Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis

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Summary

Background In February, 2017, the US Food and Drug Administration approved the blood infection marker procalcitonin for guiding antibiotic therapy in patients with acute respiratory infections. This meta-analysis of patient data from 26 randomised controlled trials was designed to assess safety of procalcitonin-guided treatment in patients with acute respiratory infections from different clinical settings.

Methods Based on a prespecified Cochrane protocol, we did a systematic literature search on the Cochrane Central Register of Controlled Trials, MEDLINE, and Embase, and pooled individual patient data from trials in which patients with respiratory infections were randomly assigned to receive antibiotics based on procalcitonin concentrations (procalcitonin-guided group) or control. The coprimary endpoints were 30-day mortality and setting-specific treatment failure. Secondary endpoints were antibiotic use, length of stay, and antibiotic side-effects.

Findings We identified 990 records from the literature search, of which 71 articles were assessed for eligibility after exclusion of 919 records. We collected data on 6708 patients from 26 eligible trials in 12 countries. Mortality at 30 days was significantly lower in procalcitonin-guided patients than in control patients (286 [9%] deaths in 3336 procalcitonin-guided patients *vs* 336 [10%] in 3372 controls; adjusted odds ratio [OR] 0·83 [95% CI 0·70 to 0·99], p=0·037). This mortality benefit was similar across subgroups by setting and type of infection ($p_{interactions}$>0·05), although mortality was very low in primary care and in patients with acute bronchitis. Procalcitonin guidance was also associated with a 2·4-day reduction in antibiotic exposure (5·7 *vs* 8·1 days [95% CI −2·71 to −2·15], p<0·0001) and a reduction in antibiotic-related side-effects (16% *vs* 22%, adjusted OR 0·68 [95% CI 0·57 to 0·82], p<0·0001).

Interpretation Use of procalcitonin to guide antibiotic treatment in patients with acute respiratory infections reduces antibiotic exposure and side-effects, and improves survival. Widespread implementation of procalcitonin protocols in patients with acute respiratory infections thus has the potential to improve antibiotic management with positive effects on clinical outcomes and on the current threat of increasing antibiotic multiresistance.

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Introduction

The US Food and Drug Administration approved the blood infection biomarker procalcitonin for the purpose of guiding antibiotic therapy in the context of acute respiratory infections and sepsis in February, 2017.[1] Procalcitonin is a calcitonin-related gene product expressed by human epithelial cells in response to bacterial infections and is conversely downregulated during viral infections.[2,3] Study findings have shown that procalcitonin concentrations fall rapidly during recovery from acute bacterial infections.[4] As a surrogate marker of host response to bacterial infections, procalcitonin has therefore been proposed as an adjunct to traditional clinical and diagnostic parameters in helping to manage patients presenting with clinical symptoms suggestive of systemic infections and to guide antibiotic prescribing practices.[5]

Acute respiratory tract illnesses are one of the leading causes of adult hospital admissions and death worldwide, and are associated with antibiotic overuse.[6] Although more than 40% of respiratory infections have a viral cause, imprecise bacterial diagnostics and provider concerns about co-infection prompt antibiotic prescription in most cases.[7] Several trials have reported significant reductions in antibiotic exposure, when procalcitonin was used to guide decisions about initiation of antibiotics in low-risk patients (eg, patients with a clinical syndrome of bronchitis in the emergency department) and duration of treatment in high-risk patients (eg, in patients with pneumonia).[8] However, although one trial[9] found a reduction in mortality associated with procalcitonin-guided antibiotic stewardship in the intensive care unit (ICU), conclusive evidence on the safety of this approach across clinical settings and different types of respiratory infections has

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Research in context

Evidence before this study

Use of the blood infection marker procalcitonin has gained much attention in the past 10 years as adjunct to clinical judgment in discriminating viral and bacterial infections and guiding both prescription and duration of antibiotic therapy. Several individual trials showed positive effects with a reduction of antibiotic exposure in patients with respiratory infections. Yet, there is ongoing concern about safety of this approach regarding mortality. Previous meta-analyses reported no significant effect on mortality, but confidence intervals were large and harm could thus not be excluded. Based on a protocol previously published in the published in the Cochrane Library, we did a systematic literature search on the Cochrane Central Register of Controlled Trials (CENTRAL; January, 2017, issue 1), MEDLINE (1966 to February, 2017), and Embase (1980 to February, 2017). We searched PubMed using the search terms "Calcitonin", "Procalcitonin", "ProCT" and "Anti-Bacterial Agents", "antibiotic", "Antibiotics", "antibacterial, "anti-bacterial", "amoxicillin, "penicillin", "ampicillin", "cotrimoxazole", "chloramphenicol", "trimethoprim", "sulphamethoxazole", "tmp smx" and "Biomarkers", "Marker", "Level", "levels", Guide", "Guidance" and "randomised controlled trial", "controlled clinical trial", "randomized", "randomised", "placebo", "drug therapy", "randomly", "trial", "groups", but not "animals", "not humans". For other data sources, we used similar key search terms as above. Individual patient data were collected from eligible randomised controlled trials that assessed adults with a clinical diagnosis of upper or lower acute respiratory tract infection.

Added value of this study

This study showed substantial relative and absolute reductions in antibiotic use in patients with respiratory infections managed by procalcitonin protocols compared with patients in the control group. Although such reductions were found in previous research, importantly in this large cohort of patients, we also found an improvement in clinical outcomes, namely a reduction in 30-day mortality and antibiotic side-effects. This analysis is the first report, to our knowledge, that shows clinical benefits beyond antibiotic reductions with the use of procalcitonin protocols.

Implications of all the available evidence

This report integrates most of the available evidence on procalcitonin in patients with acute respiratory infection from randomised trials. Given the positive results regarding antibiotic reduction and improvements in clinical outcomes, this report strengthens the rationale to use procalcitonin to support antibiotic stewardship decisions in patients with acute respiratory infections.

been impeded by insufficient statistical power in most individual trials.[9] Moreover, previous meta-analyses[10–12] concluded that although procalcitonin use was effective at reducing antibiotic exposure, results about the effect of procalcitonin-guided antibiotic stewardship on clinical outcomes were inconclusive. These meta-analyses, however, were based on aggregate data rather than individual patient-level data, restricting the ability to harmonise outcome definitions and to assess differences between subgroups, and also had a more narrow focus and thus only included a limited number of trials.

We therefore did a search and meta-analysis of individual patient data from 26 randomised-controlled trials,[9,13–37] based on a prespecified Cochrane protocol,[38,39] to comprehensively and definitively assess the safety of using procalcitonin to guide antibiotic decisions in patients with respiratory illnesses from different clinical settings and with different types of respiratory infections. This analysis is an update of a previous meta-analysis published in 2012,[39] and an extended version of this review will be published in the Cochrane Library.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, trial selection and data collection was done based on a protocol published in the Cochrane Library and the report prepared according to PRISMA individual patient data guidelines.[40,41]

We collected individual patient data from eligible randomised controlled trials that assessed adults with a clinical diagnosis of upper or lower acute respiratory tract infection including community-acquired pneumonia, hospital-acquired pneumonia, ventilator-associated pneumonia, and exacerbation of COPD and bronchitis. We excluded paediatric trials and trials that did not use procalcitonin for guiding initiation and duration of antibiotic treatment from the analysis.

The search strategy for this review was updated in Feb 10, 2017, in collaboration with Cochrane, and done in all databases from the date of their inception to Feb 10, 2017. All references were screened for eligibility. The databases searched were the Cochrane Central Register of Controlled Trials (CENTRAL; Feb 10, 2017, issue 1), MEDLINE (1966 to Feb 10, 2017), and Embase (1980 to Feb 10, 2017). There were no language or publication restrictions.

Two reviewers (YW and RS) independently assessed trial eligibility based on titles, abstracts, full-text reports, and further information from investigators as needed. Study protocols, case-report forms, and unedited databases containing individual patient data were requested from investigators of all eligible trials. Data from each trial were first checked against reported results and queries were resolved with the principal investigator, trial data manager, or statistician. Data were assessed in a consistent manner across all trials with standard definitions and parameters

and thus mortality and adverse outcome rates differed slightly from previous reports. In accordance with the Cochrane method, we used GRADE system[42] to assess risk for selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.

Data analysis

We included all patients with an acute respiratory infection randomly assigned to a procalcitonin-guided care group or a control group in the analysis. There were two prespecified primary endpoints: all-cause mortality within 30 days of randomisation and treatment failure within 30 days of randomisation. For trials with a shorter follow-up period, we used the available information (eg, treatment failure at the time of hospital discharge). Definitions of treatment failure varied by and were specific for each clinical setting. For the primary care setting, we defined treatment failure as death, hospital admission, infection-specific complications (eg, empyema for lower respiratory tract infection, or meningitis for upper respiratory tract infection), recurrent or worsening infection and patients reporting any symptoms of an ongoing respiratory infection (eg, fever, cough, or dyspnoea) at 30-day follow-up. Recurrent or worsening infection was defined as receiving another course of antibiotics in patients in whom antibiotics were discontinued, or increasing antibiotic dose or frequency in patients already receiving therapy for the same index infection. For patients initially evaluated in the emergency department or hospital, but not ICU setting, we defined treatment failure as death, subsequent ICU admission, hospital re-admission after index hospital discharge, infection-associated complications (eg, empyema or acute respiratory distress syndrome), and recurrent or worsening infection within 30 days of follow-up. In the ICU setting, we defined treatment failure as death within 30 days of follow-up and recurrent or worsening infection.

Secondary endpoints were antibiotic use defined as initiation of antibiotics, duration of antibiotics in days, and total exposure to antibiotics (total number of antibiotic days divided by total number of patients). Exploratory analyses of other clinical outcomes included length of hospital stay, ICU admission, length of ICU stay, antibiotic side-effects (appendix p 8), and number of days with restricted activities of daily living within 14 days of randomisation.

For the coprimary endpoints (mortality and treatment failure), we calculated odds ratios (ORs) and 95% CIs using multivariable hierarchical logistic regression.[43,44] Variables in the multivariate analysis were treatment group, age, sex, and type of infection. To control for variability within and between trials, we added a trial variable to the model as a random effect. Linear regression models were fitted for continuous endpoints and logistic regression models were fitted for binary secondary endpoints. Analyses were done following the intention-to-treat principle—analysing patients according to the groups to which they were randomly assigned. We excluded patients who withdrew consent and assumed no events for the few patients lost to follow-up before day 30 after randomisation. Censoring was used for patients with a follow-up shorter than 30 days for time-to-event analyses.

Prespecified sensitivity analyses were done for the quality indicators allocation concealment, blinded outcome assessment, follow-up time, and protocol adherence (<70% *vs* ≥70%). We evaluated heterogeneity of disease severity across the patient population with prespecified analyses stratified by clinical setting and diagnosis. We tested for subgroup effects by adding interaction terms to the model. Finally, heterogeneity and inconsistency was further assessed in a meta-analysis of aggregate data from all eligible trials using I^2 and Cochran's Q test.[45] All statistical analyses were done using Stata (version 9.2) and Review Manager (version 5.3).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

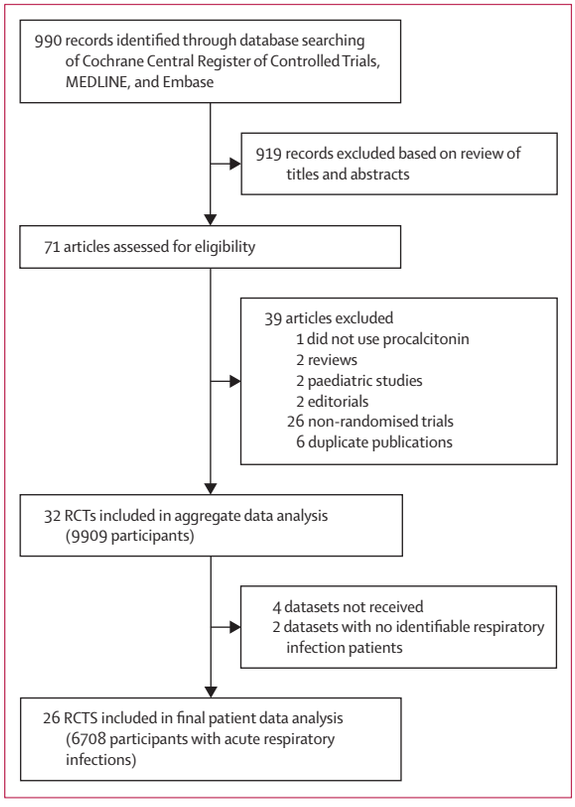

Figure 1: **Study selection**
RCT=randomised controlled trial.

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See Online for appendix

	Country	Setting, type of trial	Clinical diagnosis	Type of procalcitonin algorithm and procalcitonin cutoffs used
Bloos et al (2016)[13]	Germany	ICU, multicentre	Severe sepsis or septic shock	Discontinuation at day 4, 7, and 10; recommendation against antibiotic: <1·0 µg/L or >50% drop to previous value
Bouadma et al (2010)[14]	France	ICU, multicentre	Suspected bacterial infections during ICU stay without prior antibiotic (<24 h)	Initiation and duration; recommendation against antibiotic: <0·5 µg/L (<0·25 µg/L); recommendation for antibiotic: >0·5 µg/L (>1·0 µg/L)
Branche et al (2015)[15]	USA	ED, medical ward, single centre	Lower acute respiratory infection	Initiation and duration; recommendation against antibiotic: <0·25 µg/L (<0·1 µg/L); recommendation for antibiotic: >0·25 µg/L (>0·5 µg/L)
Briel et al (2008)[16]	Switzerland	Primary care, multicentre	Upper and lower acute respiratory infection	Initiation and duration; recommendation against antibiotic: <0·25 µg/L (<0·1 µg/L); recommendation for antibiotic: >0·25 µg/L (>0·5 µg/L)
Burkhardt et al (2010)[17]	Germany	Primary care, multicentre	Upper and lower acute respiratory infection	Initiation; recommendation against antibiotic: <0·25 µg/L; recommendation for antibiotic: >0·25 µg/L
Christ-Crain et al (2004)[18]	Switzerland	ED, single centre	Lower acute respiratory infection with x-ray confirmation	Initiation; recommendation against antibiotic: <0·25 µg/L (<0·1 µg/L); recommendation for antibiotic: >0·25 µg/L (>0·5 µg/L)
Christ-Crain et al (2006)[19]	Switzerland	ED, medical ward, single centre	Community-acquired pneumonia with x-ray confirmation	Initiation and duration; recommendation against antibiotic: <0·25 µg/L (<0·1 µg/L); recommendation for antibiotic: >0·25 µg/L (>0·5 µg/L)
Corti et al (2016)[20]	Denmark	ED, single centre	Acute exacerbation of COPD	Initiation and duration; recommendation against antibiotic <0·25 µg/L (0·15 µg/L)/80% decrease, recommendation for antibiotic >0·25 µg/L
de Jong et al (2016)[9]	Netherlands	ICU, multicentre	Critically ill patients with presumed infection	Duration; recommendation against antibiotic: <0·5 µg/L or >80% drop
Deliberato et al (2013)[21]	Brazil	ICU, single centre	Septic patients with proven bacterial infection	Duration; recommendation against antibiotic: <0·5 µg/L or >90% drop
Hochreiter et al (2009)[22]	Germany	Surgical ICU, single centre	Suspected bacterial infections and >1 systemic inflammatory response syndrome criteria	Duration; recommendation against antibiotic: <1 µg/L or >65% drop over 3 days
Kristoffersen et al (2009)[23]	Denmark	ED, medical ward, multicentre	Lower acute respiratory infection without x-ray confirmation	Initiation and duration; recommendation against antibiotic: <0·25 µg/L; recommendation for antibiotic: >0·25 µg/L (>0·5 µg/L)
Layios et al (2012)[24]	Belgium	ICU, single centre	Suspected infection	Initiation; recommendation against antibiotic: <0·5 µg/L (<0·25 µg/L); recommendation for antibiotic: >0·5 µg/L (>1·0 µg/L)
Long et al (2009)[26]	China	ED, outpatients, single centre	Community-acquired pneumonia with x-ray confirmation	Initiation and duration; recommendation against antibiotic: <0·25 µg/L; recommendation for antibiotic: >0·25 µg/L
Long et al (2011)[25]	China	ED, outpatients, single centre	Community-acquired pneumonia with x-ray confirmation	Initiation and duration; recommendation against antibiotic: <0·25 µg/L; recommendation for antibiotic: >0·25 µg/L
Long et al (2014)[27]	China	ED, single centre	Severe acute exacerbation of asthma	Initiation; recommendation against antibiotic: <0·25 µg/L (<0·1 µg/L); recommendation for antibiotic: >0·25 µg/L
Maravić-Stojković et al (2011)[28]	Serbia	ICU surgical, single centre	Infection after open heart surgery	Initiation; recommendation for antibiotic: >0·5 µg/L
Nobre et al (2008)[29]	Switzerland	ICU, single centre	Suspected severe sepsis or septic shock	Duration; recommendation against antibiotic: <0·5 µg/L (<0·25 µg/L) or >90% drop; recommendation for antibiotic: >0·5 µg/L (>1·0 µg/L)
Oliveira et al (2013)[30]	Brazil	ICU, two-centre	Severe sepsis or septic shock	Discontinuation; initial <1·0 µg/L: recommendation against antibiotic: 0·1 µg/L at day 4; initial >1·0 µg/L: recommendation against: >90% drop
Schroeder et al (2009)[31]	Germany	Surgical ICU, single centre	Severe sepsis after abdominal surgery	Duration; recommendation against antibiotic: <1 µg/L or >65% drop over 3 days
Schuetz et al (2009)[32]	Switzerland	ED, medical ward, multicentre	Lower acute respiratory infection with x-ray confirmation	Initiation and duration; recommendation against antibiotic: <0·25 µg/L (<0·1 µg/L); recommendation for antibiotic: >0·25 µg/L (>0·5 µg/L)
Shehabi et al (2014)[33]	Australia	ICU, multicentre	Suspected sepsis, undifferentiated infections	Duration; recommendation against antibiotic: <0·25 µg/L (<0·1 µg/L) or >90% drop
Stolz et al (2007)[34]	Switzerland	ED, medical ward, single centre	Exacerbated COPD	Initiation and duration; recommendation against antibiotic: <0·25 µg/L (<0·1 µg/L); recommendation for antibiotic: >0·25 µg/L (>0·5 µg/L)
Stolz et al (2009)[35]	Switzerland, USA	ICU, multicentre	Ventilator-associated pneumonia when intubated for >48 h	Duration; recommendation against antibiotic: <0·5 µg/L (<0·25 µg/L) or >80% drop; recommendation for antibiotic: >0·5 µg/L (>1·0 µg/L)
Verduri et al (2015)[36]	Italy	ED, medical ward, multicentre	Acute exacerbation of COPD	Initiation; recommendation against antibiotic:<0·1 µg/L; recommendation for antibiotic: >0·25 µg/L
Wang et al (2016)[37]	China	ICU, single centre	Acute exacerbation of COPD	All patients had initial procalcitonin <0·1 µg/L; antibiotic-group treated with antibiotic for at least 3 days, control group no antibiotic in the first 10 days

Recommendation relates to initiation or cessation of antibiotics. ICU=intensive care unit. ED=emergency department. COPD=chronic obstructive pulmonary disease.

***Table 1*: Characteristics of included trials**

Results

We identified 990 records from the literature search, of which 71 articles were assessed for eligibility after exclusion of 919 records (figure 1). Data from 6708 individual patients were obtained and included in the meta-analysis of 26 eligible trials. We excluded two trials in which patients did not have confirmed respiratory infections, and patient data were unavailable from four

additional trials. Trials were done in 12 countries: Australia, Belgium, Brazil, China, Denmark, France, Germany, Italy, the Netherlands, Serbia, Switzerland, and the USA (table 1, appendix p 1). There were two primary care trials with patients with upper respiratory tract infections and lower respiratory tract infection (n=1008), 11 trials from emergency departments and medical wards with patients with lower respiratory tract infection (n=3253), and 13 trials from ICUs with patients who were septic because of lower respiratory tract infections (n=2447). Procalcitonin-based algorithms used in the different trials were similar in concept and recommended initiation or continuation of antibiotic therapy based on procalcitonin cutoff levels. Adherence to algorithms was variable, ranging from 44% to 100% (appendix p 3). Quality of trials according to GRADE was moderate to high (appendix p 6). Caregivers and patients were blinded to the intervention in most of the trials, but half of trials did not have a blinded outcome assessment. There was no evidence of publication bias based on inspection of the funnel plot (appendix p 7).

Baseline characteristics of individual patients were similar in procalcitonin and control groups (table 2). Most patients were recruited in the emergency department or the ICU. Community-acquired pneumonia was the most frequent diagnosis in more than 40% of patients (table 2).

There were 286 deaths within 30 days in 3336 procalcitonin-guided patients (9%) compared with 336 deaths in 3372 controls (10%), resulting in a significantly lower mortality associated with procalcitonin-guided therapy (adjusted OR 0·83 [95% CI 0·70–0·99], p=0·037; table 3). This effect was consistent across clinical settings (no significant difference due to subgroup effect), although mortality could not be estimated in primary care trials in which only one death was reported in a control patient. The effects on mortality were also consistent among different types of infections (no significant difference for each interaction), excluding patients with bronchitis for whom mortality could not be assessed (table 3).

Treatment failure in procalcitonin-guided patients was numerically lower than control patients, but not significantly different (23·0% *vs* 24·9%; adjusted OR 0·90 [95% CI 0·80–1·01], p=0·068). These results were similar among subgroups by clinical setting and type of respiratory infection ($p_{interactions}$>0·05; table 3). Mortality and treatment failure results were also not significantly different from the main analysis in the sensitivity analysis based on the main quality indicators of trials with no evidence of effect modification (appendix p 5).

As an additional sensitivity analysis, a meta-analysis of the aggregate results of all 32 eligible trials was done and included the six trials initially excluded from the individual patient data analysis (figure 2). The point estimate for mortality was similar to the individual patient data analysis, but was not significant (OR 0·89 [95% CI 0·78–1·01]). The aggregate analysis of treatment failure showed a significant reduction in risk of treatment failure associated with procalcitonin-guided treatment (0·90 [0·81–0·99]). Heterogeneity for both endpoints was low suggesting similar effects among subgroups (I^2=0% for both).

	Control (n=3372)	Procalcitonin group (n=3336)
Age, years	61·2 (18·4)	60·7 (18·8)
Sex		
Men	1910 (57%)	1898 (57%)
Women	1462 (43%)	1438 (43%)
Clinical setting		
Primary care	501 (15%)	507 (15%)
Emergency department	1638 (49%)	1615 (48%)
ICU	1233 (37%)	1214 (36%)
Primary diagnosis		
Total upper acute respiratory infection	280 (8%)	292 (9%)
Common cold	156 (5%)	149 (4%)
Rhino-sinusitis, otitis	67 (2%)	73 (2%)
Pharyngitis, tonsillitis	46 (1%)	61 (2%)
Total lower acute respiratory infection	3092 (92%)	3044 (91%)
Community-acquired pneumonia	1468 (44%)	1442 (43%)
Hospital-acquired pneumonia	262 (8%)	243 (7%)
Ventilator-associated pneumonia	186 (6%)	194 (6%)
Acute bronchitis	287 (9%)	257 (8%)
Exacerbation of COPD	631 (19%)	621 (19%)
Exacerbation of asthma	127 (4%)	143 (4%)
Other lower acute respiratory infection	131 (4%)	144 (4%)
Procalcitonin dose on enrolment		
Data available	2590 (77%)	3171 (95%)
<0·1 µg/L	921 (36%)	981 (31%)
0·1–0·25 µg/L	521 (20%)	608 (19%)
>0·25–0·5 µg/L	308 (12%)	383 (12%)
>0·5–2·0 µg/L	358 (14%)	520 (16%)
>2·0 µg/L	482 (19%)	679 (21%)

Data are mean (SD) or n (%). ICU=intensive care unit. COPD=chronic obstructive pulmonary disease.

***Table 2*: Baseline characteristics of included patients**

Procalcitonin guidance was associated with a reduction in total antibiotic exposure (mean 5·7 days *vs* 8·1 days in the control group, adjusted regression coefficient –2·43 days [95% CI –2·71 to 2·15], p<0·0001; table 4, figure 3). Fewer patients in the procalcitonin group were prescribed antibiotics than in the control group and, in patients for whom antibiotics were prescribed, duration of therapy was shorter in procalcitonin-guided patients. The effect on antibiotic use differed by clinical setting. In the primary care setting, lower antibiotic exposure was mainly due to lower initial prescription rates in procalcitonin-guided patients than control patients ($p_{interaction}$<0·0001). Similarly, lower antibiotic exposure due to lower prescription rates was found in selected

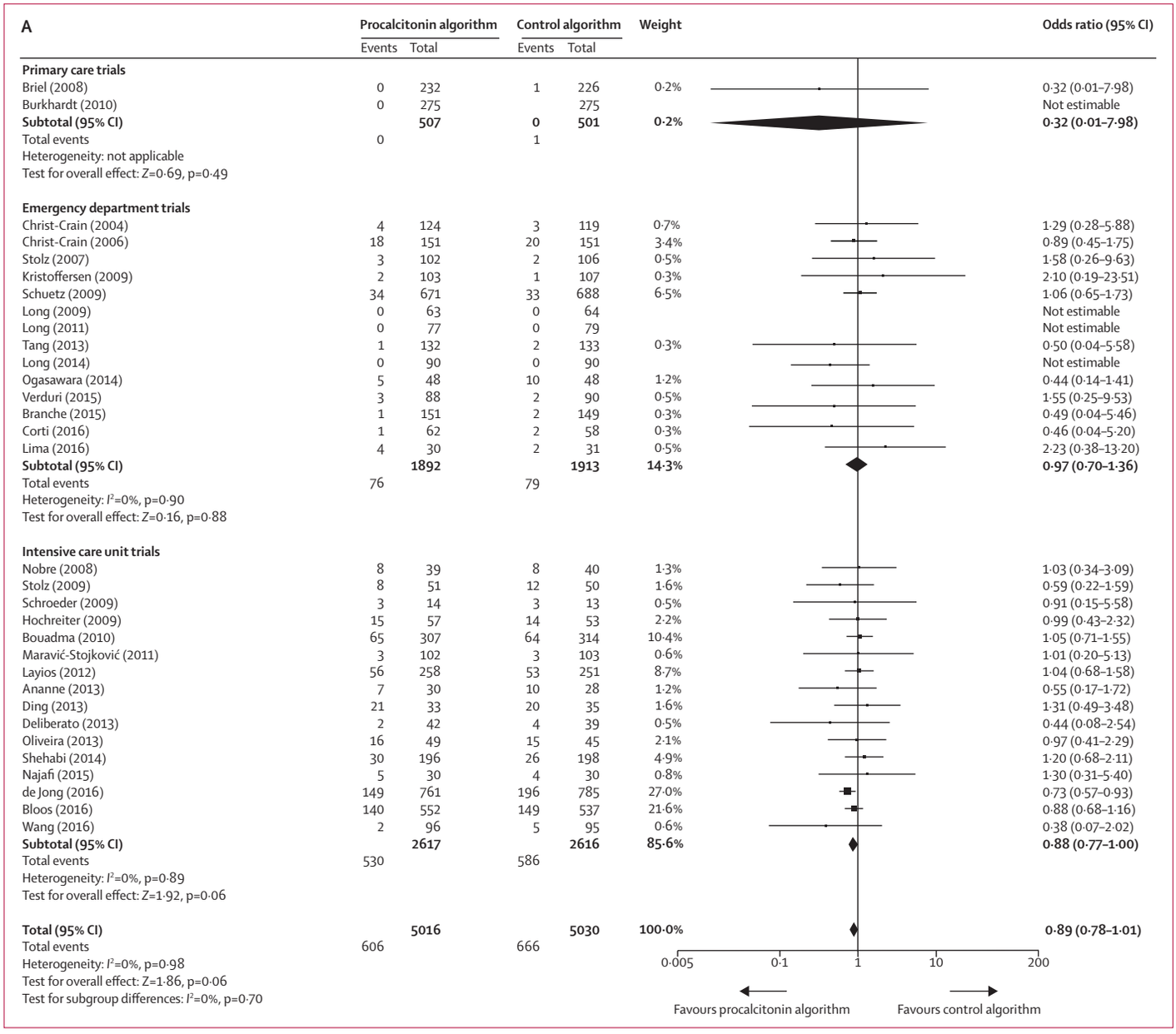
	Control (n=3372)	Procalcitonin group (n=3336)	Adjusted OR (95% CI)*, p value	$p_{interaction}$
Overall				
30-day mortality	336 (10%)	286 (9%)	0·83 (0·7 to 0·99), p=0·037	..
Treatment failure	841 (25%)	768 (23%)	0·90 (0·80 to 1·01), p=0·068	..
Length of ICU stay, days	13·3 (16·0)	13·7 (17·2)	0·39 (–0·81 to 1·58), p=0·524	..
Length of hospital stay, days	13·7 (20·6)	13·4 (18·4)	–0·19 (–0·96 to 0·58), p=0·626	..
Antibiotic-related side-effects	336/1521 (22%)	247/1513 (16%)	0·68 (0·57 to 0·82), p<0·0001	..
Setting-specific outcomes				
Primary care	501	507	..	..
30-day mortality	1 (<1%)	0 (0)	..	..
Treatment failure	164 (33%)	159 (31%)	0·96 (0·73 to 1·25), p=0·751	0·715
Days with restricted activities	8·9 (4·2)	8·9 (4·1)	0·07 (–0·44 to 0·59), p=0·777	..
Antibiotic-related side-effects	128/498 (26%)	102/506 (20%)	0·65 (0·46 to 0·91), p=0·012	0·596
Emergency department	1638	1615	..	..
30-day mortality	62 (4%)	57 (4%)	0·91 (0·63 to 1·33), p=0·635	0·546
Treatment failure	292 (18%)	259 (16%)	0·87 (0·72 to 1·05), p=0·141	0·807
Length of hospital stay, days	8·2 (10·5)	8·1 (7·5)	–0·14 (–0·73 to 0·44), p=0·631	0·684
Antibiotic-related side-effects	208/1023 (20%)	145/1007 (14%)	0·66 (0·52 to 0·83), p=0·001	0·596
Intensive care unit	1233	1214	..	..
30-day mortality	273 (22%)	229 (19%)	0·84 (0·69 to 1·02), p=0·081	0·619
Length of ICU stay, days	14·8 (16·2)	15·3 (17·5)	0·56 (–0·82 to 1·93), p=0·427	0·849
Length of hospital stay, days	26·3 (26·9)	25·8 (23·9)	–0·33 (–2·28 to 1·62), p=0·739	0·641
Disease-specific outcomes				
Community-acquired pneumonia	1468	1442	..	..
30-day mortality	206 (14%)	175 (12%)	0·82 (0·66 to 1·03), p=0·083	0·958
Treatment failure	385 (26%)	317 (22%)	0·78 (0·66 to 0·93), p=0·005	0·052
Length of ICU stay, days	10·5 (10·3)	11·9 (13·3)	1·45 (0·15 to 2·75), p=0·029	0·119
Length of hospital stay, days	13·3 (15·7)	13·9 (16·1)	0·74 (–0·25 to 1·73), p=0·143	0·094
Antibiotic-related side-effects	186/671 (28%)	127/666 (19%)	0·62 (0·48 to 0·8), p<0·0001	0·227
Exacerbation of COPD	631	621	..	..
30-day mortality	24 (4%)	19 (3%)	0·80 (0·43 to 1·48), p=0·472	0·847
Treatment failure	110 (17%)	104 (17%)	0·94 (0·7 to 1·27), p=0·704	0·676
Length of hospital stay, days	9·3 (13·9)	8·4 (7·2)	–0·6 (–1·84 to 0·64), p=0·342	0·658
Antibiotic-related side-effects	30/274 (11%)	29/275 (11%)	0·93 (0·53 to 1·63), p=0·805	0·198
Acute bronchitis	287	257	..	..
30-day mortality	0 (0)	2 (1%)	..	..
Treatment failure	55 (19%)	52 (20%)	1·11 (0·72 to 1·7), p=0·643	0·4
Length of hospital stay, days	2·6 (5·7)	2·2 (4·7)	–0·21 (–0·9 to 0·48), p=0·556	0·97
Antibiotic-related side-effects	54/250 (22%)	39/226 (17%)	0·77 (0·49 to 1·22), p=0·263	0·657
Ventilator-associated pneumonia	186	194	..	..
30-day mortality	29 (16%)	23 (12%)	0·75 (0·41 to 1·39), p=0·366	0·644
Treatment failure	51 (27%)	44 (23%)	0·78 (0·48 to 1·28), p=0·332	0·522
Length of ICU stay, days	23·5 (20·5)	21·8 (19·1)	–1·74 (–5·64 to 2·17), p=0·383	0·441
Length of hospital stay, days	33·8 (27·6)	32·0 (23·1)	–2·14 (–7·04 to 2·75), p=0·391	0·448

Data are n, mean (SD), or n (%), unless otherwise specified. OR=odds ratio. ICU=intensive care unit. COPD=chronic obstructive pulmonary disease. *Multivariable hierarchical regression with outcome of interest as dependent variable; age and respiratory tract infection diagnosis as independent variables; and trial as a random effect.

***Table 3*: Clinical endpoints overall and stratified by setting and diagnosis**

infections such as acute bronchitis. Lower antibiotic prescription rates and shorter duration of antibiotic therapy in patients contributed to the lower overall exposure in the emergency department setting. In the ICU setting and in patients diagnosed with community-acquired pneumonia, the lower exposure was mainly explained by shorter treatment durations.

There was a significant reduction in antibiotic-related side-effects in procalcitonin-guided patients (16% *vs* 22%; adjusted OR 0·68 [95% CI 0·57–0·82], p<0·0001). This



(Figure 2 continues on next page)

outcome was only assessed in primary care and emergency department trials (six trials). There was no evidence of subgroup effects ($p_{interactions}$>0·05; table 3).

Length of hospital stay (adjusted regression coefficient –0·19 days [95% CI –0·96 to 0·58], p=0·626) and ICU stay (0·39 days [–0·81 to 1·58], p=0·524) were similar in the procalcitonin and control groups and across setting-specific and disease-specific subgroups ($p_{interactions}$>0·05; table 3).

Discussion

To our knowledge, this systematic review and individual patient data meta-analysis of 26 randomised trials and 6708 patients is the first report to describe significant and relevant improvements in clinical outcomes and specifically a decreased risk for mortality for patients with acute respiratory infections, when procalcitonin was used to guide antibiotic treatment decisions. This effect was consistent across clinical settings and types of infections, and proved to be robust in different sensitivity analyses. For primary care and acute bronchitis patients, however, mortality was very low and the effect of procalcitonin could not be reliably assessed. In line with previous research, procalcitonin use was also associated with a reduction in exposure to antibiotics mainly by reduced

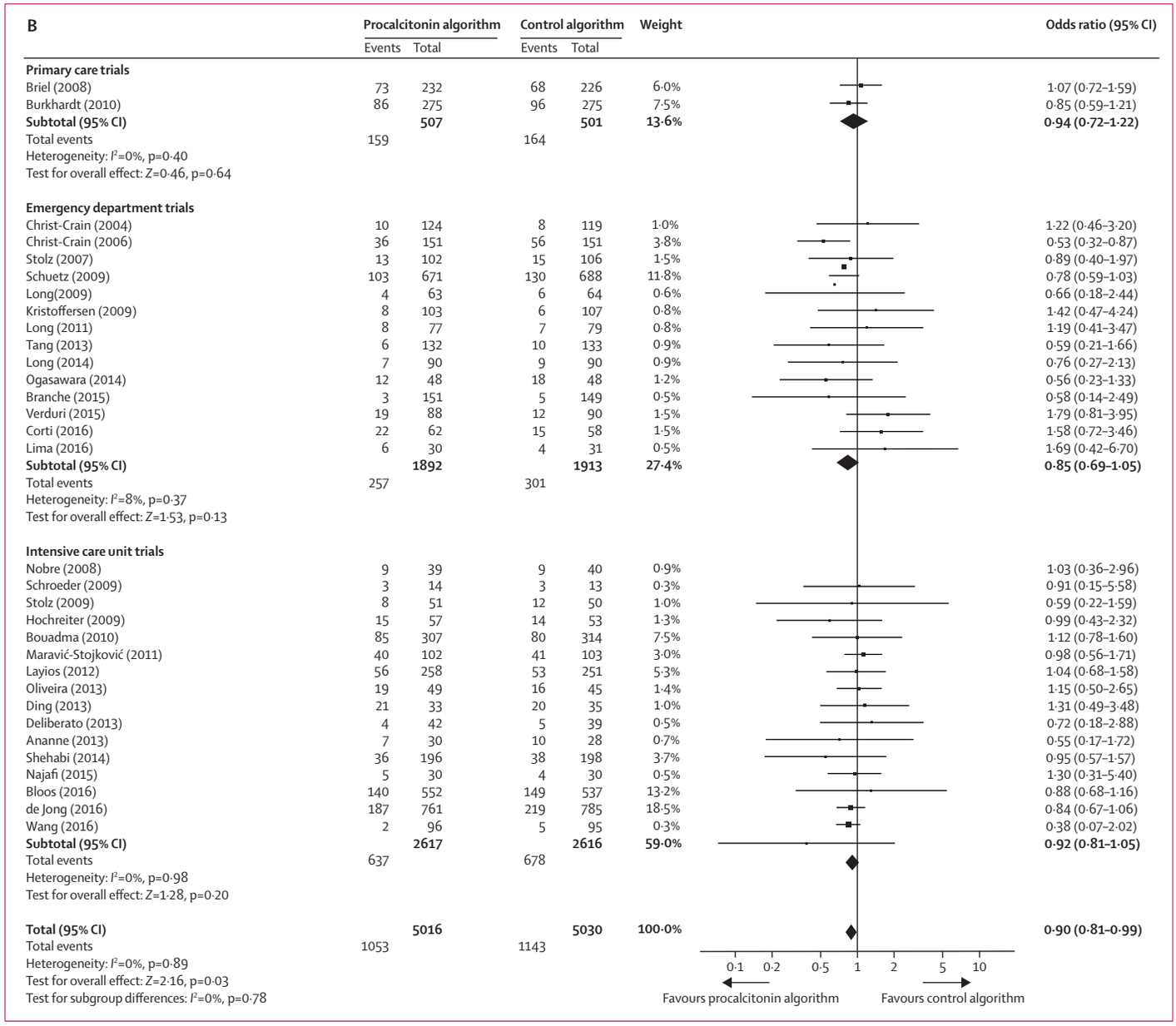


***Figure 2*: Forest plot showing overall mortality (A) and treatment failure (B) at 30 days from aggregate data meta-analysis**
Odds ratios calculated with a random-effects Mantel-Haenszel test.

antibiotic prescription in low-risk settings and low-risk patients and shorter duration and earlier discontinuation of antibiotics in high-risk patients. Procalcitonin use also resulted in reduced antibiotic side-effects, but did not have an effect on length of ICU or hospital stay.

Acute respiratory infections are caused by bacteria, viruses, and other causes and are often treated with antibiotic therapy.[6,7,46] Although early initiation of antibiotic therapy reduces morbidity associated with bacterial infections, overuse of antibiotics in patients with viral bronchitis and prolonged use in patients with bacterial infection and sepsis has contributed to the development of multidrug-resistant bacterial pathogens.[47,48] Reduction of antibiotic use without increasing the risk for adverse patient outcomes is an international priority. In the past 10 years, the infection blood biomarker procalcitonin has been proposed as an adjunct to clinical judgment and traditional clinical parameters to guide antibiotic prescribing practices in patients with acute respiratory infections. Procalcitonin measurements increase within 6–12 h of infection in response to pro-inflammatory mediator release after

	Control (n=3372)	Procalcitonin group (n=3336)	Adjusted OR or difference (95% CI), p value*	$p_{interaction}$
Overall				
Initiation of antibiotics	2894 (86%)	2351 (70%)	0·27 (0·24 to 0·32), p<0·0001	..
Duration of antibiotics, days†	9·4 (6·2)	8·0 (6·5)	–1·83 (–2·15 to –1·5), p<0·0001	..
Total exposure of antibiotics, days‡	8·1 (6·6)	5·7 (6·6)	–2·43 (–2·71 to –2·15), p<0·0001	..
Setting-specific outcomes				
Primary care	501	507	..	..
Initiation of antibiotics	316 (63%)	116 (23%)	0·13 (0·09 to 0·18), p<0·0001	<0·0001
Duration of antibiotics, days†	7·3 (2·5)	7·0 (2·8)	–0·52 (–1·07 to 0·04), p=0·068	0·064
Total exposure of antibiotics, days‡	4·6 (4·1)	1·6 (3·2)	–3·02 (–3·45 to –2·58), p<0·0001	0·101
Emergency department	1638	1615	..	..
Initiation of antibiotics	1354 (83%)	1119 (69%)	0·49 (0·41 to 0·58), p<0·0001	<0·0001
Duration of antibiotics, days†	9·8 (5·4)	7·3 (5·1)	–2·45 (–2·86 to –2·05), p<0·0001	<0·0001
Total exposure of antibiotics, days‡	8·2 (6·2)	5·2 (5·4)	–3·02 (–3·41 to –2·62), p<0·0001	<0·0001
Intensive care unit	1233	1214	..	..
Initiation of antibiotics	1224 (99%)	1116 (92%)	0·02 (0·01 to 0·05), p<0·0001	<0·0001
Duration of antibiotics, days†	9·5 (7·4)	8·8 (7·8)	–1·23 (–1·82 to –0·65), p<0·0001	<0·0001
Total exposure of antibiotics, days‡	9·5 (7·4)	8·1 (7·9)	–1·44 (–1·99 to –0·88), p<0·0001	<0·0001
Disease-specific outcomes				
Community-acquired pneumonia	1468	1442	..	..
Initiation of antibiotics	1455 (99%)	1340 (93%)	0·08 (0·04 to 0·15), p<0·0001	<0·0001
Duration of antibiotics, days†	10·5 (6·2)	8·0 (5·7)	–2·45 (–2·87 to –2·02), p<0·0001	<0·0001
Total exposure of antibiotics, days‡	10·4 (6·2)	7·5 (5·9	–2·94 (–3·38 to –2·5), p<0·0001	0·004
Exacerbation of COPD	631	621	..	..
Initiation of antibiotics	453 (72%)	266 (43%)	0·29 (0·23 to 0·36), p<0·0001	0·017
Duration of antibiotics, days†	7·4 (5·3)	7·2 (6·7)	–1·15 (–2 to –0·31), p=0·007	0·003
Total exposure of antibiotics, days‡	5·3 (5·6)	3·1 (5·6)	–2·22 (–2·83 to –1·6), p<0·0001	0·506
Acute bronchitis	287	257	..	..
Initiation of antibiotics	189 (66%)	68 (26%)	0·18 (0·12 to 0·26), p<0·0001	<0·0001
Duration of antibiotics, days†	7·1 (3·0)	6·4 (3·5)	–0·35 (–1·15 to 0·45), p=0·393	0·359
Total exposure of antibiotics, days‡	4·7 (4·2)	1·7 (3·3)	–2·95 (–3·59 to –2·31), p<0·0001	0·33
Ventilator-associated pneumonia	186	194	..	..
Initiation of antibiotics	186 (100%)	193 (100%)	..	..
Duration of antibiotics, days†	13·1 (7·9)	10·8 (8·7)	–2·22 (–3·8 to –0·65), p=0·006	0·253
Total exposure of antibiotics, days‡	13·1 (7·9)	10·8 (8·7)	–2·45 (–4·09 to –0·82), p=0·003	0·786

Data are n, mean (SD), or n (%), unless otherwise specified. OR=odds ratio. COPD=chronic obstructive pulmonary disease. *Multivariable hierarchical model adjusted for age and diagnosis and trial as a random effect. †Total days of antibiotic therapy in patients in whom antibiotics were initiated. ‡Total days of antibiotic therapy in all randomly assigned patients.

***Table 4*: Antibiotic treatment overall and stratified by setting and diagnosis**

bacterial invasion, are highest in patients who have bacteraemia, and correlate with disease severity and clinical outcome of patients with infection.[49,50] Unlike other inflammatory markers, procalcitonin release is blocked by cytokines, which characterise the typical immune response to viral infections (interferon γ).[51] Procalcitonin is therefore more specific for bacterial infections than C-reactive protein or white cell count.[52–54] Procalcitonin concentrations rapidly fall by about 50% each day during resolution of infection and are therefore useful in monitoring the clinical course and supporting decisions to discontinue antibiotic treatment.

However, an important impediment to the evaluation and validation of any sepsis marker has been the absence of a reliable reference standard for bacterial infection, particularly for respiratory infections. For procalcitonin, sensitivities and specificities of around 80% have been reported in previous observational studies using blood culture as the reference standard.[55,56] To increase sensitivity and specificity of procalcitonin, existing algorithms use a variety of cutoff points in conjunction with clinical criteria to guide antibiotic prescription.[10] Although observational research does not permit measurements of the true diagnostic accuracy of procalcitonin, interventional research is helpful to understand the clinical effect of such algorithms. Several studies have now compared antibiotic use and clinical outcomes of acute respiratory infections in patients

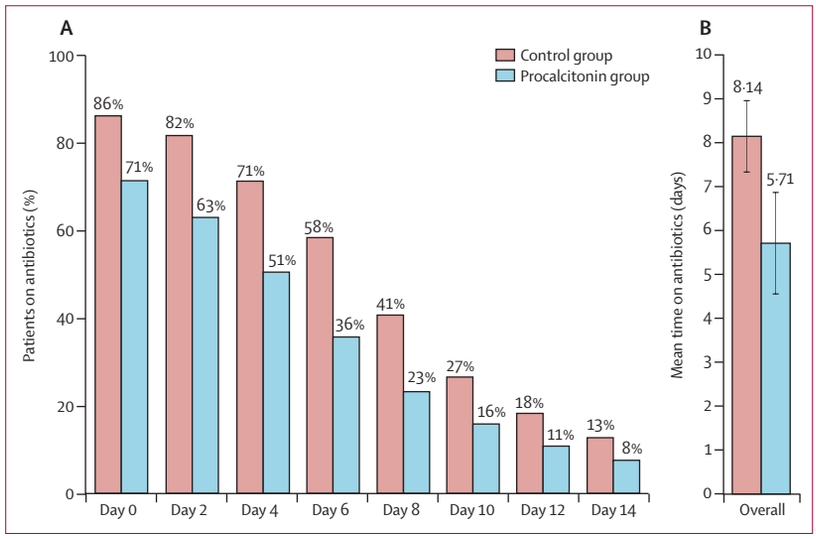


***Figure 3*: Antibiotic use**
(A) Proportions of patients on antibiotics. (B) Mean duration of antibiotic use.

managed with and without procalcitonin protocols. In these trials, procalcitonin algorithms were paired with recommendations for or against antibiotic initiation and continuation based on clinical stability and at specific procalcitonin levels or procalcitonin kinetics.[10] Although in most trials such a strategy proved to be effective in reducing antibiotic use, the safety of this approach has remained an ongoing concern.

Our analysis of the use of procalcitonin-guided care in a large aggregate patient population from different trials and countries did not conclusively reveal any associated harm, and importantly showed significantly reduced mortality with the use of procalcitonin treatment algorithms. These results are consistent with the largest trial of patients in ICUs, which also reported reduced mortality associated with procalcitonin-guided care.[9] The relative mortality reduction was 14% (ie, from 10·0% to 8·6%), and was highest in ICU trials (15%) and in patients with community-acquired pneumonia (13%) and ventilator-associated pneumonia (23%). For patients in emergency departments, the relative mortality reduction was still 8%, whereas no effect could be estimated for primary care because of the low number of events. These results were also confirmed in an aggregate data meta-analysis including 32 eligible trials. Procalcitonin thus seems to have the most clinical benefit in high-risk patient populations and no demonstrable safety concerns in low-risk groups.

There are several possible explanations for the positive effects of procalcitonin-guided antibiotic treatment on mortality in patients with acute respiratory infections. First, procalcitonin provides additional prognostic information in the assessment of patients, which influences decisions about site-of-care and timing of discharge.[29] A large US study[57] found procalcitonin kinetics over 72 h to be a strong and independent predictor of mortality. Early identification of non-responders to antibiotic and other medical treatment might also help to prevent adverse events. Secondly, increased risk for treatment failure in control patients might be related to prolonged antibiotic exposure and risk for secondary complications and re-admission to hospital.[58,59] In our analysis, procalcitonin-guided care also correlated with lower risk for antibiotic side-effects, which can be associated with both treatment failure and mortality. Third, in sick patients with evidence of an acute respiratory tract illness, a lower-than-expected procalcitonin concentration might direct clinicians to look for alternative explanations of these symptoms (eg, pulmonary embolism or heart failure). Finally, as detailed in current sepsis guidelines, several observational studies have now reported lower mortality and treatment failure risk associated with early antibiotic de-escalation in patients with sepsis than in patients with no de-escalation.[60,61]

Although most research showing the benefit of procalcitonin treatment algorithms has focused on patients in ICUs and emergency departments, the value of procalcitonin in primary care is still incompletely understood. Observational outpatient data have been largely inconclusive on the added value of procalcitonin to diagnose infection compared with other markers and clinical parameters. In our analysis, which included two non-inferiority primary care trials with 1008 patients, procalcitonin had a strong effect on antibiotic use in primary care patients. Moreover, resolution of illness as measured by days with restricted activities of daily living was similar between procalcitonin and control patients suggesting that patients not treated with antibiotics in the procalcitonin group did not need these drugs.

For the primary care setting, it could be argued that any intervention using other biomarkers or clinical parameters could reduce antibiotic use in a low-risk setting with high rates of overprescription. Studies comparing procalcitonin and C-reactive protein have reported low correlation of these markers suggesting that important differences exist, which could lead to different recommendations on antibiotic use in individual patients.[62,63] However, head-to-head studies assessing the clinical effect of procalcitonin compared with C-reactive protein guided treatment algorithms are still needed. Finally, one strategy that has had an impact in the inpatient setting is early provider notification of procalcitonin results and this strategy might improve the performance of procalcitonin-guided treatment algorithms if used in future studies done in primary care settings.

The strengths of this meta-analysis include a predefined study protocol, a comprehensive search and retrieval of all relevant trials, and a network that permitted inclusion of individual patient data from most eligible trials. We also standardised outcome definitions across trials and did appropriate subgroup and sensitivity analyses, thereby overcoming the limitation of previous meta-analyses with

aggregated data to make definitive conclusions. However, our study still had limitations. First, adherence to the procalcitonin algorithm was varied among the studies ranging from 44% to 100%. However, a sensitivity analysis found similar effects in trials with high and low adherence. Second, we limited our analysis to immunocompetent adults with acute respiratory infections, thereby reducing generalisability of our conclusions to other patient populations. Third, our patient population was substantially heterogeneous with regard to clinical setting and type of respiratory infection. This heterogeneity also limits generalisability of results particularly for the main endpoint, mortality, and specifically whether or not procalcitonin guidance results in a reduction in mortality in the primary care setting remains unproven. Finally, we did not do a cost-effectiveness analysis because cost data were not available in most trials. Future studies should investigate cost-effectiveness of procalcitonin-guided care.[56]

In conclusion, procalcitonin-guided antibiotic treatment in patients with acute respiratory infections effectively reduced antibiotic exposure and antibiotic side-effects while improving mortality. These findings were conserved across all clinical settings and clinical presentations of acute respiratory infections although mortality could not be estimated in patients in primary care and in those with bronchitis. When embedded in clinical algorithms, the use of procalcitonin has the potential to inform and improve care of patients with acute respiratory infections by reducing antibiotic exposure and the associated risk of developing subsequent antibiotic resistance and more importantly improving clinical outcomes. These findings have substantial clinical and public health implications.

Contributors

PS, MB, HCB, and BM conceived of the study and wrote the initial protocol. PS, YW, and RS did the literature search and all analysis for this report and wrote the first draft. All authors shared trial data, gave crucial feedback on the manuscript, and approved the final version. PS, MB, and BM oversaw the study.

Declaration of interests

PS, MC-C, and BM have received support from Thermo-Fisher and bioMérieux to attend meetings and fulfilled speaking engagements. BM has served as a consultant for and received research support from Thermo-Fisher. HCB and MB have received research support from Thermo-Fisher for a previous meta-analysis regarding procalcitonin. DWdL's hospital received financial support for the randomisation tool by ThermoFisher. DS, OB, and MT have received research support from Thermo-Fisher. TW and SS have received lecture fees and research support from Thermo-Fisher. CEL has received lecture fees from Brahms and Merck Sharp & Dohme-Chibret. JC has received consulting and lecture fees from Pfizer, Brahms, Wyeth, Johnson & Johnson, Nektar-Bayer, and Arpida. MW has received consulting and lectures fees from Merck Sharp & Dohme-Chibret, Janssen Cilag, Gilead, Astellas, Sanofi, and Thermo-Fisher. FT's institution received funds from Brahms. CC has received an unrestricted grant of €2000 from Thermo-Fisher Scientific, and non-financial support from bioMérieux for the ProToCOLD study. YS has received unrestricted research grants from Thermo-Fisher, bioMérieux, Orion Pharma, and Pfizer. ARF has served on advisory boards for Novavax, Hologic, Gilead, and MedImmune; and has received research funding from AstraZeneca, Sanofi Pasteur, GlaxoSmithKline, and ADMA Biologics. J-USJ declares that he was invited to the European Respiratory Society meeting 2016 by Roche Pharmaceuticals. YW, RS, LB, KBK, TW, VN, LW, DA, KR, ABr, PD, MN, ROD, CFO, VM-S, AV, BB, BC, JAHvO, ABe, ARJG, and EdJ declare no competing interests.

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