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[Intervention Review]

Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections

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ABSTRACT

Background

Acute respiratory infections (ARIs) comprise a large and heterogeneous group of infections including bacterial, viral and other aetiologies. In recent years, procalcitonin - the prohormone of calcitonin - has emerged as a promising marker for the diagnosis of bacterial infections and for improving decisions about antibiotic therapy. Several randomised controlled trials (RCTs) have demonstrated the feasibility of using procalcitonin for starting and stopping antibiotics in different patient populations with acute respiratory infections and different settings ranging from primary care to emergency departments (EDs), hospital wards and intensive care units (ICUs).

Objectives

The aim of this systematic review based on individual patient 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 2011, Issue 2) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to May 2011) and EMBASE (1974 to May 2011) to identify suitable trials.

Selection criteria

We included RCTs of adult participants with ARIs who received an antibiotic treatment either based on a procalcitonin algorithm or usual care/guidelines. Trials were excluded if they exclusively focused on paediatric patients or if they used procalcitonin for another purpose 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 the primary care setting, treatment failure was defined as death, hospitalisation, ARI-specific complications, recurrent or worsening infection, and patients reporting any symptoms of an ongoing respiratory infection at follow-up. For the ED setting, treatment failure was defined as death, ICU admission, re-hospitalisation after index hospital discharge, ARI-associated complications, 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. Secondary endpoints were antibiotic use (initiation of antibiotics, duration of antibiotics and total exposure to antibiotics (total amount of antibiotic days divided by total number of patients)), length of hospital stay for hospitalised patients, length of ICU stay for critically ill patients, and number of days with restricted activities within 14 days after randomisation for primary care patients.

For the two co-primary endpoints of all-cause mortality and treatment failure, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) using multivariable hierarchical logistic regression. The hierarchical regression model was adjusted for age and clinical diagnosis as fixed-effect. The different trials were added as random-effects into the model. We fitted corresponding linear regression models for antibiotic use. We conducted sensitivity analyses stratified by clinical setting and ARI diagnosis to assess the consistency of our results.

Main results

We included 14 trials with 4221 participants. There were 118 deaths in 2085 patients (5.7%) assigned to procalcitonin groups compared to 134 deaths in 2126 control patients (6.3%) (adjusted OR 0.94, 95% CI 0.71 to 1.23). Treatment failure occurred in 398 procalcitonin group patients (19.1%) and in 466 control patients (21.9%). Procalcitonin guidance was not associated with increased mortality or treatment failure in any clinical setting, or ARI diagnosis. These results proved robust in various sensitivity analyses. Total antibiotic exposure was significantly reduced overall (median (interquartile range) from 8 (5 to 12) to 4 (0 to 8) days; adjusted difference in days, -3.47, 95% CI -3.78 to -3.17, and across all the different clinical settings and diagnoses.

Authors' conclusions

Use of procalcitonin to guide initiation and duration of antibiotic treatment in patients with ARI was not associated with higher mortality rates or treatment failure. Antibiotic consumption was significantly reduced across different clinical settings and ARI diagnoses. Further high-quality research is needed to confirm the safety of this approach for non-European countries and patients in intensive care. Moreover, future studies should also establish cost-effectiveness by considering country-specific costs of procalcitonin measurement and potential savings in consumption of antibiotics and other healthcare resources, as well as secondary cost savings due to lower risk of side effects and reduced antimicrobial resistance.

PLAIN LANGUAGE SUMMARY

Procalcitonin testing to initiate or discontinue antibiotics in acute respiratory tract 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. Hence, procalcitonin may be used to support clinical decision making for the initiation and discontinuation of antibiotic therapy in patients with a clinical suspicion of infection. Randomised controlled trials have demonstrated that such a strategy works, particularly in patients with an infection of the respiratory tract. However, most of these individual studies did not include enough patients to allow for a conclusive assessment about safety (low statistical power). Thus, the risk for mortality and severe complications associated with procalcitonin-guided decision making remained unclear.

This systematic review included individual patient data from 14 randomised controlled trials with a total of 4211 participants. When looking at these combined data, we found no increased risk for all-cause mortality or treatment failure when procalcitonin was used to guide initiation and duration of antibiotic treatment in participants with acute respiratory infections compared to control participants.

However, we found a consistent reduction of antibiotic use, mainly due to lower prescription rates in primary care and lower duration of antibiotic courses in emergency department and intensive care unit patients. This analysis is limited to adult patients with respiratory infections excluding patients who were immuno-compromised (i.e. HIV positive, those receiving immuno-suppressive therapies or chemotherapy). Most trials were conducted in Europe and China and similar studies in other countries including the United States are warranted.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

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

Patient or population: patients with acute respiratory tract infections
Settings: primary care, emergency department, intensive care unit
Intervention: procalcitonin algorithm
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	Procalcitonin algorithm				
Mortality Follow-up: 30 days	**Study population**		**OR 0.91** (0.7 to 1.19)	4211 (14 studies)	⊕⊕⊕○ **moderate**[1,2]	
	63 per 1000	**58 per 1000** (45 to 74)				
	Moderate					
	22 per 1000	**20 per 1000** (16 to 26)				
Treatment failure Clinical assessment[3] Follow-up: 30 days	**Study population**		**OR 0.83** (0.71 to 0.97)	4211 (14 studies)	⊕⊕⊕○ **moderate**[4]	
	219 per 1000	**189 per 1000** (166 to 214)				
	Moderate					
	211 per 1000	**182 per 1000** (160 to 206)				

Antibiotic exposure Total days of antibiotic therapy in all randomised patients	The mean antibiotic exposure in the control groups was **8 days**	The mean antibiotic exposure in the intervention groups was **3.47 lower** (3.78 to 3.17 lower)		4211 (14 studies)	⊕⊕⊕○ **moderate**[4]

*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

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.

[1] There is some concern about unconcealed allocation with several trials in the emergency department setting and intensive care setting. We consider unblinded outcome assessment as not relevant for the outcome of death. See also comment for imprecision.

[2] The 95% CI does not exclude a small but still relevant harmful effect; together with some concern about risk of bias we decided to downgrade.

[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 patients 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, re-hospitalisation after index hospital discharge, ARI-associated complications (e.g. empyema or acute respiratory distress syndrome (ARDS) for lower ARI), 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] There is concern about unconcealed allocation in several emergency department and intensive care trials and about unblinded outcome assessment in emergency department trials.

BACKGROUND

Acute respiratory infections (ARIs) account for over 10% of the worldwide disease burden and are the most common reason for antibiotic therapy in primary care and hospital settings (Dixon 1985; Evans 2002; Gonzales 1997; Macfarlane 1993).

Description of the condition

ARIs 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 2012; Evans 2002). Early initiation of adequate antibiotic therapy is the cornerstone in the treatment of bacterial ARIs and associated with improved clinical outcomes (Hoare 2006; Kumar 2006; Kumar 2009; Liberati 2009b; Spurling 2010). However, overuse of antibiotics by over-prescription in outpatients with bronchitis (Arnold 2005), for instance, and prolonged duration of antibiotic therapy in patients with bacterial ARIs in the hospital and intensive care unit (ICU) settings is associated with increased resistance to common bacteria, medicalising effects, high costs and adverse drug reactions (Gonzales 1997; Goossens 2005; Lawrence 2009; Little 1007).

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 patients with pneumonia having positive cultures and some of them being false positives (Muller 2010). In this diagnostic uncertainty, surrogate biomarkers to estimate the likelihood for the presence of a bacterial infection and to grade disease severity are of great interest (Schuetz 2010b). 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 the outcomes of patients. In the case of ARIs, the clinical benefit of a diagnostic biomarker (i.e. procalcitonin) can be measured by clinical outcomes of randomised intervention studies, assuming that if the patient recovered without antibiotics then there was no relevant bacterial illness.

In recent years, procalcitonin - the prohormone of calcitonin - 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)-alpha and IL-6. Conversely, procalcitonin production is blocked by interferon gamma, a cytokine released in response to viral infections (Muller 2000). Hence, procalcitonin may be used to support clinical decision making for the initiation and discontinuation of antibiotic therapy. 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 (Schuetz 2010b; Schuetz 2011).

How the intervention might work

Procalcitonin levels correlate with the risk of relevant bacterial infections and decrease upon recovery, therefore procalcitonin testing may help physicians to decide in which patients antibiotics are needed and about the optimal duration of antibiotic therapy once treatment is started by monitoring procalcitonin levels every one to two days. Thus, use of procalcitonin in clinical protocols may decrease antibiotic consumption in two ways: by preventing unnecessary antibiotic prescriptions and by limiting durations of antibiotic treatment (Schuetz 2011).

Why it is important to do this review

Individual trials have included patients with various infections and lacked the statistical power to assess the risk for mortality and severe infectious disease complications associated with procalcitonin-guided decision making. Previous meta-analyses of RCTs investigating the effect of procalcitonin algorithms on antibiotic use focused on the critical care setting, patients with suspicion of bacterial infections and patients with sepsis and respiratory infections (Heyland 2011; Schuetz 2011; Tang 2009). However, these meta-analyses used aggregated data and were not able to investigate the effects of procalcitonin on different ARI diagnoses and on outcomes other than mortality. The safe reduction in antibiotic use is of utmost importance. To limit antibiotic overuse, rapid and accurate differentiation of clinically relevant bacterial ARIs from other causes is essential. However, proper identification of the causative micro-organisms in ARIs is challenging because clinical signs and laboratory parameters are often inconclusive and microbiological cultures often remain negative.

OBJECTIVES

We undertook a systematic review and an individual patient data meta-analysis of RCTs comparing the effects of using procalcitonin to guide initiation and duration of antibiotic treatment in patients with ARIs to patients without procalcitonin measurements. The aim of this analysis was to assess the safety and efficacy of this approach over a large range of patients with varying severity of ARIs.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective RCTs comparing a strategy to initiate or discontinue antibiotic therapy based on procalcitonin cut-off ranges with a control arm without procalcitonin measurements. Patients had to be randomised to receive antibiotics either based on procalcitonin cut-off ranges ('procalcitonin group') or a 'control group' without knowledge of procalcitonin levels, including antibiotic management based on usual care or guidelines. We did not include studies if they were non-randomised or if they used alternative biomarkers in the control arm.

Types of participants

Patients had to be adults with a clinical diagnosis of an ARI: 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, rhinosinusitis, pharyngitis, tonsillitis or otitis media. Patients with sepsis and suspected ARIs were also included in this analysis. Trials were excluded if they exclusively focused on paediatric participants or if they used procalcitonin to escalate antibiotic therapy. No exclusion was made based on language of reports or clinical setting. We included trials from primary care, the emergency department and medical and surgical ICUs.

Types of interventions

Strategies to initiate or discontinue antibiotic therapy based on procalcitonin cut-off ranges compared with usual care.

Types of outcome measures

Primary and secondary outcomes were defined up to a follow-up time of 30 days. For trials with a shorter follow-up period, the available information was used (i.e. until hospital discharge). In a sensitivity analysis, we excluded all trials with no follow-up beyond hospital discharge.

Primary outcomes

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

For the primary care setting, treatment failure was defined 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, treatment failure was defined as death, ICU admission, re-hospitalisation after index hospital discharge, ARI-associated complications (e.g. empyema or acute respiratory distress syndrome (ARDS) for lower ARIs), and recurrent or worsening infection within 30 days of follow-up. For the medical and surgical ICU setting, treatment failure was defined as death within 30 days of follow-up. In a sensitivity analysis, we used an alternate definition of treatment failure (death, hospitalisation (for primary care patients), re-hospitalisation (for hospitalised patients) and ICU admission (for non-ICU patients at randomisation)).

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 patients)).
2. Length of hospital stay for hospitalised patients.
3. Length of ICU stay for critically ill patients.
4. Number of days with restricted activities within 14 days after randomisation for primary care patients.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2011, Issue 2, part of *The Cochrane Library* www.thecochranelibrary.com (accessed 01 June 2011), which contains the Acute Respiratory Infections (ARIs) Group's Specialised Register, MEDLINE (1966 to May 2011) and EMBASE (1974 to May 2011).

MEDLINE (OVID)

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

Searching other resources

We searched reference lists of reports describing such trials. In addition, we handsearched conference proceedings (from 2006 to 2011) of the ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy), ECCMID (European Congress of Clinical Microbiology and Infectious Disease), American Thoracic Society, the American Association of Respiratory Care and the American College of Chest Physicians. We checked trial registries and contacted experts for further eligible trials. We prepared the present report according to PRISMA guidelines (Liberati 2009a).

Data collection and analysis

We requested individual patient data from the investigators of all eligible trials. We requested the protocol, case report forms and unedited databases from investigators of all eligible trials.
The overall risk of bias is presented graphically in Figure 1 and summarised in Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

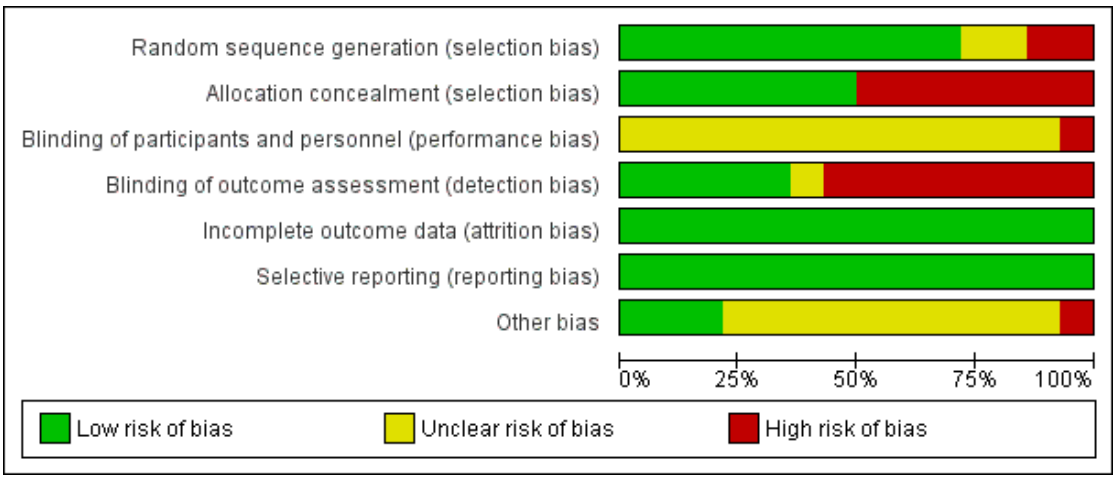
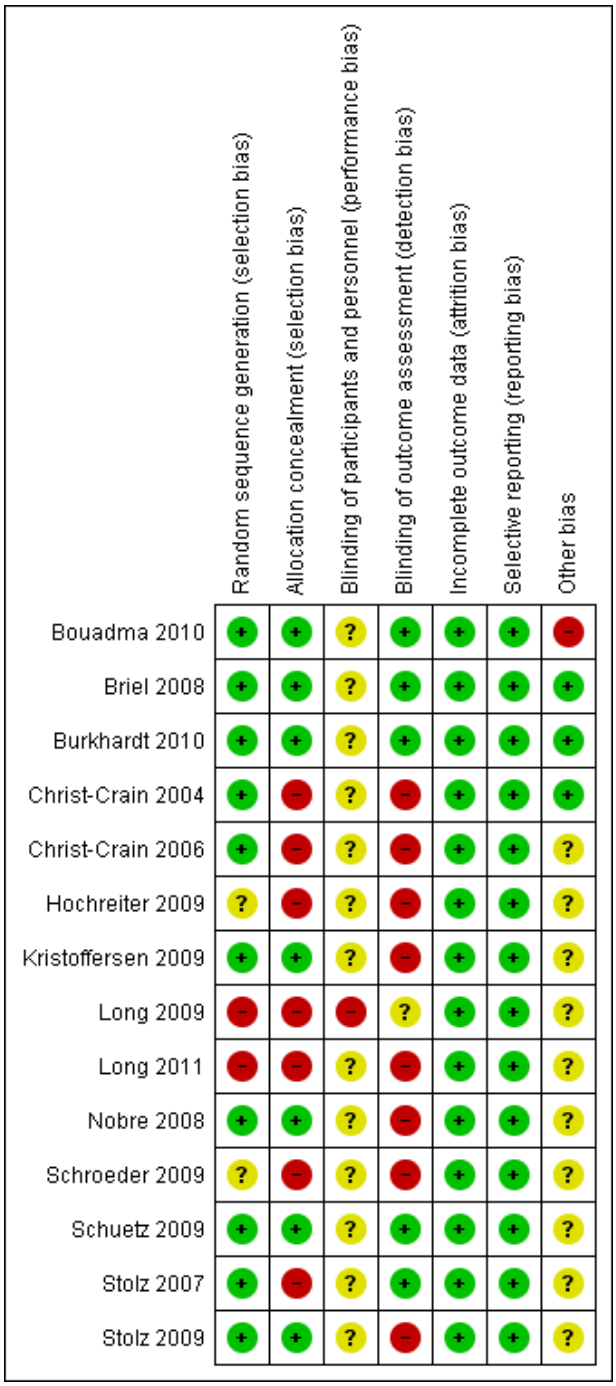


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Selection of studies

Two review authors (PS, MB) independently assessed trial eligibility based on titles, abstracts, full-text reports and further information from investigators as needed.

Data extraction and management

We first checked data from each trial against reported results and queries were resolved with the principal investigator, trial data manager or statistician. The mortality and adverse outcome rates from trials included in this meta-analysis might 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 (PS, MB) assessed the methodological quality of each included study using the Cochrane 'Risk of bias' tool (Higgins 2011) and resolved disagreements by discussion. One review author (QW) assessed the trials in which two review authors (PS, MB) were directly involved. Methodological criteria included: adequate sequence generation, concealment of treatment allocation, blinding of patients, blinding of caregivers, blinding of clinical outcome assessment, whether the study was free of selective reporting and the proportion of patients lost to follow-up. We further documented for each trial the proportion of patients in the procalcitonin group that adhered to the procalcitonin algorithm used in the study.

In addition, we assessed the quality of evidence at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

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 9.2 (College Station, Texas) and SAS version 9.1 (Cary, North Carolina) for statistical analyses.

Unit of analysis issues

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

Dealing with missing data

We assumed in our main analysis that patients lost to follow-up did not experience an event. We explored if a complete case analysis (excluding patients lost to follow-up) or an analysis assuming that patients lost to follow-up experienced an event would change the results for the primary outcomes of mortality and treatment failure in sensitivity analyses.

Assessment of heterogeneity

We performed pre-specified analyses stratified by clinical setting (i.e. primary care, emergency department, ICU) and ARI diagnosis 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 procalcitonin 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 (Higgins 2003)) in meta-analyses using aggregated data and by testing for heterogeneity using the Cochran Q test.

Assessment of reporting biases

We assessed reporting bias by trying to identify whether the study was included in a trial registry, whether a protocol is available and whether the methods section provided a list of outcomes. We compared the list of outcomes from those sources to the outcomes reported in the published paper. We also created inverted funnel plots for the primary outcomes of overall mortality and treatment failure in order to check for possible publication bias. We did not create funnel plots for the other outcomes due to the low number of included trials for each outcome.

Data synthesis

We used multivariable hierarchical logistic regression to combine patient data from the different trials (Thompson 2001; Turner 2000). Apart from the group variable indicating the use of a procalcitonin algorithm we included important prognostic factors such as patient 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 RevMan 2011.

Subgroup analysis and investigation of heterogeneity

As mentioned previously, we performed pre-specified analyses stratified by clinical setting (i.e. primary care, emergency department, ICU) and ARI diagnosis and 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 procalcitonin group as a fixed-effect.

Sensitivity analysis

We performed pre-specified sensitivity analyses based on the main quality indicators, namely allocation concealment and blinded outcome assessment. In an additional sensitivity analysis, we used an alternate definition of treatment failure (death, hospitalisation (for primary care patients), re-hospitalisation (for hospitalised patients) and ICU admission (for non-ICU patients at randomisation)). We also performed sensitivity analyses excluding trials with low adherence to procalcitonin algorithms (< 70%) or not reporting adherence, excluding all ICU trials and excluding only the largest ICU trial due to low adherence.

RESULTS

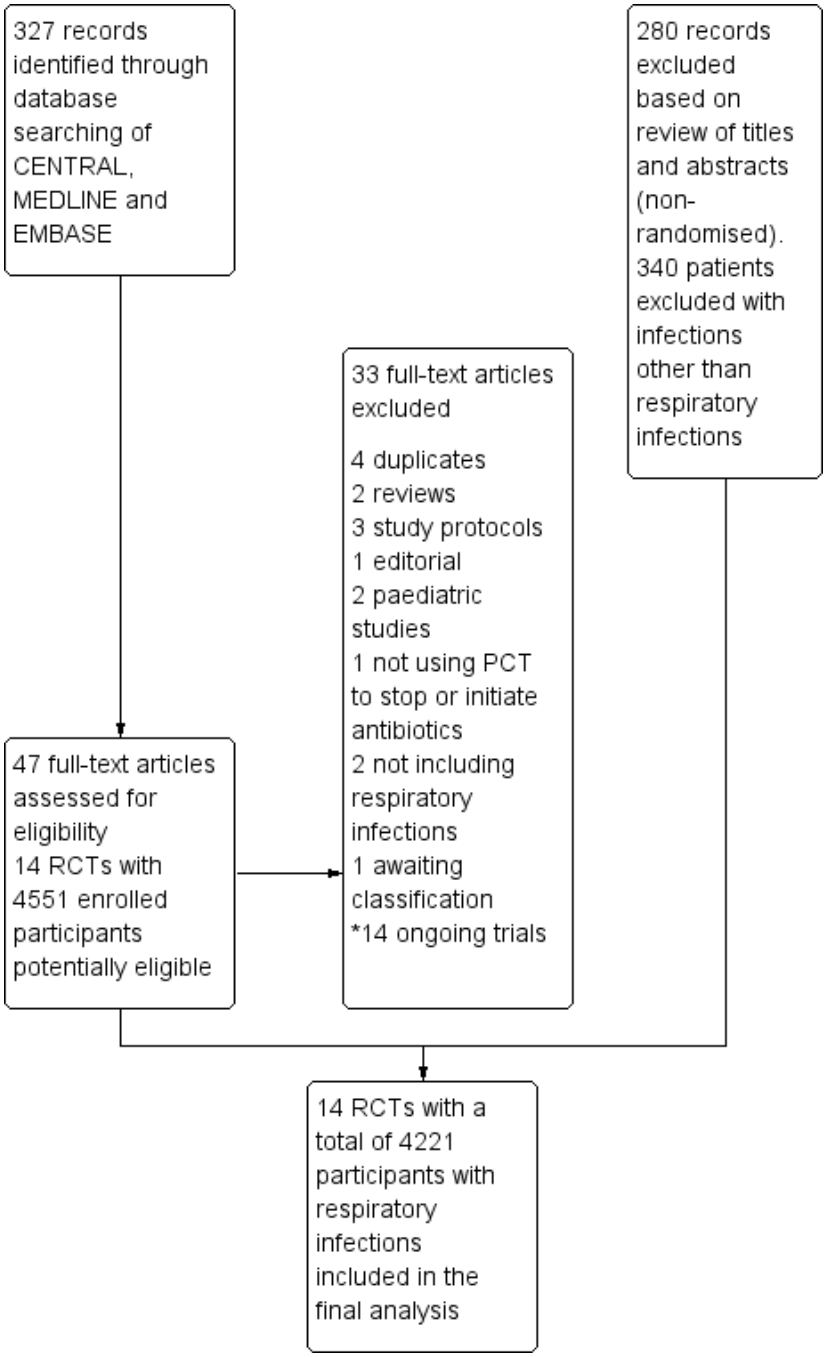
Description of studies

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

Results of the search

We identified 14 completed trials that met our inclusion criteria (Figure 3) with a total of 4551 patients. Four of the ICU trials included sepsis patients with other types of infections than ARIs; these patients (n = 340) were not considered for this analysis. Patients with initial suspicion of ARIs and other final diagnoses were included in the overall analysis. Our intention-to-treat (ITT) population consisted therefore of 4211 patients with ARIs at randomisation. We identified a further 14 ongoing RCTs on the topic with expected completion between 2012 and 2014.

Figure 3. Study flow diagram. *The 14 ongoing trials comprise of comprise 5 in paediatrics, 2 focusing on patients with community-acquired pneumonia, 1 focusing on stroke patients, 1 focusing on neutropenic patients and 5 focusing on intensive care patients.



Included studies

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 three trials following patients until hospital discharge only. The two primary care trials both employed a non-inferiority design. Procalcitonin algorithms used in the different trials were similar in concept and recommended initiation and/or continuation of antibiotic therapy based on similar procalcitonin cut-off levels (Table 1). However, there were differences: some trials in primary care and the emergency department used only a single procalcitonin 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. Adherence to algorithms was variable, ranging from 47% to 91% (Table 2).

Baseline characteristics of included patients were similar in procalcitonin and control groups with respect to important prognostic features (Table 2). Most patients were recruited in the emergency department setting and community-acquired pneumonia (CAP) was the most frequent ARI diagnosis in almost 50% of patients. Procalcitonin concentrations on admission were highest in patients from the ICU setting and lowest in primary care patients. There were no statistically significant differences in procalcitonin levels between procalcitonin and control groups overall and for individual settings (P value > 0.05 for all comparisons).

Excluded studies

We excluded two paediatric RCTs using procalcitonin for antibiotic decisions in neonates (Stocker 2010) and in a paediatric population (Esposito 2012); and four studies that were not randomised but used a before-after design (Kook 2012; Liew 2011; Schuetz 2010; Saeed 2011). We excluded one study that used PCT to guide antibiotic treatment in patients with pancreatitis (Qu 2012) and one study that included patients after heart surgery without evidence of respiratory infection (Maravić -Stojković 2011). We also excluded one trial that used procalcitonin for escalation of diagnostic measures and treatment in order to improve mortality (Jensen 2011). In addition, previous meta-analyses using aggregate data were also excluded (Heyland 2011; Jones 2007; Simmonds 2005; Simon 2004; Tang 2007; Tang 2009; Uzzan 2006).

Finally, we found one study that was published as an abstract only (poster) and thus the study awaits classification until it is published (Beni 2011).

Risk of bias in included studies

We reviewed all trials for risk of bias. The overall risk of bias is presented graphically in Figure 1 and summarised in Figure 2.

In terms of methodological quality of included trials, there were six trials with concealed allocation and five trials with blinded outcome assessment. All trials achieved complete or near-complete follow-up for mortality. None of the trials blinded patients or caregivers to group allocation. Detailed results are presented in Table 2 and we performed a number of sensitivity analyses to assess the robustness of the data (Table 3).

Allocation

All studies randomised patients to a control group or the intervention group with procalcitonin testing. Risk for selection bias was found in different studies due to weekly allocation (Christ-Crain 2004), unnumbered envelopes (Christ-Crain 2006; Stolz 2007; Stolz 2009), use of odd and even patient identification numbers (Long 2009; Long 2011) and unconcealed drawing of lots (Hochreiter 2009; Schroeder 2009).

Blinding

Blinded outcome assessment was present in the primary care trials (Briel 2008; Burkhardt 2010), in two of the emergency department trials (Schuetz 2009; Stolz 2007) and in the largest ICU trial (Bouadma 2010) (Table 2). Most trials that used all-cause mortality as the main safety outcome were not blinded. None of the trials blinded physicians in regard to group allocation because procalcitonin was used for decision making in the intervention group.

Incomplete outcome data

Trials had generally a high follow-up for mortality with only minimal patients lost to follow-up (Table 2). Three studies followed patients only until hospital discharge (Hochreiter 2009; Kristoffersen 2009; Schroeder 2009).

Selective reporting

No reporting bias found in any of the studies when comparing study protocols and final published results.

Other potential sources of bias

Another potential bias relates to low adherence to the procalcitonin algorithms. Overall, adherence was variable, ranging from 47% to 91% (Table 2). While adherence was higher in emergency department and primary care trials (Table 2), ICU trials had low adherence (Bouadma 2010) or did not report adherence (Hochreiter 2009; Schroeder 2009; Stolz 2009).

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 endpoints

Overall, there was no difference in all-cause mortality in procalcitonin group patients compared to control patients (5.7% versus 6.3%, adjusted odds ratio (OR) 0.94, 95% confidence interval (CI) 0.71 to 1.23) (Table 4). This was consistent across clinical settings and acute respiratory infection (ARI) diagnoses. We found overall a significantly lower risk for treatment failure in procalcitonin-treated patients compared to control patients (19.1% versus 21.9%, adjusted OR 0.82 (95% CI 0.71 to 0.97)). We performed several pre-defined sensitivity analyses which are summarised in Table 3. A similar, although statistically non-significant result was found when restricting the definition of treatment failure to death, intensive care unit (ICU) admission, hospitalisation or re-hospitalisation (9.1% versus 10.8%; adjusted OR 0.82, 95% CI 0.67 to 1.01).

As a sensitivity analysis and to investigate for heterogeneity among trials, we also calculated an aggregate data meta-analysis based on the aggregate results of the 14 trials. In this analysis, the results proved robust in various sensitivity analyses (Analysis 1.1; Analysis 1.2; Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4). We did not find any evidence for heterogeneity or effect modification across clinical settings or ARI diagnoses.

Secondary endpoints

Procalcitonin-guided patients had a lower antibiotic exposure overall (adjusted difference in days, -3.47, 95% CI -3.78 to -3.17), in all clinical settings and across ARI diagnoses (Table 5). In the primary care setting this was mainly due to lower initial prescription rates (adjusted OR 0.10, 95% CI 0.07 to 0.14; P < 0.0001 for interaction between primary care setting and procalcitonin group on antibiotic prescriptions). Similarly, lower antibiotic exposure due to lower prescription rates was found in selected infections such as upper ARIs (adjusted OR 0.14, 95% CI 0.09 to 0.22; P for interaction = 0.006) and acute bronchitis (adjusted OR 0.15, 95% CI 0.10 to 0.23; P for interaction = 0.001). Shorter duration of antibiotic therapy further contributed to this effect in the emergency department (adjusted difference in days -3.70, 95% CI -4.09 to -3.31; P for interaction = 0.005) and ICU setting (adjusted difference in days -3.17, 95% CI -4.28 to -2.06; P for interaction = 0.007) and in those with community-acquired pneumonia (CAP) (adjusted difference in days -3.34, 95% CI -3.79 to -2.88; P for interaction < 0.0001) and ventilator-associated pneumonia (VAP) (adjusted difference in days -2.23, 95% CI -4.06 to -0.39; P for interaction = 0.01).

In primary care patients, we found no significant difference in rates of treatment failure and days with restricted activities between groups after 14 days (Table 4). In emergency department patients, there was a significantly lower risk of treatment failure in favour of procalcitonin-guided patients (adjusted OR 0.76, 95% CI 0.61 to 0.95). There was no significant difference in the length of stay for emergency department and ICU patients.

DISCUSSION

Summary of main results

This systematic review and meta-analysis of individual patient data from 14 randomised controlled trials found no increased risk for mortality or treatment failure when procalcitonin was used to guide initiation and duration of antibiotic treatment in patients with acute respiratory infections (ARIs) compared to control patients. The upper boundary of the 95% confidence interval (CI) for treatment failure of 0.97 (or 1.01 for the alternate definition of treatment failure) makes more frequent treatment failures with procalcitonin unlikely. However, based on the available evidence, we cannot exclude a 23% relative increase in odds for mortality with the procalcitonin approach, which may correspond to an absolute risk increase for mortality of 1% in the emergency department setting (control event rate 4.5%) and of 5% in the intensive care unit (ICU) (control event rate 23.8%). Even though we consistently found no evidence for safety concerns with procalcitonin use in patient-relevant endpoints and in various sensitivity analyses, the remaining uncertainty associated with the mortality estimate in ICU patients calls for further research in this high-risk patient population. In terms of efficacy, we found a consistent reduction of antibiotic use, mainly due to lower prescription rates in primary care (predominantly among patients with upper ARIs and bronchitis); and lower duration of antibiotic courses in emergency department and ICU patients (with community-acquired pneumonia (CAP) and ventilator-associated pneumonia (VAP)).

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 patient-level data from all 14 eligible trials, standardised outcome definitions across trials and analyses based on the intention-to-treat (ITT) principle, thereby overcoming limitations of meta-analyses using aggregated data. To minimise the risk of data-driven associations, we pre-specified 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 patients with complete follow-up data.

The accuracy of procalcitonin for diagnosing bacterial infections has been called into question by previous meta-analyses of observational studies, demonstrating mixed results (Jones 2007; Simmonds 2005; Tang 2007; Uzzan 2006). 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 procalcitonin algorithms by means of randomised controlled trials (RCTs) measuring clinically robust, clearly defined, patient-level outcomes.

Despite these merits, this study has several limitations. Although we included all available randomised trial-based evidence on mortality in our pooled analysis and the point estimates in various analyses suggest no relevant difference between groups, the CIs for the overall analysis and the different subgroups are still relatively wide including both a clinically relevant reduction and increase in mortality. Thus, if one wanted to exclude, for instance, a 10% relative (or 2.3% absolute) mortality increase in ICU patients with procalcitonin guidance, an additional 5400 patients would be needed in each group (assuming a mortality rate in control ICU patients with ARIs of 23%, an alpha error of 5% and a power of 80%). There are currently several ongoing trials registered in the Clinical Trials database that may, somewhat, help address this issue. Five ongoing trials focus on procalcitonin as a guide to stop antibiotics in ICU patients with sepsis and two of those are enrolling large numbers of patients (> 1000 patients each). Hence, these trials may help to further demonstrate safety in this vulnerable patient population. For CAP, we found two smaller ongoing trials, which are unlikely to substantially impact the current analysis presented here.

We limited our analysis to adult patients with ARIs that were mostly immunocompetent and some pathogens were excluded (i.e. *Legionella* or *Pseudomonas* infections). Therefore, the results of this study may not be generalisable to immunocompromised patients, patients with specific pathogens or other infections than ARIs, or children. Previous RCTs have shown that procalcitonin guidance also reduces antibiotic exposure in a neonatal sepsis population but not in children with fever without a source (Manzano 2010). We found seven ongoing paediatric RCTs evaluating procalcitonin algorithms that should shed further light on the benefits and harms of procalcitonin use in paediatric populations.

The included trials compared the procalcitonin strategy to a control group where antibiotic therapy was guided based on 'usual practice' or based on current guideline recommendations. The magnitude of reduction of antibiotic reduction obviously correlates strongly with antibiotic prescription patterns and in regions of low antibiotic prescription the procalcitonin strategy may have smaller effects. Importantly, most trials today were conducted in Switzerland and Germany, where prescription rates tend to be lower compared with those in the United States or in most other European countries (Filippini 2006).

Quality of the evidence

Characteristics of the individual trials are presented below. Most trials had a follow-up of one month with two trials assessing outcome after 14 to 21 days and three trials following patients until hospital discharge only. The two primary care trials both employed a non-inferiority design. Procalcitonin algorithms used in the different trials were similar in concept and recommended initiation and/or continuation of antibiotic therapy based on similar procalcitonin cut-off levels (Table 1). However, there were differences: some trials in primary care (Burkhardt 2010) and the emergency department (Christ-Crain 2004) used only a single procalcitonin 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. Adherence to algorithms was variable, ranging from 47% to 91%. In terms of methodological quality of included trials, there were six trials with concealed allocation and five trials with blinded outcome assessment. All trials achieved complete or near-complete follow-up for mortality. None of the trials blinded patients or caregivers to group allocation. The overall quality of the evidence according to GRADE is moderate (Summary of findings for the main comparison).

Potential biases in the review process

Due to the differences in patient populations included in this analysis, ranging from primary care to 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. However, we did find lower rates of treatment failure overall and in the emergency department setting for patients allocated to the procalcitonin group. Sensitivity analyses using an alternate definition of treatment failure that eliminated a few of the less setting-specific components (death, ICU admission, hospitalisation or re-hospitalisation) confirmed this finding. Potential explanations are: 1) procalcitonin appears to provide additional useful information which can influence decision making in areas such as consideration of early discharge (Nobre 2008); 2) treatment failures relate to longer antibiotic courses in the control group, because previous research has shown the association of prolonged antibiotic exposure and risk for secondary complications and re-hospitalisation (Classen 2010; Roberts 2009); 3) the finding turned out to be statistically significant by chance. Perhaps the appropriately conservative interpretation of these findings is that it is improbable that procalcitonin-guided approaches increased treatment failures.

Agreements and disagreements with other studies or reviews

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.
The available evidence from RCTs, as summarised in this report, supports the use of procalcitonin for de-escalation of antibiotic therapy for patients with ARIs. The same may not be true for escalation of antibiotic therapy when procalcitonin levels increase as demonstrated in a recent large sepsis trial (Jensen 2011), where procalcitonin-guided escalation of diagnostic procedures and antimicrobial therapy in the ICU did not improve survival and lead 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 could be a safe and effective tool to guide clinical decisions for antibiotic initiation and duration of treatment. Similar to patients with suspicion of pulmonary embolism where D-dimer levels are used differently depending on the pre-test probability (Konstantinides 2008), procalcitonin should also be adapted to clinical settings and the risk of patients. In the studies included, patients at low risk for severe bacterial infections (e.g. primary care patients with upper acute respiratory infections (ARIs) or bronchitis), a procalcitonin algorithm was used to determine whether antibiotics should be initiated at all; in higher risk patients (intensive care unit (ICU) or emergency department patients with lower ARIs), procalcitonin was mainly used to determine when treatment could be safely discontinued (Schuetz 2010b).

The use of procalcitonin to guide initiation and duration of antibiotic treatment in patients with ARIs was not associated with higher mortality rates or treatment failure, but significantly reduced antibiotic consumption across different clinical settings and ARI diagnoses. Further mortality data are needed, particularly in the ICU setting, before procalcitonin-based algorithms can be considered safe. The use of procalcitonin 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.

All trials have used highly sensitive assays to measure procalcitonin 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 procalcitonin 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.

Importantly, all trials included procalcitonin into clinical algorithms and physicians could deviate from the procalcitonin algorithm if needed. Post-study surveys have been published (Schuetz 2010b) or are currently being conducted (ProREAL, ISRCTN40854211) in order to better understand the effects and challenges of procalcitonin testing in clinical practice.

Implications for research

Included trials were mostly conducted in the European setting, with two trials coming from China and one multi-national trial including US sites. Thus, further validation and adaptation of the algorithms to other countries is needed. Moreover, future studies should also establish cost-effectiveness by considering country-specific costs of procalcitonin measurement (around USD 20 to USD 30 per sample) and potential savings in consumption of antibiotics and other healthcare resources.

In addition, it would be interesting to conduct a head-to-head trial comparing a procalcitonin strategy to a strategy based on other biomarkers, such as C-reactive protein (CRP) or interleukin-6. A similar randomised controlled trial has recently been 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.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

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 patients with CAP and VAP out of 630 randomised patients: 9 post randomisation exclusions (8 withdrew consent, 1 randomised twice); 227 not considered for this analysis due to diagnosis other than ARI
Interventions	Guiding antibiotic decisions in ICU patients with repeated procalcitonin measurements **Algorithm used in this study:** investigators were encouraged to discontinue ABs when procalcitonin 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 days 28 • All-cause mortality at days 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
Notes	**Funding:** research grant from the Département à la Recherche Clinique et au Développement, Assistance Publique-Hopitaux de Paris (PHRC AOR06019), France. Brahms, Germany (manufacturer of procalcitonin 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, Télémedecine, Technologies, Boulogne,

Bouadma 2010 (*Continued*)

		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 in which group patients were and where procalcitonin 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	High risk	Low adherence to procalcitonin algorithm in procalcitonin group (47%)

Briel 2008

Methods	Randomised clinical trial, multicentre in 53 primary care practices in northwest Switzerland
Participants	**Inclusion criteria:** patients 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 being fluent in German, severe immunosuppression, cystic fibrosis, active tuberculosis and the need for immediate hospitalisation **Included in this analysis:** 458 out of 458 randomised patients
Interventions	Guiding antibiotic decisions in primary care with repeated measurements **Algorithm used in this study:** in patients with procalcitonin levels lower than 0.1 μg/L, a bacterial infection was considered highly unlikely and the use of ABs was discouraged. In patients with a procalcitonin level higher than 0.25 μg/L, a bacterial infection was considered likely and the use of ABs was recommended. For procalcitonin 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 patients, a second measurement of the procalcitonin 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 procalcitonin level had increased from the first measurement by more than 50% and the patient showed no clinical improvement. All patients given ABs based on procalcitonin level were reassessed after 3 days. Discontinuation of AB treatment was then recommended in patients with a procalcitonin level of 0.25 μg/L or lower
Outcomes	• Number of days, within the first 14 days after baseline, during which a patient'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 • Patients 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. Brahms, 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
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 in which group patients were and where procalcitonin levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded medical students performed interviews with patients 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 procalcitonin algorithm in procalcitonin group

Burkhardt 2010

Methods	Randomised clinical trial, multicentre in 15 primary care practices in the area of Hanover, Germany
Participants	**Inclusion criteria:** adult patients 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 patients: 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:** procalcitonin value < 0.25 µg/l indicated that a relevant bacterial infection of the respiratory tract is unlikely
Outcomes	• Days with impairment during everyday life and/or leisure activities 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 • Patients with any symptoms of ongoing or relapsing infection at 28 days • All-cause mortality • Hospitalisation
Notes	**Funding:** Brahms AG, Germany **Follow-up**: fixed period of 28 days **Registration:** NCT00827060 and NCT00688610

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."

Burkhardt 2010 (*Continued*)

Allocation concealment (selection bias)	Low risk	Central randomisation Quote: "In the central laboratory, the web-based randomisation of the patient into the procalcitonin group or the control group took place."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew in which group patients were and where procalcitonin 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 procalcitonin algorithm in procalcitonin group

Christ-Crain 2004

Methods	Randomised clinical trial, single-centre, emergency department at the University Hospital Basel, Switzerland
Participants	**Inclusion criteria:** patients with lower ARIs presenting at a medical emergency department **Exclusion criteria:** severely immunocompromised patients, 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 patients out of 243 randomised patients
Interventions	Guiding antibiotic decisions in emergency department patients with different ARIs with initial procalcitonin values only **Algorithm used in this study:** a procalcitonin value of 0.1 to 0.25 µg/L was regarded as an indication that bacterial infection was unlikely and we discouraged use of ABs. We deemed serum procalcitonin between 0.25 and 0.5 g/L to indicate a possible bacterial infection and the treating doctor was advised to initiate antimicrobial treatment. A procalcitonin value of 0.5 µg/L or greater was judged suggestive of the presence of bacterial infection and we strongly recommended AB treatment. For patients on antimicrobial therapy at the time of admission, we recommended discontinuation of ABs if procalcitonin 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; Brahms 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 patients 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 procalcitonin-guided antimicrobial treatment (procalcitonin 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 in which group patients were and where procalcitonin 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 procalcitonin algorithm in procalcitonin 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:** patients with cystic fibrosis or active pulmonary tuberculosis, patients with hospital-acquired pneumonia and severely immunocompromised patients **Included in this analysis:** 302 out of 302 randomised patients
Interventions	Guiding antibiotic decisions in emergency department patients with CAP with repeated procalcitonin measurements **Algorithm used in this study:** a procalcitonin 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 procalcitonin 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 procalcitonin level from 0.25 to 0.5 µg/L was considered to indicate a possible bacterial infection and the initiation or continuation of AB therapy was encouraged. A procalcitonin 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 procalcitonin levels was recommended after 6 to 24 h in all patients from whom ABs were withheld. Procalcitonin levels were reassessed after 4, 6 and 8 d. ABs were discontinued on the basis of the procalcitonin cut-offs defined above. In patients with very high procalcitonin values on admission (e.g. greater than 10 µg/L), discontinuation of ABs was encouraged if levels decreased to levels 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 patients lost to follow-up
Notes	**Funding:** funding obtained from Brahms (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

Christ-Crain 2006 (*Continued*)

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	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 in which group patients were and where procalcitonin 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: 300/302 (99%)
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol
Other bias	Unclear risk	87% adherence to procalcitonin algorithm in procalcitonin group

Hochreiter 2009

Methods	Randomised clinical trial, single-centre, intensive care unit 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:** AB therapy in the procalcitonin-guided group was discontinued if clinical signs and symptoms of infection improved and procalcitonin decreased to less than 1 µg/L, or if the procalcitonin 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)

Hochreiter 2009 (*Continued*)

Notes	**Funding:** BRAHMS AG **Follow-up:** until hospital discharge **Registration:** ISRCTN10288268

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 in which group patients were and where procalcitonin 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 procalcitonin protocol not reported/assessed

Kristoffersen 2009

Methods	Randomised clinical trial, multicentre, 3 hospitals in Denmark
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 patients: 13 post randomisation exclusions (3 no procalcitonin 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 procalcitonin results before initiating antimicrobial therapy; therefore, procalcitonin values were, in most cases, used to motivate either cessation or continuation of already initiated treatments. Discontinuation of AB treatment was recommended if procalcitonin at admission was

Kristoffersen 2009 (*Continued*)

	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 in which group patients were and where procalcitonin 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	Unclear risk	59% adherence to procalcitonin algorithm in procalcitonin group

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 $\geq$ 5 days, coexisting extrapulmonary infection requiring antibiotic therapy **Included in this analysis:** 127 out of 127 randomised patients

Long 2009 (*Continued*)

Interventions	Guiding antibiotic decisions in CAP patients with repeated levels **Algorithm used in this study:** a procalcitonin 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 procalcitonin 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 procalcitonin level of 0.25 µg/L or greater was considered to indicate a possible bacterial infection and the initiation or continuation of AB therapy was encouraged. Re-evaluation of the clinical status and measurement of procalcitonin levels was recommended after 6 to 12 h in all patients 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 patients lost to follow-up
Notes	**Funding:** training fund of Shanghai No.5 Hospital **Follow-up:** 28 days **Registration:** none

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	High risk	Open-label trial where physicians knew in which group patients were and where procalcitonin levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear 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)

Long 2009 (*Continued*)

Other bias	Unclear risk	Adherence to procalcitonin 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 patients: 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 procalcitonin 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 procalcitonin 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 procalcitonin level of 0.25 µg/L or greater was considered to indicate a possible bacterial infection and the initiation or continuation of AB therapy was encouraged. Re-evaluation of the clinical status and measurement of procalcitonin levels was recommended after 6 to 12 h in all patients 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) **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 in which group patients were and where procalcitonin levels were only communicated in the intervention arm

Long 2011 (*Continued*)

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 procalcitonin protocol not reported/assessed

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:** 1. microbiologically documented infections caused by *Pseudomonas aeruginosa*, *Acinetobacter baumanni*, *Listeria spp.*, *Legionella pneumophila*, *Pneumocystis jiroveci* or *Mycobacterium tuberculosis*, for which a prolonged duration of antibiotic therapy is standard of care (17); 2. severe infections due to viruses or parasites (e.g. haemorrhagic fever, malaria); 3. infectious conditions requiring prolonged antibiotic therapy (e.g. bacterial endocarditis, brain abscess, deep abscesses); 4. antibiotic therapy started 48 hours or more before enrolment; 5. chronic, localised infections (e.g. chronic osteomyelitis); 6. severely immunocompromised patients, such as patients infected with human immunodeficiency virus and with a CD4 count of less than 200 cells/mm^3, neutropenic patients (.500 neutrophils/mm^3) or patients on immunosuppressive therapy after solid organ transplantation; 7. withholding of life support; or 8. absence of antimicrobial treatment despite clinical suspicion of sepsis **Included in this analysis:** 52 out of 79 randomised patients: 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. Patients that presenting a favourable clinical course, investigators used pre-defined "stopping rules" based on circulating procalcitonin levels to encourage caregivers to discontinue ABs. Patients with baseline procalcitonin level greater or equal to 1 µg/L were re-evaluated at day 5. Investigators encouraged treating physicians to discontinue ABs when: 1. procalcitonin dropped more than 90% from the baseline peak level; or 2. an absolute value below 0.25 µg/L was reached Patients with procalcitonin level below 1 µg/L at baseline were re-evaluated at day 3 and treating physicians were encouraged to discontinue ABs when procalcitonin level was

Nobre 2008 (*Continued*)

	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 • Re-occurrence of the initial infection • Length of ICU stay
Notes	**Funding:** BRAHMS 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 in which group patients were and where procalcitonin 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	Unclear risk	81% adherence to procalcitonin algorithm in procalcitonin group

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 already had received antibiotic treatment prior to admission to the ICU

Schroeder 2009 (*Continued*)

	Included in this analysis: 8 out of 27 randomised patients: 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 procalcitonin-guided group, antibiotic therapy was discontinued if clinical signs and symptoms of sepsis improved and procalcitonin values either had decreased to 1 μg/L or less or had dropped to 25% to 35% of the initial procalcitonin 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 in which group patients were and where procalcitonin 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: 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 procalcitonin 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:** patients with active intravenous drug use, severe immunosuppression other than corticosteroid use, life-threatening medical co-morbidities leading to possible imminent death, patients with hospital-acquired pneumonia (development of pneumonia 48 hours after hospital admission or if they were hospitalised within 14 days before presentation) and patients with chronic infection necessitating antibiotic treatment **Included in this analysis:** 1359 out of 1381 randomised patients: 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 procalcitonin 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 procalcitonin 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 procalcitonin 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 Santé Suisse 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. BRAHMS Inc, the major manufacturer of the procalcitonin 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
Random sequence generation (selection bias)	Low risk	Independent statistician created randomisation scheme
Allocation concealment (selection bias)	Low risk	Central randomisation using a study website

Schuetz 2009 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew in which group patients were and where procalcitonin 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	Unclear risk	91% adherence to procalcitonin algorithm in procalcitonin group

Stolz 2007

Methods	Randomised clinical trial, single-centre, University Hospital Basel, Switzerland
Participants	**Inclusion criteria:** clinical diagnosis of COPD exacerbation **Exclusion criteria:** patients who were considered to be vulnerable study participants (i. e. those with psychiatric co-morbidities) 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 of226 randomised patients: 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 to indicate 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 patient's clinical condition. A procalcitonin level of 0.25 µg/L was considered to suggest 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 symptom, the worsening of symptoms, or death • Mortality • ICU admission • Hospital readmission after 30 days and 6 months

Stolz 2007 (*Continued*)

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. BRAHMS provided procalcitonin 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 in which group patients were and where procalcitonin 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
Other bias	Unclear risk	Adherence to procalcitonin 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 acquired immunodeficiency syndrome; and 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 procalcitonin level of < 0.25 µg/L suggested the absence of VAP and discontinuation of ABs was strongly encouraged. A procalcitonin 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 procalcitonin level ≥ 0.5 µg/L or decrease by < 80% as compared to day 0 was considered to indicate unresolved bacterial infection and reduction or discontinuation of AB was discouraged. A procalcitonin 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 • Sa, O_2, Pa, O_2/Fi, O_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 Brahms 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"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial where physicians knew in which group patients were and where procalcitonin levels were only communicated in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study member

Stolz 2009 (*Continued*)

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 procalcitonin protocol not reported/assessed

AB: antibiotic
ARIs: acute respiratory infections
CAP: community-acquired pneumonia
COPD: chronic obstructive pulmonary disease
CPIS: Clinical Pulmonary Infection Score
d: day
ED: emergency department
ECOPD: exacerbation of chronic obstructive pulmonary disease
h: hour
ICU: intensive care unit
ID: identification
LRTI: lower respiratory tract infection
NA: not available
ODIN: Organ Dysfunction and/or Infection score
O_2: oxygen
PaO_2/Fi: relationship between arterial oxygen tension (Pa,O2) and inspiratory oxygen fraction (FI,O2)
Pa: arterial
RTI: respiratory tract infection
SIRS: systemic inflammatory response syndrome
SOFA: Sequential Organ Failure Assessment score
VAP: ventilator-associated pneumonia

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

Study	Reason for exclusion
Esposito 2012	Not adult patients (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 a RCT; before-after study design

(*Continued)*

Liew 2011	Not a RCT
Maravić -Stojković 2011	Not a LRTI
Qu 2012	Not a respiratory infection (pancreatitis)
Saeed 2011	Not a RCT
Schuetz 2010	Not a 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

LRTI: lower respiratory tract infection
RCTs: randomised controlled trials

Characteristics of studies awaiting assessment *[ordered by study ID]*

Beni 2011

Methods	RCT
Participants	Hospital-acquired pneumonia and healthcare-associated pneumonia
Interventions	PCT testing and antibiotic stewardship
Outcomes	Antibiotic exposure
Notes	Poster presentation

PCT: procalcitonin

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

NCT00407147

Trial name or title	Procalcitonin level to discontinue antibiotics on ICU patients with no obvious site of infection
Methods	RCT
Participants	Inclusion criteria: • Suspected infection (no clear-cut source of infection) as defined by the treating physician • Empiric antibiotic treatment • No clear-cut source of infection by clinical or microbiological criteria • ICU patient • Informed consent Exclusion criteria: • Age < 18 years • Pregnancy • Haemodynamic instability defined as persistent hypotension, need for ongoing aggressive resuscitation and/or vasopressor support to maintain an adequate mean arterial blood pressure • Need for antibiotic prophylaxis • Patient withdrawn from empiric antibiotic treatment before Day 4 • Severely immuno-compromised patient (liver cirrhosis (Child-Pugh class C), immunosuppressive drugs after transplantation, neutropenia (absolute neutrophil count < 1000 counts/L), CD-4 count less than 200) • Patient with suspected bacterial or fungal endocarditis • Patient with suspected meningitis • Cardiopulmonary bypass within the last 7 days • Major surgery within the last 7 days (surgery that induces a major inflammatory response such as heart or aortic surgery or major abdominal surgery (i.e. duodenopancreatectomy) or any surgery requiring massive blood transfusion.) • Multiple trauma within the last 7 days • Cardiopulmonary resuscitation (CPR) within the last 7 days • Burns > 20% body surface area • Patient in terminal status referred for palliative care • Patient with advanced directives or Do Not Resuscitate (DNR) orders • Patient who is already enrolled in another therapeutic clinical study
Interventions	Procalcitonin-guided AB therapy
Outcomes	Primary outcome measure: Days on antibiotics beginning with day 4 until the first day without antibiotics (up to max. 28 days follow-up) (time frame: 28 days) (designated as safety issue: No) Secondary outcome measures: Days on antibiotics during ICU stay (time frame: up to 28 days) (designated as safety issue: No) Sepsis classification (time frame: up to 28 days) (designated as safety issue: No) SOFA score (modified) (time frame: up to 28 days) (designated as safety issue: No) ICU or hospital mortality up to 28 days (time frame: up to 28 days) (designated as safety issue: No) Frequency of infections (time frame: up to 28 days) (designated as safety issue: No) ICU and hospital length of stay (time frame: up to 28 days) (designated as safety issue: No)
Starting date	29 November 2006

NCT00407147 (*Continued*)

Contact information	Stefan Ebmeyer, BRAHMS AG
Notes	Quote: "The study is undertaken as prospective, randomized, controlled, multicenter trial. The study population, ICU patients with empiric antibiotic treatment due to suspected but unproven infection, is randomly assigned to either a Standard Care Group or a Procalcitonin (PCT) Guided Group. In the standard care group, antibiotic treatment would be based totally on clinical decision making with "traditional thought processes" (i.e., cultures, response to antibiotics, risk of untreated infection, other laboratory findings, etc.). The PCT guided group will use the same "traditional thought processes" and in addition the physician will be given access to a PCT value for Day 1 and Day 4 along with the recommended thresholds for likelihood of infection. In conjunction with other laboratory findings and clinical assessments the threshold of PCT is used to continue or discontinue empiric antibiotic treatment."

NCT00692848

Trial name or title	Impact of procalcitonin on the management of children aged 1 to 36 month presenting with a fever without a source
Methods	RCT
Participants	Children aged 1 to 36 months presenting with a fever without a source Inclusion criteria: • Children 1 to 36 months with rectal temperature > 38.0 °C and no identified source of infection after history and physical examination Exclusion criteria: • Acquired or congenital immunodeficiency
Interventions	Procalcitonin for deciding about initiation of antibiotic therapy
Outcomes	Primary outcome measure: Difference in prescription of antibiotics between the 2 groups, excluding those treated for a bacterial infection identified by the ED investigations Secondary outcome measures: Difference in hospitalisation rate between the 2 groups (excluding those hospitalised for an identified infection) Procalcitonin sensitivity and specificity
Starting date	November 2006
Contact information	
Notes	Quote: "Serious bacterial infections are often difficult to detect in children with fever without source. Procalcitonin is a better blood marker of infection than white blood cell count and possibly than C-reactive protein. This could lead to a reduction in antibiotic prescription. Our objective is to evaluate the impact of procalcitonin result on antibiotic prescription in children 1 to 36 month old with fever without source and our hypothesis is that it will lower the antibiotic prescription rate."

NCT00832039

Trial name or title	Placebo controlled trial of sodium selenite and procalcitonin guided antimicrobial therapy in severe sepsis (SISPCT)
Methods	RCT
Participants	Inclusion criteria: • Severe sepsis or septic shock according to American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) criteria • Onset of severe sepsis or septic shock < 24 h • Age >= 18 years • Informed consent Exclusion criteria: • Pregnant or breast-feeding women • Fertile female women without effective contraception • Participation in interventional clinical trial within the last 30 days • Current participation in any study • Former participation in this trial • Selenium intoxication • No commitment to full patient support (i.e. DNR order) • Patient's death is considered imminent due to coexisting disease • Relationship of the patient to study team member (i.e. colleague, relative) • Infection where guidelines recommend a longer duration of antimicrobial therapy (i.e. endocarditis, tuberculosis, malaria etc.) • Immunocompromised patients
Interventions	Procalcitonin testing and sodium selenite
Outcomes	Primary outcome measure: All-cause mortality (time frame: 28 days) (designated as safety issue: No) Secondary outcome measures: Mean total SOFA and SOFA sub-scores (time-frame: study duration) (designated as safety issue: No) All-cause mortality (time-frame: 90 days) (designated as safety issue: No) Frequency and duration of mechanical ventilation (time-frame: 90 days) (designated as safety issue: No) Frequency and duration of vasopressor support (time-frame: 90 days) (designated as safety issue: No) Frequency of adverse events and severe adverse events (time-frame: study duration) (designated as safety issue: Yes) Clinical cure and microbiological cure (time-frame: days 4, 7, 10, 14) (designated as safety issue: No) Duration of antimicrobial therapy (time-frame: study duration) (designated as safety issue: No) Costs of antimicrobial therapy (time-frame: study duration) (designated as safety issue: No) Time to change of antibiotic therapy (time-frame: duration of study) (designated as safety issue: No) Days alive without antimicrobial therapy (time-frame: study duration) (designated as safety issue: No) Frequency of resistance against antibiotics (VRE, MRSA, ESBL) (time-frame: study duration) (designated as safety issue: Yes) ICU length of stay (time-frame: 90 days) (designated as safety issue: No) Hospital length of stay (time-frame: 90 days) (designated as safety issue: No) Rate of surgical procedures for focus control (time-frame: study duration) (designated as safety issue: No) Rate of procedures to diagnose infections (time-frame: study duration) (designated as safety issue: No) Frequency of new infections (time-frame: study duration) (designated as safety issue: No)

NCT00832039 (*Continued*)

Starting date	28 January 2009
Contact information	Konrad Reinhart, M.D., Friedrich-Schiller-University Jena
Notes	Quote: "Detailed Description: This is a multicentre trial of the German Network Sepsis (SepNet) on patients with severe sepsis or septic shock. This study is supported by unrestricted grants The release of reactive oxygen species is an important factor in the development of sepsis induced multiorgan dysfunction syndrome. Common protection mechanisms are impaired in this syndrome. Serum levels of selenium, a cofactor of the glutathion peroxidase, are reduced. Several studies suggest a benefit of selenium application in patients with severe sepsis but data from large clinical trials are not available. After inclusion into the study, patients are randomly allocated to a placebo or selenium group. Treating physicians and patients are blinded regarding the allocation. The selenium group receives sodium selenite intravenously - 1000 µg as a bolus followed by a continuous infusion of 1000 µg per day until the end of ICU treatment but not longer than 21 days Procalcitonin (procalcitonin) is a biomarker which is elevated in the blood of patients with severe sepsis/ septic shock. Data from patients with community-acquired pneumonia demonstrated that this biomarker can be used to decide on the duration of antimicrobial therapy. Studies with small sample size seem to confirm this in ICU patients with severe sepsis. However, this needs to be confirmed in a larger cohort. All patients are randomly allocated to a procalcitonin-guided algorithm or a control group. In the procalcitonin-guided group, procalcitonin is measured at randomisation, day 4, 7, 10 and 14. Depending on the procalcitonin course, the protocol recommends to change, alter, or stop anti-infectious measures. In the control group, anti-infectious therapy is left to the discretion of the treating physician."

NCT00854932

Trial name or title	Neonatal Procalcitonin Intervention Study (NeoPInS)
Methods	RCT
Participants	Inclusion criteria: • Term and near term infants with a gestational age > 34 weeks • Suspected sepsis in the first 3 days of life requiring empiric antibiotic therapy • Parental consent Exclusion criteria: • Surgery in the first week of life • Severe congenital malformations
Interventions	Procalcitonin testing
Outcomes	Primary outcome measure: The absolute reduction of the duration of antibiotic therapy with unchanged outcome (time frame: 1 month) (designated as safety issue: Yes). Unchanged outcome = proportion of infants with a recurrence of infection requiring additional courses of antibiotic therapy within 72 hours after ending antibiotic therapy and/or death in the first month of life Secondary outcome measures: Duration of hospitalisation (time frame: 1 month) (designated as safety issue: Yes)

NCT00854932 (*Continued*)

Starting date	2 March 2009
Contact information	Contact: Martin Stocker, MD
Notes	Quote: "In neonates, clinical signs and symptoms associated with early-onset sepsis are non-specific and currently available tests have poor positive and negative predictive values. The investigators hypothesise that procalcitonin (procalcitonin) has a reliable negative predictive value to allow a reduction in duration of empiric antibiotic therapy in suspected neonatal early-onset sepsis with unchanged outcome. This study is designed as a multicentre, prospective, randomised intervention trial. The duration of antibiotic therapy in the standard group is based on the attending physician's assessment of the probability of infection during hospitalisation. In the procalcitonin group, if infection is considered to be unlikely or possible, antibiotic therapy is discontinued when 2 consecutive procalcitonin values are within the normal range."

NCT00914550

Trial name or title	Use of procalcitonin level for guidance of the treatment of suspected community acquired pneumonia
Methods	Observational model: case control
Participants	Inclusion criteria: • Adults • New radiographic findings consistent with the presence of infiltrates • Antibiotic therapy Exclusion criteria: • Critically ill patients on admission
Interventions	Procalcitonin testing
Outcomes	Primary outcome measure: Differences in antibiotic discontinuation as an effect of the caregivers learning procalcitonin levels for the therapy of new radiographic lung infiltrates
Starting date	June 2009
Contact information	
Notes	Quote: "The purpose of the study is to learn if a blood test is helpful to the doctors in deciding whether you need antibiotic therapy for possible pneumonia. The blood test is called a Procalcitonin level and sometimes the test reflects infection with certain bacteria (germs). When the doctors learn the results of these blood tests, they may be able to stop some of the antibiotic medications that they may have given to the patients. The study is designed, so that on a randomised basis (50/50 chance) the results from measuring Procalcitonin will be given to the patients' doctor. When the doctor receives these results, he/she may use this information, along with other information, to decide whether to continue antibiotic therapy."

NCT00987818

Trial name or title	Procalcitonin guided versus conventional antibiotic therapy in patients with sepsis in the ICU
Methods	RCT
Participants	Inclusion criteria: • Patients admitted to the ICU • Age > 18 years • Antibiotic therapy for sepsis with a suspected or proven focus of infection Exclusion criteria: • Age < 18 years • Pregnancy • Infection or presumed infection requiring prolonged antibiotic therapy (osteomyelitis, meningitis, endocarditis, septic arthritis, mediastinitis, tuberculosis, *Pneumocystis jiroveci* pneumonia, toxoplasmosis, legionellosis, listeriosis) • Indication for prolonged systemic prophylactic antibiotic therapy • Severe viral or parasitic infections (haemorrhagic fever, malaria) • Antibiotic therapy started 48 hours before enrolment • Severe immunocompromised patients (AIDS with a CD4 count < 200 cells/mm³, severe neutropenia (< 500 neutrophils/mm³), patients undergoing immunosuppressive therapy after solid organ transplantation) • Patients foregoing life-sustaining treatment
Interventions	Procalcitonin testing
Outcomes	Primary outcome measures: Duration of antibiotic therapy (time frame: 28 days) (designated as safety issue: Yes) Secondary outcome measures: 28-day mortality (time frame: 28 days) (designated as safety issue: Yes)
Starting date	Unclear
Contact information	Responsible Party: HJ van Leeuwen, MD PhD, Alysis Zorggroep, Rijnstate Hospital
Notes	Quote: "The adequacy of early empiric antimicrobial therapy is an important factor in determining the outcome in patients with severe sepsis. The duration of adequate antibiotic therapy in these patients however is less clear. Duration of antibiotic therapy in patients with sepsis in the ICU based on inflammatory markers has not been extensively studied Procalcitonin (procalcitonin) is an acute phase protein that has prognostic value in critically ill patients and can be used to monitor disease activity in sepsis and systemic inflammation. This study will examine the effect of procalcitonin guided antibiotic therapy compared with conventional antibiotic therapy on treatment duration in patients with sepsis admitted to the ICU."

NCT01018199

Trial name or title	Procalcitonin versus C-reactive protein to guide therapy in community acquired pneumonia (CAP-Marker)
Methods	RCT
Participants	Inclusion criteria: 1. Age ≥ 18 years 2. Signed informed consent 3. Suspected or confirmed community-acquired pneumonia Exclusion criteria: 1. Nosocomial pneumonia: development of symptoms after 48 hours of admission to the emergency department, or within 14 days after hospital discharge 2. Patients with lung cancer confirmed strongly suspected. 3. Patients with severe immunosuppression, such as severe neutropenia (< 500 neutrophils/mm^3), use of corticosteroids in doses above 0.5 mg/kg/day of prednisone or equivalent for at least 2 weeks, transplantation of solid organs or cells haematopoietic, use of immunosuppressants for any other reason (e. g. azathioprine or cyclosporine), hypogammaglobulinaemia 4. Patients with asplenia in any order 5. Pregnant 6. Patients with known HIV infection 7. Stay indicated only for social reasons 8. Patients on antibiotics for any other reason 9. Patients with multiple trauma, burns or surgery grid size in the last 5 days
Interventions	Procalcitonin testing and CRP testing
Outcomes	Primary outcome measures: Duration of antibiotic therapy for the first episode of infection (time frame: 28 days) (designated as safety issue: No) Total antibiotic exposure days per 1000 days (time frame: 28 days) (designated as safety issue: No) Days alive without antibiotics (time frame: 28 days) (designated as safety issue: No) Secondary outcome measures: All-cause 28-day mortality (time frame: 28 days) (designated as safety issue: Yes) Clinical cure rate (time frame: 28 days) (designated as safety issue: Yes) Infection relapse (diagnosed less than 48 h after antibiotic discontinuation) (time frame: 28 days) (designated as safety issue: Yes) Length of hospitalisation stay (time frame: whole hospitalisation) (designated as safety issue: No) In-hospital mortality (time frame: 28 days) (designated as safety issue: Yes) Nosocomial infection rate (time frame: 28 days) (designated as safety issue: Yes) Nosocomial superinfection (diagnosed more than 48 hours after discontinuation of the antibiotic therapy given to the first episode of infection) (time frame: 28 days) (designated as safety issue: Yes) Isolation of resistant bacteria (time frame: 28 days) (designated as safety issue: Yes) All-cause 90-day mortality (time frame: 90 days) (designated as safety issue: Yes) Costs of hospitalisation (time frame: whole hospitalisation) (designated as safety issue: Yes)
Starting date	December 2009
Contact information	Contact: Karla F Finotti, MD

NCT01018199 (*Continued*)

Notes	

NCT01025180

Trial name or title	Study of procalcitonin (procalcitonin)-guided antibiotic use in severe sepsis patients without obvious infection (Pro-SEPS)
Methods	RCT
Participants	Inclusion criteria: • Hospitalised in resuscitation ward • Severe sepsis symptomatology • At least 2 SIRS criteria • No infectious aetiology detected • At least one organ deficiency Exclusion criteria: • The presence of a pathogen agent or infectious centre clearly identified • Pregnancy • Burned • Patients with therapeutic limitation • Recent surgery • Secondary neutropenia
Interventions	Procalcitonin testing for AB guidance
Outcomes	Primary outcome measure: Rate of patients undergoing antibiotic treatment at D5 (time frame: at D5) (designated as safety issue: Yes) Secondary outcome measures: Evolution of the SOFA score between D0, D3 and D5 (time frame: D30) (designated as safety issue: Yes)
Starting date	1 December 2009
Contact information	Djillali Annane: Professor, Co-ordinator and Principal Investigator
Notes	Quote: "A recent study has demonstrated that in low respiratory infections, a strategy using prescription of antibiotics based on the pro-calcitonin level allows decreasing recourse to antibiotics by 47% without prognostic modification The aim is to evaluate the impact on antibiotics consumption of an algorithm using procalcitonin level in patients exhibiting severe sepsis symptomatology but without clearly identified hosted germs or infectious centre This multicentre study is a randomised prospective open study involving 9 ICU departments in France, comparing two strategies on antibiotic therapy treatment period one based on procalcitonin level(experimental group) the other on physician's appreciation(control group) 140 adult patients should be included with a severe sepsis symptomatology, whose infectious etiology has not been proven. The main non-inclusion criterion is: the presence of a pathogen agent or infectious centre clearly identified The primary outcome is the rate of patients undergoing antibiotic treatment at D5

NCT01025180 (*Continued*)

	Secondary outcomes: duration of the antibiotic treatment, mortality rate and duration in stay in intensive care ward and evolution of the SOFA score between D0, D3 and D5 Duration of patient enrolment is 30 days."

NCT01139489

Trial name or title	Safety and efficacy of procalcitonin guided antibiotic therapy in adult intensive care units (ICUs) (SAPS)
Methods	RCT
Participants	Inclusion criteria: • Age over 18 years old • Receiving antibiotics for no more than 24 hours for an assumed or proven infection • Informed consent Exclusion criteria: • Failure to obtain written consent to participate • Patients receiving prolonged antibiotic therapies (> 3 weeks, e.g. endocarditis, cerebral/hepatic abscess) • Patients with severe infections due to viruses or parasites (e.g. dengue, *Toxoplasma gondii*, *Plasmodium* spp.) • Patients infected with *Mycobacterium tuberculosis* • Patients entering the ICU for postoperative observation and/or on antibiotic prophylaxis with an estimated length of stay less then 24 h • Patients suffering from cystic fibrosis • Severely immunocompromised patients such as patients with HIV and with a CD4 count of less than 200 cells/mm, neutropenic patients (< 500 neutrophils per mL) or patients with solid organ transplantation • Moribund patients
Interventions	Procalcitonin-guided AB therapy
Outcomes	Primary outcome measures: Mortality (time frame: 28 days) (designated as safety issue: Yes) Consumption of antibiotics expressed as the defined daily dosage and duration of antibiotic therapy expressed in days of therapy (time frame: between day 1 and day 28) (designated as safety issue: Yes) Secondary outcome measures: Length of ICU stay (time frame: between day 1 and day 28) (designated as safety issue: Yes) Acquisition costs of antibiotics (time frame: between day 1 and day 28) (designated as safety issue: No), expressed in Euros Acquisition costs of procalcitonin (time frame: between day 1 and day 28) (designated as safety issue: No), expressed in Euros
Starting date	November 2009
Contact information	Contact: Albertus Beishuizen, Dr; beishuizen@vumc.nl
Notes	Quote: "This is a randomised controlled trial comparing standard-of-care therapy of infections in critically ill patients with a procalcitonin-guided approach evaluating efficacy (antibiotics consumption) and safety (mortality)."

NCT01379547

Trial name or title	Procalcitonin to shorten antibiotics duration in ICU patients (ProShort)
Methods	RCT
Participants	Inclusion criteria: • All patients with laboratory or image-confirmed severe infection at admission or during stay in ICU will be eligible for inclusion Definition of laboratory or image-confirmed severe infection: 1. 2 or more of 4 signs of inflammation: temperature > 38.3 ℃ or < 36 ℃; heart rate > 90 beats/min; respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg; WBC > 12,000 cells/mm³, < 4000 cells/mm³, or > 10% bands 2. Initial procalcitonin > 0.5 μg/L 3. Presence of either laboratory or image evidence of infection Laboratory evidence: Sign of inflammation in urine, CSF, ascites, pleural effusion or local abscess Image evidence: Compatible findings on chest X ray, ultrasound, CT or MR image Exclusion criteria: • Age less than 20 years • Known pregnancy • Presence of DNR order • Expected ICU stay less than 3 days • Neutropenia (ANC count < 500/mm³) • Specific infections for which long-term antibiotic treatment is strongly recommended: lung abscess or empyema, bacterial meningitis, osteomyelitis, infective endocarditis, local abscess, mediastinitis
Interventions	
Outcomes	Primary outcome measures: Average antibiotics duration (time frame: 28 days) (designated as safety issue: No) 28-day mortality rate (time frame: 28 days) (designated as safety issue: Yes) Safety endpoints Secondary outcome measures: Proportion of antibiotics use in both arms (time frame: 28 days) (designated as safety issue: No) Length of ICU stay (time frame: 90 days) (designated as safety issue: Yes) Recurrence of fever within 72 hours of antibiotics discontinuation (time frame: 28 days) (designated as safety issue: Yes) APACHE-II score or SOFA score (time frame: 28 days) (designated as safety issue: Yes) Reinfection between 72 hours and 28 days post antibiotics discontinuation (time frame: 28 days) (designated as safety issue: Yes) 90-day all-cause mortality (time frame: 90 days) (designated as safety issue: Yes) 90-day infection-related readmission rate (time frame: 90 days) (designated as safety issue: Yes)
Starting date	21 June 2011
Contact information	Chien-Chang Lee, Attending Physician/Assistant Professor, Department of Emergency Medicine, National Taiwan University Hospital

NCT01379547 (*Continued*)

Notes	Quote: "The trial is aimed to show that implementation of a procalcitonin-guided antibiotics algorithm may result in shortened antibiotics course in ICU sepsis patients without inferior outcome as compared to the conventional therapy."

AB: antibiotic
ACCP: American College of Chest Physicians
ANC: absolute neutrophil count
CRP: C-reactive protein
CSF: cerebrospinal fluid
CT: computerised tomography
d: day
DNR: do not resuscitate
ED: emergency department
ESBL: extended spectrum beta lactamase
h: hour
ICU: intensive care unit
MR: magnetic resonance
MRSA: methicillin-resistant *Staphylococcus aureus*
$O_{2.}$ oxygen
Pa: arterial
RCT: randomised controlled trial
SCCM: Society of Critical Care
SIRS: systemic inflammatory response syndrome
SOFA: Sequential Organ Failure Assessment score
VRE: vancomycin-resistant Enterococcus
WBC: white blood cells

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	14	4211	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.70, 1.19]
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	7	2605	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.72, 1.52]
1.3 Intensive care unit trials	5	598	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.53, 1.17]
2 Treatment failure at 30 days	14	4211	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.71, 0.97]
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	7	2605	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.96]
2.3 Intensive care unit trials	5	598	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.53, 1.17]

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	14	4211	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.70, 1.19]
1.1 Adherence to procalcitonin algorithm > 70%	6	2964	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.66, 1.38]
1.2 Adherence to procalcitonin algorithm < 70% or not available	8	1247	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.58, 1.28]
2 Treatment failure at 30 days stratified by adherence	14	4211	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.71, 0.97]
2.1 Adherence to procalcitonin algorithm > 70%	6	2964	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.99]
2.2 Adherence to procalcitonin algorithm < 70% or not available	8	1247	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.64, 1.22]
3 Mortality at 30 days stratified by allocation concealment	14	4211	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.70, 1.19]
3.1 Trials with concealed allocation	7	3124	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.64, 1.20]
3.2 Trials without concealed allocation	7	1087	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.59, 1.75]
4 Treatment failure at 30 days stratified by allocation concealment	14	4211	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.71, 0.97]

4.1 Trials with concealed allocation	7	3124	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.72, 1.01]
4.2 Trials without concealed allocation	7	1087	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.53, 1.05]

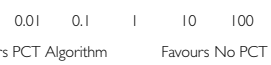
Analysis 1.1. Comparison 1 Procalcitonin algorithm versus no procalcitonin algorithm stratified by clinical setting, Outcome 1 Mortality at 30 days.

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

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

Outcome: 1 Mortality at 30 days

Study or subgroup	PCT Algorithm n/N	No PCT Algorithm n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Primary care trials					
Briel 2008	0/232	1/226		0.7 %	0.32 [0.01, 7.98]
Burkhardt 2010	0/275	0/275			Not estimable
Subtotal (95% CI)	**507**	**501**		**0.7 %**	**0.32 [0.01, 7.98]**
Total events: 0 (PCT Algorithm), 1 (No PCT Algorithm)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
2 Emergency department trials					
Christ-Crain 2004	4/124	3/119		3.1 %	1.29 [0.28, 5.88]
Christ-Crain 2006	18/151	20/151		15.6 %	0.89 [0.45, 1.75]
Stolz 2007	3/102	2/106		2.2 %	1.58 [0.26, 9.63]
Schuetz 2009	34/671	33/688		30.1 %	1.06 [0.65, 1.73]
Kristoffersen 2009	2/103	1/107		1.2 %	2.10 [0.19, 23.51]
Long 2009	0/63	0/64			Not estimable
Long 2011	0/77	0/79			Not estimable
Subtotal (95% CI)	**1291**	**1314**		**52.3 %**	**1.05 [0.72, 1.52]**
Total events: 61 (PCT Algorithm), 59 (No PCT Algorithm)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.82, df = 4 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 0.26 (P = 0.80)					
3 Intensive care unit trials					
Nobre 2008	5/25	8/27		4.4 %	0.59 [0.16, 2.14]
Hochreiter 2009	7/24	5/19		4.0 %	1.15 [0.30, 4.44]
Schroeder 2009	0/4	0/4			Not estimable



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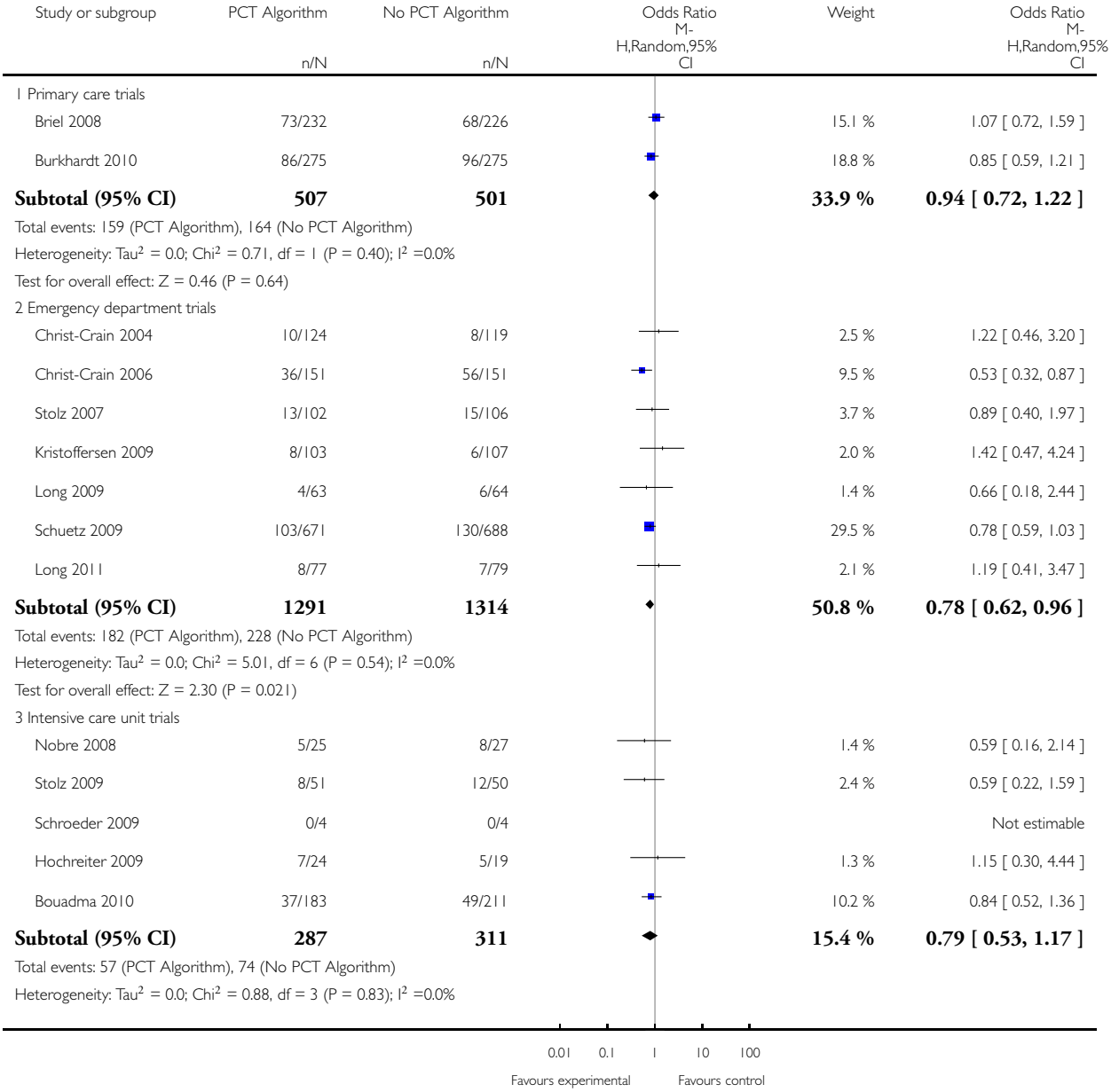
Study or subgroup	PCT Algorithm n/N	No PCT Algorithm n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Stolz 2009	8/51	12/50		7.3 %	0.59 [0.22, 1.59]
Bouadma 2010	37/183	49/211		31.2 %	0.84 [0.52, 1.36]
Subtotal (95% CI)	**287**	**311**		**47.0 %**	**0.79 [0.53, 1.17]**
Total events: 57 (PCT Algorithm), 74 (No PCT Algorithm)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.88$, df = 3 (P = 0.83); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.18 (P = 0.24)					
Total (95% CI)	**2085**	**2126**		**100.0 %**	**0.91 [0.70, 1.19]**
Total events: 118 (PCT Algorithm), 134 (No PCT Algorithm)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.18$, df = 9 (P = 0.96); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.68 (P = 0.50)					
Test for subgroup differences: $Chi^2 = 1.48$, df = 2 (P = 0.48), $I^2 = 0.0\%$					

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

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

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

Outcome: 2 Treatment failure at 30 days



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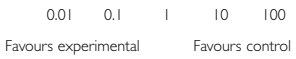
Study or subgroup	PCT Algorithm n/N	No PCT Algorithm n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Test for overall effect: Z = 1.18 (P = 0.24)					
Total (95% CI)	**2085**	**2126**		**100.0 %**	**0.83 [0.71, 0.97]**
Total events: 398 (PCT Algorithm), 466 (No PCT Algorithm)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 7.88, df = 12 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 2.37 (P = 0.018)					
Test for subgroup differences: Chi^2 = 1.28, df = 2 (P = 0.53), I^2 =0.0%					



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

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

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

Outcome: 1 Mortality at 30 days stratified by adherence

Study or subgroup	PCT Algorithm n/N	No PCT Algorithm n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Adherence to procalcitonin algorithm > 70%					
Christ-Crain 2004	4/124	3/119		3.1 %	1.29 [0.28, 5.88]
Christ-Crain 2006	18/151	20/151		15.6 %	0.89 [0.45, 1.75]
Briel 2008	0/232	1/226		0.7 %	0.32 [0.01, 7.98]
Nobre 2008	5/25	8/27		4.4 %	0.59 [0.16, 2.14]
Schuetz 2009	34/671	33/688		30.1 %	1.06 [0.65, 1.73]
Burkhardt 2010	0/275	0/275			Not estimable
Subtotal (95% CI)	**1478**	**1486**		**54.0 %**	**0.96 [0.66, 1.38]**
Total events: 61 (PCT Algorithm), 65 (No PCT Algorithm)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.33, df = 4 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 0.24 (P = 0.81)					
2 Adherence to procalcitonin algorithm < 70% or not available					

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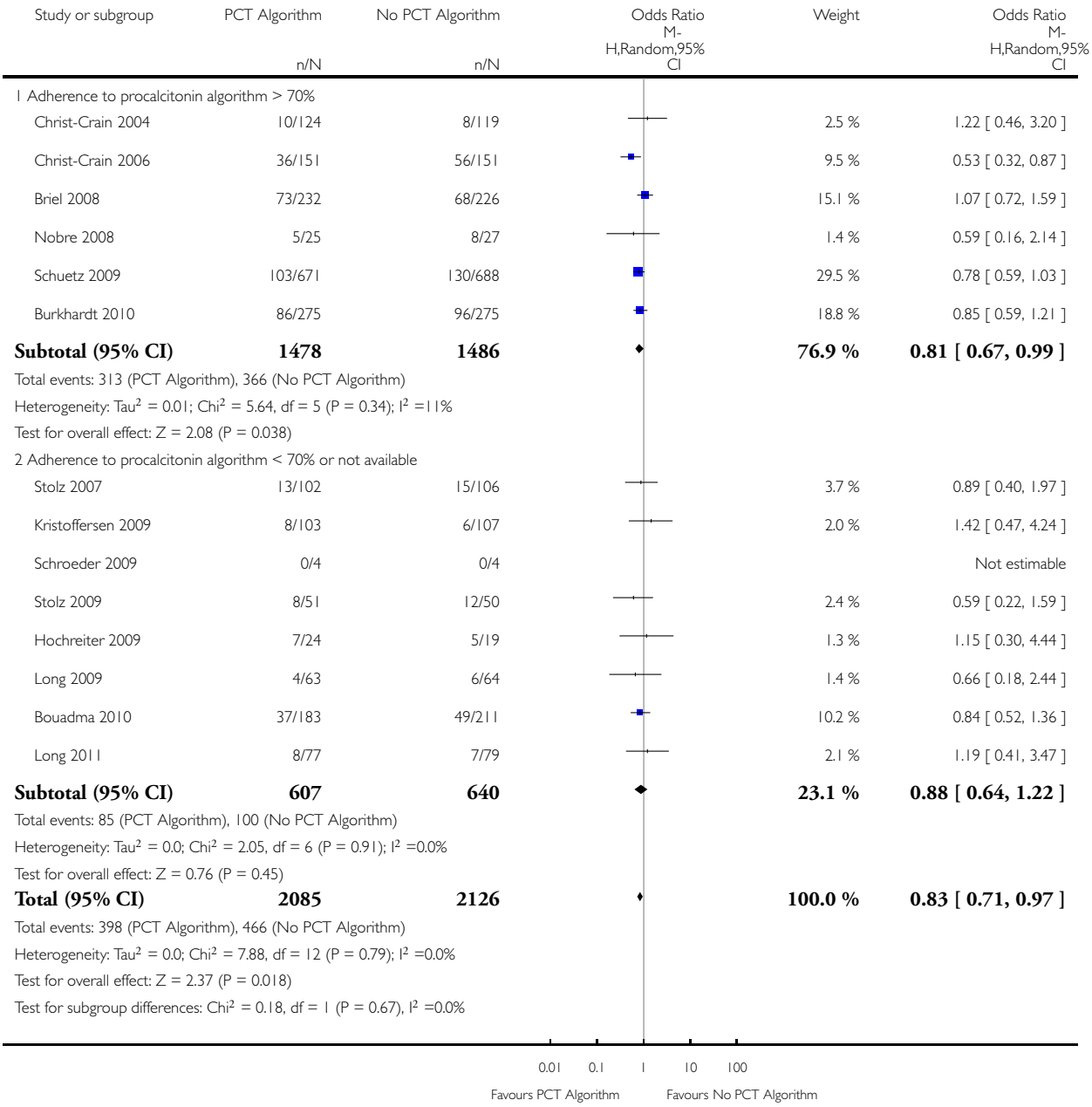
Study or subgroup	PCT Algorithm n/N	No PCT Algorithm n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Stolz 2007	3/102	2/106		2.2 %	1.58 [0.26, 9.63]
Long 2009	0/63	0/64			Not estimable
Stolz 2009	8/51	12/50		7.3 %	0.59 [0.22, 1.59]
Kristoffersen 2009	2/103	1/107		1.2 %	2.10 [0.19, 23.51]
Hochreiter 2009	7/24	5/19		4.0 %	1.15 [0.30, 4.44]
Schroeder 2009	0/4	0/4			Not estimable
Bouadma 2010	37/183	49/211		31.2 %	0.84 [0.52, 1.36]
Long 2011	0/77	0/79			Not estimable
Subtotal (95% CI)	**607**	**640**		**46.0 %**	**0.86 [0.58, 1.28]**
Total events: 57 (PCT Algorithm), 69 (No PCT Algorithm)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.70$, df = 4 (P = 0.79); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.74 (P = 0.46)					
Total (95% CI)	**2085**	**2126**		**100.0 %**	**0.91 [0.70, 1.19]**
Total events: 118 (PCT Algorithm), 134 (No PCT Algorithm)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.18$, df = 9 (P = 0.96); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.68 (P = 0.50)					
Test for subgroup differences: $Chi^2 = 0.14$, df = 1 (P = 0.70), $I^2 = 0.0\%$					

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

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

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

Outcome: 2 Treatment failure at 30 days stratified by adherence

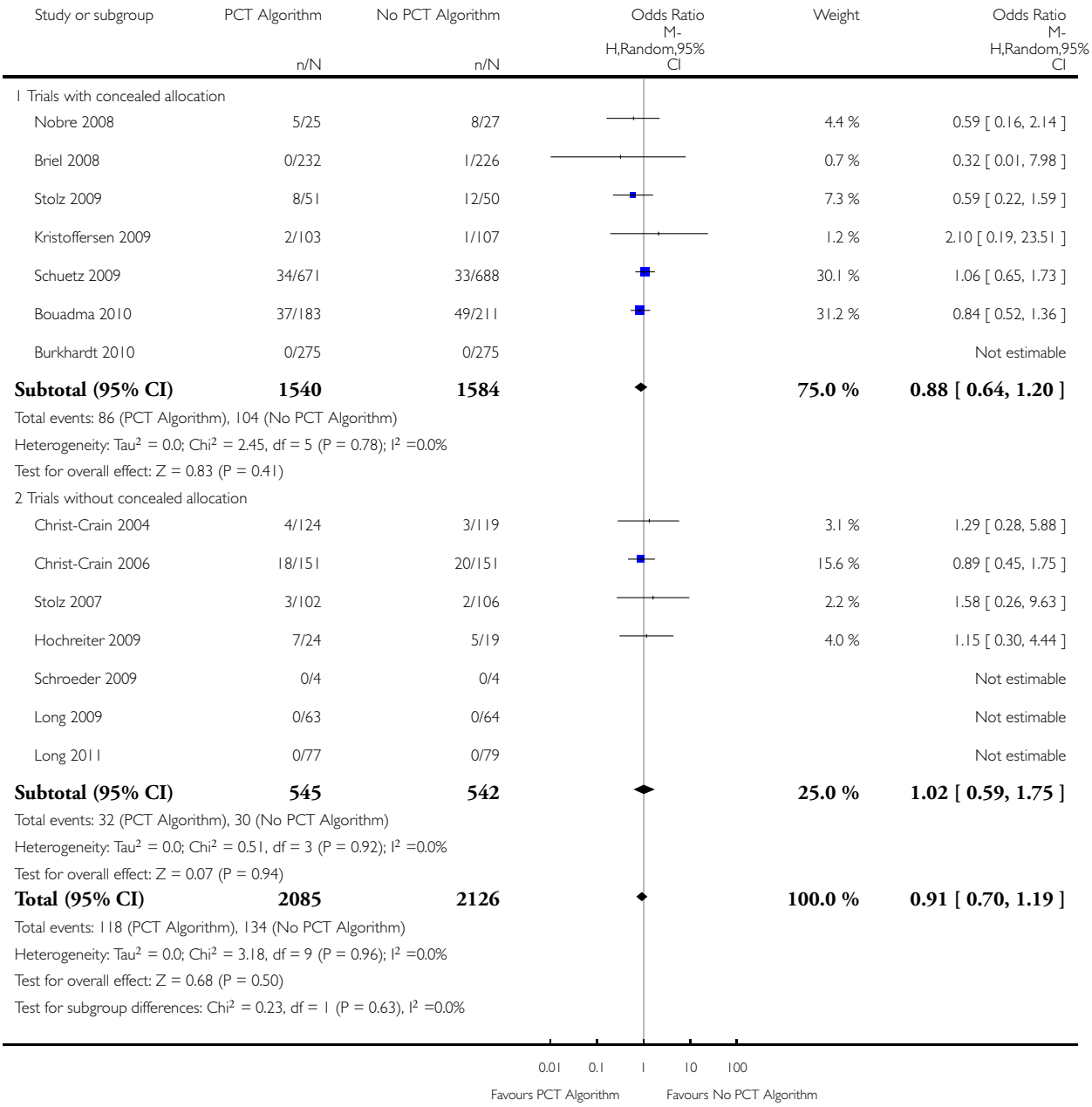


Analysis 2.3. Comparison 2 Procalcitonin algorithm versus no procalcitonin algorithm, sensitivity analyses, Outcome 3 Mortality at 30 days stratified by allocation concealment.

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

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

Outcome: 3 Mortality at 30 days stratified by allocation concealment

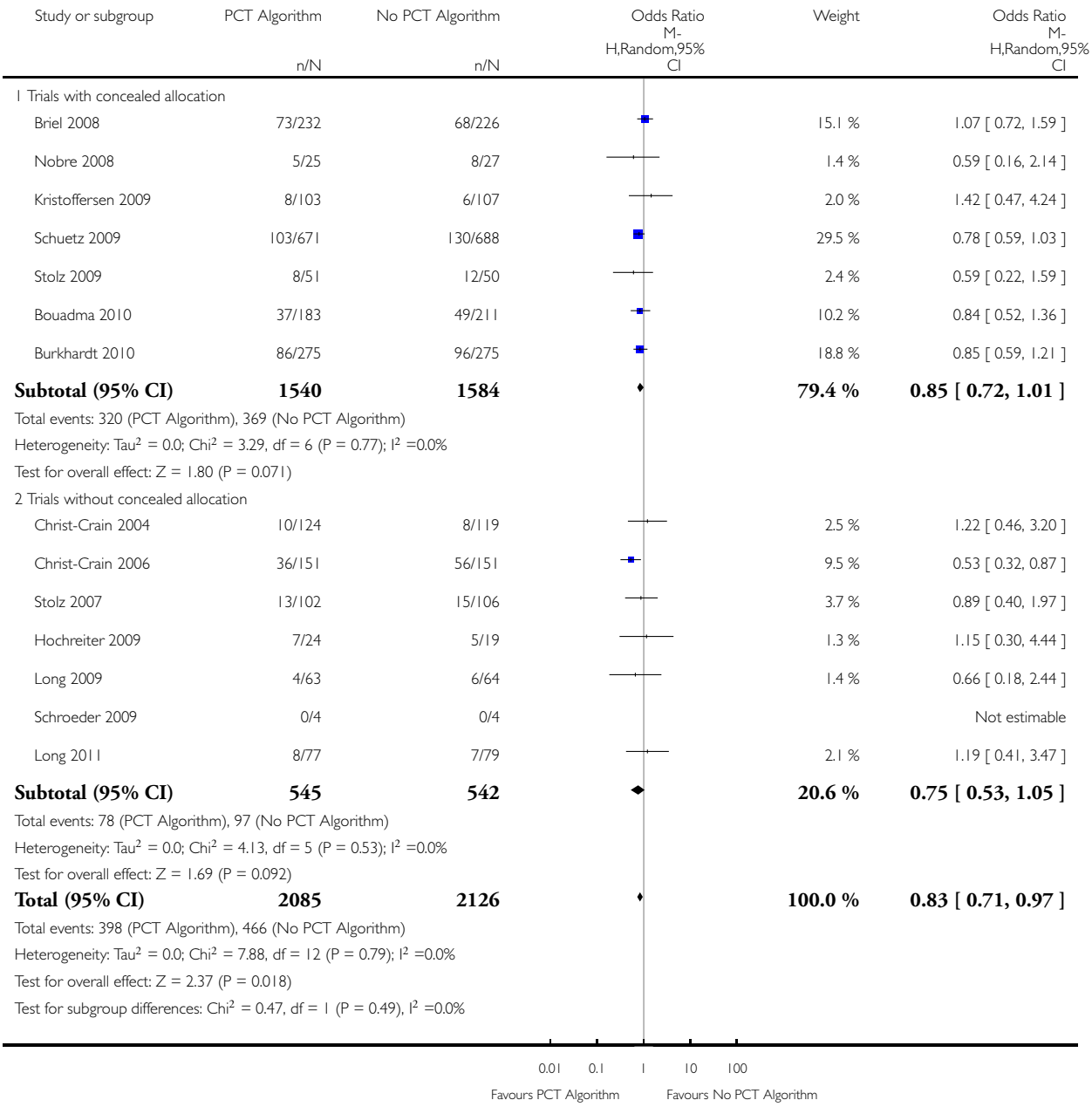


Analysis 2.4. Comparison 2 Procalcitonin algorithm versus no procalcitonin algorithm, sensitivity analyses, Outcome 4 Treatment failure at 30 days stratified by allocation concealment.

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

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

Outcome: 4 Treatment failure at 30 days stratified by allocation concealment



ADDITIONAL TABLES

Table 1. Characteristics of included trials

First author (year)	Country	Setting, type of trial	Clinical diagnosis	Type of procalcitonin algorithm and procalcitonin cut-offs used (µg/L)	No. ARI patients (study total)	Primary endpoint	Follow-up time
Briel 2008	Switzerland	Primary care, multicentre	Upper and lower ARIs	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
Burkhardt (2010)	Germany	Primary care, multicentre	Upper and lower ARIs	Initiation; R against AB: < 0.25; R for AB: > 0.25	550 (571)[a]	Days with restricted activities	1 month
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)	243 (243)	AB use	2 weeks
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)	302 (302)	AB use	6 weeks
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)[b]	AB use	2 to 3 weeks
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)[c]	AB use	Hospital stay

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

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	AB use	1 month
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)	1359 (1381)[d]	AB use	1 month
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)[e]	AB use	1 month
Nobre (2008)	Switzerland	Medical 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)[f]	AB use	1 month
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)[g]	AB use	Hospital stay
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)[h]	AB use	Hospital stay
Stolz (2010)	Switzerland, USA	Medical ICU, multicentre	Clinically diagnosed VAP	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
Bouadma (2010)	France	Medical ICU, multicentre	Suspected bacterial infections during ICU stay	Initiation and duration; R against AB: < 0.5 (< 0.25); R for AB:	394 (630)[i]	All-cause mortality	2 months

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

			without prior AB (> 24 h)	> 0.5 (> 1.0)			

[a] 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).
[b] 18 post randomisation exclusions due to absence of COPD according to GOLD criteria.
[c] 13 post randomisation exclusions (3 no procalcitonin testing, 6 not meeting inclusion criteria, 4 withdrew informed consent).
[d] 22 post randomisation exclusions due to withdrawal of consent.
[e] 16 post randomisation exclusions (6 lost to follow-up, 7 withdrew consent, 3 with final diagnosis other than CAP).
[f] 27 not considered for this analysis due to a diagnosis other than ARI.
[g] 19 not considered for this analysis due to diagnosis other than ARI.
[h] 67 not considered for this analysis due to diagnosis other than ARI.
[i] 9 post randomisation exclusions (8 withdrew consent, 1 randomised twice); 227 not considered for this analysis due to diagnosis other than ARI.
AB: antibiotic
ARI: acute respiratory infection
CAP: community-acquired pneumonia
COPD: chronic obstructive pulmonary disease
d: days
ED: emergency department
h: hours
ICU: intensive care unit
R: recommendation for or against antibiotics
SIRS: systemic inflammation response system
VAP: ventilator-associated pneumonia

Table 2. Baseline characteristics of included patients

Parameter	Procalcitonin group (n = 2085)	Control group (n = 2126)
Demographics		
Age (year), mean (SD)	59.4 (20.1)	60.1 (19.4)
Gender (male), No (%)	1152 (55.3%)	1130 (53.2%)
Clinical setting, No (%)		
Primary care	507 (24.3%)	501 (23.6%)
Emergency department	1291 (61.9%)	1314 (61.8%)
ICU	287 (13.8%)	311 (14.6%)
Primary diagnosis		
Total upper ARI, No (%)	282 (13.5%)	267 (12.6%)

Table 2. Baseline characteristics of included patients (*Continued*)

Common cold	149 (7.2%)	156 (7.3%)
Rhino-sinusitis, otitis	72 (3.5%)	65 (3.1%)
Pharyngitis, tonsillitis	61 (2.9%)	46 (2.2%)
Total lower ARI, No (%)	1752 (86.1%)	1815 (87.2%)
Community-acquired pneumonia	999 (47.9%)	1028 (48.4%)
Hospital-acquired pneumonia	31 (1.5%)	48 (2.3%)
Ventilator-associated pneumonia	126 (6%)	116 (5.5%)
Acute bronchitis	249 (11.9%)	282 (13.3%)
Exacerbation of COPD	288 (13.8%)	296 (13.9%)
Exacerbation of asthma	20 (1%)	10 (0.5%)
Unspecified lower ARI	39 (1.9%)	35 (1.7%)
Other final diagnosis, No (%)	51 (2.5%)	44 (2.1%)
Procalcitonin (µg/L), mean, median (SD, IQR)		
Overall	2.7, 0.2 (13.1, 0.1 to 0.8)	2.3, 0.2 (9.3, 0.1 to 0.8)
Primary care	0.1, 0.1 (0.9, 0.05 to 0.1)	0.2, 0.1 (1.8, 0.05 to 0.1)
Emergency department	2.4, 0.3 (10.7, 0.1 to 0.9)	2.5, 0.3 (10.0, 0.1 to 0.9)
Intensive care unit	9.3, 1.4 (26.4, 0.4 to 5.8)	6.4, 1.2 (9.3, 0.3 to 4.7)

ARI: acute respiratory infection
COPD: chronic obstructive pulmonary disease
ICU: intensive care unit
SD: standard deviation
IQR: interquartile range

Table 3. Sensitivity analysis

	Procalcitonin group	Control group	Adjusted OR (95% CI)[a]	P for interaction*
Main analysis (assumption that patients lost to follow-up did not experience an event)				
Mortality	118/2085 (5.7%)	134/2126 (6.3%)	0.94 (0.71 to 1.23)	
Treatment failure	398/2085 (19.1%)	466/2126 (21.9%)	0.82 (0.71 to 0.97)	
Assumption that patients lost to follow-up experienced an event (death or treatment failure)				
Mortality	47/1188 (4%)	44/1195 (3.7%)	0.97 (0.6 to 1.55)	
Treatment failure	410/2085 (19.7%)	476/2126 (22.4%)	0.84 (0.72 to 0.98)	
Exclusion of patients lost to follow-up (complete case analysis)				
30 days mortality	118/2072 (5.7%)	134/2116 (6.3%)	0.94 (0.71 to 1.23)	
Treatment failure	397/2072 (19.2%)	466/2116 (22%)	0.83 (0.71 to 0.96)	
Excluding ProRATA (Bouadma 2010)				
Mortality	81/1902 (4.3%)	85/1915 (4.4%)	0.97 (0.61 to 1.55)	0.81
Treatment failure	361/1902 (19%)	417/1915 (21.8%)	0.84 (0.71 to 0.98)	0.94
Excluding all ICU trials				
Mortality	61/1798 (3.4%)	60/1815 (3.3%)	0.97 (0.61 to 1.55)	0.55
Treatment failure	341/1798 (19%)	392/1815 (21.6%)	0.84 (0.72 to 1.00)	0.88
Excluding all trials with low adherence (< 70%) or not reporting adherence				
Mortality	61/1478 (4.1%)	65/1486 (4.4%)	0.97 (0.61 to 1.55)	0.96
Treatment failure	313/1478 (21.2%)	366/1486 (24.6%)	0.82 (0.69 to 0.98)	0.66
Excluding all trials without allocation concealment				
Mortality	78/1489 (5.2%)	92/1534 (6%)	0.93 (0.59 to 1.49)	0.72
Treatment failure	312/1489 (21%)	357/1534 (23.3%)	0.85 (0.72 to 1.02)	0.43
Excluding all trials without blinded outcome assessment				

Table 3. Sensitivity analysis (*Continued*)

Mortality	74/1463 (5.1%)	85/1506 (5.6%)	0.93 (0.59 to 1.49)	0.87
Treatment failure	312/1463 (21.3%)	358/1506 (23.8%)	0.85 (0.71 to 1.01)	0.47
Excluding all trials with no follow-up beyond hospital discharge				
Mortality	109/1954 (5.6%)	128/1996 (6.4%)	0.97 (0.6 to 1.55)	0.25
Treatment failure	383/1954 (19.6%)	455/1996 (22.8%)	0.82 (0.71 to 0.96)	0.26

*Analyses with individual patient data from all trials and added interaction terms (e.g. low adherence x procalcitonin group) in the regression model to test for effect modifications. P values < 0.05 indicate evidence for effect modification.

CI: confidence interval

ICU: intensive care unit

OR: odds ratio

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

	Procalcitonin group	Control group	Adjusted OR (95% CI)[a]	P
Overall	**n = 2085**	**n = 2126**		
Mortality, No (%)	118 (5.7%)	134 (6.3%)	0.94 (0.71 to 1.23)	0.754
Treatment failure, No (%)[b]	398 (19.1%)	466 (21.9%)	0.82 (0.71 to 0.97)	0.02
Setting-specific				
Primary care	**n = 507**	**n = 501**		
Mortality, No (%)	0 (0%)	1 (0.2%)	-	-
Treatment failure, No (%)[c]	159 (31.4%)	164 (32.7%)	0.95 (0.73 to 1.24)	0.687
Days with restricted activities, median (IQR)	9 (6 to 14)	9 (5 to 14)	0.05 (-0.46 to 0.56)[d]	0.854
Emergency department	**n = 1291**	**n = 1314**		
Mortality, No (%)	61 (4.7%)	59 (4.5%)	1.03 (0.7 to 1.5)	0.895
Mortality or ICU admission, No (%)	126 (9.8%)	147 (11.2%)	0.83 (0.64 to 1.08)	0.161

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

Treatment failure, No (%)[e]	182 (14.1%)	228 (17.4%)	0.76 (0.61 to 0.95)	0.014
Length of hospital stay, median (IQR)[f]	8 (4 to 13)	8 (4 to 13)	-0.42 (-1.2 to 0.35)[d]	0.283
Intensive care unit	**n = 287**	**n = 311**		
Mortality, No (%)	57 (19.9%)	74 (23.8%)	0.84 (0.54 to 1.31)	0.443
Length of ICU stay, median (IQR)	12 (6 to 23)	12 (6 to 22)	1.01 (-1.26 to 3.28)[d]	0.385
Length of hospital stay, median (IQR)	21 (11 to 38)	24 (14 to 38)	-1.36 (-4.5 to 1.77)[d]	0.393
Disease-specific				
Upper ARI	**n = 282**	**n = 267**		
Mortality, No (%)	0 (0%)	1 (0.4%)	-	-
Treatment failure, No (%)[c]	93 (33.0%)	92 (34.5%)	0.95 (0.73 to 1.24)	0.687
Community-acquired pneumonia	**n = 999**	**n = 1028**		
Mortality, No (%)	92 (9.2%)	111 (10.8%)	0.89 (0.64 to 1.23)	0.471
Ventilator-associated pneumonia	**n = 126**	**n = 116**		
Mortality, No (%)	8 (6.3%)	12 (10.3%)	0.69 (0.25 to 1.94)	0.486
Acute bronchitis	**n = 249**	**n = 282**		
Mortality, No (%)	0 (0%)	2 (0.8%)	-	-
Exacerbation of COPD	**n = 288**	**n = 296**		
Mortality, No (%)	9 (3.1%)	8 (2.7%)	1.15 (0.43 to 3.09)	0.774

[a] Multivariable hierarchical regression with outcome of interest as dependent variable, procalcitonin group; age and ARI diagnosis as independent variables; and trial as a random-effects.

[b] Treatment failure was defined according to clinical setting: primary care (death, hospitalisation, ARI-specific complications, recurrent or worsening infection and discomfort at 30 days), emergency department (mortality, ICU admission, re-hospitalisation, complications, recurrent or worsening infection within 30 days), intensive care unit (all-cause mortality within 30 days).

[c] Treatment failure was defined as death, hospitalisation, ARI-specific complications, recurrent or worsening infection and discomfort at 30 days.
[d] Adjusted difference in days from hierarchical linear regression with procalcitonin group, age and ARI diagnosis as a fixed-effect and trial as a random-effect.
[e] Treatment failure is defined as mortality, ICU admission, re-hospitalisation, complications, recurrent or worsening infection within 30 days.
[f] Two trials focusing on outpatients were excluded from this analysis (Long 2009; Long 2011).
ARI: acute respiratory infection
CI: confidence interval
COPD: chronic obstructive pulmonary disease
ICU: intensive care unit
IQR: interquartile range
OR: odds ratio

Table 5. Antibiotic treatment overall and stratified by setting and ARI diagnosis

Parameter	Procalcitonin group	Control group	Adjusted OR or difference (95% CI)[c]	P of the regression model
Overall	**n = 2085**	**n = 2126**		
Initiation of antibiotics, n (%)	1341 (64%)	1778 (84%)	0.24 (0.20 to 0.29)	< 0.001
[a] Duration of antibiotics (days), median (IQR)	7 (4 to 10)	10 (7 to 13)	-2.75 (-3.12 to -2.39)	< 0.001
[b] Total exposure of antibiotics (days), median (IQR)	4 (0 to 8)	8 (5 to 12)	-3.47 (-3.78 to -3.17)	< 0.001
Setting-specific				
Primary care	**n = 507**	**n = 501**		
Initiation of antibiotics, n (%)	116 (23%)	316 (63%)	0.10 (0.07 to 0.14)	< 0.001
[a] Duration of antibiotics (days), median (IQR)	7 (5 to 8)	7 (6 to 8)	-0.6 (-1.17 to -0.03)	0.04
[b] Total exposure of antibiotics (days), median (IQR)	0 (0 to 0)	6 (0 to 7)	-3.06 (-3.48 to -2.65)	< 0.001
Emergency department	**n = 1291**	**n = 1314**		
Initiation of antibiotics, n (%)	939 (73%)	1151 (88%)	0.34 (0.28 to 0.43)	< 0.001

Table 5. Antibiotic treatment overall and stratified by setting and ARI diagnosis (*Continued*)

[a]Duration of antibiotics (days), median (IQR)	7 (4 to 10)	10 (7 to 12)	-3.7 (-4.09 to -3.31)	< 0.001
[b]Total exposure of antibiotics (days), median (IQR)	5 (0 to 8)	9 (5 to 12)	-2.96 (-3.38 to -2.54)	< 0.001
Intensive care unit	**n = 287**	**n = 311**		
Initiation of antibiotics, n (%)	286 (100%)	311 (100%)	-	-
[a]Duration of antibiotics (days), median (IQR)	8 (5 to 15)	12 (8 to 18)	-3.17 (-4.28 to -2.06)	< 0.001
[b]Total exposure of antibiotics (days), median (IQR)	8 (5 to 15)	12 (8 to 18)	-3.21 (-4.32 to -2.10)	< 0.001
Disease-specific				
Upper ARI	**n = 282**	**n = 267**		
Initiation of antibiotics, n (%)	43 (15%)	129 (48%)	0.14 (0.09 to 0.22)	< 0.001
[a]Duration of antibiotics (days), median (IQR)	7 (5 to 8)	7 (6 to 7)	-1.16 (-2.08 to -0.24)	0.013
[b]Total exposure of antibiotics (days), median (IQR)	0 (0 to 0)	0 (0 to 7)	-2.64 (-3.16 to -2.11)	< 0.001
Community-acquired pneumonia	**n = 999**	**n = 1028**		
Initiation of antibiotics, n (%)	898 (90%)	1019 (99%)	0.07 (0.03 to 0.14)	< 0.001
[a]Duration of antibiotics (days), median (IQR)	7 (5 to 10)	10 (8 to 14)	-3.34 (-3.79 to -2.88)	< 0.001
[b]Total exposure of antibiotics (days), median (IQR)	6 (4 to 10)	10 (8 to 14)	-3.98 (-4.44 to -3.52)	< 0.001
Ventilator-associated pneumonia	**n = 126**	**n = 116**		

Table 5. Antibiotic treatment overall and stratified by setting and ARI diagnosis (*Continued*)

Initiation of antibiotics, n (%)	125 (99%)	116 (100%)	-	-
[a]Duration of antibiotics (days), median (IQR)	11 (6 to 17)	14 (9 to 19.5)	-2.23 (-4.06 to -0.39)	0.017
[b]Total exposure of antibiotics (days), median (IQR)	11 (6 to 17)	14 (9 to 19.5)	-2.34 (-4.18 to -0.5)	0.013
Acute bronchitis	**n = 249**	**n = 282**		
Initiation of antibiotics, n (%)	61 (24%)	185 (66%)	0.15 (0.10 to 0.23)	< 0.001
[a]Duration of antibiotics (days), median (IQR)	7 (4 to 9)	7 (5 to 8)	-0.38 (-1.21 to 0.46)	0.375
[b]Total exposure of antibiotics (days), median (IQR)	0 (0 to 0)	5 (0 to 7)	-3.06 (-3.69 to -2.43)	< 0.001
Exacerbation of COPD	**n = 288**	**n = 296**		
Initiation of antibiotics, n (%)	137 (48%)	216 (73%)	0.32 (0.23 to 0.46)	< 0.001
[a]Duration of antibiotics (days), median (IQR)	6 (3 to 9)	8 (6 to 10)	-1.58 (-2.33 to -0.82)	< 0.001
[b]Total exposure of antibiotics (days), median (IQR)	0 (0 to 6)	7 (0 to 10)	-3.03 (-3.76 to -2.3)	< 0.001

[a]Total days of antibiotic therapy in patients in whom antibiotics were initiated.
[b]Total days of antibiotic therapy in all randomised patients.
[c]Multivariable hierarchical model adjusted for age and diagnosis and trial as a random-effect.
ARI: acute respiratory infection
CI: confidence interval
COPD: chronic obstructive pulmonary disease
IQR: interquartile range
OR: odds ratio

CONTRIBUTIONS OF AUTHORS

PS, BM, HCB and MB conceived of the study and wrote the initial protocol. MCC, DS LB, MW, CET, JC, FT, KBB, LW, OB, TW, SS, VN and MT are investigators on included trials or were in charge of the statistical analyses; they reviewed the protocol, provided data from their respective trials and resolved queries about their trial data. NB is a research librarian experienced in the design of sensitive search strategies. PS and MB performed the statistical analyses and drafted the manuscript. All authors amended and commented on the manuscript and approved the final version. PS, BM, HCB and MB oversaw the study and act as guarantors.

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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 did not assess the secondary endpoint of side effects from antibiotic treatment, because it was not reported consistently 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 editorial process, we added further sensitivity analyses to investigate the robustness of our results. Specifically, we performed sensitivity analyses excluding trials with low adherence to procalcitonin algorithms (< 70%) or not reporting adherence, excluding all ICU trials, and excluding only the largest ICU trial due to low adherence (Bouadma 2010). We also performed sensitivity analyses assuming losses to follow-up as having the event (death or treatment failure) and sensitivity analyses

with respect to methodological quality criteria (allocation concealment and blinded outcome assessment). 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 procalcitonin algorithms.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [*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