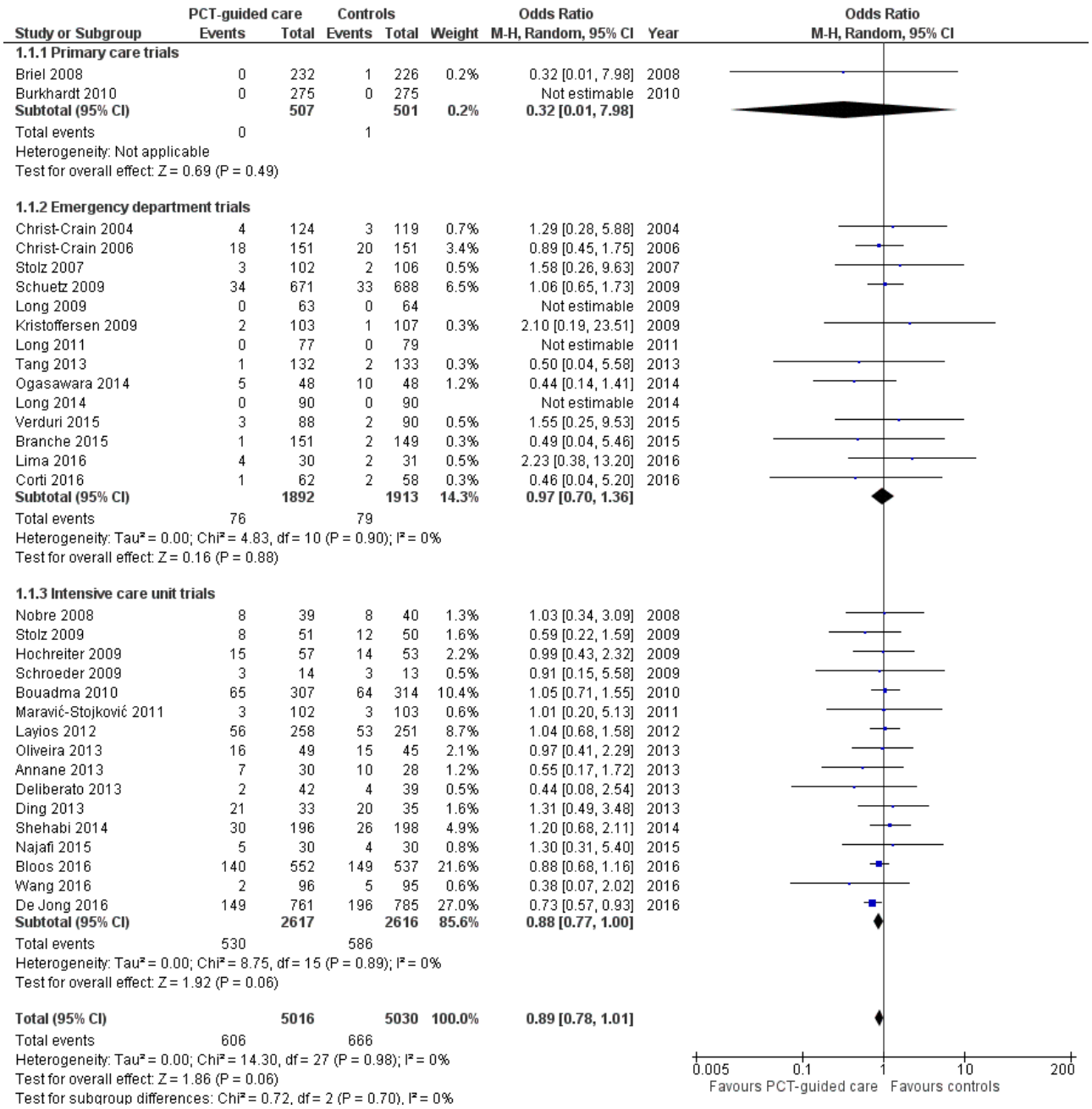
See: **Summary of findings for the main comparison** Procalcitonin algorithm compared to standard care for guiding antibiotic therapy in acute respiratory tract infections

Primary outcomes

1. All-cause mortality following randomisation up to a follow-up time of 30 days

There were 286 deaths in 3336 PCT-guided participants (8.6%) compared to 336 in 3372 controls (10.0%) resulting in a significantly lower mortality associated with PCT-guided therapy (adjusted odds ratio (OR) 0.83, 95% confidence interval (CI) 0.70 to 0.99, P = 0.037) (Table 4). This effect was consistent across clinical settings (P for interaction > 0.05), although mortality could not be estimated in primary care trials because only one death was reported in a control group participant. The effect on mortality was also consistent among different ARI diagnoses (CAP, COPD, bronchitis, VAP) (P for interaction > 0.05). As a further sensitivity analysis and to investigate heterogeneity among trials, we also calculated an aggregate data meta-analysis based on the aggregate results of all 32 potentially eligible trials (thus not limited to ARI participants only). In this analysis, the results proved robust, although the mortality estimate did not reach statistical significance (OR 0.89, 95% CI 0.78 to 1.01; Analysis 1.1; Figure 5). There was no evidence of heterogeneity (I^2 = 0%).

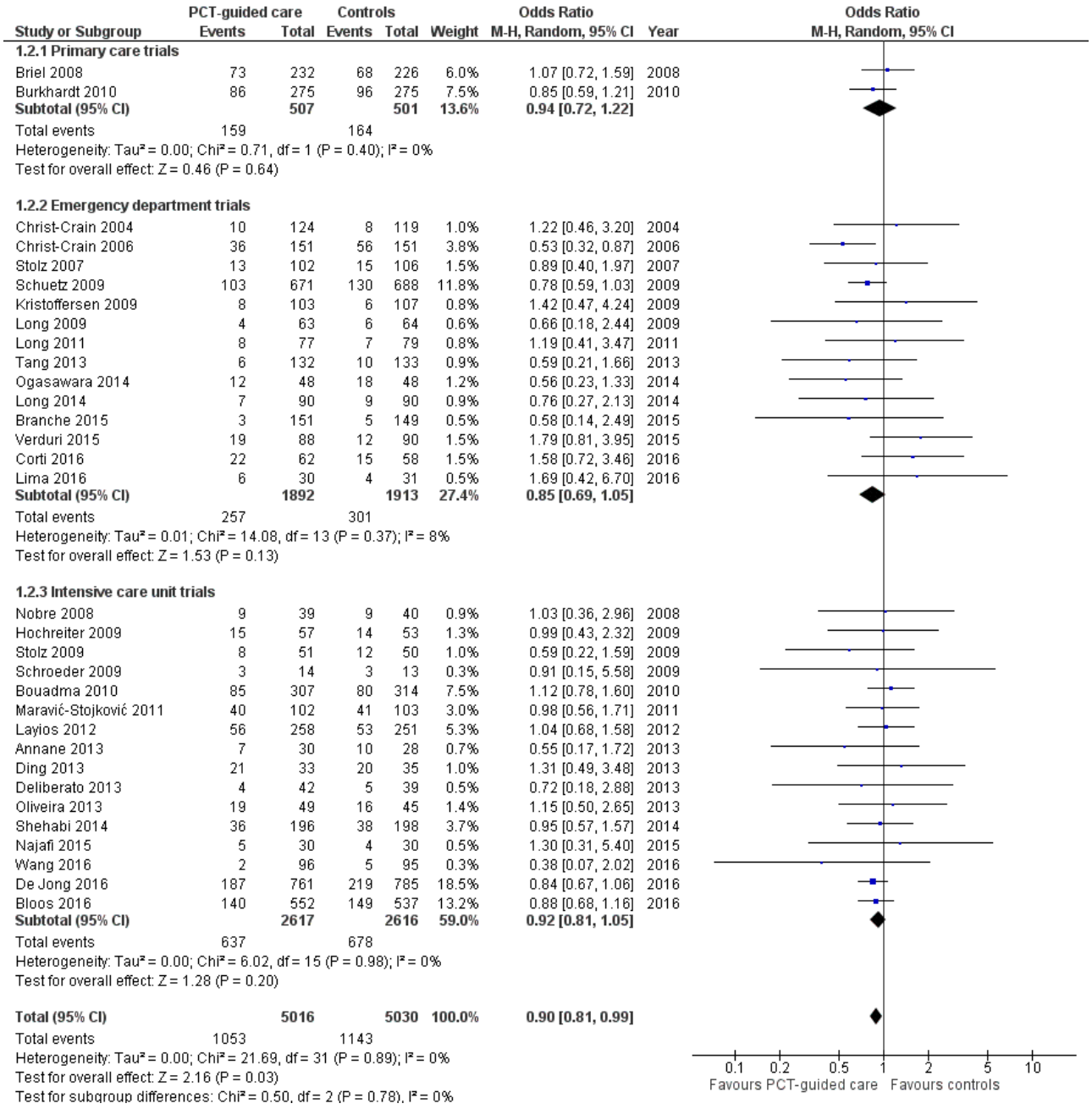
Figure 5. Forest plot of comparison: 1 Procalcitonin algorithm versus no procalcitonin algorithm stratified by clinical setting, outcome: 1.1 Mortality at 30 days.



2. Setting-specific treatment failure within 30 days of inclusion

Treatment failure was not significantly lower in PCT-guided participants (23.0% versus 24.9%, adjusted OR 0.90, 95% CI 0.80 to 1.01, P = 0.068). These results were similar among subgroups by clinical setting and type of respiratory infection (P for interaction > 0.05). With an OR of 0.90 (95% CI 0.81 to 0.99), treatment failure was significantly lower in PCT group participants in an aggregate data meta-analysis based on all 32 potentially eligible trials (thus relying on the original definition of treatment failure as used in the trials). There was no evidence of heterogeneity (I^2 = 0%) (Figure 6). We also performed several predefined sensitivity analyses, which showed no evidence for interactions (see summary in Table 5).

Figure 6. Forest plot of comparison: 1 Procalcitonin algorithm versus no procalcitonin algorithm stratified by clinical setting, outcome: 1.2 Treatment failure at 30 days.



Secondary outcomes

1. Antibiotic use (initiation of antibiotics, duration of antibiotics, and total exposure to antibiotics (total amount of antibiotic days divided by total number of participants))

Procalcitonin guidance was associated with a reduction in total antibiotic exposure (mean 8.1 days compared to 5.7 days, regression coefficient -2.43 days (95% CI -2.71 to -2.15), P < 0.001). Also, duration of antibiotic treatment in treated participants was shorter (mean 9.4 days compared to 8.0 days, adjusted coefficient -1.83 days (95% CI -2.15 to -1.5), P < 0.001) (Table 6).

2. Length of hospital stay for hospitalised participants

However, the effect on antibiotic consumption differed according to clinical setting. In the primary care setting, lower antibiotic exposure was mainly due to lower initial prescription rates (P < 0.001 for interaction between primary care setting and PCT group on antibiotic prescriptions). Similarly, lower antibiotic exposure due to lower prescription rates was found in selected infections such as acute bronchitis (adjusted OR 0.18, 95% CI 0.12 to 0.26; P for interaction < 0.001). Lower antibiotic prescription rates (adjusted OR 0.49, 95% CI 0.41 to 0.58) and shorter duration of antibiotic therapy in participants with initiation of antibiotic

(adjusted coefficient -2.45 days, 95% CI -2.86 to -2.05) contributed to the lower overall exposure in the emergency department setting.

Length of hospital stay and ICU stay were similar in both groups with no evidence for different effects in subgroups (P for interaction > 0.05).

3. Length of ICU stay for critically ill participants

For the ICU setting, the lower exposure was mainly explained by shorter treatment durations (adjusted difference in days -1.23, 95% CI -1.82 to -0.65). Similarly, for CAP, the lower exposure was mainly explained by shorter durations (adjusted difference in days -2.45, 95% CI -2.87 to -2.02).

4. Number of days with restricted activities within 14 days after randomisation for primary care participants

For studies conducted in the primary care setting, there was no difference in days with restricted activities of daily living between PCT and control group participants (days, 8.9 ± 4.2 versus 8.9 ± 4.1, regression coefficient 0.07 (95% CI -0.44 to 0.59), P = 0.777).

5. Antibiotic-related side effects

There was also a significant reduction in antibiotic-related side effects (16.3% versus 22.1%, adjusted OR 0.68, 95% CI 0.57 to 0.82, P < 0.001). This outcome was only assessed in some of the primary care and emergency department trials (n = 6), and not in ICU trials. There was no evidence for subgroup effects (P for interaction > 0.05).

DISCUSSION

Summary of main results

This updated systematic review and meta-analysis included 32 trials, of which 26 trials were used for the main individual participant data analysis. Trials were conducted in 12 countries and included different clinical settings and types of respiratory infections. There was mostly low risk for random sequence generation, allocation concealment, incomplete outcome data, and selective reporting. There was unclear risk in all studies for blinding of personnel, and mostly high risk for blinding of outcome assessment. The results indicate a significant reduction in mortality (high-quality evidence according to GRADE, Summary of findings for the main comparison) and non-significant result for treatment failure (moderate-quality evidence according to GRADE, Summary of findings for the main comparison) when PCT was used to guide initiation and duration of antibiotic treatment in ARI participants compared to control participants. Additionally, antibiotic consumption and side effects from antibiotics were significantly reduced across different clinical settings and types of ARIs. There was no effect on length of hospital stay and ICU length of stay. Results were similar in subgroup and sensitivity analyses including an aggregate data analysis with all 32 potentially eligible trials. Limitations include incomplete individual participant data, with four research groups not agreeing to the sharing of individual participant data; incomplete follow-up information in some of the trials where no outcome assessment was done after 30 days of enrolment; differences in definitions of treatment failure among trials; and exclusion of some patient populations such as immunosuppressed people. Still, results from this updated individual participant data meta-analysis support the use of PCT in the context of antibiotic stewardship in people with ARIs.

Overall completeness and applicability of evidence

The strengths of our review include an explicit study protocol, a comprehensive search to retrieve all relevant trials, access to individual participant-level data from all but four of the included trials, and standardised outcome definitions across trials, thereby overcoming limitations of meta-analyses using aggregated data. To minimise the risk of data-driven associations, we prespecified a limited number of prognostic factors and subgroup variables for our statistical model. We allowed for potential clustering effects by using random-effects models for included trials. Our results proved robust in sensitivity analyses focusing on high-quality trials and on participants with complete follow-up data.

The accuracy of PCT for diagnosing bacterial infections has been called into question by previous meta-analyses of observational studies, which demonstrated mixed results (Jones 2007; Simmonds 2005; Tang 2007; Uzzan 2006). However, a more recent meta-analysis using positive culture as the reference method found moderate to high discrimination of systematic inflammatory response syndrome and sepsis (Wacker 2013). Since there are no available gold standards for the diagnosis of the clinical conditions included in our analysis, most studies used clinical consensus criteria, which may differ among studies. Rather than relying on these imperfect diagnostic criteria, we were able to assess the value of PCT algorithms by means of RCTs measuring clinically relevant, participant-level outcomes.

Despite these merits, this review has several limitations. We limited our analysis to adults with ARIs who were mostly immunocompetent, and excluded some pathogens (i.e. *Legionella* or *Pseudomonas* infections). The results of these trials may therefore not be generalised to people who are immunocompromised, with specific pathogens or infections other than ARIs, or children. Previous RCTs have shown that PCT guidance also reduces antibiotic exposure in a neonatal sepsis population but not in children with fever without a source (Manzano 2010). We found several ongoing RCTs in children evaluating PCT algorithms that should shed further light on the benefits and harms of PCT use for children. The included trials compared the PCT strategy to a control group where antibiotic therapy was guided based on 'usual practice' or based on current guideline recommendations. The magnitude of antibiotic reduction obviously correlates strongly with antibiotic prescription patterns, and in regions of low antibiotic prescription the PCT strategy may have smaller effects.

Quality of the evidence

Characteristics of the individual trials are presented in Table 1. Most trials had a follow-up of one month, with two trials assessing outcome after 14 to 21 days and several trials following participants until hospital discharge (or ICU discharge) only. Procalcitonin algorithms used in the different trials were similar in concept and recommended initiation and/or continuation of antibiotic therapy based on similar PCT cut-off levels (Table 1). However, there were differences: some trials in primary care and the emergency department used only a single PCT measurement on admission to guide initiation of antibiotics (Burkhardt 2010; Christ-Crain 2004), while the other trials (predominantly in hospitalised participants with severe infections) used repeated measurements for guiding the duration of treatment. Adherence to algorithms was variable. In terms of methodological quality, trials had concealed allocation, but in several trials blinded outcome assessment was

not done. All trials achieved complete or near-complete follow-up for mortality. None of the trials blinded participants or physicians to group allocation. The overall quality of the evidence according to GRADE was moderate to high (Summary of findings for the main comparison).

Potential biases in the review process

Due to the differences in patient populations included in this analysis, which ranged from primary care to the ICU, we adapted the definition of treatment failure to clinical settings by including setting-specific components in this composite outcome. This may challenge the clinical interpretation in the overall analysis.

Agreements and disagreements with other studies or reviews

While mortality did not differ significantly in our initial meta-analysis (adjusted OR 0.94, 95% CI 0.71 to 1.23) (Schuetz 2012), we found a significantly lower mortality rate in PCT-guided participants in this update. This result was robust in subgroup analyses and in our sensitivity analysis. Also, when considering all trials in the aggregate data analysis, mortality tended to be reduced, although not significantly (OR 0.89, 95% CI 0.78 to 1.01). Importantly, the largest-yet ICU trial from the Netherlands has reported a significantly lower mortality in PCT-guided participants (De Jong 2016).

Two of the included individual trials reported reduced length of stay, particularly within the ICU. Yet, despite a marked reduction in the duration of antibiotic therapy across trials and settings, there was no difference in length of ICU and hospital stay between the two groups in our comprehensive analysis. One might expect that clinically stable patients with discontinued intravenous antibiotics could be safely discharged unless there are extenuating circumstances. Perceived needs by physicians to further monitor these patients in the unit or inability to transfer patients to other inpatient or aftercare locations may partly explain this finding.

There is ongoing controversy about the diagnostic performance of PCT and other blood markers to correctly identify patients with a bacterial infection. In fact, several observational studies have questioned the added value of PCT in addition to clinical signs, such as a primary care study authored by van Vugt and colleagues reporting no additional benefit of PCT to a clinical assessment (van Vugt 2013). Importantly, in the context of respiratory infections, diagnostic studies are limited by the lack of a reference standard, with blood cultures only detecting a minority of cases (e.g. only 10% to 20% of patients with clinically and radiologically confirmed CAP have positive blood cultures) (Muller 2010; Wacker 2013). Interventional research, such as the trials included in the current analysis, do not rely on a reference standard but compare resource use (e.g. antibiotics) and clinical outcomes in people with and without use of the diagnostic marker. For the primary care setting, PCT had a very strong effect on antibiotic consumption (reduction of antibiotic exposure by 70%, from 4.6 to 1.6 days) without compromising disease resolution and patient safety. Of note, we were not able to assess the effect of PCT on mortality due to the very low risk situation with only one non-survivor (control group) among the 1008 included participants.

The available evidence from RCTs, as summarised in this report, supports the use of PCT for de-escalation of antibiotic therapy for people with ARIs. The same may not be true for escalation of antibiotic therapy when PCT levels increase as demonstrated in a recent large sepsis trial (Jensen 2011), where PCT-guided escalation of diagnostic procedures and antimicrobial therapy in the ICU did not improve survival and led to organ-related harm and prolonged ICU stays.

AUTHORS' CONCLUSIONS

Implications for practice

Emerging bacterial resistance to multiple antibiotic agents calls for more stringent efforts to reduce the empiric use of antimicrobial agents in self limited and non-bacterial diseases and to shorten the duration of antibiotic treatment in bacterial infection with clinical resolution. The results of our study suggest that procalcitonin (PCT) is a safe and effective tool to guide clinical decisions for antibiotic initiation and duration of treatment. In all trials, PCT was used to inform physicians about the need for initiation or discontinuation of antibiotic therapy, or both. However, there were differences in PCT protocols among trials depending on the clinical setting (see Table 1 for details about PCT recommendations used in the individual trials) (Schuetz 2011a; Schuetz 2015). In brief, PCT was mainly used to inform about initiation of antibiotic treatment in primary care trials, and re-measurement of PCT was recommended in participants not being treated with antibiotics and not showing a resolution of illness at follow-up. In the emergency room and hospital ward setting, PCT was used to inform about initiation of antibiotic treatment (mainly in low-risk patients with bronchitis or chronic obstructive pulmonary disease exacerbation), and also about discontinuation of treatment in community-acquired pneumonia patients. In intensive care unit patients, PCT was mainly used to monitor treatment and discontinue antibiotics in participants with clinical improvement and a drop in PCT levels. Thus for clinical practice, PCT should also be adapted to clinical settings and the risk of patients - similar to patients with suspicion of pulmonary embolism where D-dimer levels are used differently depending on the pre-test probability (Konstantinides 2008).

The use of PCT to guide initiation and duration of antibiotic treatment in people with acute respiratory infections (ARIs) was associated with lower mortality rates and significantly reduced antibiotic consumption and associated side effects across different clinical settings and ARI diagnoses. Of note, mortality was very low in primary care patients, and we were thus not able to assess the effect of PCT on mortality. The use of PCT embedded in clinical algorithms has the potential to improve the antibiotic management of ARI patients and has substantial clinical and public health implications to reduce antibiotic exposure and the associated risk of antibiotic resistance. Several assays for the measurement of PCT are currently available (Schuetz 2017), and the US Food and Drug Administration recently cleared the Vidas assay, among others, for antibiotic stewardship and prognostication of patients using a PCT kinetics algorithm (Schuetz 2016). Importantly, all trials have used highly sensitive assays to measure PCT in order to have optimal sensitivity and thus test performance. Factors such as accessibility and time taken to get reports of the tests are equally important in whether PCT will be used in the clinical decision-making process for antibiotic therapy in ARIs. In this regard, a point-of-care test would be important, especially for the primary care setting (Kutz 2016).

Importantly, all trials included PCT into clinical algorithms, and physicians could deviate from the PCT algorithm if needed.

Poststudy surveys have been published in order to better understand the effects and challenges of PCT testing in clinical practice (Albrich 2012; Balk 2017).

Implications for research

Future studies should establish cost-effectiveness by considering country-specific costs of PCT measurement (around USD 20 to USD 30 per sample) and potential savings in consumption of antibiotics and other healthcare resources (Stojanovic 2017).

In addition, it would be interesting to conduct a head-to-head trial comparing a PCT strategy to a strategy based on another biomarker, such as C-reactive protein (CRP) or interleukin-6 (Meili 2015; Meili 2016). A similar randomised controlled trial was recently conducted in primary care in the Netherlands with a treatment algorithm based on either CRP levels, communication training, or both, compared to a control group (Cals 2009). The trial authors reported a 42% relative reduction in antibiotic use with CRP guidance, which was similar to the effect of communication training in this setting. However, the usefulness of CRP for antibiotic guidance outside the primary care setting is not yet supported by controlled intervention trials.

While there is strong evidence for the use of PCT in respiratory infections, its role in other infections remains unclear. Several studies have investigated PCT as a diagnostic and antibiotic stewardship marker in different types of infections (Albrich 2012; Drozdov 2015; Sager 2017). However, larger trials powered for safety are needed to understand the effect of PCT outside respiratory infections.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Annane 2013

Methods	Randomised, multicentre, single-blind clinical trial in 8 French ICUs
Participants	**Inclusion criteria:** Adults admitted to a participating ICU were eligible if they, < 48 h, had SIRS, acute dysfunction of at least 1 organ, absence of indisputable clinical infection, and negative microbial cultures **Exclusion criteria:** Pregnancy, burns over ≥ 15% of body surface area, trauma, outpatient or inpatient cardiac arrest, post-orthopaedic surgery status, drug-related neutropenia, withdrawal of life-supportive therapies or a decision to withhold them, indisputable clinical infection or antibiotic exposure ≥ 48 h during the time shortly before ICU admission **Included in this study:** 62/1250 screened patients were eligible for the study, of whom 31 were randomised to each arm. 4 post randomisation exclusion (4 withdrew their consent)
Interventions	Guiding antibiotic decisions in ICU patients with non-microbiologically proven apparent severe sepsis **Algorithm used in this study:** In the experimental arm, both initiation and discontinuation of antibiotics were guided by a PCT-based algorithm, applied at 6 h and on day 3 and day 5 post randomisation. Briefly, antibiotic therapy was not to be started or was to be halted when PCT was < 0.25 µg/L, was strongly discouraged when PCT was ≥ 0.25 to < 0.5 µg/L, was recommended when PCT was ≥ 0.5 to < 5 µg/L, and was strongly recommended when PCT was ≥ 5 µg/L. Owing to the fact that surgery can increase PCT levels, for 12 participants enrolled in the 48-hour postoperative period, the respective PCT cut-offs were < 4 µg/L, ≥ 4 to < 9 µg/L, and ≥ 9 µg/L. Investigators were strongly advised not to overrule the algorithm every day up to the study day 5. In the control arm, the decision to start or stop antibiotic therapy was at the discretion of the participant's physician, without knowledge of the participant's PCT concentrations.
Outcomes	• proportion of participants receiving antibiotics at day 5 post randomisation • death at day 5, at ICU discharge, and at hospital discharge • proportion of participants started on antibiotics post randomisation • duration of antibiotic exposure • SOFA score at day 3 and day 5

Annane 2013 *(Continued)*

- proportion of participants with infection acquired between randomisation and day 3, day 5, and ICU discharge
- ICU and hospital length-of-stay

Notes	**Funding:** Research grant partly by Thermo Fisher B·R·A·H·M·S France. The sponsor had no input in study design, conduct, or reporting. **Follow-up time:** Until hospital discharge or 30 days' post randomisation, whichever came first **Registration:** NCT01025180

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised in a 1:1 ratio according to a computer-generated list. Randomisation was centralised through a secured web site and performed by an independent statistician.
Allocation concealment (selection bias)	Low risk	Centralised randomisation using permutation blocks
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The control arm remained blinded to PCT levels. Masking of antibiotic therapy was not feasible in this study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Investigators remained blinded to PCT levels in the control arm, but no blinding of overall outcome assessment was mentioned in the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for participants on antibiotic on day 5 was: 58/62. 4 participants withdrew their consent.
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol. Trial registered (NCT01025180).
Other bias	Unclear risk	Moderate adherence in the PCT arm: physicians were non-compliant with the PCT-based algorithm in 19% of participants at 6 h, 17% on day 3, and 37% on day 5. The study was stopped prematurely owing to the low incidence of eligible patients. As a consequence, the study population is small with low statistical power.

Bloos 2016

Methods	Randomised, investigator-initiated, multicentre, partially blinded clinical trial, in 33 multidisciplinary ICUs across Germany
Participants	**Inclusion criteria:** Adults with severe sepsis or septic shock (severe sepsis was defined as SIRS caused by infection combined with acute organ dysfunction. Septic shock was defined as sepsis in combination with arterial hypotension or need for vasopressor therapy despite adequate fluid resuscitation) **Exclusion criteria:** Pregnant or lactating women, patients with selenium intoxication, individuals with infections for which guidelines recommend a longer duration of antimicrobial therapy, immunocompromised patients, and those without commitment to full therapy or where death was imminent owing to coexisting diseases were excluded from the trial.

Bloos 2016 *(Continued)*

	Included in this study: 1180 participants were randomised; 91 participants were excluded from the final analysis because informed consent was not obtainable in the deferred consent process, resulting in 1089 participants with valid data.
Interventions	Guiding antibiotic decisions and effect of sodium selenite administration in people with severe sepsis or septic shock **Algorithm used in this study:** Using a 2 × 2 factorial design, participants were randomly assigned to receive intravenous sodium selenite or placebo as well as antimicrobial therapy guided by a PCT algorithm or conventional antimicrobial therapy. In participants randomised to the PCT guidance arm, PCT was measured locally on days 0, 1, 4, 7, 10, and 14 after randomisation if the participant was still in the ICU. Procalcitonin concentration on day 0 or day 1 served as the baseline value. Depending on the PCT results, an algorithm provided recommendations to change or discontinue antimicrobial therapy or trigger diagnostic procedures to optimise source control. On day 4, no change in antimicrobial therapy was recommended if the PCT level dropped by at least 50% compared with the baseline value. Otherwise, change or optimisation of antimicrobial therapy or interventions regarding source control were recommended. On the other days, stopping antimicrobial therapy was recommended if the PCT level was 1 ng/mL or lower or if the PCT level dropped by at least 50% compared with the previous value. Otherwise, change or optimisation of antimicrobial therapy or interventions regarding source control were recommended. The treating physician was allowed to overrule the algorithm recommendation. In the group without PCT guidance, no PCT measurements were obtained until day 14; changes in antimicrobial therapy were made at the discretion of the treating physician. Investigators agreed to treat all participants according to the Guidelines of the Germany Sepsis Society, which included recommendations to re-evaluate antimicrobial therapy after 48 to 72 hours and to restrict duration of antimicrobial therapy to no more than 10 days.
Outcomes	• death from any cause by 28 days after inclusion • 90-day all-cause mortality • mean total SOFA score and its sub scores • duration of ICU and hospital stay • ventilator-, vasopressor-, and dialysis-free days until day 90 • duration and costs of antimicrobial therapy • duration until change of antimicrobial therapy • antimicrobial exposure days • days free of antimicrobial therapy • frequency of surgical source control • frequency of diagnostic procedures for localisation of the infection focus • clinical and microbiologic treatment response • secondary infections • emergence of antibiotic-resistant bacteria
Notes	**Funding:** The study infrastructure was partially funded by grant 01 KI 0106 from the German Federal Ministry of Education and Research. Biosyn (Germany) and Thermo Fisher (Germany) provided study medication and financial support via unrestricted grants. **Follow-up:** 90 days **Trial registration:** NCT00832039

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Web-based, centralised randomisation
Allocation concealment (selection bias)	Low risk	quote "Using a 2 × 2 factorial design, we randomly assigned patients to receive intravenous sodium selenite or placebo as well as antimicrobial therapy guided by a PCT algorithm or conventional antimicrobial therapy without

Bloos 2016 *(Continued)*

		PCT guidance with an allocation ratio of 1:1:1:1 by use of a central randomisation web server. Randomisation was stratified by study centre, sex, and sepsis severity"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Due to the study design, blinding of physicians was not feasible. Procalcitonin values were only available in participants with study intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment was mentioned in study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Postrandomisation exclusions were about even among intervention arms with a very low dropout rate for mortality
Selective reporting (reporting bias)	Low risk	Outcomes correspond to trial registration (NCT00832039)
Other bias	Unclear risk	Overruling of the PCT algorithm was very high (adherence was lower than 50%)

Bouadma 2010

Methods	Randomised, multicentre clinical trial in 9 French ICUs
Participants	**Inclusion criteria:** Patients with suspected bacterial infections during ICU stay without prior AB (> 24 h) **Exclusion criteria:** Aged under 18 years; known pregnancy; expected stay in the ICU of less than 3 days; bone marrow transplant or chemotherapy-induced neutropenia (< 500 neutrophils per mL); infections for which long-term antibiotic treatment is strongly recommended (i.e. infective endocarditis, osteoarticular infections, anterior mediastinitis after cardiac surgery, hepatic or cerebral abscesses, chronic prostatitis, or infection with *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*, or *Toxoplasma gondii*); poor chance of survival, defined as a simplified acute physiology score (SAPS II) of more than 65 points at screening; and do-not-resuscitate orders. **Included in this analysis:** 394 participants with CAP and VAP out of 630 randomised participants; 9 post randomisation exclusions (8 withdrew consent, 1 randomised twice), and 227 not considered for this analysis due to diagnosis other than ARI
Interventions	Guiding antibiotic decisions in ICU patients with repeated PCT measurements **Algorithm used in this study:** Investigators were encouraged to discontinue ABs when PCT concentration was less than 80% of the peak concentration or an absolute concentration of less than 0.5 µg/L was reached.
Outcomes	• all-cause mortality at day 28 • all-cause mortality at day 60 • antibiotic use • relapse or superinfection (days 1 to 28) • number of days without mechanical ventilation (days 1 to 28) • SOFA score (days 1, 7, 14, and 28) • length of stay in the ICU and hospital

Bouadma 2010 *(Continued)*

Notes	**Funding:** Research grant from the Département à la Recherche Clinique et au Développement, Assistance Publique-Hopitaux de Paris (PHRC AOR06019), France. B·R·A·H·M·S, Germany (manufacturer of PCT assay) provided all assay-related materials free of charge for the study (Kryptor machines if not already available on-site and kits and maintenance required for study-related measurements). **Follow-up:** Fixed period of 60 days for mortality **Registration:** NCT00472667

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent, centralised, computer-generated randomisation sequence (CleanWEB, Telemedicine Technologies, Boulogne, France)
Allocation concealment (selection bias)	Low risk	Centralised randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Although treatment assignments were not masked, all investigators were unaware of aggregate outcomes during the study and primary endpoints were strictly defined and not patient-reported." Quote: "An adjudication committee comprised of 4 specialists in infectious diseases and critical care medicine who were masked to the randomisation assignment reviewed and validated all infectious episode classifications by consensus."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 393/394 (100%)
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol. Trial registered (NCT00472667).
Other bias	Unclear risk	Low adherence to PCT algorithm in PCT group (47%)

Branche 2015

Methods	Single-centre, randomised, open-label clinical trial in Rochester, NY, USA
Participants	**Inclusion criteria:** Adults ≥ 21 years of age with symptoms compatible with LRTI (i.e. admission diagnosis of pneumonia, acute exacerbations of COPD, bronchitis, asthma, influenza, viral syndrome, respiratory failure, and congestive heart failure CHF) were identified by reviewing the daily admission census. **Exclusion criteria:** Patients with characteristics indicative of a high risk for bacterial infection (i.e. ICU requirement, active chemotherapy or radiation, immunosuppression, definitive infiltrate on chest radiograph, enrolment systolic blood pressure of < 90 mmHg, and ≥ 15% band forms in peripheral blood). Patients who had conditions known to increase PCT levels (i.e. trauma, renal failure, and pancreatitis) or who had received antibiotics prior to admission were also excluded.

Branche 2015 *(Continued)*

	Included in this study: 300/685 screened patients were eligible for the study, of whom 151 were randomised to the intervention group and 149 to the non-intervention group
Interventions	Guiding antibiotic decisions in hospitalised patients with respiratory infections **Algorithm used in this study:** In the intervention group serum PCT and viral/atypical pathogen PCR testing were performed on admission (in addition to all standard-of-care diagnostic tests). Antibiotic decisions were made based on a PCT algorithm (for PCT values of ≤ 0.1 ng/mL, initiation of antibiotic treatment is strongly discouraged; for values of 0.11 to 0.24 ng/mL, initiation is discouraged; for values of 0.25 to 0.49 ng/mL, initiation is encouraged; and for values of ≥ 0.5 ng/ mL, initiation is strongly encouraged). In the standard care group standard-of-care testing (bacterial and viral cultures of respiratory samples, hospital influenza/RSV duplex PCR, and urine *Legionella* antigen analysis) were obtained on admission and antibiotic decisions were made by the attending physician. Participants in the standard care group had PCT and viral testing samples frozen and tested at study termination.
Outcomes	• duration of antibiotic therapy • length of hospital stay • respiratory complications • ICU care • death • healthcare utilisation
Notes	**Funding:** This work was supported by Rochester General Hospital (KIDD Fund); the National Institutes of Health, National Institute of Allergy and Infectious Diseases (contract HHSN27220120005C); and BioFire (FilmArray respiratory panel instrument). **Follow up time:** Study personnel reviewed the EMR daily until hospital discharge. Participants were contacted by phone at 30 days and 3 months by personnel blinded to randomisation, who collected information about healthcare utilisation, antibiotic use and complications, and return to baseline health. **Registration:** NCT01907659

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were stratified by the presence of COPD and were randomly assigned at a ratio of 1:1, using blocks of 4, to receive standard care or the intervention.
Allocation concealment (selection bias)	Low risk	Small block size (4) for randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding was not feasible due to the study design. Although the control arm remained blinded, there was a risk for spillover care resulting from providers caring for participants in both arms.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants in the standard care group had blood samples frozen and tested at study termination, making the data only available at the end of the study. Phone follow-up by personnel blinded to randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Over 3 months of follow-up 36 participants were lost to follow-up, 13 died, and 4 withdrew their consent (237/300 completed 3-month follow-up).
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol. Trial registered (NCT01907659).
Other bias	High risk	Low overall adherence to the PCT algorithm (64%)

Branche 2015 *(Continued)*

	Small sample size

Briel 2008

Methods	Randomised clinical trial, multicentre in 53 primary care practices in northwest Switzerland
Participants	**Inclusion criteria:** People with upper or lower ARIs in primary care and the physician's intention to prescribe antibiotics on the basis of evidence-based guidelines **Exclusion criteria:** Antibiotic use within the previous 28 days, psychiatric disorders or inability to give written informed consent, not being available for follow-up, not fluent in German, severe immunosuppression, cystic fibrosis, active tuberculosis, and the need for immediate hospitalisation **Included in this analysis:** 458 out of 458 randomised participants
Interventions	Guiding antibiotic decisions in primary care with repeated measurements **Algorithm used in this study:** In participants with PCT levels lower than 0.1 µg/L, a bacterial infection was considered highly unlikely and the use of ABs was discouraged. In participants with a PCT level higher than 0.25 µg/L, a bacterial infection was considered likely and the use of ABs was recommended. For PCT concentrations of 0.1 to 0.25 µg/L, a bacterial infection was considered unlikely and the use of ABs was not recommended. When ABs were withheld from participants, a second measurement of the PCT level was mandatory within 6 to 24 hours for safety reasons. The use of ABs was recommended if this second measurement was higher than 0.25 µg/L or if the PCT level had increased from the first measurement by more than 50% and the participant showed no clinical improvement. All participants given ABs based on PCT level were reassessed after 3 days. Discontinuation of AB treatment was then recommended in participants with a PCT level of 0.25 µg/L or lower.
Outcomes	• number of days, within the first 14 days after baseline, during which a participant's daily activities (work or recreation) were restricted by a respiratory tract infection • degree of discomfort from infection (scored on a scale from 0 (no discomfort) to 10 (a great deal of discomfort)) at 14 days • days of work missed within 14 days • days with adverse effects from medication (abdominal pain, diarrhoea, vomiting, skin rash) within 14 days • antibiotic use • participants with any symptoms of ongoing or relapsing infection at 28 days • all-cause mortality • hospitalisation
Notes	**Funding:** Swiss National Science Foundation (Grant 3300C0-107772) and Association for the Promotion of Science and Postgraduate Training of the University Hospital Basel, Switzerland. B·R·A·H·M·S, Germany provided assay and kit material related to the study. **Follow-up:** Fixed period of 28 days **Registration:** ISRCTN73182671

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent statistician generated the randomisation sequence.

Briel 2008 *(Continued)*

Allocation concealment (selection bias)	Low risk	Centralised randomisation communicated by phone to physician.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded medical students performed interviews with participants at 14 and 28 days.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 454/458 (99%)
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol.
Other bias	Low risk	85% adherence to PCT algorithm in PCT group

Burkhardt 2010

Methods	Randomised clinical trial, multicentre in 15 primary care practices in the Hanover, Germany area
Participants	**Inclusion criteria:** Adults with upper or lower ARIs in primary care **Exclusion criteria:** Treatment with antibiotics during the previous 2 weeks, chronic liver disease, major surgery that had required hospitalisation during the last 4 weeks, autoimmune or systemic disorders, dialysis, medullary C-cell carcinoma and other inflammatory diseases **Included in this analysis:** 550 out of 571 randomised participants; 21 post randomisation exclusions (2 withdrew consent, 1 due to loss of sample, 15 with autoimmune, inflammatory, or systemic disease, 2 with advanced liver disease, 1 with prior use of antibiotics)
Interventions	Guiding antibiotic decisions in primary care with initial measurement only **Algorithm used in this study:** PCT value < 0.25 µg/L indicated that a relevant bacterial infection of the respiratory tract is unlikely.
Outcomes	• days with impairment during everyday life or leisure activities, or both, due to the infection of the respiratory tract within the first 14 days according to self assessment • revisit to the physician's office with a respiratory tract infection within 28 days • number of days with antibiotic-induced side effects • antibiotic use • change of antibiotics within 28 days • participants with any symptoms of ongoing or relapsing infection at 28 days • all-cause mortality • hospitalisation
Notes	**Funding:** B·R·A·H·M·S AG, Germany **Follow-up**: Fixed period of 28 days **Registration:** NCT00827060 and NCT00688610

Burkhardt 2010 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated Quote: "Baseline adaptive randomisation was realised through a web-based randomisation data bank (IOMTech GmbH, Berlin, Germany), which had been programmed specifically for that purpose."
Allocation concealment (selection bias)	Low risk	Central randomisation Quote: "In the central laboratory, the web-based randomisation of the patient into the PCT group or the control group took place."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Structured interviews by blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 546/550 (99%)
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol.
Other bias	Low risk	87% adherence to PCT algorithm in PCT group

Christ-Crain 2004

Methods	Randomised clinical trial, single-centre, emergency department at the University Hospital Basel, Switzerland
Participants	**Inclusion criteria:** People with lower ARIs presenting at a medical emergency department **Exclusion criteria:** Severely immunocompromised people, i.e. with HIV infection and a CD4 count less than 200 cells per mL, neutropenic patients, and stem cell transplant recipients; those with cystic fibrosis or active tuberculosis; and individuals with nosocomial pneumonia **Included in this analysis:** 243 participants out of 243 randomised participants
Interventions	Guiding antibiotic decisions in emergency department patients with different ARIs with initial PCT values only **Algorithm used in this study:** A PCT value of 0.1 to 0.25 µg/L was regarded as an indication that bacterial infection was unlikely and use of ABs was discouraged. A serum PCT between 0.25 and 0.5 g/L was deemed indicative of a possible bacterial infection, and the treating doctor was advised to initiate antimicrobial treatment. A PCT value of 0.5 µg/L or greater was judged suggestive of the presence of bacterial infection and AB treatment was strongly recommended. For participants on antimicrobial therapy at the time of admission, discontinuation of ABs was recommended if PCT concentrations were less than 0.25 µg/L.

Christ-Crain 2004 *(Continued)*

Outcomes	• antibiotic use • all-cause mortality • ICU admission • frequency and length of hospital admission • quality of life • rate of re-exacerbation in COPD patients
Notes	**Funding:** Freiwillige Akademische Gesellschaft Basel, Switzerland; Department of Internal Medicine and the Divisions of Endocrinology and Pneumology, University Hospital Basel; B·R·A·H·M·S AG, Germany and Orgenium Laboratories, Finland, provided assay material and partial support of the investigator-initiated study. **Follow-up**: Fixed period of 10 to 14 days; in participants with acute exacerbations of COPD the follow-up period comprised 4 to 6 months **Registration:** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We randomly assigned eligible patients either standard antimicrobial therapy (standard group) or PCT-guided antimicrobial treatment (PCT group) according to a computer-generated week wise-randomisation scheme."
Allocation concealment (selection bias)	High risk	Recruiting physicians were aware of group allocation based on week-wise randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 230/243 (95%)
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol.
Other bias	Low risk	83% adherence to PCT algorithm in PCT group

Christ-Crain 2006

Methods	Randomised clinical trial, single-centre, emergency department at the University Hospital Basel, Switzerland
Participants	**Inclusion criteria:** CAP with X-ray confirmation in the emergency department **Exclusion criteria:** People with cystic fibrosis or active pulmonary tuberculosis, people with hospital-acquired pneumonia, and severely immunocompromised individuals

Christ-Crain 2006 *(Continued)*

	Included in this analysis: 302 out of 302 randomised participants
Interventions	Guiding antibiotic decisions in emergency department patients with CAP with repeated PCT measurements **Algorithm used in this study:** a PCT level of less than 0.1 µg/L suggested the absence of bacterial infection, and the initiation or continuation of ABs was strongly discouraged. A PCT level between 0.1 and 0.25 µg/L indicated that bacterial infection was unlikely, and the initiation or continuation of ABs was discouraged. A PCT level from 0.25 to 0.5 µg/L was considered indicative of a possible bacterial infection, and the initiation or continuation of AB therapy was encouraged. A PCT level greater than 0.5 µg/L strongly suggested the presence of bacterial infection, and AB treatment and continuation was strongly encouraged. Re-evaluation of the clinical status and measurement of serum PCT levels were recommended after 6 to 24 h in all participants from whom ABs were withheld. PCT levels were reassessed after 4, 6, and 8 d. Antibiotics were discontinued on the basis of the PCT cut-offs defined above. In participants with very high PCT values on admission (e.g. greater than 10 µg/L), discontinuation of ABs was encouraged if levels decreased to less than 10% of the initial value (e.g. 1 µg/L, instead of less than 0.25 µg/L).
Outcomes	• antibiotic use • mortality • ICU admission • hospital readmission • complications due to CAP • cure defined as resolution of clinical, laboratory, and radiographic signs of CAP • improvement was defined as reduction of clinical signs and symptoms, improvement of laboratory findings, and reduction of the number or intensity of radiographic signs of CAP • treatment success represented the sum of the rates for cure and improvement. Treatment failure included death, recurrence, relapse, or persistence of clinical, laboratory, and radiologic signs of CAP and participants lost to follow-up
Notes	**Funding:** Funding obtained from B·R·A·H·M·S (Hennigsdorf, Germany), Pfizer (Schweiz AG), and Mepha (Schweiz AG) was used for assay material and salaries of technical personnel involved in laboratory work and for shipping and handling of data and specimens and presentation of data at scientific meetings. Additional support, which provided more than two-thirds of the total study costs, was granted by funds from the Departments of Internal Medicine and Emergency Medicine, the Stiftung Forschung Infektionskrankheiten (SFI), and mainly from the Departments of Endocrinology and Pulmonary Medicine, University Hospital Basel, Switzerland. **Follow-up:** Fixed period of 6 weeks **Registration:** ISRCTN04176397

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent statistician created randomisation list.
Allocation concealment (selection bias)	Unclear risk	Quote: "On admission, patients were randomly assigned to one of the two groups by sealed, opaque envelopes." Envelopes were not numbered.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias)	High risk	Non-blinded study members

Christ-Crain 2006 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 300/302 (99%)
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol.
Other bias	Low risk	87% adherence to PCT algorithm in PCT group

Corti 2016

Methods	Randomised, single-centre clinical trial in an ED of a university hospital in Denmark
Participants	**Inclusion criteria:** 1) 18 years old and 2) admitted with an AECOPD (clinician's diagnosis at admission), defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) **Exclusion criteria:** 1) person unable to understand or respond to oral or written information; 2) previously been enrolled in the study; and 3) do-not-resuscitate order in place **Included in this analysis:** 120/630 screened people with AECOPD were randomised and used for the ITT analysis (62 in the PCT group, 58 in the control group).
Interventions	The aim was to assess whether PCT-guided antibiotic treatment could reduce the overall use of antibiotics among people hospitalised for AECOPD. **Algorithm used in this study:** In the control group, antibiotic therapy followed treatment strategies for AECOPD according to GOLD guidelines. In the PCT group, initiation or continuation of antibiotics was strongly discouraged if PCT was 0.15 ng/mL or lower and discouraged if levels were between 0.15 ng/mL and 0.25 ng/mL. Initiation or continuation of antibiotics was encouraged if PCT was > 0.25 ng/mL. In participants with PCT over 5 ng/mL on admission, the algorithm recommended stopping antibiotics when PCT levels decreased by 80% of the peak value.
Outcomes	• fraction of participants using antibiotics for at least 5 days within 28 days after inclusion • cumulative number of days with any antibiotic therapy within 28 days • fraction of participants using antibiotics for a) at least 1 day, b) at least 3 days, c) at least 7 days • length of hospital stay • adverse events (composite endpoint of mortality, readmission, ICU admission all within 28 days
Notes	**Funding:** Thermo Fisher Scientific, MA, USA, and bioMérieux Denmark ApS supported the study non-financially. **Follow-up:** 28 days **Registration:** NCT01950936

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were allocated according to the random part of the civil registration number in Denmark
Allocation concealment (selection bias)	Low risk	The randomisation algorithm was concealed to treating clinicians and participants
Blinding of participants and personnel (performance bias)	Unclear risk	Blinding was not feasible, but PCT was only measured in the intervention arm

Corti 2016 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mentioning of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 120/120 (100%)
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol. Trial registered (NCT01950936)
Other bias	High risk	Moderate adherence to the PCT algorithm in PCT group (61.1%)

De Jong 2016

Methods	Randomised, multicentre, controlled, open-label intervention trial in 15 hospitals in the Netherlands
Participants	**Inclusion criteria:** Eligible patients had to be at least 18 years of age, be admitted to the ICU, and have received their first dose of antibiotics no longer than 24 h before inclusion to the trial for an assumed or proven infection. **Exclusion criteria:** Patients were excluded in cases of systemic antibiotics as prophylaxis only, antibiotics solely as part of selective decontamination of the digestive tract, prolonged therapy (e.g. endocarditis), expected ICU stay of less than 24 h, severe immunosuppression, severe infections (due to viruses, parasites, or *Mycobacterium tuberculosis*), and moribund patients. Patients who received corticosteroids were not excluded. **Included in this study:** 1575/4507 screened patients were enrolled in the study (776 in the PCT group, 799 in the control group) for an intention-to-treat analysis.
Interventions	Guiding antibiotic decisions in critically ill ICU patients **Algorithm used in this study:** Antibiotics in the standard-of care group were stopped according to local or national guidelines and according to the discretion of attending physicians. Procalcitonin concentration was not measured in the standard-of-care group. For participants randomly assigned to the PCT-guided group, once-a-day measurements of PCT concentrations were taken and made available to the attending physicians, including a baseline measurement as close to initiation of antibiotics as possible, at least within 24 h. The study protocol advised stopping the prescribed antibiotics if PCT concentration had decreased by 80% or more of its peak value (relative stopping threshold) or when it reached a value of 0.5 µg/L or lower (absolute stopping threshold). The attending physician was free to decide whether to continue antibiotic treatment in participants who had reached these thresholds.
Outcomes	• consumption of antibiotics (expressed as defined daily doses) • duration of antibiotic treatment (defined as the number of 24-hour periods between start and end of antibiotic treatment) • percentage of participants who had a recurrent infection • length of stay in hospital and ICU • costs of antibiotics • costs of PCT tests
Notes	**Funding:** Thermo Fisher Scientific **Follow-up:** 1-year follow-up **Trial Registration:** NCT01139489

Risk of bias

De Jong 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done centrally by use of a computer-generated list produced by an independent research organisation (the Julius Centre for Human Research, Utrecht, Netherlands).
Allocation concealment (selection bias)	Low risk	Centralised randomisation by an independent organisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and investigators were aware of treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment mentioned in the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1546 of 1575 participants included in the intention-to-treat population analysis
Selective reporting (reporting bias)	Low risk	The outcomes correspond to the trial registration (NCT01139489).
Other bias	High risk	Physicians did not adhere to the stopping advice in more than half of the participants. About 30% of participants randomly assigned to the PCT group were discharged from ICU before the algorithm recommended stopping antibiotic treatment.

Deliberato 2013

Methods	Randomised, single-centre, controlled clinical trial at an ICU of a tertiary care, private hospital in São Paulo, Brazil
Participants	**Inclusion criteria:** People with microbiologically confirmed infections (blood, urine, tracheal aspirate, or bronchoalveolar lavage fluid cultures) with sepsis, severe sepsis, and septic shock **Exclusion criteria were:** Onset of antibiotic therapy more than 48 hours before the date when the cultures were performed; people under 18 years old; known pregnancy; infections requiring prolonged antibiotic therapy, such as bacterial endocarditis, hepatic or brain abscess, deep abscess, mediastinitis, and osteomyelitis; severe infection caused by viruses, parasites, fungi, or mycobacteria; chronic localised infections, such as chronic osteomyelitis or chronic prostatitis; people without indication for ICU admission, as determined by the attending physician; and negative cultures (blood, urine, tracheal aspirate, or bronchoalveolar lavage fluid) in people with suspected sepsis, severe sepsis, or septic shock **Included in this study:** 81/265 eligible patients randomised for a intention-to-treat analysis; after further exclusions, 51/265 patients remained for per-protocol analysis.
Interventions	Guiding antibiotic decisions in ICU patients with proven bacterial infection **Algorithm used in this study:** All participants received antibiotic therapy. For the control group, stopping antibiotic therapy was at the discretion of the attending physician. For the intervention group, physicians were guided by the PCT protocol to stop antibiotic treatment. The protocol stated 2 conditions: 1) PCT dropped more than 90% from the peak level, or 2) an absolute value < 0.5 ng/mL was reached.

Deliberato 2013 *(Continued)*

Outcomes	• duration of antibiotic therapy • in-hospital mortality • ICU mortality • ICU length of stay • recurrence of the initial infection • analysis of the CRP levels along with the PCT protocol • therapy costs
Notes	**Funding:** No funding declared in the main article. **Follow-up time:** Data were recorded from 2 days before the bacteraemia (when applicable), with day 0 defined as the day sepsis was diagnosed, until 14 days after or at ICU discharge, whichever came first. **Registration:** NCT01494675

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A blind randomisation scheme was used where a black box contained 100 folders, and 2 authors randomly drew 1 folder as soon as an informed consent was present.
Allocation concealment (selection bias)	Low risk	Folders were randomly and blindly assigned as “PCT group” or “standard group”. 2 of the authors would randomly draw 1 folder from a black box containing 100 folders (50 “PCT group” and 50 “control group”).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of the treating physicians was not feasible in this study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of the outcome assessment mentioned in the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the intention-to-treat analysis the follow-up for mortality was 81/81 (100%).
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol. Trial registered (NCT01494675).
Other bias	High risk	Low adherence to the PCT algorithm (47.6%) Single-centre study where not all attending physicians agreed to participate (also a reason for exclusions in the PCT arm in the per-protocol analysis and low adherence)

Ding 2013

Methods	Randomised, single-centre, open-label, controlled clinical trial in HeNan Hospital, China
Participants	**Inclusion criteria:** All patients with suspected AE-IPF admitted to the respiratory department were assessed for eligibility from January 2009 to December 2011. Acute exacerbation of idiopathic pulmonary fibrosis was defined according to the criteria established by the Idiopathic Pulmonary Fibrosis Clinical Research Network: (1) previous or concurrent diagnosis of idiopathic pulmonary fibrosis; (2) unexplained worsening or development of dyspnoea within 30 days; (3) high-resolution computed tomog-

Ding 2013 *(Continued)*

	raphy with new bilateral ground-glass; (4) abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with usual interstitial pneumonia pattern; (5) no evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage; (6) exclusion of left heart failure, pulmonary embolism, and identifiable cause of acute lung injury. **Exclusion criteria:** Patients treated with antibiotics during the previous 2 weeks were excluded. **Included in this study:** 68 of 78 randomised participants finished at follow-up.
Interventions	Guiding antibiotic decisions in people with acute exacerbation of idiopathic pulmonary fibrosis **Algorithm used in this study:** Serum PCT level was measured every 3 days. The first PCT measurement was available before the clinical decision to start antibiotics treatment. Participants whose serum PCT value exceeded the threshold of 0.25 ng/mL were administered antibiotics and were treated until PCT value fell to ≤ 0.25 ng/mL. In the routine treatment group, the decision to administer antibiotics was guided by the clinical experience of the clinician, typically by conventional laboratory tests such as sputum bacteriology and white blood cell count.
Outcomes	• length of hospitalisation • the numbers of participants exposed to antibiotics treatment • duration of antibiotic treatment • cases of mechanical ventilation
Notes	**Funding:** No funding declared in the main paper. **Follow-up:** 30 days **Trial registration:** No trial registration found for this clinical trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned to either PCT-guided antibiotic treatment or a control group receiving routine antibiotic therapy by the statistician using computer-generated random numbers.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding was performed. "In the routine treatment group, patients were treated by antibiotics according to the clinical experience of clinicians typically guided by conventional laboratory tests, such as sputum bacteriology and white blood cell count."
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment was mentioned in this study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Postrandomisation exclusion rate was relatively high but similar in both study arms (6 in the intervention arm versus 4 in the control group).
Selective reporting (reporting bias)	Unclear risk	No trial registration was found for this trial.
Other bias	Low risk	100% adherence to PCT protocol in the per-protocol analysed participants (all protocol violations were defined as "withdrawn").

Hochreiter 2009

Methods	Randomised clinical trial, single-centre, ICU in Germany
Participants	**Inclusion criteria:** Patients in the surgical ICU with suspected bacterial infections and > 1 SIRS criteria **Exclusion criteria:** Patients who refused study consent, whose antibiotic treatment had been initiated before intensive care admission, or who had therapy limitations **Included in this analysis:** 43 (110); 67 not considered for this analysis due to diagnosis other than ARI
Interventions	Guiding antibiotic decisions in postoperative patients in a surgical ICU **Algorithm used in this study:** Antibiotic therapy in the PCT-guided group was discontinued if clinical signs and symptoms of infection improved and PCT decreased to less than 1 µg/L, or if the PCT value was more than 1 µg/L, but had dropped to 25% to 35% of the initial value over 3 days.
Outcomes	• antibiotic use • mortality (ICU-free days alive)
Notes	**Funding:** B·R·A·H·M·S AG **Follow-up:** Until hospital discharge **Registration:** ISRCTN10288268

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Unconcealed drawing of lots
Allocation concealment (selection bias)	High risk	Unconcealed drawing of lots
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	High risk	Non-blinded study members
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 393/394 (100%)
Selective reporting (reporting bias)	Low risk	No selective reporting (oral verification with first author)
Other bias	Unclear risk	Adherence to PCT protocol not reported/assessed

Kristoffersen 2009

Methods	Randomised clinical trial, multicentre, 3 hospitals in Denmark

Kristoffersen 2009 *(Continued)*

Participants	**Inclusion criteria:** Hospitalised patients with suspected pneumonia (no X-ray confirmation); quote: "The assessment of eligibility (i.e. the clinical diagnosis) was made by the admitting physician and was based on medical history and physical examination." **Exclusion criteria:** Not meeting the diagnostic criteria **Included in this analysis:** 210 out of 223 randomised participants; 13 post randomisation exclusions (3 no PCT testing, 6 not meeting inclusion criteria, 4 withdrew informed consent)
Interventions	Guiding antibiotic decisions in CAP patients with initial values only **Algorithm used in this study:** Physicians were not asked to wait for PCT results before initiating antimicrobial therapy, therefore PCT values were, in most cases, used to motivate either cessation or continuation of already initiated treatments. Discontinuation of AB treatment was recommended if PCT at admission was below 0.25 µg/L, despite delays in test results.
Outcomes	• antibiotic use • mortality • ICU admission
Notes	**Funding:** The Danish Medical Research Council and the Danish Lung Association provided financial support. **Follow-up:** Until hospital discharge **Registration:** NCT00415753

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	High risk	Non-blinded study members
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 210/210 (100% until discharge)
Selective reporting (reporting bias)	Low risk	No selective reporting (oral verification with first author)
Other bias	High risk	59% adherence to PCT algorithm in PCT group

Layios 2012

Methods	Randomised, single-centre, prospective, controlled clinical study in 5 ICUs in Belgium
Participants	**Inclusion criteria:** Patients older than 18 yrs of age and hospitalised for > 2 days in 1 of the 5 ICUs **Included in this study:** Of 509 randomised participants, 441 developed infection, and PCT was obtained and analysed in 389 of these participants.
Interventions	Guiding antibiotic decisions in ICU patients **Algorithm used in this study:** According to the proposal by Mueller and colleagues, for participants in the PCT group, the use of antibiotics was more or less strongly discouraged if PCT level was < 0.25 µg/L or 0.50 µg/L, respectively, and more or less recommended if PCT level was above 1 µg/L or 0.50 µg/L, respectively. This strategy was applied to all infectious episodes encountered during participants' ICU stay.
Outcomes	• difference of antibiotic consumption between the PCT group and the control group • usefulness of PCT levels in the ICU diagnostic algorithm in deciding whether or not to initiate antibiotics whenever infection was suspected and determination of concordance of the infection's diagnostic ratings by the ICU physician and the infectious disease specialist, bearing in mind that the latter was blinded to PCT results in all of the cases
Notes	**Funding:** No information provided. **Follow-up:** During ICU stay **Trial registration:** No trial registration found.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on method of randomisation provided.
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Procalcitonin levels in the control arm were blinded for treating physicians, but the study arm to which participants had been assigned was not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	At the end of ICU stay, participants' charts were reviewed by infectious disease specialists blinded to PCT results, who classified them as confirmed, probable, possible, or no infection using all the clinical data and biological results including microbiological cultures and results from investigational procedures.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality 509/509 (100%)
Selective reporting (reporting bias)	Unclear risk	No trial registration found for this research article.
Other bias	High risk	Low adherence to PCT algorithm (46.3%)

Lima 2016

Methods	Randomised, single-centre, prospective, controlled clinical trial in Minas Gerais, Brazil
Participants	**Inclusion criteria:** Presence of febrile neutropenia (axillary temperature ˜37.8°C, neutrophils count < 500 cells/mm^3) in people with diagnosis of haematological disease (except people undergoing allogeneic stem cell transplantation); with expected duration of neutropenia of more than 3 days; ongoing broad-spectrum antibiotic therapy according to institutional guideline, based on Infectious Diseases Society of America; and no current use of therapeutic antibiotics or antifungals with the last day of use was > 14 days before inclusion in the study **Exclusion criteria:** Severe organ dysfunction (e.g. hypotension, ICU admission, trans-retinoic acid syndrome, respiratory insufficiency, and disseminated intravascular coagulation); previous proven or probable invasive fungal infection according to the Springer Ann Hematol (2016) European Organisation for Research and Treatment of Cancer-Mycosis Study Group (EORTC-MSG) criteria; infections due to *Pseudomonas spp*, *Acinetobacter spp*, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*, *Toxoplasma gondii*, or HIV; infections requiring antibodies for a long time (e.g. infectious endocarditis, osteomyelitis); grade 3 or 4 oral mucositis, since this condition increases the risk of *S aureus* bacteraemia; and pregnancy **Included in this study:** 62 randomised participants, 1 post randomisation exclusion due to withdrawal of informed consent
Interventions	Guiding antibiotic decisions in people with febrile neutropenia **Algorithm used in this study:** Attending physicians were encouraged to discontinue antibiotics in participants when both of the following criteria were met: (i) no febrile episodes for 2 consecutive days (if no longer neutropenia) or 3 consecutive days (if still neutropenia), and (ii) PCT concentration at least 90% lower than highest baseline levels or lower than 0.5 ng/mL for 2 consecutive days, regardless of the initial levels. The final decision to discontinue antibiotics was left at the attending physician's discretion. Procalcitonin levels were measured for 2 additional days following antibiotics interruption to monitor a possible relapse of infection. For safety reasons, at least 5 days of antibiotic therapy were ensured for all included participants. Participants with bacteraemia were treated for at least 7 days. In the control group, duration of antibiotic therapy was based on institutional protocol, according to Infectious Diseases Society of America recommendations.
Outcomes	• antibiotic exposure, measured by the duration of the first course of antibiotic therapy (in days) and days without antibiotics during follow-up (28 days) • clinical cure rate • infection relapse rate (infection diagnosed 48 h or more after antibiotic discontinuation) • superinfection rate (defined as occurrence of infection due to 1 or more different pathogens, in the same or in another site, during the first antibiotic therapy) • length of hospital stay from inclusion (in days) • all-cause 28- and 90-day mortality
Notes	**Funding:** This work was supported by Funda of the de Amparo a Pesquisa do Eatado dc MiDaa Ocrais (.APQ-01956-10). **Follow-up:** 3 months **Trial registration:** NCT00928291

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised on the third day of follow-up, in a 1:1 ratio for the PCT group and the control group.
Allocation concealment (selection bias)	Low risk	Randomisation was performed using a table of random, computer-generated numbers, and sealed, opaque envelopes were used.

Lima 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	For participants randomised into the control group, results of PCT serum levels were kept concealed during the study and were only revealed for the final analysis. However, physicians were aware of the study group.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment was mentioned in the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Most randomised participants finished follow-up. Only 1 post randomisation exclusion
Selective reporting (reporting bias)	Low risk	Outcomes correspond to trial registration.
Other bias	Low risk	High adherence to the PCT protocol (73.3%)

Long 2009

Methods	Randomised clinical trial, single-centre, emergency department outpatients in China
Participants	**Inclusion criteria:** CAP with X-ray confirmation **Exclusion criteria:** Use of antibiotic therapy in 2 weeks before enrolment, systemic immune deficiency, organ dysfunction, tumour, mental illness, CAP onset ≥ 5 days, coexisting extrapulmonary infection requiring antibiotic therapy **Included in this analysis:** 127 out of 127 randomised participants
Interventions	Guiding antibiotic decisions in CAP patients with repeated levels **Algorithm used in this study:** A PCT level of less than 0.1 µg/L suggested the absence of bacterial infection, and the initiation or continuation of ABs was strongly discouraged. A PCT level between 0.1 and 0.25 µg/L indicated that bacterial infection was unlikely, and the initiation or continuation of ABs was discouraged. A PCT level of 0.25 µg/L or greater was considered indicative of a possible bacterial infection, and the initiation or continuation of AB therapy was encouraged. Re-evaluation of the clinical status and measurement of PCT levels was recommended after 6 to 12 h in all participants from whom ABs were withheld.
Outcomes	• antibiotic use • mortality • ICU admission • treatment success represented the sum of the rates for cure and improvement. Cure was defined as resolution of clinical, laboratory, and radiographic signs of CAP. Improvement was defined as reduction of clinical signs and symptoms, improvement of laboratory findings, and reduction of the number or intensity of radiographic signs of CAP. • treatment failure included death, recurrence, relapse, or persistence of clinical, laboratory, and radiologic signs of CAP and participants lost to follow-up
Notes	**Funding:** Training fund of Shanghai No. 5 Hospital **Follow-up:** 28 days **Registration:** None

Long 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Odd and even patient ID numbers
Allocation concealment (selection bias)	High risk	Odd and even patient ID numbers
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	High risk	Non-blinded study members
Incomplete outcome data (attrition bias) All outcomes	Low risk	210/210 (100% until discharge)
Selective reporting (reporting bias)	Low risk	No selective reporting (oral verification with first author)
Other bias	Unclear risk	Adherence to PCT protocol not reported/assessed.

Long 2011

Methods	Randomised clinical trial, single-centre, emergency department outpatients in China
Participants	**Inclusion criteria:** CAP with X-ray confirmation in an outpatient setting **Exclusion criteria:** Pregnancy, commencement of antibiotic therapy ≥ 48 h before enrolment, systemic immune deficiency, withholding of life-support, and active tuberculosis **Included in this analysis:** 156 out of 172 randomised participants; 16 post randomisation exclusions (6 lost to follow-up, 7 withdrew consent, 3 with final diagnosis other than CAP)
Interventions	Guiding antibiotic decisions in CAP patients with repeated levels **Algorithm used in this study:** A PCT level of less than 0.1 µg/L suggested the absence of bacterial infection, and the initiation or continuation of ABs was strongly discouraged. A PCT level between 0.1 and 0.25 µg/L indicated that bacterial infection was unlikely, and the initiation or continuation of ABs was discouraged. A PCT level of 0.25 µg/L or greater was considered indicative of a possible bacterial infection, and the initiation or continuation of AB therapy was encouraged. Re-evaluation of the clinical status and measurement of PCT levels was recommended after 6 to 12 h in all participants from whom ABs were withheld.
Outcomes	• antibiotic use • mortality • ICU admission
Notes	**Funding:** The study was sponsored by a grant from the Shanghai Fifth People's Hospital Science Foundation (09YRCPY11).

Long 2011 *(Continued)*

Follow-up: Fixed period of 4 weeks

Registration: NA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Odd and even patient ID numbers
Allocation concealment (selection bias)	High risk	Odd and even patient ID numbers
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	High risk	Non-blinded study members
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 156 (156) (100%)
Selective reporting (reporting bias)	Low risk	No selective reporting (oral verification with first author)
Other bias	Unclear risk	Adherence to PCT protocol not reported/assessed.

Long 2014

Methods	Randomised, single-centre, open-label, controlled clinical trial in Shanghai, China
Participants	**Inclusion criteria:** People aged 18 to 65 years with severe acute exacerbations of asthma. A severe asthma exacerbation was defined as at least 1 of the following: need for systemic corticosteroids, or an increase from a stable maintenance dose, for at least 3 days and/or hospitalisation or ED visit because of asthma requiring systemic corticosteroids. **Exclusion criteria:** People with antibiotic use within the previous 14 days, psychiatric disorders or other inability to give written informed consent, not being available for follow-up, severe immunosuppression, heart failure, cystic fibrosis, active tuberculosis, pregnancy, and chest radiography–confirmed pneumonia **Included in this study:** 180/216 screened individuals were eligible for the study (90 intervention group, 90 non-intervention group); 169 finished the follow-up.
Interventions	Guiding antibiotic decisions in people with acute severe exacerbation of asthma **Algorithm used in this study:** Antibiotic treatment was strongly discouraged when serum PCT level was less than 0.1 µg/L; antibiotic treatment was discouraged when serum PCT level was less than 0.25 µg/L; and antibiotic treatment was encouraged when serum PCT level was higher than 0.25 µg/L. When antibiotics were withheld from participants, a second measurement of the PCT level was mandatory within 6 to 24 hours for safety reasons. The use of antibiotics was recommended if this second measurement was higher than 0.25 µg/L. Physicians were permitted to overrule the algorithm, but they had to indicate the reasons for overruling. The control group received antibiotic according to the discretion of the treating physician, who was unaware of the participant's PCT levels.

Long 2014 *(Continued)*

Outcomes	• antibiotic use, expressed as rate of antibiotic prescriptions in percentage and relative risk of antibiotic exposure • measures of treatment success • length of hospital stay • clinical, laboratory, and spirometry outcomes at discharge • results of spirometry at the 12-month follow-up examination, as well as the results of the Asthma Control Test, the results of the Asthma Quality of Life Questionnaire at the 12-month follow-up visit • clinical events during the 12-month follow-up period, including numbers of asthma exacerbations, ED visits, hospitalisations, and need for systemic corticosteroid use for treatment of asthma
Notes	**Funding:** The study was sponsored by a grant from the Shanghai Fifth People's Hospital Science Foundation and Minhang District Natural Science Foundation of Shanghai. The funding bodies had no involvement in the design, collection, analysis, or interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication. **Follow-up time:** 12 months **Registration:** ChiCTR-TRC-12002534

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation to either intervention was conducted according to computer-generated random numbers produced by an independent statistician.
Allocation concealment (selection bias)	Low risk	After randomisation, an opaque, sealed, sequentially numbered envelope containing the PCT or control protocol was prepared for each participant according to group assignment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label study with blinding of PCT level in the control group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment mentioned in the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	169/180 participants completed 1-year follow-up visit (11 participants lost to follow-up).
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol. Trial registered (ChiCTR-TRC-12002534).
Other bias	Low risk	High adherence to PCT algorithm (93.3%)

Maravić-Stojković 2011

Methods	Randomised, single-centre, open-label, controlled clinical trial at a 200-bed academic tertiary care hospital in Belgrade, Serbia
Participants	**Inclusion criteria:** People scheduled to undergo open heart surgery on cardio-pulmonal bypass. We assessed people who were selected for elective cardiac surgery at the 200-bed academic tertiary care hospital. The criterion for inclusion in the study was the type of operation: coronary artery bypass grafting (CABG) surgery, valve reconstruction, combined CABG and valve procedures. Entry criteria in-

Maravić-Stojković 2011 *(Continued)*

	cluded stable and unstable angina pectoris, valve insufficiency, left ventricle ejection fraction (LVEF) above 30%, and epidemiological status with saprophyte bacteria. **Exclusion criteria:** People selected for redo cardiac operations, thoracic aortic surgery, as well as people having active endocarditis and people with LVEF < 30%. People with preoperative signs of infection (leukocyte count > 12,000/L; body temperature > 38°C) were also excluded. **Included in this study:** 205/205 included participants finished for follow-up (102 PCT group/103 standard group).
Interventions	Guiding antibiotic decisions in patients after cardiac surgery **Algorithm used in this study:** Antibiotic prophylaxis was performed in all participants. The participants were divided at the time of surgery into the standard group and the PCT group. In the standard group, the antibiotic use was applied according to the criteria based on the laboratory and clinical signs; no antibiotic therapy was administrated routinely in the absence of clinical signs of infection or a bacteriologic positive sample. In the PCT group, the use of antibiotics was encouraged or discouraged on the basis of serum PCT concentrations. A serum PCT concentration of 0.5 ng/mL or less indicated the absence of bacterial infection, at which point the use of antibiotics was discouraged.
Outcomes	• proportion of participants treated with antibiotics • overall cost of antibiotics per 1 patient • total cost of antibiotics per 1 hospital day after operation • ICU stays and hospital stay • rehospitalisation • incidence of infections • severe non-infection complications • mortality rate
Notes	**Funding:** No funding is mentioned in the main article. **Follow-up:** 1 year **Trial registration:** No trial registration found.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	The participants were divided at the time of surgery into the standard group and the PCT group by centralised randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of physicians due to the study design
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment mentioned in the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 205/205 (100%)
Selective reporting (reporting bias)	Unclear risk	No trial registration found.

Maravić-Stojković 2011 *(Continued)*

Other bias	Unclear risk	No information about adherence

Najafi 2015

Methods	Randomised, single-centre, single-blinded clinical trial in a 30-bed ICU in Tehran, Iran
Participants	**Inclusion criteria:** Patients with at least 2 of 4 criteria including body temperature above 38°C or below 36°C; tachycardia > 90/min; tachypnoea > 20/min; and leukocytosis > 12×10^9/L or a leftward shift with more than 10% band cells or leukopenia < 4×10^9/L were defined as patient with SIRS. **Exclusion criteria:** Documented infection, pus from wound or abscess, empyema, thrombophlebitis, infection due to viral or parasites, hypoxaemia (PO_2 < 60 mmHg), oliguria (urine output < 30 mL/h), Glasgow Coma Scale 3 without sedation, parenteral antibiotic usage 24 hours before admission to ICU, hospitalisation 48 hours before enrolment, conditions requiring prolonged antibiotic therapy such as endocarditis, chronic localised infection such as osteomyelitis, and severely immunocompromised patients **Included in this study:** 60 participants were randomised (30 in the intervention group and 30 in the control group).
Interventions	Guiding antibiotic decisions in critically ill ICU patients **Algorithm used in this study:** In case group, according to serum level of PCT, participants were divided into 3 groups as: PCT level 0.5 ng/mL or less (group A), PCT value of 0.5 to 2 ng/mL (group B), and PCT level 2 ng/mL or more (group C). Group A indicated a low probability of bacterial infection; use of antibiotics was discouraged, and PCT level was rechecked after 12 hours. In group B, with a medium probability of infection, antibiotic therapy was not administered, and PCT level was rechecked after 8 hours. In group C, with a high probability of bacterial infection, participants underwent antibiotic treatment. If the PCT level was higher than 2 ng/mL after recheck in group A and B, antibiotics therapy was administered; if the PCT level was lower than 2 ng/mL, participants underwent close observation, and PCT was rechecked until culture results were obtained.
Outcomes	• use of antibiotic treatment • change in clinical status • early mortality
Notes	**Funding:** No funding declared in the original research article. **Follow-up:** No precise follow-up found in the original research article. **Trial registration:** No trial registration found in the original research article.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All participants were randomly divided into 2 groups by computer-based random number generation.
Allocation concealment (selection bias)	Low risk	All participants were randomly divided into 2 groups by computer-based random number generation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Procalcitonin was only measured in the intervention arm, but blinding was not feasible due to the study design.
Blinding of outcome assessment (detection bias)	High risk	No blinding of outcome assessment was mentioned in the study.

Najafi 2015 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants finished the study and were assessed for the primary outcome.
Selective reporting (reporting bias)	Unclear risk	No trial registration was found for this study.
Other bias	Unclear risk	Adherence to the PCT algorithm was not known.

Nobre 2008

Methods	Randomised clinical trial, single-centre, medical ICU in Switzerland
Participants	**Inclusion criteria:** Suspected severe sepsis or septic shock in the ICU **Exclusion criteria:** • microbiologically documented infections caused by *Pseudomonas aeruginosa*,*Acinetobacter baumannii*,*Listeria spp*,*Legionella pneumophila*,*Pneumocystis jirovecii*, or*Mycobacterium tuberculosis*, for which a prolonged duration of antibiotic therapy is standard of care • severe infections due to viruses or parasites (e.g. haemorrhagic fever, malaria) • infectious conditions requiring prolonged antibiotic therapy (e.g. bacterial endocarditis, brain abscess, deep abscesses) • antibiotic therapy started 48 hours or more before enrolment • chronic, localised infections (e.g. chronic osteomyelitis) • severely immunocompromised patients, such as patients infected with HIV and with a CD4 count < 200 cells/mm^3, neutropenic patients (0.500 neutrophils/mm^3), or patients on immunosuppressive therapy after solid organ transplantation • withholding of life-support • absence of antimicrobial treatment despite clinical suspicion of sepsis **Included in this analysis:** 52 out of 79 randomised participants; 27 not considered for this analysis due to a diagnosis other than RTI
Interventions	Guiding antibiotic decisions in ICU patients with repeated measurements **Algorithm used in this study:** Procalcitonin levels measured at baseline and daily. For participants presenting a favourable clinical course, investigators used predefined “stopping rules” based on circulating PCT levels to encourage physicians to discontinue ABs. Participants with baseline PCT level ≥ 1 µg/L were re-evaluated at day 5. Investigators encouraged treating physicians to discontinue ABs when: 1. PCT dropped more than 90% from the baseline peak level; or 2. an absolute value below 0.25 µg/L was reached. Participants with PCT level below 1 µg/L at baseline were re-evaluated at day 3; treating physicians were encouraged to discontinue ABs when PCT level was below 0.1 µg/L and careful clinical evaluation ruled out severe infection.
Outcomes	• all-cause mortality at day 28 • clinical cure defined as clinical signs and symptoms present at baseline that had resolved by the final clinical assessment • reoccurrence of the initial infection • length of ICU stay

Nobre 2008 *(Continued)*

Notes	**Funding:** B·R·A·H·M·S AG **Follow-up:** Fixed follow-up period of 28 days **Registration:** NCT00250666

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based random number generation
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	High risk	Non-blinded study members
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 52/52 (100%)
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol.
Other bias	Low risk	81% adherence to PCT algorithm in PCT group

Ogasawara 2014

Methods	Randomised, single-centre, prospective, open-label, non-inferiority clinical trial in Shizuoka, Japan
Participants	**Inclusion criteria:** Patients at risk for aspiration, who had been hospitalised after developing pneumonia, were enrolled. Aspiration pneumonia was clinically diagnosed on the basis of the findings on computed tomography (e.g. bronchopneumonia in the dorsal lower lobes), combined with a history of aspiration pneumonia, stroke or dementia, poor systemic condition, or any combination of these (e.g. bedridden patients or patients fed by a nasogastric tube or percutaneous endoscopic gastrostomy). Selection criteria included the following: at least 1 month had elapsed since the last treatment for relapsed pneumonia, and ventilator use was not scheduled for the pneumonia treatment **Exclusion criteria:** Patients with a known severe allergy to any drugs; patients with sepsis or a severe infectious disease; patients with severe underlying diseases (e.g. malignancy, COPD, heart failure) that affected the prognosis; and patients who could not safely have cessation of oral intake or hydration as a treatment for aspiration pneumonia because of dementia **Included in this study:** The study enrolled 105 participants; 2 participants withdrew their informed consent, 5 were excluded because of other final diagnoses, and 1 was excluded because of a defect in the PCT data. The ITT population thus comprised 96 participants: 48 in the PCT group and 48 in the control group
Interventions	Guiding antibiotic decisions in patients with aspiration pneumonia and assessment of the continuation of oral intake

Ogasawara 2014 *(Continued)*

	Algorithm used in this study: Procalcitonin levels were measured via outsourcing to SRL (Tokyo, Japan); the results were obtained 2 or 3 days after admission. In the PCT group, if the PCT levels upon admission were < 0.5 ng/mL, 0.5 to 1.0 ng/mL, or > 1.0 ng/mL, the duration of antibiotic therapy was determined to be 3, 5, or 7 days, respectively. If the PCT level upon admission was 45.0 ng/mL, antibiotic treatment was continued until it was less than 10% of the peak PCT level reached. In the control group, antibiotic therapy followed the recommendations of the Japanese Respiratory Society guideline for management of community-acquired pneumonia in adults. Antibiotic therapy was discontinued if 3 of the following 4 criteria were met: fever declined (body temperature < 37.0°C), normalisation of leukocyte count, decrease in the CRP level to 30% of the maximum, and an obvious improvement as observed by chest radiography. In both groups, the choice of antibiotic regimen was left to the discretion of the treating physician.
Outcomes	• primary non-inferiority endpoint was a composite of a relapse of aspiration pneumonia and death from any cause occurring within 30 days of admission • antibiotic exposure • adverse events from antibiotic therapy
Notes	**Funding:** No funding declared in the main research paper. **Follow-up:** 30 days **Trial registration:** UMIN000004800

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated in 1:1 ratio
Allocation concealment (selection bias)	Unclear risk	No clear mention of allocation concealment is made in the main article. Citation "Following enrolment, the patients were randomly allocated in a 1:1 ratio to groups assigned different durations of antibiotic therapy…"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Procalcitonin was only measured in the intervention arm, but study design was open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment mentioned in the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Most participants were followed for 30 days. Reasons for post randomisation exclusions are clearly reported in the article.
Selective reporting (reporting bias)	Low risk	Outcomes correspond to trial registration.
Other bias	Unclear risk	As cited by authors under limitations, time until analysis of PCT concentrations was available was relatively long (3 days). Adherence to PCT algorithm not known

Oliveira 2013

Methods	Randomised, multicentre, open-label, controlled clinical trial in the ICUs of 2 university hospitals in Brazil
Participants	**Inclusion criteria:** All adult patients 18 years of age or older with suspected severe sepsis or septic shock were assessed for potential inclusion. **Exclusion criteria:** Confirmed microbiological infection by *Pseudomonas aeruginosa*,*Acinetobacter baumannii*, *Listeria spp*,*Mycobacterium tuberculosis*, or fungi; *Staphylococcus aureus* bacteraemia; suspected or confirmed severe infections caused by viruses or parasites; infections that required long-term treatment, regardless of the aetiologic agent (e.g. bacterial endocarditis); localised chronic infections (e.g. chronic osteomyelitis); > 48 hours of antibiotic treatment; immunosuppressed patients (such as those diagnosed with HIV), patients with neutropenia (< 500 neutrophils/mm^3), patients post-solid organ transplant, patients under immunosuppressive therapy, and patients who received more than 1 mg/kg of prednisone or equivalent; patients under palliative care; patients who suffered multiple trauma, burns, or major surgery in the previous 5 days; patients diagnosed with pulmonary neoplasias, carcinoid tumours, or medullary tumours of the thyroid; and patients who remained in the ICU for 24 hours or less **Included in this study:** 94/355 patients assessed for eligibility were included in the final analysis (49 in the PCT group and 45 in the CRP group).
Interventions	Guiding antibiotic decisions with CRP versus PCT in septic patients **Algorithm used in this study:** Antibiotic therapy was discontinued following a protocol based on serum levels of these markers, according to the allocation group. For both groups, at least 7 full days of antibiotic therapy were ensured in participants with SOFA score greater than 10 and/or bacteraemia at inclusion, and participants with evident resolution of the infectious process had antibiotics stopped after 7 days, despite biomarker levels.
Outcomes	• duration of antibiotic therapy for the first episode of infection • total number of days on antibiotic therapy • days off antibiotic therapy • death from any cause during the 28 days of follow-up in the hospital • length of stay (LOS) in the ICU and LOS in the hospital • clinical cure, recurrent infection, and nosocomial infection
Notes	**Funding:** Supported in part by the Minas Gerais Research Foundation (Fundação de Amparo à Pesquisa do Estado de Minas Gerais, FAPEMIG) **Follow-up:** 28 days or until death or hospital discharge **Trial registration:** NCT00934011

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a computer-generated random number table.
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes were used for the randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding due to the study design
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment mentioned in the study.

Oliveira 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the ITT analysis.
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol. Trial registered (NCT00934011).
Other bias	Low risk	High adherence to the PCT protocol (87.8%)

Schroeder 2009

Methods	Randomised clinical trial, single-centre, surgical ICU in Germany
Participants	**Inclusion criteria:** Patients after abdominal surgery with antibiotic treatment because of severe sepsis in the surgical ICU **Exclusion criteria:** Patients were excluded if they did not meet the respective inclusion criteria, refused informed consent, or had already received antibiotic treatment prior to admission to the ICU. **Included in this analysis:** 8 out of 27 randomised participants; 19 not considered for this analysis due to diagnosis other than RTI
Interventions	Guiding antibiotic decisions in postoperative patients in a surgical ICU **Algorithm used in this study:** In the PCT-guided group, antibiotic therapy was discontinued if clinical signs and symptoms of sepsis improved and PCT values had either decreased to 1 µg/L or less or had dropped to 25% to 35% of the initial PCT concentration over 3 consecutive days.
Outcomes	• antibiotic use • mortality (ICU-free days alive)
Notes	**Funding:** NA **Follow-up:** Until hospital discharge **Registration:** None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unconcealed drawing of lots
Allocation concealment (selection bias)	High risk	Unconcealed drawing of lots
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	High risk	Non-blinded study members

Schroeder 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 8/8 (100% until discharge)
Selective reporting (reporting bias)	Low risk	No selective reporting (oral verification with first author)
Other bias	Unclear risk	Adherence to PCT protocol not reported/assessed.

Schuetz 2009

Methods	Randomised clinical trial, multicentre, 6 sites in Switzerland
Participants	**Inclusion criteria:** Clinical diagnosis of CAP, ECOPD, bronchitis with X-ray confirmation **Exclusion criteria:** People with active intravenous drug use, severe immunosuppression other than corticosteroid use, life-threatening medical comorbidity leading to possible imminent death, hospital-acquired pneumonia (development of pneumonia 48 hours after hospital admission or if they were hospitalised within 14 days before presentation), and chronic infection necessitating antibiotic treatment **Included in this analysis:** 1359 out of 1381 randomised participants; 22 post randomisation exclusions due to withdrawal of consent
Interventions	Guiding antibiotic decisions in emergency department patients with different ARIs with repeated measurements **Algorithm used in this study:** Initiation or continuation of ABs was strongly discouraged if PCT was less than 0.1 µg/L and discouraged if levels were 0.25 µg/L or lower. Initiation or continuation of ABs was strongly encouraged if PCT was higher than 0.5 µg/L and encouraged if levels were higher than 0.25 µg/L. If ABs were withheld, hospitalised patients were clinically re-evaluated and PCT measurement was repeated after 6 to 24 hours.
Outcomes	• composite of overall adverse outcomes including death from any cause, ICU admission for any reason, disease-specific complications, and recurrence of LRTI in need of ABs • any of above outcomes • length of stay • side effects from antibiotics
Notes	**Funding:** This work was supported in part by grant SNF 3200BO-116177/1 from the Swiss National Science Foundation and contributions from santésuisse and the Gottfried and Julia Bangerter-Rhyner-Foundation, the University Hospital Basel, the Medical University Clinic Liestal, the Medical Clinic Buergerspital Solothurn, the Cantonal Hospitals Muensterlingen, Aarau and Lucerne, respectively, the Swiss Society for Internal Medicine, and the Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Basel. B·R·A·H·M·S Inc, the major manufacturer of the PCT assay, provided all assay-related material, Kryptor machines if not already available onsite, and kits and maintenance required for 10,000 measurements related to the study. **Follow-up:** Fixed follow-up period after 30 days and 180 days **Registration:** ISRCTN95122877

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Schuetz 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	Independent statistician created randomisation scheme.
Allocation concealment (selection bias)	Low risk	Central randomisation using a study web site
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Interviews by blinded medical students, data safety monitoring board
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 1358/1359 (100%)
Selective reporting (reporting bias)	Low risk	Outcomes match previously published protocol.
Other bias	Low risk	91% adherence to PCT algorithm in PCT group

Shehabi 2014

Methods	Randomised, multicentre, single-blind, controlled clinical trial in 11 ICUs in Australia
Participants	**Inclusion criteria:** Patients older than 18 years of age, admitted to ICU within the previous 72 hours, receiving parenteral and/or enteral antibiotics for a suspected bacterial infection (with 2 or more SIRS criteria) and expected to remain in the ICU for longer than 24 hours were eligible. **Exclusion criteria:** Patients receiving antibiotics for surgical prophylaxis or with proven bacterial infection requiring more than 3 weeks' antibiotic therapy, isolated systemic fungal or systemic viral infection in the absence of bacterial infection, neutropenia with a neutrophil count less than 1000 cells/mL, receiving immunosuppressive agents, cardiac surgery or trauma or heat stroke within 48 hours, medullary thyroid or small cell lung cancer, patient not expected to survive to hospital discharge, or known pregnancy **Included in this study:** Of 400 randomised participants, 394 finished 90 days' follow-up for survival. 6 withdrew their consent.
Interventions	Guiding antibiotic decisions in critically ill patients in the ICU with undifferentiated infection or suspected sepsis **Algorithm used in this study:** Cessation of antibiotics was recommended if initial or any subsequent PCT was negative (<0.10 ng/mL) or if initial or any subsequent PCT was between 0.10 to 0.25 ng/mL, and infection was highly unlikely; Subsequent PCT level declined more than 90% from baseline, and 2. Assess antibiotic appropriateness and/or adequacy of source control if PCT level at 48 hours is 70% of baseline value. Daily PCT results were made available to the treating clinician for participants randomised to the PCT group. Antibiotic prescription in both the standard care and PCT groups was according to the Australian Antibiotics Therapeutic Guidelines and the antimicrobial stewardship (implemented by infectious diseases twice-weekly rounds and on-need consultations). The algorithm was implemented only in the ICU.
Outcomes	• time to antibiotic cessation at 28 days, hospital discharge, or death, whichever came first after randomisation • antibiotic-free days at day 28 after randomisation

Shehabi 2014 *(Continued)*

- number of antibiotic daily defined doses at day 28
- ICU and hospital length of stay
- mortality and 90-day all-cause mortality
- additional a priori outcomes included the relationship between baseline (taken at randomisation) PCT and sepsis severity, microbiologically confirmed infections within 72 hours, and the predictive value of baseline and serial PCT of mortality
- readmission
- emergence of resistant micro-organisms
- number of algorithm violations

Notes	**Funding:** Funded by a competitive grant from the Intensive Care Foundation of Australia and New Zealand. Material support was provided by Roche Diagnostics, Thermo Fisher Scientific, and bio-Mérieux. Roche Diagnostics and Thermo Fisher Scientific provided additional unrestricted grant funding. **Follow-up:** 90 days' post randomisation for survival **Trial registration:** ACTRN12610000809033

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were variable block randomised 1:1 via a secured central study web site into either a PCT-guided or clinician-guided group.
Allocation concealment (selection bias)	Low risk	Central randomisation with variable blocks
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	For the standard care group, clinicians were blinded to the PCT levels, but the physicians were aware of the participants' study group due to the study design.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data were collected by professional research personnel at each site and entered into a central secured database at the Clinical Informatics and Data Management Unit, Department of Epidemiology and Preventive Medicine, Monash University and analysed by a blinded biostatistician at Monash University, Melbourne, Australia. The study was monitored by an independent data safety and monitoring committee, with no interim analysis performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The follow-up for mortality was 394/394 (100%).
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol. Trial registered (ACTRN12610000809033).
Other bias	Low risk	High adherence to the PCT algorithm (97%). "The proportion of study days where the PCT algorithm was not followed was less than 3%, the majority of which was due to missed PCT sampling."

Stolz 2007

Methods	Randomised clinical trial, single-centre, University Hospital Basel, Switzerland
Participants	**Inclusion criteria:** Clinical diagnosis of COPD exacerbation

Stolz 2007 *(Continued)*

	Exclusion criteria: People who were considered to be vulnerable study participants (i.e. those with psychiatric comorbidity) were excluded from the study. Other exclusion criteria were immunosuppression, asthma, cystic fibrosis, and the presence of infiltrates on chest radiographs on hospital admission. **Included in this analysis:** 208 out of 226 randomised participants; 18 post randomisation exclusions due to absence of COPD according to GOLD criteria
Interventions	Guiding antibiotic decisions in COPD patients with repeated measurements **Algorithm used in this study:** Procalcitonin level of 0.1 µg/L was considered indicative of the absence of bacterial infection, and the use of ABs was discouraged. A level of 0.1 to 0.25 µg/L indicated possible bacterial infection, and the use of ABs was discouraged or encouraged, respectively, based on the stability of the participant's clinical condition. A PCT level of 0.25 µg/L was considered suggestive of the presence of bacterial infection, and AB treatment was encouraged.
Outcomes	• antibiotic use • "clinical success" defined as improvement of symptoms compared to exacerbation status • "clinical failure" defined as the absence of the attenuation of symptoms, the worsening of symptoms, or death • mortality • ICU admission • hospital readmission after 30 days and 6 months
Notes	**Funding:** This study was funded by the Clinic of Pulmonary Medicine; the Clinic of Endocrinology, Diabetes and Clinical Nutrition; and the Emergency Department of the University Hospital Basel. B·R·A·H·M·S provided PCT assays for this investigator-driven study. **Follow-up:** Short-term follow-up visit after 14 to 21 days; long-term follow-up visit at 6 months **Registration:** ISRCTN77261143

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent statistician created randomisation list.
Allocation concealment (selection bias)	High risk	Sealed envelopes, not numbered
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 208/208 (100%)
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol.

Stolz 2007 *(Continued)*

Other bias	Unclear risk	Adherence to PCT protocol not reported/assessed.

Stolz 2009

Methods	Randomised clinical trial, multicentre with 7 European and US intensive care units
Participants	**Inclusion criteria:** VAP when intubated for > 48 h **Exclusion criteria:** Patients were excluded it they 1) were pregnant; 2) were enrolled in another trial; 3) had received immunosuppressants or long-term corticosteroid therapy (> 0.5 mg/kg per day for > 1 month); 4) were severely immunosuppressed, including AIDS; or 5) had a coexisting extrapulmonary infection diagnosed between day 1 and 3 requiring antibiotic therapy for > 3 days. **Included in this analysis:** 101 (101) (100%)
Interventions	Guiding antibiotic decisions in VAP patients with repeated measurements **Algorithm used in this study:** A PCT level of < 0.25 µg/L suggested the absence of VAP, and discontinuation of ABs was strongly encouraged. A PCT level between 0.25 µg/L and 0.5 µg/L or a decrease by ≥ 80% as compared to day 0 indicated that bacterial infection was unlikely, and reduction or discontinuation of ABs was encouraged. A PCT level ≥ 0.5 µg/L or decrease by < 80% as compared to day 0 was considered indicative of unresolved bacterial infection, and reduction or discontinuation of AB was discouraged. A PCT level of > 1 µg/L strongly suggested unresolved bacterial infection, and AB discontinuation was strongly discouraged.
Outcomes	• antibiotic-free days alive • any antibiotic exposure after inclusion, i.e. total antibiotic exposure days and total antibiotic agent days, regardless of indication • the number of mechanical ventilation-free days • the number of ICU-free days alive • the evolution of the signs and symptoms potentially linked to pulmonary infection • SaO_2, PaO_2/FiO_2 • the evolution of the SOFA, ODIN, and CPIS scores • length of hospital stay • the VAP-related clinical deterioration rate and overall mortality at 28 days
Notes	**Funding:** Funding was granted by the Clinic of Pulmonary Medicine, University Hospital Basel. Funding obtained from B·R·A·H·M·S AG (Hennigsdorf, Germany) **Follow-up:** Fixed follow-up period of 28 days **Registration:** ISRCTN61015974

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent statistician created randomisation list.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was through arbitrary allocation to one of the two treatment assignments based on sealed, opaque envelopes. Block size was 20 envelopes. Treating physicians were not aware of envelope contents before randomisation"

Stolz 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew to which group participants had been assigned and where PCT levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study member
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for mortality: 101/101 (100%)
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol.
Other bias	Unclear risk	Adherence to PCT protocol not reported/assessed.

Tang 2013

Methods	Randomised, single-centre, single-blinded, controlled clinical trial in the emergency department of the Fifth People's Hospital of Shanghai, China
Participants	**Inclusion criteria:** 1) ≥ 18 years old; 2) has any, or all, of the following clinical features as defined by the Global Initiative for National Asthma (GINA) Guidelines: dyspnoea, wheeze, acute cough, increased work of breathing, increased requirement for beta2-agonist from baseline use, O_2 saturation < 95%, a peak expiratory flow (PEF) at randomisation ≤ 80% of their known best (within the last 12 months) or, in the absence of this information, of their predicted PEF **Exclusion criteria:** 1) treatment with antibiotics within 2 weeks prior to recruitment; 2) bacterial infection in other parts of body than the respiratory system; 3) chest X-ray-confirmed pneumonia; 4) suffering from other chronic respiratory diseases; 5) suffering from severe organ dysfunction **Included in this study:** 265 people were eligible, and 255 participants completed the study.
Interventions	Guiding antibiotic decisions in patients with acute exacerbation of asthma **Algorithm used in this study:** Participants in the PCT group were treated with antibiotics based on their PCT serum level according to the following guidelines: antibiotics treatment was strongly discouraged when serum PCT level was < 0.1 µg/L; antibiotics treatment was discouraged when serum PCT level was < 0.25 µg/L; antibiotics treatment was encouraged when serum PCT level was > 0.25 µg/L.
Outcomes	• antibiotic prescription rate and the relative risk of antibiotic exposure • clinical, laboratory, and lung function outcomes at the follow-up visit (6 weeks) • secondary ED visits, hospital readmissions, repeated need for steroids or dosage increase, need for antibiotics, white blood cell count, PCT levels, and FEV1% were assessed during the 6-week follow-up period
Notes	**Funding:** The study was sponsored by a grant from the Shanghai Fifth People's Hospital Science Foundation and Minhang District Natural Science Foundation of Shanghai. **Follow-up:** 6 weeks **Trial registration:** ICTRP ChiCTR-TRC-12002534

Risk of bias

Bias	Authors' judgement	Support for judgement

Tang 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Allocation to either intervention was conducted according to computer-generated random numbers produced by an independent statistician.
Allocation concealment (selection bias)	Low risk	After randomisation, an opaque, sealed, and sequentially numbered envelope containing the PCT or control protocol was prepared for each participant according to the group.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Attending physicians responsible for participants in the control group remained unaware of the participants' PCT concentrations throughout the study, but blinding was not feasible due to the study design.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants, laboratory technicians, investigators, and research designers were blinded to participant assignments until the data analysis was completed. There were no protocol violations during the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	265/265 participants completed follow-up for mortality.
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol: ICTRP ChiCTR-TRC-12002534.
Other bias	Low risk	100% adherence to the PCT algorithm. "There were no protocol violations during the study."

Verduri 2015

Methods	Randomised, multicentre, open, controlled, parallel-group, non-inferiority trial involving 18 university/city hospital pulmonary departments in Italy
Participants	**Inclusion criteria:** Study participants were male or female, 18 years of age, current or former smokers, and diagnosed with COPD stages I-IV as defined by GOLD guidelines available at the time the study was designed, with protocol deviation. Participants were hospitalised for severe ECOPD requiring antibiotic treatment, i.e. type 1 exacerbation (increased dyspnoea, sputum volume, and sputum purulence verified by the attending clinician) according to Anthonisen, and/or characterised by respiratory failure. Exacerbation of chronic obstructive pulmonary disease was defined as "an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication". **Exclusion criteria:** Bronchial asthma, unstable concomitant disease (cardiovascular, renal, hepatic, gastrointestinal, neurological, metabolic, musculoskeletal, neoplastic, respiratory, or other disease), pregnancy and breastfeeding, clinically significant laboratory abnormalities suggestive of unstable concomitant disease, survival for 1 year unlikely, and inability to give written consent. Antibiotic pretreatment before hospital admission and radiographic signs of pneumonia did not preclude eligibility for the study. **Included in this study**: 183 participants were randomised, of which 178 participants, 88 in the PCT group and 90 in the standard care group, were analysed.
Interventions	Guiding antibiotic decisions in people with severe exacerbations of COPD **Algorithm used in this study:** On admission, all patients received a 3-day course of antibiotics (either amoxicillin plus clavulanate or quinolones) according to 2005 international guidelines. Procalcitonin levels were measured on hospital admission, on day 1, and on day 2. On day 2 each eligible patient was randomly assigned to 1 of the 2 treatment plans. quote "Participants randomised to the standard group continued antibiotic therapy for 10 days, whereas participants randomised to the PCT group either continued treatment for 10 days or stopped on day 3, depending on their PCT levels, according to previously recommended cut-off values. Specifi-

Verduri 2015 *(Continued)*

	cally, participants continued antibiotic treatment for 10 days if 1 or more of the PCT values on the first 3 days of hospitalisation were 0.25 µg/L. When PCT values were < 0.25 µg/L but > 0.1 µg/L on any occasion, antibiotic treatment was continued for 10 days if participants were clinically unstable or had acute respiratory failure; otherwise, treatment was stopped on day 3. If all PCT values were consistently < 0.1 µg/L, treatment was stopped on day 3." All participants were also treated with systemic corticosteroids for 14 days, plus regular inhaled short-acting or long-acting bronchodilators.
Outcomes	• percentage of participants with at least 1 exacerbation within 6 months after the index exacerbation • hospital readmission • admission to the ICU • change in lung function (ΔFEV1) • length of hospital stay • death from any cause
Notes	**Funding:** The trial was approved and funded by the Agenzia Italiana del Farmaco (AIFA), the Italian agency for drugs, which is an official body of the Italian Ministry of Health. **Follow-up:** Follow-up visits were scheduled on day 1, day 3, and 6 months after discharge; telephone interviews were conducted at 2, 4, and 5 months after discharge. **Trial registration:** NCT01125098

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was web based, and only statisticians and the web site administrator knew the randomisation sequence
Allocation concealment (selection bias)	Low risk	Eligible patients were randomly assigned to receive standard antibiotic therapy (standard group) or PCT-guided antibiotic treatment (PCT group) according to a 1:1 permuted block computer-generated scheme, stratified according to hospital
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding was not feasible due to the study design
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment mentioned in the study. The authors state that: "... because we anticipated that the primary outcome (exacerbations of COPD) would be strong and easy to identify, and thus unlikely to be biased by investigator influence, we did not adopt any procedure to reduce bias during the follow-up part of the trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	187 of 192 randomised participants were included in final analysis.
Selective reporting (reporting bias)	Low risk	Results correspond to the trial registration.
Other bias	Low risk	High adherence to the PCT protocol (95.5%) The study planned to enrol 400 participants to have enough statistical power for the primary endpoint, but randomised only 183.

Wang 2016

Methods	Randomised, single-centre, single-blinded, controlled clinical trial in the Beijing Luhe Hospital, China
Participants	**Inclusion criteria:** Patients with AECOPD who were 40 years of age, had sound understanding and language abilities, and who had a PCT level < 0.1 ng/mL were included. **Exclusion criteria:** Fever (38°C), tracheal intubation within 24 h after hospital admission, a PCT level of 0.1 ng/mL on admission, pneumonia, chronic renal failure, history of malignant disease, immunosuppressive therapy, and refusal to participate **Included in this study:** 194 randomised participants. 191 finished the 30-day follow-up.
Interventions	Guiding antibiotic decisions in patients with acute exacerbation of chronic obstructive pulmonary disease **Algorithm used in this study:** Patients with a PCT concentration < 0.1 ng/mL were randomised. Antibiotics were withheld from participants in the control group. However, antibiotics could be administered later for participants whose clinical condition was unstable or who had a worsening of symptoms and signs, and for those with positive evidence of bacteria as assessed by the attending physicians. In the antibiotic group, antibiotics were administered routinely.
Outcomes	• treatment success rate on day 10 after admission • symptoms assessed by visual analogue scale (at hospital admission, 3 days after hospitalisation, and on the day of hospital discharge) • length of hospital stay • intubation rate • mortality during hospitalisation and the 30-day follow-up period • rate of antibiotic use • readmission due to AECOPD in the 30-day follow-up period
Notes	**Funding:** The study was sponsored by the National Science Fund for Distinguished Young Scholars (81425001/H0104) for Dr Bin Cao. **Follow-up:** 30 days after hospital discharge **Trial registration:** ChiCTR-TRC-14004726

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer digital table method was used to generate randomisation numbers.
Allocation concealment (selection bias)	Low risk	Researchers in this study had 24-hour access to randomisation numbers, allowing immediate and concealed allocation to the trial.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding feasible due to the study protocol.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Individuals responsible for allocation concealment were not allowed to take part in the measurement of results, but no overall blinding of the outcome assessment was mentioned in this study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3 participants were excluded during the 30-day follow-up, due to a diagnosis of pneumonia according to chest X-ray.
Selective reporting (reporting bias)	Low risk	Outcomes correspond to the trial registration (ChiCTR-TRC-14004726).

Wang 2016 *(Continued)*

Other bias	Low risk	High adherence to the PCT protocol (82.3%)

AB: antibiotic
AECOPD: acute exacerbation of chronic obstructive pulmonary disease
AE-IPF: acute exacerbation of idiopathic pulmonary fibrosis
ARIs: acute respiratory infections
CAP: community-acquired pneumonia
COPD: chronic obstructive pulmonary disease
CPIS: Clinical Pulmonary Infection Score
CRP: C-reactive protein
d: day
ED: emergency department
ECOPD: exacerbation of chronic obstructive pulmonary disease
EMR: electronic medical record
FEV1%: forced expiratory volume for 1 second expressed as a percentage of the forced vital capacity
GOLD: Global Initiative for Chronic Obstructive Lung Disease
h: hour
ICU: intensive care unit
ID: identification
ITT: intention-to-treat
LRTI: lower respiratory tract infection
NA: not available
ODIN: Organ Dysfunction and/or Infection
PaO_2/FiO_2: relationship between arterial oxygen tension (PaO_2) and inspiratory oxygen fraction (FiO_2)
Pa: arterial
PCR: polymerase chain reaction
PCT: procalcitonin
RSV: respiratory Syncytial virus
RTI: respiratory tract infection
SaO_2: oxygen saturation
SIRS: systemic inflammatory response syndrome
SOFA: Sequential Organ Failure Assessment
VAP: ventilator-associated pneumonia

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Dharaniyadewi 2013	Poster presentation only
Esposito 2012	Not adult participants (paediatrics)
Heyland 2011	Meta-analysis of previous RCTs
Jensen 2011	Not using procalcitonin to de-escalate antibiotic therapy but for improving mortality by escalation of therapy
Jones 2007	Meta-analysis of observational studies
Kook 2012	Not an RCT; before-after study design
Liew 2011	Not an RCT
Liu 2013	Not an RCT
Qu 2012	Not a respiratory infection (pancreatitis)

Study	Reason for exclusion
Saeed 2011	Not an RCT
Schuetz 2010	Not an RCT; before-after study design (post study survey)
Simmonds 2005	Meta-analysis of observational studies
Simon 2004	Meta-analysis of observational studies
Stocker 2010	Included a paediatric population only
Tang 2007	Meta-analysis of observational studies
Tang 2009	Meta-analysis of RCTs
Uzzan 2006	Meta-analysis of observational studies

RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT02130986

Trial name or title	PCT Antibiotic Consensus Trial (ProACT)
Methods	Randomised, single-blind, multicentre study
Participants	**Inclusion criteria:** 1. ≥ 18 years old 2. a primary clinical diagnosis in the ED of acute LRTI (< 28 days duration) 3. clinician willing to consider PCT in antibiotic decision making **Exclusion criteria:** 1. systemic antibiotics before ED presentation (all prophylactic antibiotic regimens, OR received > 1 dose within 72 hours prior to ED presentation) 2. current vasopressor use 3. mechanical ventilation (via endotracheal tube) 4. known severe immunosuppression 5. accompanying non-respiratory infections 6. known lung abscess or empyema 7. chronic dialysis 8. metastatic cancer 9. surgery in the past 7 days (excluding minor surgery such as skin biopsy) 10.incarcerated or homeless 11.enrolled in ProACT in the past 30 days
Interventions	**Algorithm used in this study:** Procalcitonin versus usual care group in patients with LRTI in the ED. Procalcitonin cut-offs: < 0.1 ng/L. Antibiotics strongly discouraged 0.1 to 0.25 ng/L. Antibiotics discouraged > 0.25 to 0.5 ng/L. Antibiotics recommended

NCT02130986 *(Continued)*

	> 0.5 ng/L. Antibiotics strongly recommended
Outcomes	• total antibiotic exposure days (time frame: 30 days). Total antibiotic exposure, defined as the total number of antibiotic days by day 30 • combined endpoint of adverse outcomes that could be attributable to withholding antibiotics in LRTI (time frame: 30 days) • rate of antibiotic initiation by the initial ED clinician (time frame: during initial ED visit)
Starting date	November 2014
Contact information	Elizabeth A Gimbel, BS; gimbele@upmc.edu Kourtney A Wofford, BA; woffordka@upmc.edu
Notes	**Collaborators:** University of Pittsburgh National Institute of General Medical Sciences (NIGMS), bioMérieux **Registration:** NCT02130986

NCT02261610

Trial name or title	Pulmonary embolism and PCT. PE-PCT study
Methods	Single-centre, prospective, randomised trial in France
Participants	**Inclusion criteria:** 1. age over 18 years 2. CT diagnosis of pulmonary embolism with signs of pulmonary infarction 3. temperature > 37.8 4. prior agreement with the patient signing a consent **Exclusion criteria:** 1. pregnant women 2. refusal of the patient 3. pulmonary neoplasia 4. antibiotic ongoing for more than 24 hours at the time of diagnosis of pulmonary embolism 5. cardiogenic shock (hypotension with mean arterial pressure less than 65 bpm) 6. suspicion of infection other than lung associated (urinary tract infection; prostatitis; ear, nose, and throat infection; sinusitis, etc.) 7. patient under guardianship 8. patient unable to give consent
Interventions	**Algorithm used in this study:** Procalcitonin algorithm to guide antibiotic therapy. In the control group, the use of antibiotics will be guided by clinical criteria
Outcomes	• percentage of participants treated with antibiotics in each group (time frame: at day 1) • percentage of deaths (time frame: at day 1) • percentage of antibiotics stop (time frame: at day 1) • rate of new hospitalisations during the following month (time frame: at 1 month)
Starting date	November 2014
Contact information	Patrick Lacarin; placarin@chu-clermontferrand.fr

NCT02261610 *(Continued)*

Notes	**Collaborators:** Thermo Fisher Scientific **Registration:** NCT02261610

NCT02332577

Trial name or title	Study to compare the efficacy of pristinamycin (Pyostacine) versus amoxicillin in the treatment of acute community acquired pneumonia
Methods	A multicentre, non-inferiority, randomised, double-blind, phase IV study in France and Tunisia
Participants	**Inclusion criteria:** 1. male or female older than 18 years with a presumed bacterial acute community-acquired pneumonia presenting a PORT score of II or III (Fine II or III) **Exclusion criteria:** 1. patients diagnosed with legionellosis 2. having received over 24 hours of systemic antibiotic therapy during the week preceding the start of study treatment 3. associated neoplasm (active cancer (of whatever type, solid or haematological) or diagnosed within the year other than baso-cellular skin cancer) 4. severe or very severe COPD (GOLD3 and GOLD4) 5. history of bacterial pneumonia in the past 12 months 6. bronchopulmonary diseases likely to interfere with the assessment of the therapeutic response 7. known hypersensitivity to streptogramins, penicillin and other beta-lactam antibiotics or excipients of the treatments studied 8. history of severe skin reaction after taking pristinamycin or amoxicillin 9. kidney disease (chronic kidney failure or creatinine clearance ≤ 30 mL/minute) 10. patients treated with allopurinol, colchicine, immunosuppressants (cyclosporin, tacrolimus, mycophenolate mofetil, methotrexate, bio therapies), oral anticoagulants in the previous 6 months or during the study 11. known HIV infection, whatever the stage
Interventions	**Algorithm used in this study**: pristinamycin + placebo versus amoxicillin + placebo. To evaluate the clinical efficacy of pristinamycin at a dose of 2 g x 2/day for 2 days then 1 g x 3/day for 5 to 7 days versus amoxicillin 1 g x 3/day for 7 to 9 days, 5 to 9 days after the end of treatment
Outcomes	• percentage of cured participants established from the clinical course and pulmonary radiological course (time frame: 5 to 9 days post-treatment) • percentage of cured participants evaluated by bacteriological documentation and PCT levels (time frame: 5 to 9 days post-treatment) • percentage of cured participants evaluated by bacteriological documentation for pneumococcus (time frame: 5 to 9 days post-treatment) • percentage of participants with relapse (time frame: at day 30) • mortality rate (time frame: at day 30) • number of documented failures (time frame: 5 to 9 days post-treatment) • proportion of participants with adverse events (time frame: up to day 30)
Starting date	April 2015
Contact information	Contact-Us@sanofi.com
Notes	**Collaborators:** Clinical Sciences & Operations

NCT02332577 *(Continued)*

	Registration: NCT02332577

NCT02440828

Trial name or title	Addition of tobramycin inhalation in the treatment of ventilator associated pneumonia (VAPORISE)
Methods	Randomised trial, parallel assignment, double-blind (participant, investigator) in the Netherlands and Spain
Participants	**Inclusion criteria**: 1) mechanical ventilation 48 hours or more; and 2) new or progressive radiologic pulmonary infiltrate; together with at least 2 of the following 3 criteria (< 24 h): • temperature > 38°C; • leukocytosis > 12,000/mm^3 or leukopenia < 4000/mm^3; • purulent respiratory secretions. **Exclusion criteria:** 1. patients with allergy to tobramycin 2. pregnancy 3. expected to die within 72 hours after enrolment
Interventions	**Algorithm used in this study:** Experimental arm: tobramycin inhalation twice daily; tobramycin inhalation (Bramitob) 300 mg and standard intravenous antibiotics treatment. Intervention: drug: tobramycin inhalation Placebo comparator: placebo twice daily; placebo inhalation and standard intravenous antibiotics treatment. Intervention: drug: placebo
Outcomes	• response after 72 h of treatment (time frame: 72 hours) • mortality rate (time frame: day 30) 30-day and 90-day mortality rate • ICU survival (time frame: day 90) • absence of hospital admittance at day 60 (time frame: day 60) • discharge from the ICU (time frame: up to 60 days) • adverse events • day of normalisation of CRP • eradication of pathogens • Clinical Pulmonary Infectious Score • APACHE II score • Multiple Organ Dysfunction Score • SOFA score • Lung Injury Score • day of normalisation of PCT • day of normalisation of chest X-ray
Starting date	March 2015
Contact information	Rogier Hoek, MD; r.hoek@erasmusmc.nl Menno Van der Eerden, MD, PhD; m.vandereerden@erasmusmc.nl
Notes	**Collaborators:** Chiesi Farmaceutici S.p.A. **Registration:** NCT02440828

NCT02787603

Trial name or title	PCT in Early Antibiotic Interruption in Patient With Bacterial Pulmonary infeCtion and Acute Heart Failure (EPICAD)
Methods	Randomised trial with parallel assignment, open label in Brazil
Participants	**Inclusion criteria:** 1. Decompensated acute heart failure diagnosis and suspected pulmonary infection 2. BNP ≥ 500 pg/mL or NT-proBNP ≥ 450 pg/mL for patients ≤ 50 years old 3. BNP ≥ 500 pg/mL or NT-proBNP ≥ 900 pg/mL for patients 51 to 75 years old 4. BNP ≥ 500 pg/mL or NT-proBNP ≥ 1800 pg/mL for patients > 75 years old **Exclusion criteria:** 1. antibiotic use (oral or endovenous) in the last 15 days 2. acute coronary syndrome 3. creatinine > 3.0 mg/dL or haemodialysis 4. pregnancy 5. second suspected infection 6. suspected pulmonary thromboembolism 7. cancer 8. myocarditis
Interventions	**Algorithm used in this study**: Experimental: group A: interruption of antibiotic treatment based on PCT measurement No intervention: group B: antibiotic therapy period determined by the physician without knowledge of PCT levels
Outcomes	• total period of antibiotic therapy (time frame: 30 days) • hospitalisation (time frame: 30 days) • mortality (time frame: 30 days) • PCT levels during antibiotic therapy (time frame: 5 days)
Starting date	January 2015
Contact information	Mucio Tavares, PhD, MD; mucio@incor.usp.br Aline Bossa, MSc; aline.bossa@incor.usp.br
Notes	**Collaborators:** University of Sao Paulo General Hospital, bioMérieux **Registration:** NCT02787603

NCT02862314

Trial name or title	PCT Pneumonia/Pneumonitis Associated With ASPIration (PROPASPI)
Methods	Randomised trial, parallel assignment, open label in France
Participants	**Inclusion criteria:** 1. aged 18 or older

NCT02862314 *(Continued)*

	2. have undergone oro-tracheal intubation for a coma (Glasgow Coma Score ≤ 8) 3. with mechanical ventilation initiated in the first 48 hours following hospital admission **Exclusion criteria:** 1. pregnancy 2. patients under legal custody 3. patients without health insurance 4. patients included in another interventional clinical study involving infections or antibiotics and having the same primary parameter 5. moribund patients 6. situation in which the PCT concentration could be increased without correlation to an infectious process (polytraumatised patients) 7. surgical interventions within the last 4 days 8. cardiorespiratory arrest 9. administration of antithymocyte globulin 10. immunodepressed patients (bone marrow transplant patients, patients with severe neutropenia) 11. patients with an absolute indication for administration of antibiotics at the moment of ICU admission (meningitis, pneumonia) or a chronic infection for which long-term antibiotic treatment is necessary (endocarditis, osteoarticular infections, mediastinitis, deep abscesses, pneumocystis infection, toxoplasmosis, tuberculosis) 12. patients with haemodynamic instability of septic origin or a respiratory insufficiency (defined by a ratio $PaO_2/FiO_2 \leq 200$ mmHg and pulmonary positive ≥ 5 cmH_2O)
Interventions	**Algorithm used in this study:** Experimental: PCT group. The PCT concentration is measured at inclusion. No intervention: control group. Concentrations of PCT are not measured.
Outcomes	• duration of antibiotic treatment (time frame: during the first 15 days following admission to the ICU)
Starting date	February 2015
Contact information	Gilles Capellier, MDPH; gilles.capellier@univ-fcomte.fr Sophie Depierre; sdepierre@chu-besancon.fr
Notes	**Collaborators:** Centre Hospitalier Universitaire de Besancon **Registration:** NCT02862314

NCT02931409

Trial name or title	Intra-operative PEEP optimisation: effects on postoperative pulmonary complications and inflammatory response
Methods	Randomised trial, parallel assignment, single-blind in Hungary
Participants	**Inclusion criteria:** 1. patients with bladder cancer undergoing radical cystectomy and urinary diversion (ileal conduit or orthotopic bladder substitute) **Exclusion criteria:**

NCT02931409 *(Continued)*

	1. age < 18 years 2. American society of Anesthesiology risk class IV 3. history of severe COPD (GOLD grade III or IV) 4. history of severe or uncontrolled bronchial asthma 5. history of severe restrictive pulmonary disease 6. pulmonary metastases 7. history of any thoracic surgery 8. need for thoracic drainage before surgery 9. renal replacement therapy prior to surgery 10. congestive heart failure (NYHA grade III or IV) 11. extreme obesity (BMI > 35 kg/m^2) 12. lack of patient's consent
Interventions	**Algorithm used in this study:** Experimental: Optimal PEEP patients submitted to general anaesthesia and open radical cystectomy and urinary diversion (20 participants) will be submitted an alveolar recruitment maneuver using the sustained airway pressure by the CPAP method, applying 30 cmH_2O PEEP for 30 seconds followed by a decremental PEEP titration procedure directed by static pulmonary compliance (Cstat). During PEEP titration procedure, PEEP will be decreased from 14 cmH_2O by 2 cmH_2O every 4 minutes, until a final PEEP of 6 cmH_2O. Optimal PEEP is considered to be a PEEP value resulting the highest possible Cstat measured by ventilator. After PEEP titration procedure, a lung protective mechanical ventilation will be performed using optimal PEEP and low tidal volumes. Active comparator: Standard PEEP. Patients submitted to general anaesthesia and open radical cystectomy and urinary diversion (20 participants) will be submitted an alveolar recruitment manoeuvre using the sustained airway pressure by the CPAP method, applying 30 cmH_2O PEEP for 30 seconds followed by a standard lung protective mechanical ventilation using a PEEP value of 6 cmH_2O and low tidal volumes (6 mL/kg)
Outcomes	• Postoperative Pulmonary Complications: new infiltrates or atelectasis on chest X-ray, abnormal breathing sounds on auscultation, excessive bronchial secretions, unexplained fever, respiratory failure or need for non-invasive or invasive ventilatory support. • Procalcitonin Kinetics: serum procalcitonin levels during and after surgery
Starting date	October 2016
Contact information	Zoltán Ruszkai, MD; ruszkai.zoltan@peterfykh.hu
Notes	**Collaborator:** Péterfy Sándor Hospital, Szeged University **Registration:** NCT02931409

AB: antibiotic
ACCP: American College of Chest Physicians
APACHE II: Acute Physiology and Chronic Health Evaluation II
BMI: body mass index
BNP: B-type natriuretic peptide
COPD: chronic obstructive pulmonary disease
CPAP: continuous positive airway pressure
CRP: C-reactive protein
CT: computed tomography
d: day
ED: emergency department
ESBL: extended-spectrum beta-lactamase
h: hour
GOLD: Global Initiative for Chronic Obstructive Lung Disease

ICU: intensive care unit
LRTI: lower respiratory tract infection
NT-proBNP: N-terminal pro-B-type natriuretic peptide
NYHA: New York Heart Association
Pa: arterial
PaO_2/FiO_2: relationship between arterial oxygen tension (PaO_2) and inspiratory oxygen fraction (FiO_2)
PCT: procalcitonin
PEEP: positive end-expiratory pressure
PORT: Pneumonia Patient Outcomes Research Team
RCT: randomised controlled trial
SIRS: systemic inflammatory response syndrome
SOFA: Sequential Organ Failure Assessment score

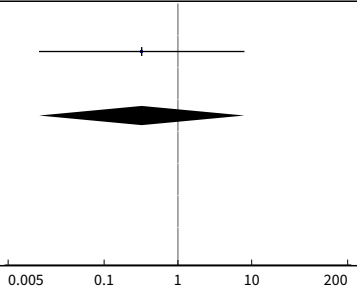
DATA AND ANALYSES

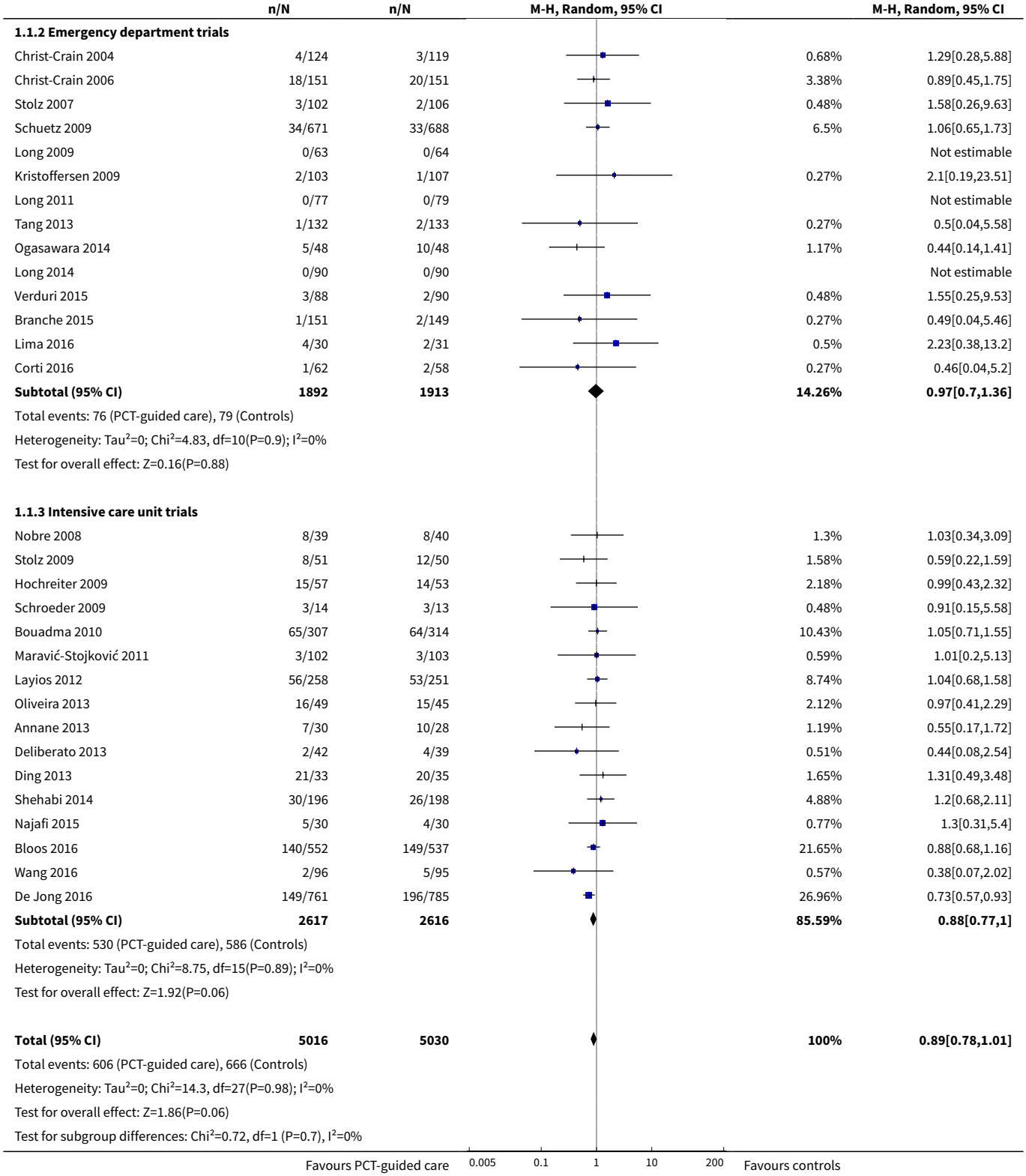
Comparison 1. Procalcitonin algorithm versus no procalcitonin algorithm stratified by clinical setting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at 30 days	32	10046	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.78, 1.01]
1.1 Primary care trials	2	1008	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.98]
1.2 Emergency department trials	14	3805	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.70, 1.36]
1.3 Intensive care unit trials	16	5233	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.77, 1.00]
2 Treatment failure at 30 days	32	10046	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.81, 0.99]
2.1 Primary care trials	2	1008	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.72, 1.22]
2.2 Emergency department trials	14	3805	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.69, 1.05]
2.3 Intensive care unit trials	16	5233	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.81, 1.05]

Analysis 1.1. Comparison 1 Procalcitonin algorithm versus no procalcitonin algorithm stratified by clinical setting, Outcome 1 Mortality at 30 days.

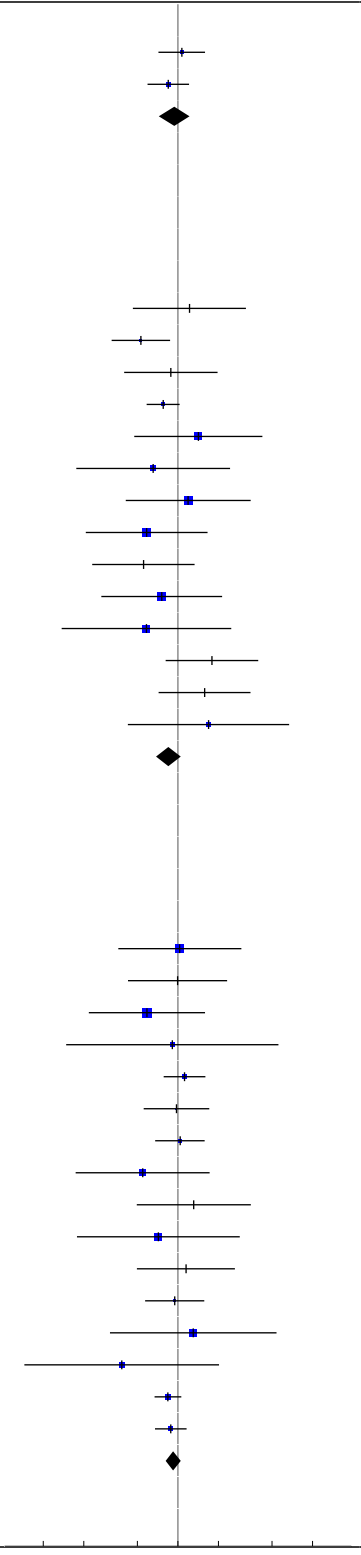
Study or subgroup	PCT-guided care n/N	Controls n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Primary care trials					
Briel 2008	0/232	1/226		0.15%	0.32[0.01,7.98]
Burkhardt 2010	0/275	0/275			Not estimable
Subtotal (95% CI)	**507**	**501**		**0.15%**	**0.32[0.01,7.98]**
Total events: 0 (PCT-guided care), 1 (Controls)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					

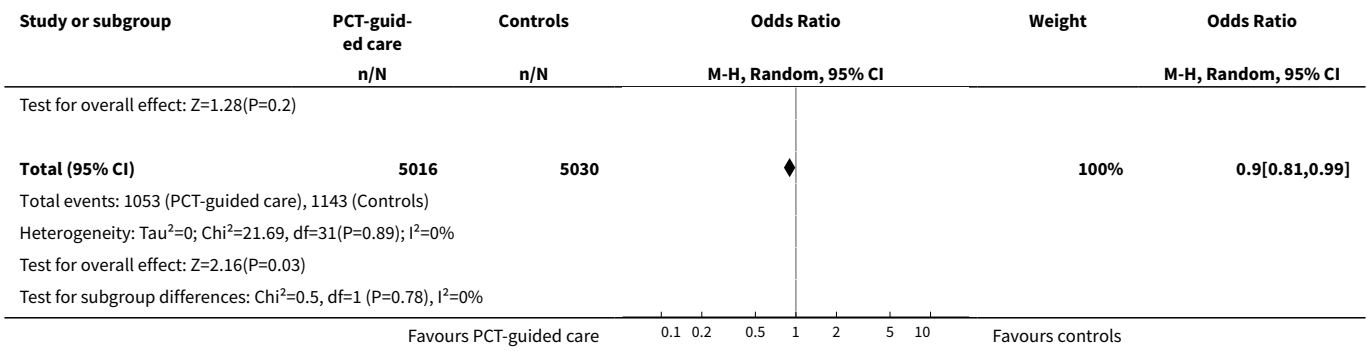




Analysis 1.2. Comparison 1 Procalcitonin algorithm versus no procalcitonin algorithm stratified by clinical setting, Outcome 2 Treatment failure at 30 days.

Study or subgroup	PCT-guided care n/N	Controls n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Primary care trials					
Briel 2008	73/232	68/226		6.05%	1.07[0.72,1.59]
Burkhardt 2010	86/275	96/275		7.53%	0.85[0.59,1.21]
Subtotal (95% CI)	**507**	**501**		**13.58%**	**0.94[0.72,1.22]**
Total events: 159 (PCT-guided care), 164 (Controls)					
Heterogeneity: Tau^2=0; Chi^2=0.71, df=1(P=0.4); I^2=0%					
Test for overall effect: Z=0.46(P=0.64)					
1.2.2 Emergency department trials					
Christ-Crain 2004	10/124	8/119		1.02%	1.22[0.46,3.2]
Christ-Crain 2006	36/151	56/151		3.82%	0.53[0.32,0.87]
Stolz 2007	13/102	15/106		1.5%	0.89[0.4,1.97]
Schuetz 2009	103/671	130/688		11.84%	0.78[0.59,1.03]
Kristoffersen 2009	8/103	6/107		0.79%	1.42[0.47,4.24]
Long 2009	4/63	6/64		0.55%	0.66[0.18,2.44]
Long 2011	8/77	7/79		0.84%	1.19[0.41,3.47]
Tang 2013	6/132	10/133		0.88%	0.59[0.21,1.66]
Ogasawara 2014	12/48	18/48		1.24%	0.56[0.23,1.33]
Long 2014	7/90	9/90		0.89%	0.76[0.27,2.13]
Branche 2015	3/151	5/149		0.45%	0.58[0.14,2.49]
Verduri 2015	19/88	12/90		1.52%	1.79[0.81,3.95]
Corti 2016	22/62	15/58		1.55%	1.58[0.72,3.46]
Lima 2016	6/30	4/31		0.5%	1.69[0.42,6.7]
Subtotal (95% CI)	**1892**	**1913**		**27.39%**	**0.85[0.69,1.05]**
Total events: 257 (PCT-guided care), 301 (Controls)					
Heterogeneity: Tau^2=0.01; Chi^2=14.08, df=13(P=0.37); I^2=7.65%					
Test for overall effect: Z=1.53(P=0.13)					
1.2.3 Intensive care unit trials					
Nobre 2008	9/39	9/40		0.86%	1.03[0.36,2.96]
Hochreiter 2009	15/57	14/53		1.32%	0.99[0.43,2.32]
Stolz 2009	8/51	12/50		0.96%	0.59[0.22,1.59]
Schroeder 2009	3/14	3/13		0.29%	0.91[0.15,5.58]
Bouadma 2010	85/307	80/314		7.51%	1.12[0.78,1.6]
Maravić-Stojković 2011	40/102	41/103		3.04%	0.98[0.56,1.71]
Layios 2012	56/258	53/251		5.31%	1.04[0.68,1.58]
Annane 2013	7/30	10/28		0.73%	0.55[0.17,1.72]
Ding 2013	21/33	20/35		1%	1.31[0.49,3.48]
Deliberato 2013	4/42	5/39		0.49%	0.72[0.18,2.88]
Oliveira 2013	19/49	16/45		1.36%	1.15[0.5,2.65]
Shehabi 2014	36/196	38/198		3.72%	0.95[0.57,1.57]
Najafi 2015	5/30	4/30		0.47%	1.3[0.31,5.4]
Wang 2016	2/96	5/95		0.34%	0.38[0.07,2.02]
De Jong 2016	187/761	219/785		18.48%	0.84[0.67,1.06]
Bloos 2016	140/552	149/537		13.15%	0.88[0.68,1.16]
Subtotal (95% CI)	**2617**	**2616**		**59.03%**	**0.92[0.81,1.05]**
Total events: 637 (PCT-guided care), 678 (Controls)					
Heterogeneity: Tau^2=0; Chi^2=6.02, df=15(P=0.98); I^2=0%					





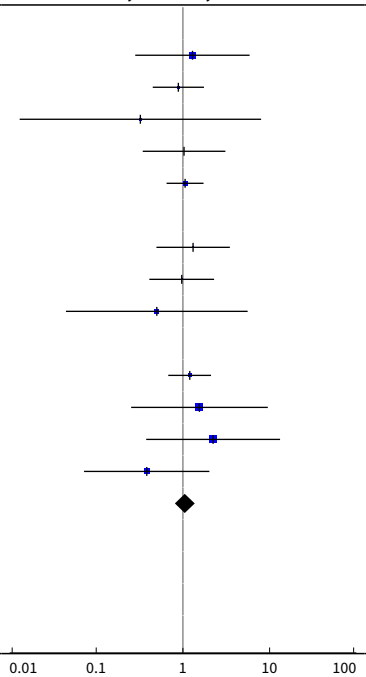
Comparison 2. Procalcitonin algorithm versus no procalcitonin algorithm, sensitivity analyses

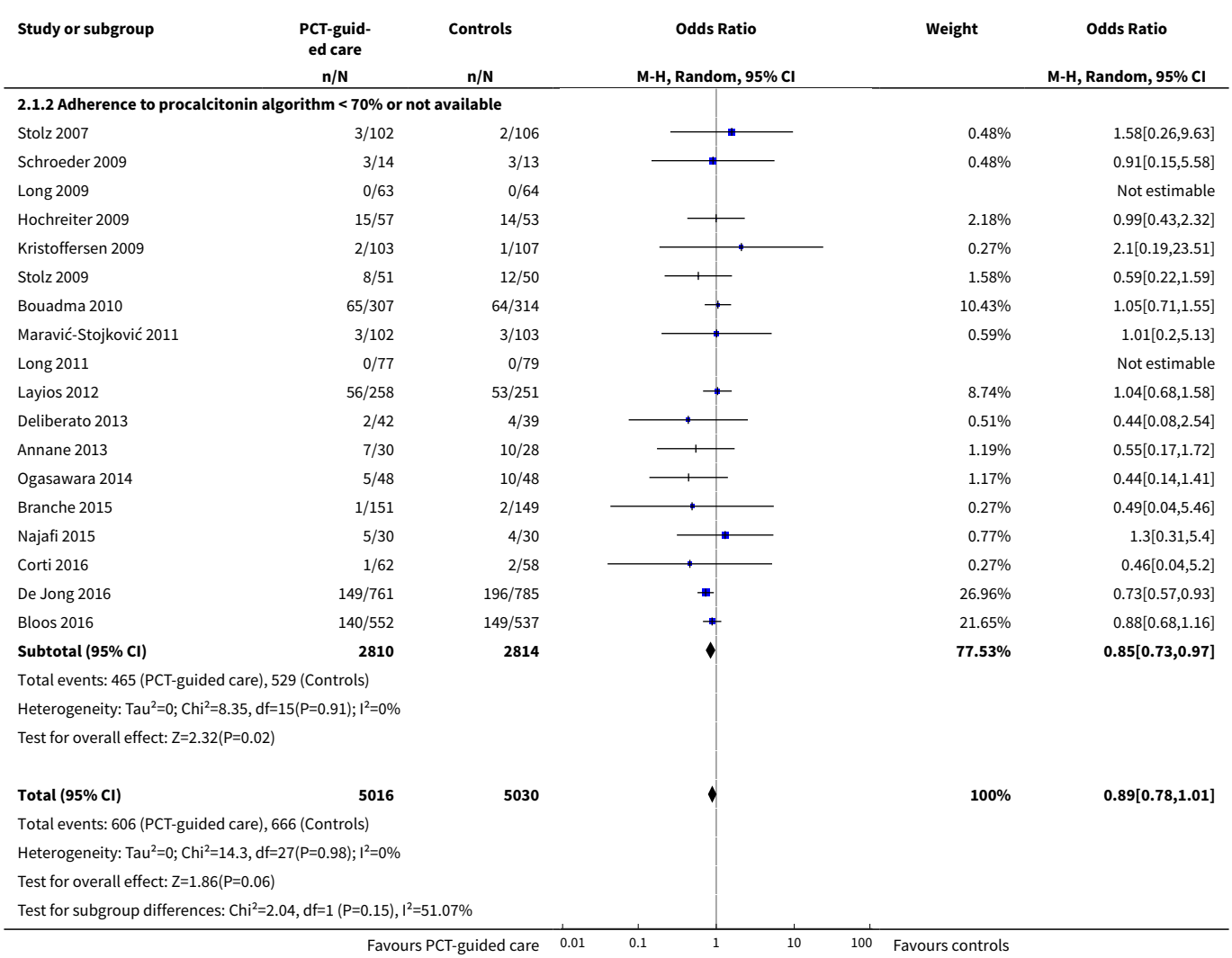
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at 30 days stratified by adherence	32	10046	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.78, 1.01]
1.1 Adherence to procalcitonin algorithm > 70%	14	4422	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.81, 1.37]
1.2 Adherence to procalcitonin algorithm < 70% or not available	18	5624	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.73, 0.97]
2 Treatment failure at 30 days stratified by adherence	32	10046	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.81, 0.99]
2.1 Adherence to procalcitonin algorithm > 70%	14	4422	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.75, 1.02]
2.2 Adherence to procalcitonin algorithm < 70% or not available	18	5624	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.81, 1.04]
3 Mortality at 30 days stratified by allocation concealment	32	10046	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.78, 1.01]
3.1 Trials with concealed allocation	22	7968	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.01]
3.2 Trials without concealed allocation	10	2078	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.70, 1.28]
4 Treatment failure at 30 days stratified by allocation concealment	32	10046	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.81, 0.99]
4.1 Trials with concealed allocation	22	7968	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.02]
4.2 Trials without concealed allocation	10	2078	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.64, 1.04]
5 Mortality at 30 days stratified by blinded outcome assessment	32	10046	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.78, 1.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Trials with blinded outcome assessment	9	4664	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.84, 1.32]
5.2 Trials without blinded outcome assessment	23	5382	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.70, 0.95]
6 Treatment failure at 30 days stratified by blinded outcome assessment	32	10046	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.81, 0.99]
6.1 Trials with blinded outcome assessment	9	4664	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.79, 1.06]
6.2 Trials without blinded outcome assessment	23	5382	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.77, 1.01]
7 Mortality at 30 days stratified by follow up	32	10046	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.78, 1.00]
7.1 Trials with 1 month follow up for mortality	18	7337	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.74, 0.98]
7.2 Trials with different follow up for mortality	14	2709	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.30]

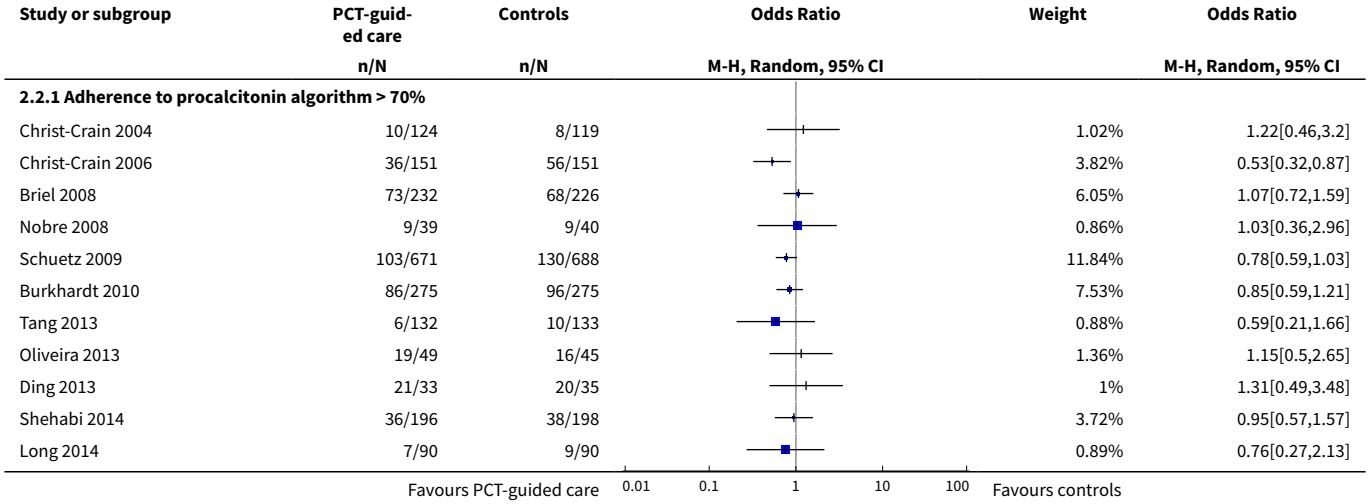
Analysis 2.1. Comparison 2 Procalcitonin algorithm versus no procalcitonin algorithm, sensitivity analyses, Outcome 1 Mortality at 30 days stratified by adherence.

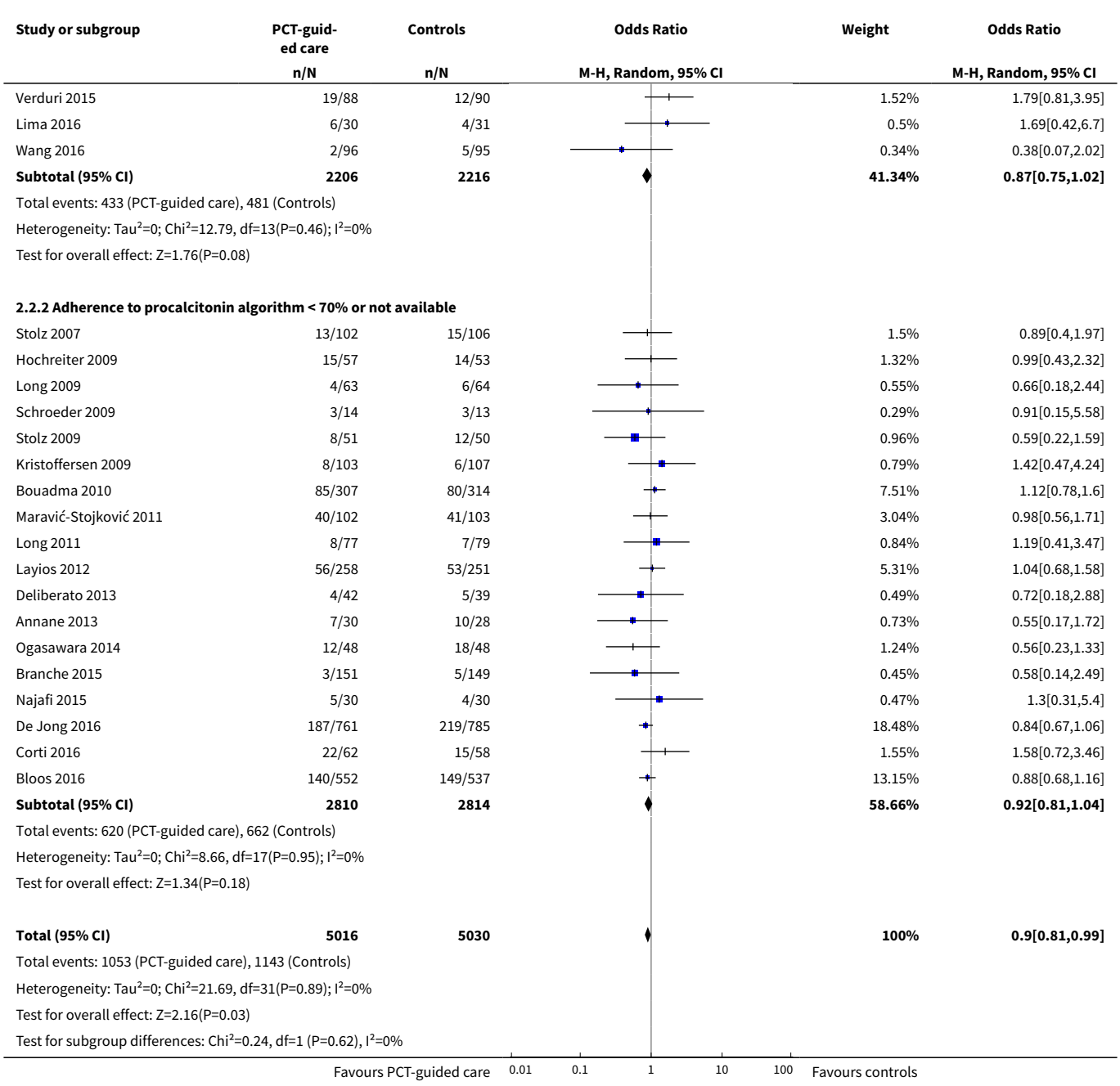
Study or subgroup	PCT-guided care n/N	Controls n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
2.1.1 Adherence to procalcitonin algorithm > 70%					
Christ-Crain 2004	4/124	3/119		0.68%	1.29[0.28,5.88]
Christ-Crain 2006	18/151	20/151		3.38%	0.89[0.45,1.75]
Briel 2008	0/232	1/226		0.15%	0.32[0.01,7.98]
Nobre 2008	8/39	8/40		1.3%	1.03[0.34,3.09]
Schuetz 2009	34/671	33/688		6.5%	1.06[0.65,1.73]
Burkhardt 2010	0/275	0/275			Not estimable
Ding 2013	21/33	20/35		1.65%	1.31[0.49,3.48]
Oliveira 2013	16/49	15/45		2.12%	0.97[0.41,2.29]
Tang 2013	1/132	2/133		0.27%	0.5[0.04,5.58]
Long 2014	0/90	0/90			Not estimable
Shehabi 2014	30/196	26/198		4.88%	1.2[0.68,2.11]
Verduri 2015	3/88	2/90		0.48%	1.55[0.25,9.53]
Lima 2016	4/30	2/31		0.5%	2.23[0.38,13.2]
Wang 2016	2/96	5/95		0.57%	0.38[0.07,2.02]
Subtotal (95% CI)	**2206**	**2216**		**22.47%**	**1.05[0.81,1.37]**
Total events: 141 (PCT-guided care), 137 (Controls)					
Heterogeneity: Tau^2=0; Chi^2=3.91, df=11(P=0.97); I^2=0%					
Test for overall effect: Z=0.38(P=0.71)					



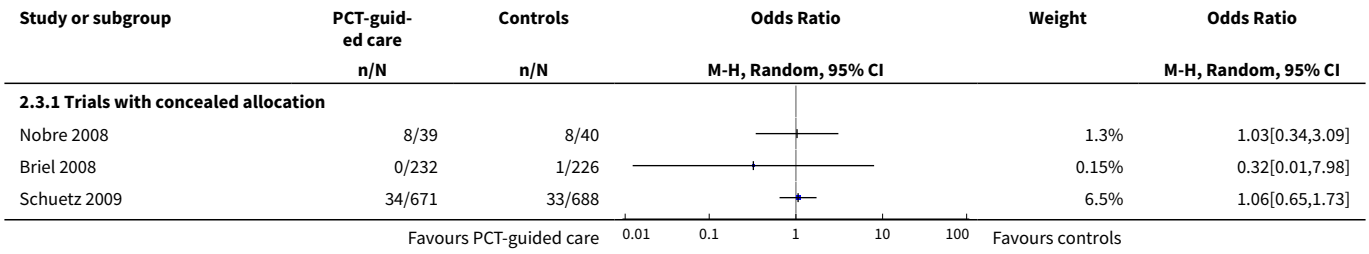


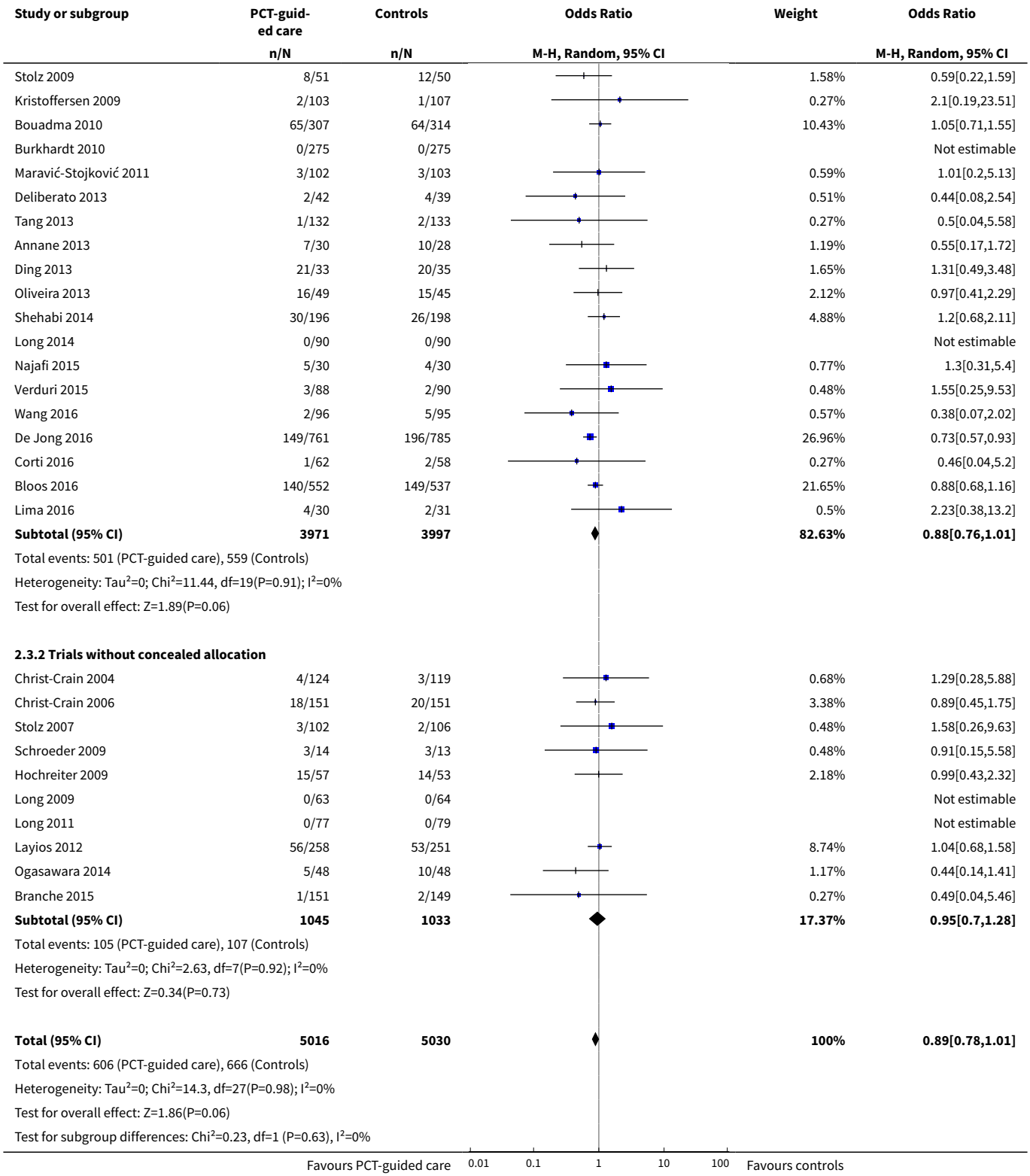
Analysis 2.2. Comparison 2 Procalcitonin algorithm versus no procalcitonin algorithm, sensitivity analyses, Outcome 2 Treatment failure at 30 days stratified by adherence.





Analysis 2.3. Comparison 2 Procalcitonin algorithm versus no procalcitonin algorithm, sensitivity analyses, Outcome 3 Mortality at 30 days stratified by allocation concealment.

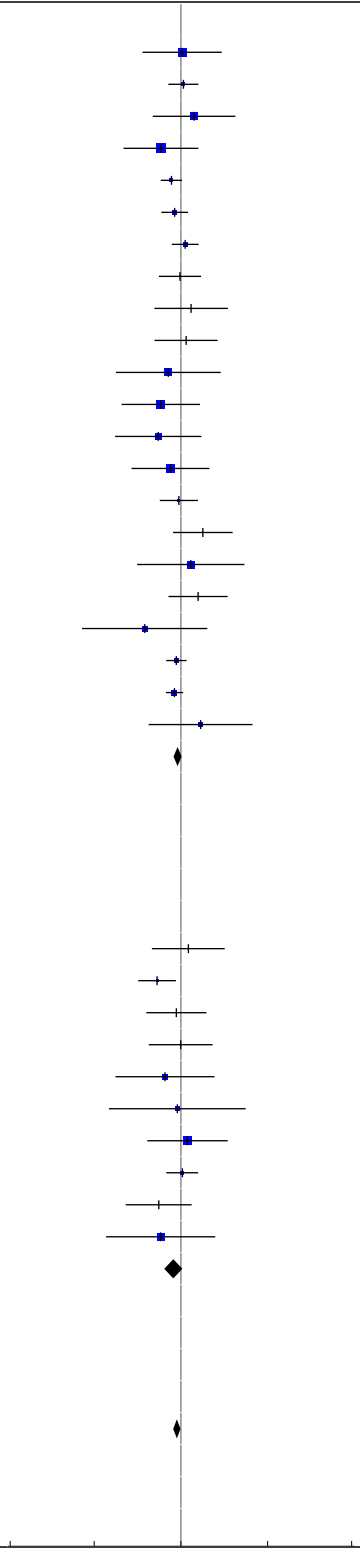




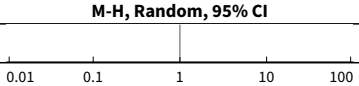
Study or subgroup	PCT-guided care n/N	Controls n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Stolz 2009	8/51	12/50		1.58%	0.59[0.22,1.59]
Kristoffersen 2009	2/103	1/107		0.27%	2.1[0.19,23.51]
Bouadma 2010	65/307	64/314		10.43%	1.05[0.71,1.55]
Burkhardt 2010	0/275	0/275			Not estimable
Maravić-Stojković 2011	3/102	3/103		0.59%	1.01[0.2,5.13]
Deliberato 2013	2/42	4/39		0.51%	0.44[0.08,2.54]
Tang 2013	1/132	2/133		0.27%	0.5[0.04,5.58]
Annane 2013	7/30	10/28		1.19%	0.55[0.17,1.72]
Ding 2013	21/33	20/35		1.65%	1.31[0.49,3.48]
Oliveira 2013	16/49	15/45		2.12%	0.97[0.41,2.29]
Shehabi 2014	30/196	26/198		4.88%	1.2[0.68,2.11]
Long 2014	0/90	0/90			Not estimable
Najafi 2015	5/30	4/30		0.77%	1.3[0.31,5.4]
Verduri 2015	3/88	2/90		0.48%	1.55[0.25,9.53]
Wang 2016	2/96	5/95		0.57%	0.38[0.07,2.02]
De Jong 2016	149/761	196/785		26.96%	0.73[0.57,0.93]
Corti 2016	1/62	2/58		0.27%	0.46[0.04,5.2]
Bloos 2016	140/552	149/537		21.65%	0.88[0.68,1.16]
Lima 2016	4/30	2/31		0.5%	2.23[0.38,13.2]
Subtotal (95% CI)	**3971**	**3997**		**82.63%**	**0.88[0.76,1.01]**
Total events: 501 (PCT-guided care), 559 (Controls)					
Heterogeneity: Tau²=0; Chi²=11.44, df=19(P=0.91); I²=0%					
Test for overall effect: Z=1.89(P=0.06)					
2.3.2 Trials without concealed allocation					
Christ-Crain 2004	4/124	3/119		0.68%	1.29[0.28,5.88]
Christ-Crain 2006	18/151	20/151		3.38%	0.89[0.45,1.75]
Stolz 2007	3/102	2/106		0.48%	1.58[0.26,9.63]
Schroeder 2009	3/14	3/13		0.48%	0.91[0.15,5.58]
Hochreiter 2009	15/57	14/53		2.18%	0.99[0.43,2.32]
Long 2009	0/63	0/64			Not estimable
Long 2011	0/77	0/79			Not estimable
Layios 2012	56/258	53/251		8.74%	1.04[0.68,1.58]
Ogasawara 2014	5/48	10/48		1.17%	0.44[0.14,1.41]
Branche 2015	1/151	2/149		0.27%	0.49[0.04,5.46]
Subtotal (95% CI)	**1045**	**1033**		**17.37%**	**0.95[0.7,1.28]**
Total events: 105 (PCT-guided care), 107 (Controls)					
Heterogeneity: Tau²=0; Chi²=2.63, df=7(P=0.92); I²=0%					
Test for overall effect: Z=0.34(P=0.73)					
Total (95% CI)	**5016**	**5030**		**100%**	**0.89[0.78,1.01]**
Total events: 606 (PCT-guided care), 666 (Controls)					
Heterogeneity: Tau²=0; Chi²=14.3, df=27(P=0.98); I²=0%					
Test for overall effect: Z=1.86(P=0.06)					
Test for subgroup differences: Chi²=0.23, df=1 (P=0.63), I²=0%					

Analysis 2.4. Comparison 2 Procalcitonin algorithm versus no procalcitonin algorithm, sensitivity analyses, Outcome 4 Treatment failure at 30 days stratified by allocation concealment.

Study or subgroup	PCT-guided care n/N	Controls n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
2.4.1 Trials with concealed allocation					
Nobre 2008	9/39	9/40		0.86%	1.03[0.36,2.96]
Briel 2008	73/232	68/226		6.05%	1.07[0.72,1.59]
Kristoffersen 2009	8/103	6/107		0.79%	1.42[0.47,4.24]
Stolz 2009	8/51	12/50		0.96%	0.59[0.22,1.59]
Schuetz 2009	103/671	130/688		11.84%	0.78[0.59,1.03]
Burkhardt 2010	86/275	96/275		7.53%	0.85[0.59,1.21]
Bouadma 2010	85/307	80/314		7.51%	1.12[0.78,1.6]
Maravić-Stojković 2011	40/102	41/103		3.04%	0.98[0.56,1.71]
Ding 2013	21/33	20/35		1%	1.31[0.49,3.48]
Oliveira 2013	19/49	16/45		1.36%	1.15[0.5,2.65]
Deliberato 2013	4/42	5/39		0.49%	0.72[0.18,2.88]
Tang 2013	6/132	10/133		0.88%	0.59[0.21,1.66]
Annane 2013	7/30	10/28		0.73%	0.55[0.17,1.72]
Long 2014	7/90	9/90		0.89%	0.76[0.27,2.13]
Shehabi 2014	36/196	38/198		3.72%	0.95[0.57,1.57]
Verduri 2015	19/88	12/90		1.52%	1.79[0.81,3.95]
Najafi 2015	5/30	4/30		0.47%	1.3[0.31,5.4]
Corti 2016	22/62	15/58		1.55%	1.58[0.72,3.46]
Wang 2016	2/96	5/95		0.34%	0.38[0.07,2.02]
Bloos 2016	140/552	149/537		13.15%	0.88[0.68,1.16]
De Jong 2016	187/761	219/785		18.48%	0.84[0.67,1.06]
Lima 2016	6/30	4/31		0.5%	1.69[0.42,6.7]
Subtotal (95% CI)	**3971**	**3997**		**83.66%**	**0.91[0.82,1.02]**
Total events: 893 (PCT-guided care), 958 (Controls)					
Heterogeneity: Tau^2=0; Chi^2=14.46, df=21(P=0.85); I^2=0%					
Test for overall effect: Z=1.63(P=0.1)					
2.4.2 Trials without concealed allocation					
Christ-Crain 2004	10/124	8/119		1.02%	1.22[0.46,3.2]
Christ-Crain 2006	36/151	56/151		3.82%	0.53[0.32,0.87]
Stolz 2007	13/102	15/106		1.5%	0.89[0.4,1.97]
Hochreiter 2009	15/57	14/53		1.32%	0.99[0.43,2.32]
Long 2009	4/63	6/64		0.55%	0.66[0.18,2.44]
Schroeder 2009	3/14	3/13		0.29%	0.91[0.15,5.58]
Long 2011	8/77	7/79		0.84%	1.19[0.41,3.47]
Layios 2012	56/258	53/251		5.31%	1.04[0.68,1.58]
Ogasawara 2014	12/48	18/48		1.24%	0.56[0.23,1.33]
Branche 2015	3/151	5/149		0.45%	0.58[0.14,2.49]
Subtotal (95% CI)	**1045**	**1033**		**16.34%**	**0.82[0.64,1.04]**
Total events: 160 (PCT-guided care), 185 (Controls)					
Heterogeneity: Tau^2=0; Chi^2=6.52, df=9(P=0.69); I^2=0%					
Test for overall effect: Z=1.64(P=0.1)					
Total (95% CI)	**5016**	**5030**		**100%**	**0.9[0.81,0.99]**
Total events: 1053 (PCT-guided care), 1143 (Controls)					
Heterogeneity: Tau^2=0; Chi^2=21.69, df=31(P=0.89); I^2=0%					
Test for overall effect: Z=2.16(P=0.03)					



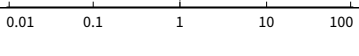
Study or subgroup	PCT-guided care n/N	Controls n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=0.71, df=1 (P=0.4), I²=0%					



Favours PCT-guided care | Favours controls

Analysis 2.5. Comparison 2 Procalcitonin algorithm versus no procalcitonin algorithm, sensitivity analyses, Outcome 5 Mortality at 30 days stratified by blinded outcome assessment.

Study or subgroup	PCT-guided care n/N	Controls n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.5.1 Trials with blinded outcome assessment					
Stolz 2007	3/102	2/106		0.36%	1.58[0.26,9.63]
Briel 2008	0/232	1/226		0.29%	0.32[0.01,7.98]
Schuetz 2009	34/671	33/688		5.88%	1.06[0.65,1.73]
Bouadma 2010	65/307	64/314		9.47%	1.05[0.71,1.55]
Burkhardt 2010	0/275	0/275			Not estimable
Layios 2012	56/258	53/251		7.99%	1.04[0.68,1.58]
Tang 2013	1/132	2/133		0.38%	0.5[0.04,5.58]
Shehabi 2014	30/196	26/198		4.16%	1.2[0.68,2.11]
Branche 2015	1/151	2/149		0.38%	0.49[0.04,5.46]
Subtotal (95% CI)	**2324**	**2340**		**28.91%**	**1.05[0.84,1.32]**
Total events: 190 (PCT-guided care), 183 (Controls)					
Heterogeneity: Tau²=0; Chi²=1.66, df=7(P=0.98); I²=0%					
Test for overall effect: Z=0.46(P=0.65)					
2.5.2 Trials without blinded outcome assessment					
Christ-Crain 2004	4/124	3/119		0.56%	1.29[0.28,5.88]
Christ-Crain 2006	18/151	20/151		3.35%	0.89[0.45,1.75]
Nobre 2008	8/39	8/40		1.19%	1.03[0.34,3.09]
Long 2009	0/63	0/64			Not estimable
Schroeder 2009	3/14	3/13		0.46%	0.91[0.15,5.58]
Stolz 2009	8/51	12/50		1.94%	0.59[0.22,1.59]
Hochreiter 2009	15/57	14/53		2.03%	0.99[0.43,2.32]
Kristoffersen 2009	2/103	1/107		0.18%	2.1[0.19,23.51]
Long 2011	0/77	0/79			Not estimable
Maravić-Stojković 2011	3/102	3/103		0.55%	1.01[0.2,5.13]
Annane 2013	7/30	10/28		1.51%	0.55[0.17,1.72]
Ding 2013	21/33	20/35		1.34%	1.31[0.49,3.48]
Oliveira 2013	16/49	15/45		2%	0.97[0.41,2.29]
Deliberato 2013	2/42	4/39		0.75%	0.44[0.08,2.54]
Ogasawara 2014	5/48	10/48		1.7%	0.44[0.14,1.41]
Long 2014	0/90	0/90			Not estimable
Najafi 2015	5/30	4/30		0.63%	1.3[0.31,5.4]
Verduri 2015	3/88	2/90		0.36%	1.55[0.25,9.53]
Lima 2016	4/30	2/31		0.32%	2.23[0.38,13.2]
Wang 2016	2/96	5/95		0.93%	0.38[0.07,2.02]
Bloos 2016	140/552	149/537		21.41%	0.88[0.68,1.16]
De Jong 2016	149/761	196/785		29.47%	0.73[0.57,0.93]
Corti 2016	1/62	2/58		0.39%	0.46[0.04,5.2]
Subtotal (95% CI)	**2692**	**2690**		**71.09%**	**0.82[0.7,0.95]**



Favours PCT-guided care | Favours controls

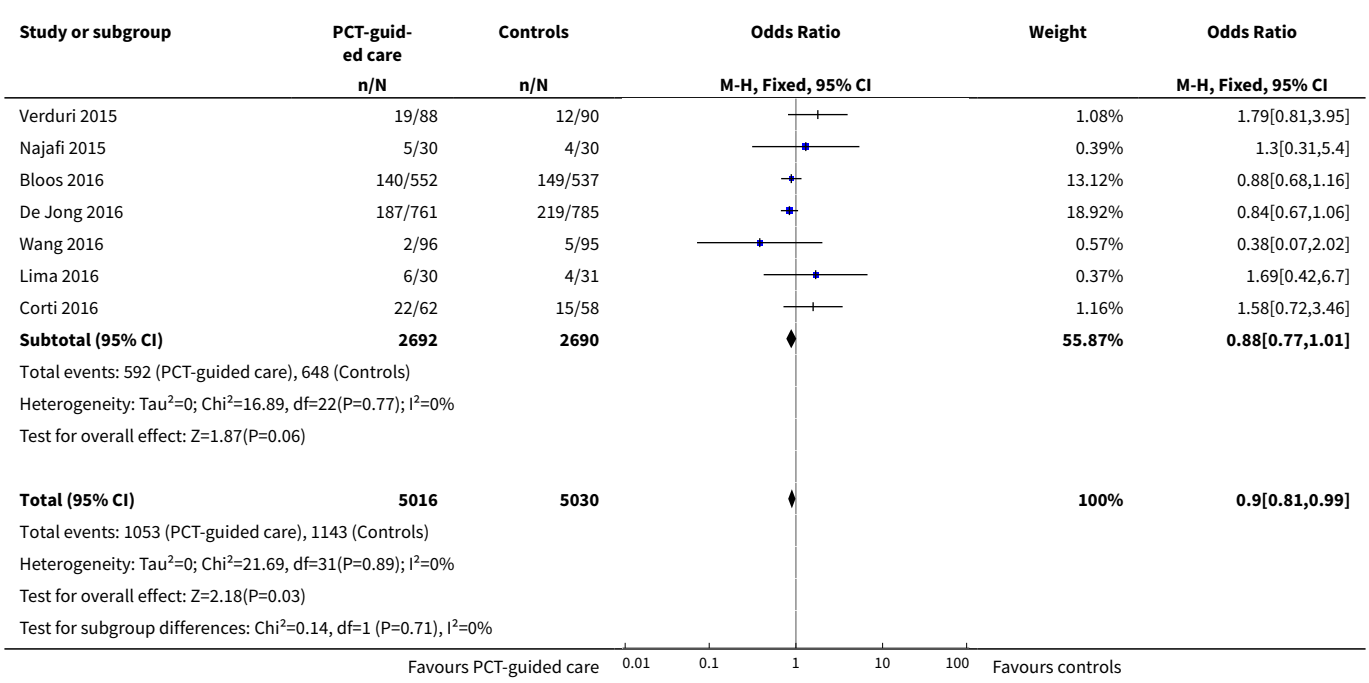
Study or subgroup	PCT-guided care n/N	Controls n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Total events: 416 (PCT-guided care), 483 (Controls)					
Heterogeneity: Tau²=0; Chi²=9.22, df=19(P=0.97); I²=0%					
Test for overall effect: Z=2.6(P=0.01)					
Total (95% CI)	**5016**	**5030**		**100%**	**0.89[0.78,1]**
Total events: 606 (PCT-guided care), 666 (Controls)					
Heterogeneity: Tau²=0; Chi²=14.3, df=27(P=0.98); I²=0%					
Test for overall effect: Z=1.89(P=0.06)					
Test for subgroup differences: Chi²=3.4, df=1 (P=0.07), I²=70.55%					

Favours PCT-guided care 0.01 0.1 1 10 100 Favours controls

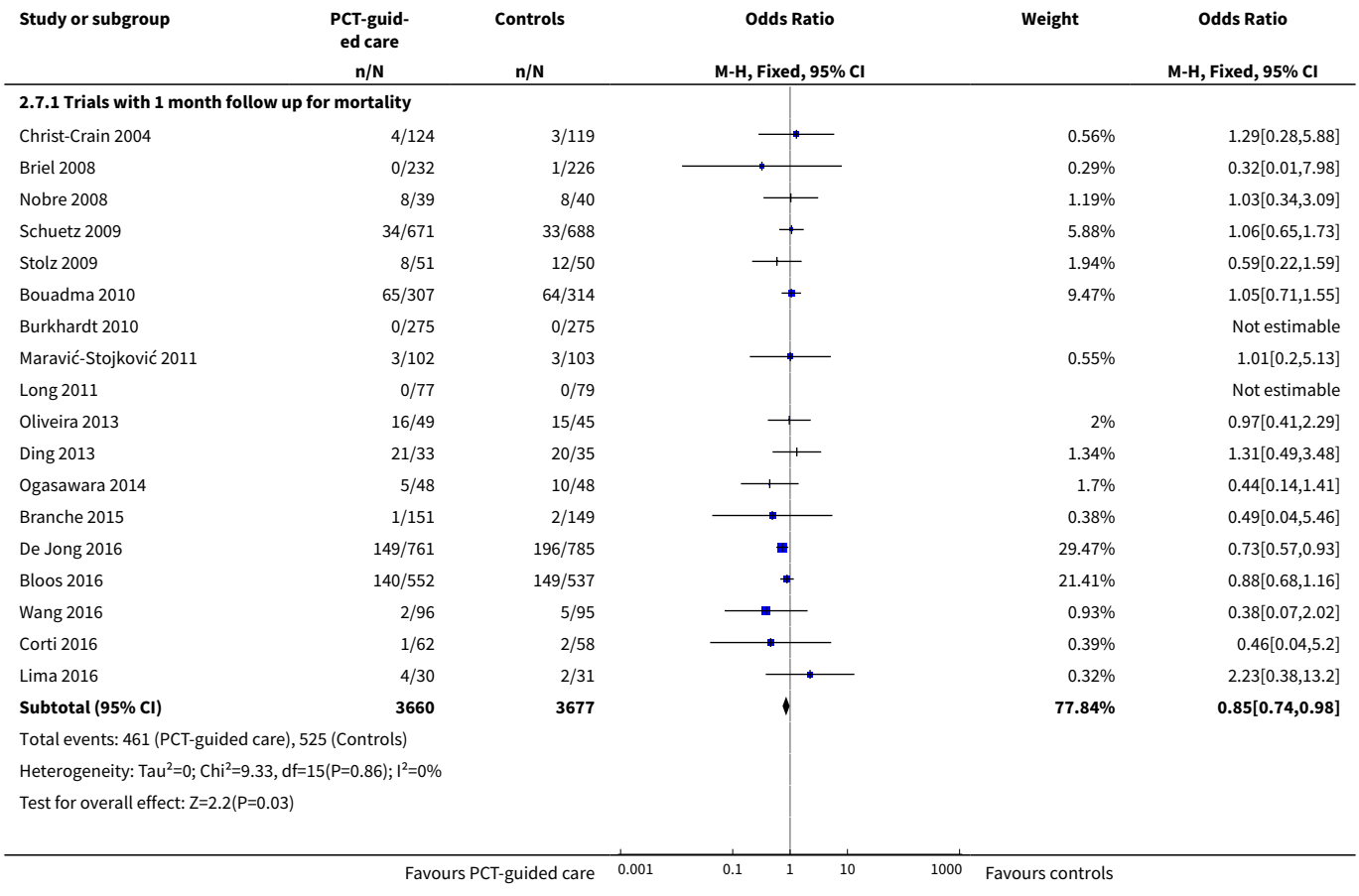
Analysis 2.6. Comparison 2 Procalcitonin algorithm versus no procalcitonin algorithm, sensitivity analyses, Outcome 6 Treatment failure at 30 days stratified by blinded outcome assessment.

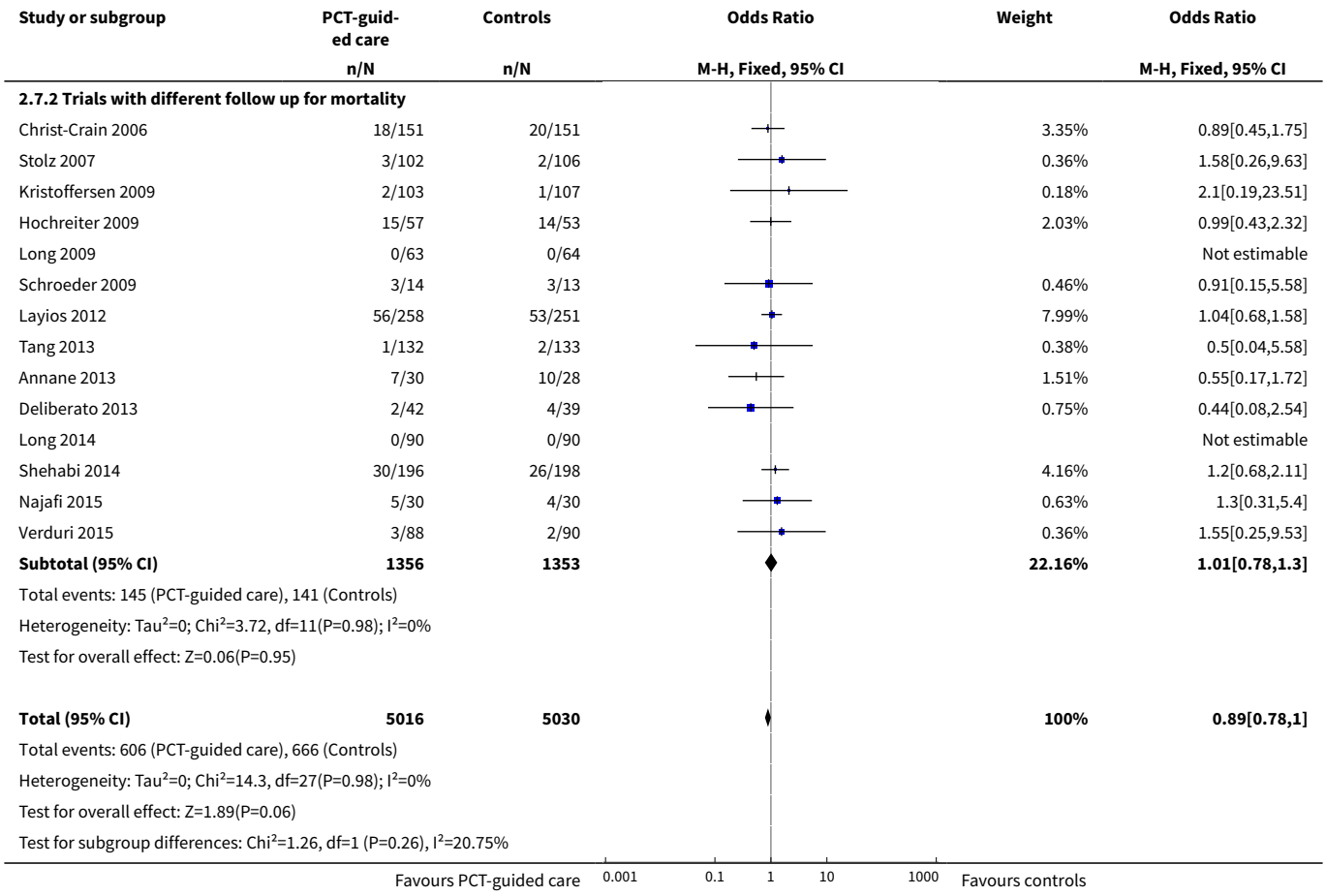
Study or subgroup	PCT-guided care n/N	Controls n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.6.1 Trials with blinded outcome assessment					
Stolz 2007	13/102	15/106		1.49%	0.89[0.4,1.97]
Briel 2008	73/232	68/226		5.49%	1.07[0.72,1.59]
Schuetz 2009	103/671	130/688		12.65%	0.78[0.59,1.03]
Burkhardt 2010	86/275	96/275		7.68%	0.85[0.59,1.21]
Bouadma 2010	85/307	80/314		6.66%	1.12[0.78,1.6]
Layios 2012	56/258	53/251		4.9%	1.04[0.68,1.58]
Tang 2013	6/132	10/133		1.11%	0.59[0.21,1.66]
Shehabi 2014	36/196	38/198		3.59%	0.95[0.57,1.57]
Branche 2015	3/151	5/149		0.57%	0.58[0.14,2.49]
Subtotal (95% CI)	**2324**	**2340**		**44.13%**	**0.92[0.79,1.06]**
Total events: 461 (PCT-guided care), 495 (Controls)					
Heterogeneity: Tau²=0; Chi²=4.66, df=8(P=0.79); I²=0%					
Test for overall effect: Z=1.17(P=0.24)					
2.6.2 Trials without blinded outcome assessment					
Christ-Crain 2004	10/124	8/119		0.87%	1.22[0.46,3.2]
Christ-Crain 2006	36/151	56/151		4.96%	0.53[0.32,0.87]
Nobre 2008	9/39	9/40		0.8%	1.03[0.36,2.96]
Hochreiter 2009	15/57	14/53		1.24%	0.99[0.43,2.32]
Schroeder 2009	3/14	3/13		0.28%	0.91[0.15,5.58]
Stolz 2009	8/51	12/50		1.19%	0.59[0.22,1.59]
Kristoffersen 2009	8/103	6/107		0.63%	1.42[0.47,4.24]
Long 2009	4/63	6/64		0.65%	0.66[0.18,2.44]
Maravić-Stojković 2011	40/102	41/103		2.89%	0.98[0.56,1.71]
Long 2011	8/77	7/79		0.72%	1.19[0.41,3.47]
Annane 2013	7/30	10/28		0.92%	0.55[0.17,1.72]
Oliveira 2013	19/49	16/45		1.19%	1.15[0.5,2.65]
Ding 2013	21/33	20/35		0.82%	1.31[0.49,3.48]
Deliberato 2013	4/42	5/39		0.55%	0.72[0.18,2.88]
Ogasawara 2014	12/48	18/48		1.57%	0.56[0.23,1.33]
Long 2014	7/90	9/90		0.97%	0.76[0.27,2.13]

Favours PCT-guided care 0.01 0.1 1 10 100 Favours controls



Analysis 2.7. Comparison 2 Procalcitonin algorithm versus no procalcitonin algorithm, sensitivity analyses, Outcome 7 Mortality at 30 days stratified by follow up.





ADDITIONAL TABLES

Table 1. Characteristics of included trials

Study ID	Country	Setting, type of trial	Clinical diagnosis	Type of PCTalgorithm and PCTcut-offs used (µg/L)	N: ARI participants (study total)	Primary endpoint	Follow-up time	Reasons for exclusion of patients
Annane 2013	France	ICU, multicentre	Severe sepsis without overt source of infection and negative blood culture	Initiation and duration; R against AB: < 0.5 (< 0.25); R for AB: > 0.5 (> 5.0)	0 (62)	Participants on AB on day 5 post randomisation	Hospital stay	62 non-ARI patients (4 of them with post randomisation consent withdrawal)
Bloos 2016	Germany	ICU, multicentre	Severe sepsis or septic shock	Discontinuation at day 4, 7, and 10; R against AB: < 1.0 or > 50% drop to previous value	219 (1180)	28-day mortality	3 months	91 post randomisation exclusions (informed consent not obtainable), 870 not ARI patients
Bouadma 2010	France	ICU, multicentre	Suspected bacterial infections during ICU stay without prior AB (> 24 h)	Initiation and duration; R against AB: < 0.5 (< 0.25); R for AB: > 0.5 (> 1.0)	394 (630)	All-cause mortality	2 months	9 post randomisation exclusions (8 withdrew consent, 1 randomised twice); 227 non-ARI patients
Branche 2015	USA	ED, medical ward, single centre	Lower ARI	Initiation and duration; R against AB: < 0.25 (< 0.1); R for AB: > 0.25 (> 0.5)	265 (300)	Antibiotic exposure and safety	3 months	35 non-ARI patients
Briel 2008	Switzerland	Primary care, multicentre	Upper and lower ARI	Initiation and duration; R against AB: < 0.25 (< 0.1); R for AB: > 0.25 (> 0.5)	458 (458)	Days with restricted activities	1 month	No exclusions
Burkhardt 2010	Germany	Primary care, multicentre	Upper and lower ARI	Initiation; R against AB: < 0.25; R for AB: > 0.25	550 (571)	Days with restricted activities	1 month	21 post randomisation exclusions (2 withdrew consent, 1 due to loss of sample, 15 with autoimmune, inflammatory, or systemic disease, 2 with advanced liver disease, 1 with prior use of antibiotics)

Table 1. Characteristics of included trials *(Continued)*

Christ-Crain 2004	Switzerland	ED, single centre	Lower ARI with X-ray confirmation	Initiation; R against AB: < 0.25 (< 0.1); R for AB: > 0.25 (> 0.5)	219 (243)	AB use	2 weeks	24 non-ARI patients
Christ-Crain 2006	Switzerland	ED, medical ward, single centre	CAP with X-ray confirmation	Initiation and duration; R against AB: < 0.25 (< 0.1); R for AB: > 0.25 (> 0.5)	286 (302)	AB use	6 weeks	16 non-ARI patients
Corti 2016	Denmark	ED, single centre	AECOPD	Initiation and duration; R against AB < 0.25 (0.15)/80% decrease; R for AB > 0.25	120 (120)	AB use	28 days	No exclusions
De Jong 2016	Netherlands	ICU, multicentre	Critically ill patients with presumed infection	Duration; R against AB: < 0.5 or > 80% drop	994 (1575)	AB use	1 year	29 post randomisation exclusions (25 protocol violations, 4 withdrew informed consent), 552 non-ARI patients
Deliberato 2013	Brazil	ICU, single centre	Septic patients with proven bacterial infection	Duration; R against AB: < 0.5 or > 90% drop	66 (81)	AB use	ICU discharge or 14 days' post randomisation	15 non-ARI patients
Ding 2013	China	ICU, single centre	Acute exacerbation of pulmonary fibrosis	Initiation and duration; R against AB: < 0.25; R for AB: > 0.25	0 (78)	AB use	1 month	10 post randomisation exclusions (7 lost to follow-up, 3 withdrew informed consent), 68 data not shared
Hochreiter 2009	Germany	Surgical ICU, single centre	Suspected bacterial infections and > 1 SIRS criteria	Duration; R against AB: < 1 or > 65% drop over 3 d	43 (110)	AB use	Hospital stay	67 non-ARI patients
Kristoffersen 2009	Denmark	ED, medical ward, multicentre	Lower ARI without X-ray confirmation	Initiation and duration; R against AB: < 0.25; R for AB: > 0.25 (> 0.5)	210 (223)	AB use	Hospital stay	13 post randomisation exclusions (3 no PCT testing, 6 not meeting inclusion criteria, 4 withdrew informed consent)

Table 1. Characteristics of included trials *(Continued)*

Layios 2012	Belgium	ICU, single centre	Suspected infection	Initiation; R against AB: < 0.5 (< 0.25); R for AB: > 0.5 (> 1.0)	160 (509)	AB use	1 month	120 no PCT measurements, 10 missing data, 219 non-ARI patients
Lima 2016	Brazil	ED, medical ward, single centre	Febrile neutropenia	Duration; R against AB: < 0.5 for 2 days or > 90% drop than highest measured concentration	0 (62)	AB use	28 days	1 post randomisation exclusion (withdrew informed consent), 62 non-ARI patients
Long 2009	China	ED, outpatients, single centre	CAP with X-ray confirmation	Initiation and duration; R against AB: < 0.25; R for AB: > 0.25	127 (149)	AB use	1 month	22 post randomisation exclusions due to withdrawal of consent
Long 2011	China	ED, outpatients, single centre	CAP with X-ray confirmation	Initiation and duration; R against AB: < 0.25; R for AB: > 0.25	156 (172)	AB use	1 month	16 post randomisation exclusions (6 lost to follow-up, 7 withdrew consent, 3 with final diagnosis other than CAP)
Long 2014	China	ED, single centre	Severe acute exacerbation of asthma	Initiation; R against AB: < 0.25 (< 0.1); R for AB: > 0.25	180 (180)	AB use	1 year	No exclusions
Maravić-Stojković 2011	Serbia	ICU surgical, single centre	Infection after open heart surgery	Initiation; R for AB: > 0.5	5 (205)	AB use, AB cost	Hospital stay	200 non-ARI patients
Najafi 2015	Iran	ICU, single centre	SIRS without apparent source of infection	Initiation; R for AB: > 2	0 (60)	AB use	Hospital stay	60 patient data not shared
Nobre 2008	Switzerland	ICU, single centre	Suspected severe sepsis or septic shock	Duration; R against AB: < 0.5 (< 0.25) or > 80% drop; R for AB: > 0.5 (> 1.0)	52 (79)	AB use	1 month	27 non-ARI patients
Ogasawara 2014	Japan	Medical ward, single centre	Aspiration pneumonia	Predefined duration; AB for 3 d: < 0.5; AB for 5 d: 0.5 to 1.0; AB for 7 d: > 1	0 (105)	Relapse and 30-day mortality	1 month	9 post randomisation exclusions (2 withdrew consent, 7 others), 96 data not shared
Oliveira 2013	Brazil	ICU, multicentre	Severe sepsis or septic shock	Discontinuation; initial < 1.0: R against AB: 0.1 at day 4; ini-	58 (97)	AB use	28 days or hospital discharge	3 post randomisation exclusions (2 withdrew consent, 1 technical prob-

Table 1. Characteristics of included trials *(Continued)*

				tial > 1.0: R against: > 90% drop				lems), 36 patients with a final diagnosis other than ARI
Schroeder 2009	Germany	Surgical ICU, single centre	Severe sepsis following abdominal surgery	Duration; R against AB: < 1 or > 65% drop over 3 d	8 (27)	AB use	Hospital stay	19 non-ARI patients
Schuetz 2009	Switzerland	ED, medical ward, multicentre	Lower ARI with X-ray confirmation	Initiation and duration; R against AB: < 0.25 (< 0.1); R for AB: > 0.25 (> 0.5)	1304 (1381)	AB use	1 month	22 post randomisation exclusions due to withdrawal of consent, 55 non-ARI patients
Shehabi 2014	Australia	ICU, multicentre	Suspected sepsis, undifferentiated infections	Duration; R against AB: < 0.25 (< 0.1) or > 90% drop	156 (400)	AB use	3 months	6 post randomisation exclusions (6 withdrew consent), 238 non-ARI patients
Stolz 2007	Switzerland	ED, medical ward, single centre	Exacerbated COPD	Initiation and duration; R against AB: < 0.25 (< 0.1); R for AB: > 0.25 (> 0.5)	208 (226)	AB use	2 to 3 weeks	18 post randomisation exclusions (absence of COPD)
Stolz 2009	Switzerland, USA	ICU, multicentre	VAP when intubated > 48 h	Duration; R against AB: < 0.5 (< 0.25) or > 80% drop; R for AB: > 0.5 (> 1.0)	101 (101)	AB-free days alive	1 month	No exclusions
Tang 2013	China	ED, single centre	Exacerbation of asthma	Initiation and duration; R against AB: < 0.25 (< 0.1); R for AB: > 0.25	0 (265)	AB use	6 weeks	10 post randomisation exclusions (5 lost to follow-up, 3 died, 2 withdrew consent), 255 data not shared
Verduri 2015	Italy	ED, medical ward, multicentre	AECOPD	Initiation; R against AB:< 0.1; R for AB: > 0.25	178 (183)	Number of exacerbations	6 months	5 post randomisation exclusions (5 lost to follow-up because they did not meet the inclusion criteria)
Wang 2016	China	ICU, single centre	AECOPD	All participants had initial PCT < 0.1; AB group treated with AB for at least 3 days, control group no AB in the first 10 days	191 (194)	Treatment success within 10 days	30 days	3 post randomisation exclusions (3 with pneumonia according to CT scan)

AB: antibiotic
AECOPD: acute exacerbation of chronic obstructive pulmonary disease
ARI: acute respiratory infection
CAP: community-acquired pneumonia
COPD: chronic obstructive pulmonary disease
CT: computed tomography
d: days
ED: emergency department
h: hours
ICU: intensive care unit
PCT: procalcitonin
R: recommendation for or against antibiotics
SIRS: systemic inflammatory response syndrome
VAP: ventilator-associated pneumonia

Table 2. Baseline characteristics of included participants

Parameter	Control (n = 3372)	PCT group (n = 3336)
Demographics		
Age (year), mean (SD)	61.2 ± 18.4	60.7 ± 18.8
Male gender, n (%)	1910 (56.6%)	1898 (56.9%)
Clinical setting, no (%)		
Primary care	501 (14.9%)	507 (15.2%)
Emergency department	1638 (48.6%)	1615 (48.4%)
Intensive care unit	1233 (36.6%)	1214 (36.4%)
Primary diagnosis		
Total upper ARI, n (%)	280 (8.3%)	292 (8.8%)
Common cold	156 (4.6%)	149 (4.5%)
Rhino-sinusitis, otitis	67 (2.0%)	73 (2.2%)
Pharyngitis, tonsillitis	46 (1.4%)	61 (1.8%)
Total lower ARI, n (%)	3092 (91.7%)	3044 (91.2%)
Community-acquired pneumonia	1468 (43.5%)	1442 (43.2%)
Hospital-acquired pneumonia	262 (7.8%)	243 (7.3%)
Ventilator-associated pneumonia	186 (5.5%)	194 (5.8%)
Acute bronchitis	287 (8.5%)	257 (7.7%)
Exacerbation of COPD	631 (18.7%)	621 (18.6%)
Exacerbation of asthma	127 (3.8%)	143 (4.3%)
Other lower ARI	131 (3.9%)	144 (4.3%)
Procalcitonin upon enrolment		
PCT< 0.1 ug/L	921 (35.6%)	981 (30.9%)
PCT 0.1 to 0.25 ug/L	521 (20.1%)	608 (19.2%)
PCT > 0.25 to 0.5 ug/L	308 (11.9%)	383 (12.1%)
PCT > 0.5 to 2.0 ug/L	358 (13.8%)	520 (16.4%)
PCT > 2.0 ug/L	482 (18.6%)	679 (21.4%)

ARI: acute respiratory infection

COPD: chronic obstructive pulmonary disease
PCT: procalcitonin
SD: standard deviation

Table 3. Quality assessment of trials

Study ID	Allocation concealment	Blinded outcome assessment	Follow-up for mortality	Adherence to PCT algorithm in PCT group	Follow-up for mortality
Annane 2013	Yes (central randomisation)	No	58/58 (100%)	63% adherence	LOS
Bloos 2016	Yes (central randomisation)	No	1045/1089 (96%)	49.6% adherence	28 days and 90 days
Bouadma 2010	Yes (central randomisation)	Yes	393/394 (100%)	47% adherence	28 days and 60 days
Branche 2015	Yes (central randomisation using blocks of 4)	No	250/300 (83.3%)	64% adherence	1 month and 3 months
Briel 2008	Yes (central randomisation)	Yes	454/458 (99%)	85% adherence	28 days
Burkhardt 2010	Yes (central randomisation)	Yes	546/550 (99%)	87% adherence	28 days
Christ-Crain 2004	No (alternating weeks)	No	230/243 (95%)	83% adherence	10 to 14 days
Christ-Crain 2006	Yes (sequentially numbered, opaque, sealed envelopes)	No	300/302 (99%)	87% adherence	56 days
Corti 2016	Yes (randomisation algorithm was concealed to treating clinicians and participants)	No	120/120 (100%)	61.1% adherence	28 days
De Jong 2016	Yes (central randomisation)	No	1546/1546 (100%)	44% adherence	28 days and 1 year
Deliberato 2013	Yes (opaque, sealed envelopes)	No	81/81 (100%)	52% adherence	LOS
Ding 2013	Yes (central randomisation)	No	68/78 (87.2%)	Not reported	30 days
Hochreiter 2009	No (unconcealed drawing of lots)	No	43/43 (100% until discharge)	Not reported	LOS
Kristoffersen 2009	Yes (central randomisation)	No	210/210 (100% until discharge)	59% adherence	LOS
Layios 2012	Not reported	No	509/509 (100%)	Not reported	Intensive care unit LOS
Lima 2016	Yes (sequentially numbered, opaque, sealed envelopes)	No	61/62 (98.4%)	73.3% adherence	28 days and 90 days
Long 2009	No (odd and even patient ID numbers)	No	127/127 (100%)	Not reported	Not reported

Table 3. Quality assessment of trials *(Continued)*

Long 2011	No (odd and even patient ID numbers)	No	156/156 (100%)	Not reported	28 days
Long 2014	Yes (central randomisation)	No	169/180 (93.9%)	96.6% adherence	LOS and 1 year
Maravić-Stojković 2011	Yes (central randomisation)	No	205/205 (100%)	Not reported	30 days and LOS
Najafi 2015	Yes (central randomisation)	No	30/30 (100%)	Not reported	LOS
Nobre 2008	Yes (sequentially numbered, opaque, sealed envelopes)	No	52/52 (100%)	81% adherence	28 days and LOS
Ogasawara 2014	Not reported	No	96/96 (100%)	Not reported	30 days
Oliveira 2013	Yes (central randomisation)	No	94/94 (100%)	86.2% adherence	28 days
Schroeder 2009	No (unconcealed drawing of lots)	No	8/8 (100% until discharge)	Not reported	LOS
Schuetz 2009	Yes (central randomisation)	Yes	1358/1359 (100%)	91% adherence	28 days
Shehabi 2014	Yes (central randomisation)	Yes	394/394 (100%)	Not reported	LOS and 90 days
Stolz 2007	Yes (sequentially numbered, opaque, sealed envelopes)	Yes	208/208 (100%)	Not reported	6 months
Stolz 2009	Yes (sequentially numbered, opaque, sealed envelopes)	No	101/101 (100%)	Not reported	28 days
Tang 2013	Yes (sequentially numbered, opaque, sealed envelopes)	Yes	258/265 (97.4%)	Not reported	6 weeks
Verduri 2015	Yes (central randomisation)	No	178/178 (100%)	Not reported	6 months
Wang 2016	Yes (those responsible for allocation concealment were not involved in the measurement of results)	No	191/191 (100%)	82.3% adherence (17 participants in the control group received AB)	30 days

LOS: length of stay
PCT: procalcitonin

Table 4. Clinical endpoints overall and stratified by setting and ARI diagnosis

	Control group	PCT group	Measures of effect: adjusted OR or difference (95% CI), P value	P for interaction
Overall	3372	3336		
30 days mortality, n (%)	336 (10.0%)	286 (8.6%)	0.83 (0.70 to 0.99), P = 0.037	NA

Table 4. Clinical endpoints overall and stratified by setting and ARI diagnosis *(Continued)*

Treatment failure, n (%)	841 (24.9%)	768 (23.0%)	0.90 (0.80 to 1.01), P = 0.068	NA
Length of ICU stay, mean (±SD)	13.3 ± 16.0	13.7 ± 17.2	0.39 (-0.81 to 1.58), P = 0.524	NA
Length of hospital stay, mean (±SD)	13.7 ± 20.6	13.4 ± 18.4	-0.19 (-0.96 to 0.58), P = 0.626	NA
Antibiotic-related side effects, n (%)	336 (22.1%)	247 (16.3%)	0.68 (0.57 to 0.82), P < 0.001	NA
According to setting				
Primary care	501	507		
30 days mortality, n (%)	1 (0.2%)	0 (0.0%)	NA	NA
Treatment failure, n (%)	164 (32.7%)	159 (31.4%)	0.96 (0.73 to 1.25), P = 0.751	0.715
Days with restricted activities, mean (±SD)	8.9 ± 4.2	8.9 ± 4.1	0.07 (-0.44 to 0.59), P = 0.777	NA
Antibiotic-related side effects, n (%)	128 (25.7%)	102 (20.2%)	0.65 (0.46 to 0.91), P = 0.012	0.596
Emergency department	1638	1615		
30 days mortality, n (%)	62 (3.8%)	57 (3.5%)	0.91 (0.63 to 1.33), P = 0.635	0.546
Treatment failure, n (%)	292 (17.8%)	259 (16.0%)	0.87 (0.72 to 1.05), P = 0.141	0.807
Length of hospital stay, mean (±SD)	8.2 ± 10.5	8.1 ± 7.5	-0.14 (-0.73 to 0.44), P = 0.631	0.684
Antibiotic-related side effects, n (%)	208 (20.3%)	145 (14.4%)	0.66 (0.52 to 0.83), P = 0.001	0.596
Intensive care unit	1233	1214		
30 days mortality, n (%)	273 (22.3%)	229 (19.0%)	0.84 (0.69 to 1.02), P = 0.081	0.619
Length of ICU stay, mean (±SD)	14.8 ± 16.2	15.3 ± 17.5	0.56 (-0.82 to 1.93), P = 0.427	0.849
Length of hospital stay, mean (±SD)	26.3 ± 26.9	25.8 ± 23.9	-0.33 (-2.28 to 1.62), P = 0.739	0.641
According to diagnosis				
Community-acquired pneumonia	1468	1442		
30 days mortality, n (%)	206 (14.1%)	175 (12.2%)	0.82 (0.66 to 1.03), P = 0.083	0.958
Treatment failure, n (%)	385 (26.2%)	317 (22.0%)	0.78 (0.66 to 0.93), P = 0.005	0.052
Length of ICU stay, mean (±SD)	10.5 ± 10.3	11.9 ± 13.3	1.45 (0.15 to 2.75), P = 0.029	0.119
Length of hospital stay, mean (±SD)	13.3 ± 15.7	13.9 ± 16.1	0.74 (-0.25 to 1.73), P = 0.143	0.094
Antibiotic-related side effects, n (%)	186 (27.7%)	127 (19.1%)	0.62 (0.48 to 0.80), P < 0.001	0.227
Exacerbation of COPD	631	621		
30 days mortality, n (%)	24 (3.8%)	19 (3.1%)	0.8 (0.43 to 1.48), P = 0.472	0.847

Table 4. Clinical endpoints overall and stratified by setting and ARI diagnosis *(Continued)*

Treatment failure, n (%)	110 (17.4%)	104 (16.7%)	0.94 (0.70 to 1.27), P = 0.704	0.676
Length of hospital stay, mean (±SD)	9.3 ± 13.9	8.4 ± 7.2	-0.60 (-1.84 to 0.64), P = 0.342	0.658
Antibiotic-related side effects, n (%)	30 (10.9%)	29 (10.5%)	0.93 (0.53 to 1.63), P = 0.805	0.198
Acute bronchitis	287	257		
30 days mortality, n (%)	0 (0.0%)	2 (0.8%)	NA	NA
Treatment failure, n (%)	55 (19.2%)	52 (20.2%)	1.11 (0.72 to 1.70), P = 0.643	0.4
Length of hospital stay, mean (±SD)	2.6 ± 5.7	2.2 ± 4.7	-0.21 (-0.90 to 0.48), P = 0.556	0.97
Antibiotic-related side effects, n (%)	54 (21.6%)	39 (17.3%)	0.77 (0.49 to 1.22), P = 0.263	0.657
Ventilator-associated pneumonia	186	194		
30 days mortality, n (%)	29 (15.6%)	23 (12.0%)	0.75 (0.41 to 1.39), P = 0.366	0.644
Treatment failure, n (%)	51 (27.4%)	44 (22.7%)	0.78 (0.48 to 1.28), P = 0.332	0.522
Length of ICU stay, mean (±SD)	23.5 ± 20.5	21.8 ± 19.1	-1.74 (-5.64 to 2.17), P = 0.383	0.441
Length of hospital stay, mean (±SD)	33.8 ± 27.6	32.0 ± 23.1	-2.14 (-7.04 to 2.75), P = 0.391	0.448

Measures of effect: dichotomous outcomes are reported as adjusted OR (95% CI) and continuous outcomes are adjusted mean differences and confidence intervals
ARI: acute respiratory infection
CI: confidence interval
COPD: chronic obstructive pulmonary disease
ICU: intensive care unit
NA: not applicable
OR: odds ratio
PCT: procalcitonin
SD: standard deviation

Table 5. Sensitivity analysis

Mortality				
Main analysis	**Control group**	**PCT group**	**Adjusted OR (95% CI), P value**	**P for interaction**
All participants	336 (10.0%)	286 (8.6%)	0.83 (0.70 to 0.99), P = 0.037	NA
Adherence				
High adherence	82 (4.5%)	75 (4.1%)	0.88 (0.63 to 1.22), P = 0.434	0.617
Low adherence (< 70% or not reporting)	254 (16.4%)	211 (14.0%)	0.83 (0.67 to 1.02), P = 0.073	
Allocation				

Table 5. Sensitivity analysis *(Continued)*

Low risk for allocation concealment bias	305 (10.6%)	250 (8.8%)	0.80 (0.67 to 0.97), P = 0.021	0.229
High risk for allocation concealment bias (or not reporting)	31 (6.5%)	36 (7.3%)	1.12 (0.66 to 1.91), P = 0.672	
Blinding				
Blinded outcome assessment	113 (6.5%)	102 (5.9%)	0.85 (0.64 to 1.13), P = 0.259	0.537
No blinded outcome assessment	223 (13.8%)	184 (11.5%)	0.81 (0.65 to 1.01), P = 0.062	
Follow-up				
Follow up for mortality at 1 month	275 (10.7%)	224 (8.9%)	0.81 (0.67 to 0.99), P = 0.039	0.325
Follow up for mortality < 1 month	61 (7.6%)	62 (7.6%)	0.94 (0.64 to 1.38), P = 0.756	

Treatment failure	**Control group**	**PCT group**	**Adjusted OR (95% CI), P value**	**P for interaction**
All participants	841 (24.9%)	768 (23.0%)	0.90 (0.80 to 1.01), P = 0.068	NA
Adherence				
High adherence	419 (23.1%)	381 (21.0%)	0.89 (0.76 to 1.04), P = 0.148	0.752
Low adherence (< 70% or not reporting)	422 (27.1%)	387 (25.5%)	0.92 (0.77 to 1.08), P = 0.301	
Allocation				
Low risk for allocation concealment bias	776 (26.8%)	699 (24.6%)	0.89 (0.79 to 1.01), P = 0.069	0.486
High risk for allocation concealment bias (or not reporting)	65 (13.6%)	69 (13.8%)	0.99 (0.68 to 1.44), P = 0.939	
Blinding				
Blinded outcome assessment	412 (23.5%)	367 (21.1%)	0.88 (0.75 to 1.03), P = 0.117	0.574
No blinded outcome assessment	429 (26.5%)	401 (25.1%)	0.94 (0.79 to 1.11), P = 0.438	

CI: confidence interval
NA: not applicable
OR: odds ratio
PCT: procalcitonin

Table 6. Antibiotic treatment overall and stratified by setting and ARI diagnosis

Parameter	**Control group**	**PCT group**	**Measures of effect: adjusted OR or difference (95% CI), P value**	**P for interaction**

Table 6. Antibiotic treatment overall and stratified by setting and ARI diagnosis *(Continued)*

Overall	3372	3336		
Initiation of antibiotics, n (%)	2894 (86.3%)	2351 (71.5%)	0.27 (0.24 to 0.32), P < 0.001	
Duration of antibiotics (days), mean (±SD)	9.4 ± 6.2	8.0 ± 6.5	-1.83 (-2.15 to -1.50), P < 0.001	
Total exposure of antibiotics (days), mean (±SD)	8.1 ± 6.6	5.7 ± 6.6	-2.43 (-2.71 to -2.15), P < 0.001	
Setting-specific outcomes				
Primary care	501	507		
Initiation of antibiotics, n (%)	316 (63.1%)	116 (22.9%)	0.13 (0.09 to 0.18), P < 0.001	< 0.001
Duration of antibiotics (days), mean (±SD)	7.3 ± 2.5	7.0 ± 2.8	-0.52 (-1.07 to 0.04), P = 0.068	0.064
Total exposure of antibiotics (days), mean (±SD)	4.6 ± 4.1	1.6 ± 3.2	-3.02 (-3.45 to -2.58), P < 0.001	0.101
Emergency department	1638	1615		
Initiation of antibiotics, n (%)	1354 (83.2%)	1119 (71.3%)	0.49 (0.41 to 0.58), P < 0.001	< 0.001
Duration of antibiotics (days), mean (±SD)	9.8 ± 5.4	7.3 ± 5.1	-2.45 (-2.86 to -2.05), P < 0.001	< 0.001
Total exposure of antibiotics (days), mean (±SD)	8.2 ± 6.2	5.2 ± 5.4	-3.02 (-3.41 to -2.62), P < 0.001	< 0.001
Intensive care unit	1233	1214		
Initiation of antibiotics, n (%)	1224 (99.8%)	1116 (91.9%)	0.02 (0.01 to 0.05), P < 0.001	< 0.001
Duration of antibiotics (days), mean (±SD)	9.5 ± 7.4	8.8 ± 7.8	-1.23 (-1.82 to -0.65), P < 0.001	< 0.001
Total exposure of antibiotics (days), mean (±SD)	9.5 ± 7.4	8.1 ± 7.9	-1.44 (-1.99 to -0.88), P < 0.001	< 0.001
Disease-specific outcomes				
Community-acquired pneumonia	1468	1442		
Initiation of antibiotics, n (%)	1455 (99.4%)	1340 (92.9%)	0.08 (0.04 to 0.15), P < 0.001	< 0.001
Duration of antibiotics (days), mean (±SD)	10.5 ± 6.2	8.0 ± 5.7	-2.45 (-2.87 to -2.02), P < 0.001	< 0.001
Total exposure of antibiotics (days), mean (±SD)	10.4 ± 6.2	7.5 ± 5.9	-2.94 (-3.38 to -2.50), P < 0.001	0.004
Exacerbation of COPD	631	621		
Initiation of antibiotics, n (%)	453 (71.8%)	266 (42.8%)	0.29 (0.23 to 0.36), P < 0.001	0.017

Table 6. Antibiotic treatment overall and stratified by setting and ARI diagnosis *(Continued)*

Duration of antibiotics (days), mean (±SD)	7.4 ± 5.3	7.2 ± 6.7	-1.15 (-2.00 to -0.31), P = 0.007	0.003
Total exposure of antibiotics (days), mean (±SD)	5.3 ± 5.6	3.1 ± 5.6	-2.22 (-2.83 to -1.60), P < 0.001	0.506
Acute bronchitis	287	257		
Initiation of antibiotics, n (%)	189 (65.9%)	68 (26.5%)	0.18 (0.12 to 0.26), P < 0.001	< 0.001
Duration of antibiotics (days), mean (±SD)	7.1 ± 3.0	6.4 ± 3.5	-0.35 (-1.15 to 0.45), P = 0.393	0.359
Total exposure of antibiotics (days), mean (±SD)	4.7 ± 4.2	1.7 ± 3.3	-2.95 (-3.59 to -2.31), P < 0.001	0.33
Ventilator-associated pneumonia	186	194		
Initiation of antibiotics, n (%)	186 (100.0%)	193 (99.5%)	NA	NA
Duration of antibiotics (days), mean (±SD)	13.1 ± 7.9	10.8 ± 8.7	-2.22 (-3.80 to -0.65), P = 0.006	0.253
Total exposure of antibiotics (days), mean (±SD)	13.1 ± 7.9	10.8 ± 8.7	-2.45 (-4.09 to -0.82), P = 0.003	0.786

Note: Duration refers to the total days of antibiotic therapy in participants in whom antibiotics were initiated. Total exposure refers to the total days of antibiotic therapy in all randomised participants.
Measures of effect: dichotomous outcomes are reported as adjusted OR (95% CI) and continuous outcomes are adjusted mean differences and confidence intervals
ARI: acute respiratory infection
CI: confidence interval
COPD: chronic obstructive pulmonary disease
NA: not applicable
OR: odds ratio
PCT: procalcitonin
SD: standard deviation

APPENDICES

Appendix 1. CENTRAL (Cochrane Library via Wiley) search strategy

[mh Calcitonin] OR Procalcitonin:ti,ab OR ProCT:ti,ab OR (calcitonin:ti,ab AND (precursor:ti,ab OR precursors:ti,ab))

AND

[mh "Anti-Bacterial Agents"] OR (antibiotic OR Antibiotics OR antibacterial OR anti-bacterial OR amoxicillin OR amoxycillin OR penicillin OR ampicillin OR cotrimoxazole OR chloramphenicol OR trimethoprim OR sulphamethoxazole OR "tmp smx" OR tmp-smx):ti,ab

AND

[mh Biomarkers] OR (Biomarker OR Biomarkers OR Marker OR Level OR Levels OR Guide OR Guidance):ti,ab

Appendix 2. MEDLINE (Ovid) search strategy

exp Calcitonin/ OR Procalcitonin.tw. OR ProCT.tw. OR (calcitonin.tw. AND (precursor.tw. OR precursors.tw.))

AND

exp Anti-Bacterial Agents/ OR (antibiotic OR Antibiotics OR antibacterial OR anti-bacterial OR amoxicillin or amoxycillin OR penicillin OR ampicillin OR cotrimoxazole OR chloramphenicol OR trimethoprim OR sulphamethoxazole OR tmp smx OR tmp-smx).tw,nm.

AND

exp Biomarkers/ OR (Biomarker OR Biomarkers OR Marker OR Level OR Levels OR Guide OR Guidance).tw.

AND

((randomised controlled trial or controlled clinical trial).pt. or randomized.ab. or randomised.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) NOT (exp animals/ not humans.sh.)

Appendix 3. Embase.com (Elsevier) search strategy

'Calcitonin'/exp OR Procalcitonin:ti,ab OR ProCT:ti,ab OR (calcitonin:ti,ab AND (precursor:ti,ab OR precursors:ti,ab))

AND

'antiinfective agent'/exp OR (antibiotic OR Antibiotics OR antibacterial OR anti-bacterial OR amoxicillin OR amoxycillin OR penicillin OR ampicillin OR cotrimoxazole OR chloramphenicol OR trimethoprim OR sulphamethoxazole OR "tmp smx" OR tmp-smx):ti,ab

AND

'biological marker'/exp OR (Biomarker OR Biomarkers OR Marker OR Level OR Levels OR Guide OR Guidance):ti,ab

AND

random* OR factorial OR crossover OR placebo OR blind OR blinded OR assign OR assigned OR allocate OR allocated OR 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'randomised controlled trial'/exp OR 'single-blind procedure'/exp NOT ('animal'/exp NOT ('animal'/exp AND 'human'/exp))

Appendix 4. Previous MEDLINE (Ovid) search strategy

Search used for previous versions of this Cochrane Review

1 procalcitonin.tw.

2 calcitonin precursor*.tw.

3 exp Anti-Bacterial Agents/

4 antibiotic.tw.

5 1 or 2

6 3 or 4

7 5 and 6

F E E D B A C K

Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections, 22 October 2017

Summary

In the 2012 update of this review (Schuetz, 2012), (Maravic-Stojkovic, 2011) was excluded due to “[no] evidence of respiratory infection”. In this 2017 update, (Maravic-Stojkovic, 2011) has now been included. The reasons for this change do not seem to be explicitly provided in the review. The “What’s new” section does say “new trials” were included but (Maravic-Stojkovic, 2011) had already been published, identified and excluded in the previous review.

Schuetz, P., Müller, B., Christ-Crain, M., Stolz, D., Tamm, M., Bouadma, L., … Briel, M. (2012). Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database of Systematic Reviews. doi:10.1002/14651858.cd007498.pub2

Maravic-Stojkovic, V., Lausevic-Vuk, L., Jovic, M., Rankovic, A., Borzanovic, M., & Marinkovic, J. (2011). Procalcitonin-based therapeutic strategy to reduce antibiotic use in patients after cardiac surgery: A randomized controlled trial. Srpski Arhiv Za Celokupno Lekarstvo, 139(11-12), 736–742. doi:10.2298/sarh1112736m

Best,

Martin Vuillème
Affiliation: Volunteer translator

I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment.

Reply

Based on the 2012 review of abstracts we did not believe that the Maravic dataset would have "patients with acute respiratory tract infection included" (our main inclusion criterion) based on the description in the abstract "The prospective study included 205 patients who underwent open heart surgery. The patients were randomly assigned for procalcitonin-guided antibiotic treatment (PCT-group; n=102) or standard care (standard group; n=103). On the basis of serum procalcitonin concentrations, usage of antibiotics was encouraged (PCT≥0.5 ng/mL) or discouraged."

For the 2017 update we decided to check again all trials with investigators and indeed found that 5 out of the 205 patients had hospital-acquired pneumonia (HAP) – these 5 patients were then included in the final analysis.

Thus – the 5 patients from the Maravic study should have been included in the 2012 review already but slipped our attention due to the focus of the study on cardiac surgery patients.

Contributors

Philipp Scheutz

Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections, 15 March 2019

Summary

This review reports findings in the summary of findings table for four outcomes (mortality, treatment failure, anitbiotic-related side effects, anitbiotic exposure) but data and meta-analyses are only included for the first two. Can the study level findings and meta-analyses please be made available for the third and fourth outcomes? This review is being considered by the WHO Essential Diagnostics List and seeing this data is very important.

Do you have any affiliation with or involvement in any organisation with a financial interest in the subject matter of your comment?: No

Jon Deeks, Professor of Biostatistics, University of Birmingham

Reply

Thank you for your comments. Currently, we only have these results for our individual patient data analysis, but will include analyses for the third and fourth outcomes using random-effects in our next update.

Contributors

Philipp Scheutz

WHAT'S NEW

Date	Event	Description
17 May 2019	Feedback has been incorporated	Feedback comment and reply added to the review.

HISTORY

Protocol first published: Issue 4, 2008
Review first published: Issue 9, 2012

Date	Event	Description
26 October 2017	Amended	Correction to Sumary of findings table GRADE icon.
26 October 2017	Feedback has been incorporated	Feedback comment and reply added to the review.

Date	Event	Description
10 February 2017	New citation required and conclusions have changed	Procalcitonin-guided antibiotic treatment improves clinical outcomes and reduces antibiotic consumption.
10 February 2017	New search has been performed	We updated our searches and analyses. We included 12 new trials in individual participant analysis (Bloos 2016; Branche 2015; Corti 2016; De Jong 2016; Deliberato 2013; Layios 2012; Long 2014; Maravić-Stojković 2011; Oliveira 2013; Shehabi 2014; Verduri 2015; Wang 2016). We identified six new trials that were excluded from individual participant analysis (Annane 2013; Ding 2013; Lima 2016; Najafi 2015; Ogasawara 2014; Tang 2013). We identified seven new ongoing trials (NCT02130986; NCT02261610; NCT02332577; NCT02440828; NCT02787603; NCT02862314; NCT02931409). Our new results show that mortality is significantly lower in the procalcitonin group.

CONTRIBUTIONS OF AUTHORS

Philipp Schuetz, Beat Mueller, Heiner Bucher, and Matthias Briel conceived the study and wrote the initial protocol.

Philipp Schuetz and Matthias Briel performed the analysis of the initial review, and Philipp Schuetz, Yannick Wirz, and Ramon Sager performed the analysis of the 2017 update including the writing of the manuscript. Philipp Schuetz, Mirjam Christ-Crain, Daiana Stolz, Michael Tamm, Lila Bouadma, Charles E Luyt, Michel Wolff, Jean Chastre, Florence Tubach, Kristina B Kristoffersen, Olaf Burkhardt, Tobias Welte, Stefan Schroeder, Vandack Nobre, Long Wei, Heiner C Bucher, Djillali Annane, Konrad Reinhart, Angela Branche, Pierre Damas, Maarten Nijsten, Dylan W de Lange, Rodrigo O Deliberato, Stella SS Lima, Vera Maravić-Stojković, Alessia Verduri, Bin Cao, Yahya Shehabi, Albertus Beishuizen, Jens-Ulrik S Jensen, Caspar Corti, Matthias Briel, Beat Mueller, Jos A Van Oers, Ann R Falsey, and Evelien de Jong are investigators of included trials, provided data from their respective trials, and resolved queries about their trial data.

All authors amended and commented on the manuscript and approved the final version. Philipp Schuetz, Beat Mueller, and Matthias Briel oversaw the study and act as guarantors.

DECLARATIONS OF INTEREST

Philipp Schuetz received support (paid to his employer) from Thermo Fisher, Roche Diagnostics, Abbott and bioMerieux to attend meetings and fulfil speaking engagements. These conflicts breach Cochrane's Commercial Sponsorship Policy (Clause 3), therefore Philipp Schuetz will step down as lead author at the next update of the review. Dr Schuetz's declared conflicts were referred to the Funding Arbiter Panel and Cochrane's Deputy Editor-in-Chief who have agreed this course of action but as an exception which does not set a precedent for similar situations in the future.
Beat Mueller reports that within the last 3 years he was part of the speaker bureau of B·R·A·H·M·S and bioMérieux to give educational talks. His institution received compensation for flight and travel expenses, and to cover his absence from work.
Yannick Wirz: None known.
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No commercial sponsor had any involvement in the design and conduct of this review, namely collection, management, analysis, and interpretation of the data; and preparation, decision to submit, review, or approval of the manuscript.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the co-primary endpoint of combined disease-specific failure at 30 days (mentioned in the protocol) to setting-specific treatment failure at 30 days as defined above for reasons of standardisation across trials. We limited the analysis of the secondary outcome number of 'sick days' (days with restricted activities from the ARI within 14 days following randomisation) to the primary care trials because other trials did not assess this outcome.

In addition, based on referee comments during the initial editorial process of the initial review (Schuetz 2012), we added further sensitivity analyses to investigate the robustness of our results. Specifically, we performed sensitivity analyses excluding trials with low adherence to PCT algorithms (< 70%) or not reporting adherence. We also performed sensitivity analyses with respect to methodological quality criteria (allocation concealment and blinded outcome assessment). We further performed a sensitivity analysis excluding trials with a follow-up time for mortality different than one month. We conducted meta-analyses with aggregated data of included trials to further investigate heterogeneity (inconsistency measure I^2 statistic and Cochran Q test) of intervention effects and trial subgroups based on adherence to PCT algorithms.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [adverse effects] [*therapeutic use]; Bacterial Infections [blood] [*drug therapy] [mortality]; Biomarkers [blood]; Calcitonin [*blood]; Calcitonin Gene-Related Peptide; Cause of Death; Protein Precursors [*blood]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [blood] [*drug therapy] [mortality]; Treatment Failure

MeSH check words

Humans