

Procalcitonin to Guide Initiation and Duration of Antibiotic Treatment in Acute Respiratory Infections: An Individual Patient Data Meta-Analysis

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Background. Procalcitonin algorithms may reduce antibiotic use for acute respiratory tract infections (ARIs). We undertook an individual patient data meta-analysis to assess safety of this approach in different ARI diagnoses and different clinical settings.

Methods. We identified clinical trials in which patients with ARI were assigned to receive antibiotics based on a procalcitonin algorithm or usual care by searching the Cochrane Register, MEDLINE, and EMBASE. Individual patient data from 4221 adults with ARIs in 14 trials were verified and reanalyzed to assess risk of mortality and treatment failure—overall and within different clinical settings and types of ARIs.

Results. Overall, there were 118 deaths in 2085 patients (5.7%) assigned to procalcitonin groups compared with 134 deaths in 2126 control patients (6.3%; adjusted odds ratio, 0.94; 95% confidence interval CI, .71–1.23). Treatment failure occurred in 398 procalcitonin group patients (19.1%) and in 466 control patients (21.9%; adjusted odds ratio, 0.82; 95% CI, .71–.97). Procalcitonin guidance was not associated with increased mortality or treatment failure in any clinical setting or ARI diagnosis. Total antibiotic exposure per patient was significantly reduced overall (median [interquartile range], from 8 [5–12] to 4 [0–8] days; adjusted difference in days, –3.47 [95% CI, –3.78 to –3.17]) and across all clinical settings and ARI diagnoses.

Conclusions. Use of procalcitonin to guide initiation and duration of antibiotic treatment in patients with ARIs was effective in reducing antibiotic exposure across settings without an increase in the risk of mortality or treatment failure. Further high-quality trials are needed in critical-care patients.

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Acute respiratory infections (ARIs) comprise a large and heterogeneous group of infections, including bacterial infections, viral infections, and infections of other etiologies. Early initiation of adequate antibiotic therapy is the cornerstone in the treatment of bacterial ARIs and is associated with improved clinical outcomes [1, 2]. However, overuse of antibiotics by overprescription in outpatients with bronchitis [3], for instance, and prolonged duration of antibiotic therapy in patients with bacterial ARIs in the hospital and intensive care setting is associated with increased resistance for common bacteria, high costs, and adverse drug reactions [4, 5]. The safe reduction in antibiotic use is therefore of utmost importance.

In recent years, procalcitonin (PCT) has emerged as a promising marker for the diagnosis of bacterial infections because higher levels are found in severe bacterial infections than in viral infections and nonspecific inflammatory diseases [6, 7]. Hence, PCT may be used to support clinical decision making for the initiation and discontinuation of antibiotic therapy [8]. Randomized controlled trials (RCTs) have demonstrated the feasibility of such a strategy in different ARI patient populations and different settings ranging from primary care [9, 10] to emergency departments (EDs), hospital wards [11–17], and intensive care units (ICUs) [18–22]. Most individual trials, however, lacked the statistical power to assess the risk for mortality and severe infectious disease complications associated with PCT-guided decision making.

We undertook an individual patient data meta-analysis of trials comparing the effects of using PCT to guide initiation and duration of antibiotic treatment in patients with ARI assigned to routine PCT measurement or standard of care without PCT measurement. 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

Trial Selection and Data Collection

The predefined protocol for this meta-analysis of individual patient data is published in the Cochrane Library [23]. We prepared the present report according to PRISMA guidelines [24].

Patients in eligible randomized or quasi-randomized trials had to be adults with a clinical diagnosis of either upper or lower ARI (for detailed definitions see Supplementary Appendix 1). Trials were excluded if they exclusively focused on pediatric patients or if they used PCT for a purpose other than to guide initiation and duration of antibiotic treatment. There were no exclusions based on language or publication status of reports.

We identified suitable trials by a formal search of the Cochrane Controlled Trials Registry (CCTR), MEDLINE, and EMBASE (all from their inception to May 2011) and through

use of reference lists of reports describing such trials. The full electronic search strategy is published with our study protocol [23].

Two reviewers (P. S. and M. B.) independently assessed trial eligibility based on titles, abstracts, full-text reports, and further information from investigators as needed. We requested the protocol, case report forms, and unedited databases containing individual patient data from investigators of all eligible trials. The mortality and adverse outcome rates from trials included in this individual patient data meta-analysis might differ slightly from previous reports because we treated data in a consistent manner across all trials.

Patients and Endpoints

Our patient population consisted of all randomized patients with initial suspicion of ARI independent of the final diagnosis. We prespecified 2 primary endpoints: all-cause mortality and setting-specific treatment failure at 30 days. For trials with a shorter follow-up period, the available information was used (eg, until hospital discharge (Table 1)). Mortality is the most important safety endpoint but relatively rare in some settings; therefore we decided on treatment failure as a coprimary endpoint that is more frequent but needs to be defined according to patient setting. For the primary-care setting, treatment failure was defined as death, hospitalization, ARI-specific complications (eg, empyema for lower ARI, meningitis for upper ARI), recurrent or worsening infection, and patients reporting any symptoms of an ongoing respiratory infection (eg, fever, cough, dyspnea) at follow-up. For the ED setting, treatment failure was defined as death, ICU admission, rehospitalization after index hospital discharge, ARI-associated complications (eg, empyema or acute respiratory distress syndrome for lower ARI), or 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 hospitalized patients, length of ICU stay for critically ill patients, and number of days with restricted activities within 14 days after randomization for primary-care patients.

Statistical Analysis

All patients were analyzed in the study group to which they were randomized. For patients lost to follow-up, we assumed in our main analysis that they did not experience an event. For the primary endpoint of mortality from any cause, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) using multivariable hierarchical logistic regression [25, 26]. Apart from the group variable indicating the use of a PCT

Table 1. Characteristics of Included Trials

First Author (Year)	Country	Setting, Type of Trial	Clinical Diagnosis	Type of PCT Algorithm (PCT Cut-offs Used to Recommend Initiation and Duration [$\mu\text{g/L}$])	No. of ARI Patients (Study Total)	Primary Endpoint	Follow-up Time
Briel (2008) [9]	Switzerland	Primary care, multicenter	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 mo
Burkhardt (2010) [10]	Germany	Primary care, multicenter	Upper and lower ARIs	Initiation; R against AB: <0.25 ; R for AB: >0.25	550 (571) ^a	Days with restricted activities	1 mo
Christ-Crain (2004) [11]	Switzerland	ED, single center	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 wk
Christ-Crain (2006) [12]	Switzerland	ED, medical ward, single center	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 wk
Stolz (2007) [13]	Switzerland	ED, medical ward, single center	Exacerbated COPD	Initiation and duration; R against AB: <0.25 (<0.1); R for AB: >0.25 (>0.5)	208 (226) ^b	AB use	2–3 wk
Kristoffersen (2009) [14]	Denmark	ED, medical ward, multicenter	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
Long (2009) [16]	China	ED, outpatients, single center	CAP with x-ray confirmation	Initiation and duration; R against AB: <0.25 ; R for AB: >0.25	127	AB use	1 mo
Schuetz (2009) [17]	Switzerland	ED, medical ward, multicenter	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 mo
Long (2011) [15]	China	ED, outpatients, single center	CAP with x-ray confirmation	Initiation and duration; R against AB: <0.25 ; R for AB: >0.25	156 (172) ^e	AB use	1 mo
Nobre (2008) [18]	Switzerland	ICU, single center	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 mo
Schroeder (2009) [21]	Germany	Surgical ICU, single center	Severe sepsis following abdominal surgery	Duration; R against AB: <1 or $>65\%$ drop over 3d	8 (27) ^g	AB use	Hospital stay
Hochreiter (2009) [22]	Germany	Surgical ICU, single center	Suspected bacterial infections and >1 SIRS criteria	Duration; R against AB: <1 or $>65\%$ drop over 3d	43 (110) ^h	AB use	Hospital stay
Stolz (2010) [19]	Switzerland, United States	ICU, multicenter	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 mo
Bouadma (2010) [20]	France	ICU, multicenter	Suspected bacterial infections during ICU stay without prior AB (>24 h)	Initiation and duration; R against AB: <0.5 (<0.25); R for AB: >0.5 (>1.0)	394 (630) ⁱ	All-cause mortality	2 mo

Abbreviations: AB, antibiotic; ARI, acute respiratory infection; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; ED, emergency department; ICU, intensive care unit; PCT, procalcitonin; R, recommendation for or against antibiotics; SIRS, systemic inflammation response system; VAP, ventilator-associated pneumonia.

^a Twenty-one postrandomization 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 Eighteen postrandomization exclusions due to absence of COPD according to GOLD criteria.

^c Thirteen postrandomization exclusions (3 no PCT testing, 6 not meeting inclusion criteria, 4 withdrew informed consent).

^d Twenty-two postrandomization exclusions due to withdrawal of consent.

^e Sixteen postrandomization exclusions (6 lost to follow-up, 7 withdrew consent, 3 with final diagnosis other than CAP).

^f Twenty-seven not considered for this analysis due to a diagnosis other than ARI.

^g Nineteen not considered for this analysis due to diagnosis other than ARI.

^h Sixty-seven not considered for this analysis due to diagnosis other than ARI.

ⁱ Nine postrandomization exclusions (8 withdrew consent, 1 randomized twice); 227 not considered for this analysis due to diagnosis other than ARI.

algorithm, we included important prognostic factors such as patient age and ARI diagnosis as additional fixed effects; to account for within-and between-trial variability, we added trial to the model as a random effect. We fitted corresponding linear and logistic regression models for continuous and binary secondary endpoints, respectively. We performed prespecified sensitivity analyses based on the main quality indicators, namely allocation concealment and blinded outcome assessment; we conducted a complete case analysis and an analysis assuming that patients lost to follow-up experienced an event. In an additional sensitivity analysis, we used an alternate definition of treatment failure (death, hospitalization [for primary-care patients], rehospitalization [for hospitalized patients], and ICU admission [for non-ICU patients at randomization]). We also performed sensitivity analyses

excluding trials with low adherence to PCT algorithms (<70%) or not reporting adherence, excluding all ICU trials, and excluding only the largest ICU trial due to low adherence [20]. To further investigate the consistency of results across our heterogeneous patient population in terms of disease severity, we performed prespecified analyses stratified by clinical setting 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 PCT group as fixed effects. We conducted meta-analyses with aggregate data of included trials to investigate inconsistency and heterogeneity of effects by means of I^2 and the Cochran Q test [27].

We used Stata version 9.2 and SAS version 9.1 for statistical analyses.

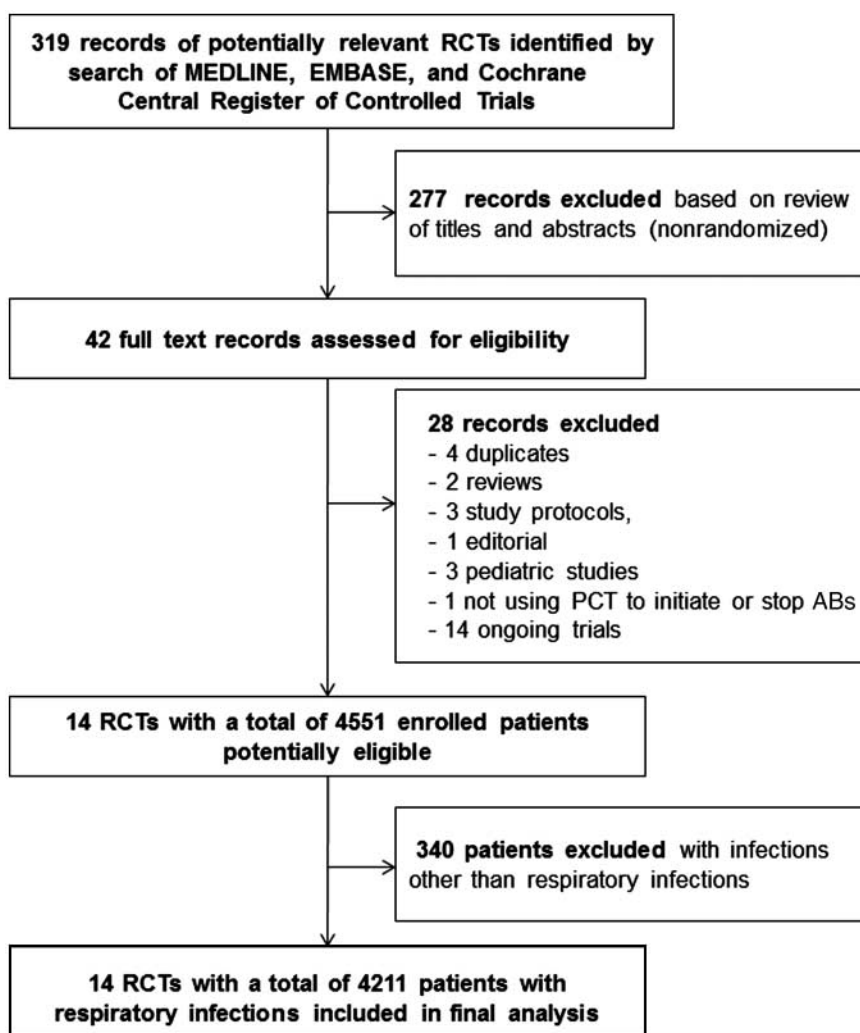


Figure 1. Trial flow. The 14 ongoing trials comprise 5 in pediatrics, 2 focusing on patients with community acquired pneumonia, 1 focusing on stroke patients, 1 focusing on neutropenic patients, and 5 focusing on intensive-care patients. Abbreviations: ABs, antibiotics; PCT, procalcitonin; RCT, randomized controlled trial.

Table 2. Methodological Quality of Included Trials

First Author (Year)	Allocation Concealment	Blinded Outcome Assessment	Follow-up for Mortality	Adherence to PCT Algorithm in PCT Group
Briel (2008) [9]	Yes (central randomization, by phone)	Yes	454/458 (99%)	85% adherence
Burkhardt (2010) [10]	Yes (central randomization, by fax)	Yes	546/550 (99%)	87% adherence
Christ-Crain (2004) [11]	No (weekly randomization)	No	230/243 (95%)	83% adherence
Christ-Crain (2006) [12]	No (envelopes)	No	300/302 (99%)	87% adherence
Stolz (2007) [13]	No (envelopes)	Yes	208/208 (100%)	Not reported
Kristoffersen (2009) [14]	Yes (central randomization, web-based)	No	210/210 (100% until discharge)	59% adherence
Long (2009) [16]	No (odd and even patient ID numbers)	No	127/127 (100%)	Not reported
Schuetz (2009) [17]	Yes (central randomization, web-based)	Yes	1358/1359 (100%)	91% adherence
Long (2011) [15]	No (odd and even patient ID numbers)	No	156/156 (100%)	Not reported
Nobre (2008) [18]	Yes (sequentially numbered, opaque, sealed envelopes)	No	52/52 (100%)	81% adherence
Schroeder (2009) [21]	No (unconcealed drawing of lots)	No	8/8 (100% until discharge)	Not reported
Hochreiter (2009) [22]	No (unconcealed drawing of lots)	No	43/43 (100% until discharge)	Not reported
Stolz (2010) [19]	No (envelopes)	No	101/101 (100%)	Not reported
Bouadma (2010) [20]	Yes (central randomization, web-based)	Yes	393/394 (100%)	47% adherence

Abbreviations: ID, identification; PCT, procalcitonin.

RESULTS

We identified 14 completed trials with a total of 4551 patients that met the inclusion criteria (Figure 1). Four of the ICU trials [18, 20–22] included patients with sepsis not related to ARI; these patients (n = 340) were not considered for this analysis. Patients with initial suspicion of ARI and other final diagnoses were included in the overall analysis. Our intention-to-treat population consisted therefore of 4211 patients with ARI at randomization. We further identified 14 ongoing RCTs on the topic with expected completion between 2012 and 2014.

Characteristics of the individual trials are presented in Table 1. Most trials had a follow up of 1 month, with 2 trials assessing outcome after 14–21 days and 3 trials following patients until hospital discharge only. Both primary-care trials, 1 trial conducted in the ED [17], and 1 ICU trial [20] employed a noninferiority design. The PCT algorithms used in the different trials were similar in concept and recommended initiation and/or continuation of antibiotic therapy based on similar PCT cut-off levels (Table 1). However, there were differences: some trials in primary care [10] and the ED [11] used only a single PCT measurement on admission to guide initiation of antibiotics, whereas the other trials (predominantly in hospitalized patients with severe infections) used repeated measurements for guiding the duration of treatment. Adherence to algorithms was variable, ranging from 47%–91% (Table 2). In terms of methodological quality of included trials, there were 6 trials with concealed allocation and 5 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.

Baseline characteristics of included patients were similar in PCT and control groups with respect to important prognostic features (Table 3). Most patients were recruited in the ED setting, and community-acquired pneumonia (CAP) was the most frequent ARI diagnosis, occurring in almost 50% of patients. The PCT concentrations on admission were highest in patients from the ICU setting and lowest in primary-care patients. There were no statistically significant differences in PCT levels between PCT and control groups overall and for individual settings ($P > .05$ for all comparisons).

Primary Endpoints

Overall, there was no difference in mortality in PCT group patients compared with control patients (5.7% vs 6.3%; adjusted OR, 0.94; 95% CI, .71–1.23; Table 4). This was consistent across clinical settings and ARI diagnoses (see Kaplan–Meier curves in Supplementary Appendix 2). We found overall a significantly lower risk for treatment failure in PCT-treated patients compared with control patients (19.1% vs 21.9%; adjusted OR, 0.82; 95% CI, .71–.97). Statistically significant differences in treatment failure were also found for the ED setting and CAP patients (Table 4, lower part). A similar, although statistically not significant, result was found when restricting the definition of treatment failure to death, ICU admission, hospitalization, or rehospitalization (9.1% vs

Table 3. Baseline Characteristics of Included Patients

Parameter	PCT Group (n = 2085)	Control Group (n = 2126)
Demographics		
Age in years, mean (SD)	59.4 (20.1)	60.1 (19.4)
Men, 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)
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 (1.0)	10 (0.5)
Unspecified lower ARI	39 (1.9)	35 (1.7)
Other final diagnosis, No. (%)	51 (2.5)	44 (2.1)
Procalcitonin in µg/L, mean, median (SD; IQR)		
Overall	2.7, 0.2 (13.1; 0.1–0.8)	2.3, 0.2 (9.3; 0.1–0.8)
Primary care	0.1, 0.1 (0.9; 0.05–0.1)	0.2, 0.1 (1.8; 0.05–0.1)
Emergency department	2.4, 0.3 (10.7; 0.1–0.9)	2.5, 0.3 (10.0; 0.1–0.9)
Intensive care unit	9.3, 1.4 (26.4; 0.4–5.8)	6.4, 1.2 (9.3; 0.3–4.7)

Abbreviations: ARI, acute respiratory infection; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; PCT, procalcitonin; SD, standard deviation.

10.8%; adjusted OR, 0.82; 95% CI, .67–1.01). These results proved robust in various sensitivity analyses. We found no evidence for heterogeneity or effect modification across clinical settings or ARI diagnoses (Supplementary Appendices 3 and 4).

Secondary Endpoints

The PCT-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 (Figure 2; Table 5). In the primary-care setting, this was mainly due to lower initial prescription rates (adjusted OR, 0.10; 95% CI, .07–.14; $P < .0001$ for interaction between primary-care setting and PCT group on antibiotic prescriptions). Similarly, lower antibiotic exposure due to lower prescription rates were found in selected infections, such as upper ARI (adjusted OR, 0.14; 95% CI, .09–.22; P for interaction = .006) and acute bronchitis (adjusted OR, 0.15; 95% CI, .10–.23; P for interaction = .001). Shorter duration of antibiotic therapy further contributed to this effect in patients admitted

to the ED (adjusted difference in days –3.70; 95% CI, –4.09 to –3.31; P for interaction = .005) and the ICU setting (adjusted difference in days, –3.17; 95% CI, –4.28 to –2.06; P for interaction = .007) and in those with CAP (adjusted difference in days, –3.34; 95% CI, –3.79 to –2.88; P for interaction < .0001) and ventilator-associated pneumonia (VAP; adjusted difference in days –2.23; 95% CI, –4.06 to –.39; P for interaction = .01).

In primary-care patients, we found no significant difference in rates of treatment failure and days with restricted activities after 14 days between groups (Table 4). In ED patients, there was a significantly lower risk of treatment failure in favor of PCT-guided patients (adjusted OR, 0.76; 95% CI, .61–.95). There was no difference in the length of stay for ED and ICU patients.

DISCUSSION

This systematic review and individual patient data meta-analysis of 14 trials found no increased risk for mortality or

Table 4. Clinical Endpoints Overall and Stratified by Setting and Acute Respiratory Infection Diagnosis

	PCT Group	Control Group	Adjusted OR (95% CI) ^a	P Value
Overall	n = 2085	n = 2126
Mortality, No. (%)	118 (5.7)	134 (6.3)	0.94 (.71–1.23)	.75
Treatment failure, No. (%) ^b	398 (19.1)	466 (21.9)	0.82 (.71–.97)	.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 (.73–1.24)	.69
Days with restricted activities, median (IQR)	9 (6–14)	9 (5–14)	0.05 (–.46 to .56) ^d	.85
Emergency department	n = 1291	n = 1314		
Mortality, No. (%)	61 (4.7)	59 (4.5)	1.03 (.7–1.5)	.90
Mortality or ICU admission, No. (%)	126 (9.8)	147 (11.2)	0.83 (.64–1.08)	.16
Treatment failure, No. (%) ^e	182 (14.1)	228 (17.4)	0.76 (.61–.95)	.01
Length of hospital stay, median (IQR) ^f	8 (4–13)	8 (4–13)	–0.42 (–1.2 to .35) ^d	.28
Intensive care unit	n = 287	n = 311		
Mortality, No. (%)	57 (19.9)	74 (23.8)	0.84 (.54–1.31)	.44
Length of ICU stay, median (IQR)	12 (6–23)	12 (6–22)	1.01 (–1.26 to 3.28) ^d	.39
Length of hospital stay, median (IQR)	21 (11–38)	24 (14–38)	–1.36 (–4.5 to 1.77) ^d	.39
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 (.73–1.24)	.69
Community-acquired pneumonia	n = 999	n = 1028		
Mortality, No. (%)	92 (9.2)	111 (10.8)	0.89 (.64–1.23)	.47
Treatment failure, No. (%) ^b	190 (19.0)	240 (23.4)	0.77 (.62–.96)	.02
Ventilator-associated pneumonia	n = 126	n = 116		
Mortality, No. (%)	8 (6.3)	12 (10.3)	0.69 (.25–1.94)	.49
Treatment failure, No. (%) ^b	8 (6.3)	12 (10.3)	0.69 (.25–1.94)	.49
Acute bronchitis	n = 249	n = 282		
Mortality, No. (%)	0 (0)	2 (0.8)
Treatment failure, No. (%) ^b	51 (20.5)	54 (19.2)	1.09 (.70–1.70)	.71
Exacerbation of COPD	n = 288	n = 296		
Mortality, No. (%)	9 (3.1)	8 (2.7)	1.15 (.43–3.09)	.77
Treatment failure, No. (%) ^b	35 (13.7)	45 (15.2)	0.75 (.46–1.22)	.25

Abbreviations: ARI, acute respiratory infection; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio; PCT, procalcitonin.

^a Multivariable hierarchical regression with outcome of interest as dependent variable; PCT group, age, and ARI diagnosis as independent variables; and trial as a random effect.

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

^c Treatment failure was defined as death, hospitalization, ARI-specific complications, recurrent or worsening infection, and discomfort at 30 days.

^d Adjusted difference in days from hierarchical linear regression with PCT group, age, and ARI diagnosis as fixed effects and trial as a random effect.

^e Treatment failure is defined as mortality, ICU admission, rehospitalization, complications, recurrent or worsening infection within 30 days.

^f Two trials focusing on outpatients were excluded from this analysis [15, 16].

treatment failure when PCT was used to guide initiation and duration of antibiotic treatment in patients with ARI compared with control patients. The upper boundary of the 95% CI for treatment failure of .97 makes more frequent treatment failures with PCT unlikely. For mortality, however, the relatively wide CI does not exclude a 23% relative increase in odds

with the PCT approach. This may correspond to an absolute risk increase for mortality of 1% in the ED setting, assuming an event rate of 4.5%, and an absolute risk increase of 4% in the ICU setting, assuming an event rate of 23.8%. The remaining uncertainty associated with the mortality estimate for ICU patients calls for further research in this high-risk patient

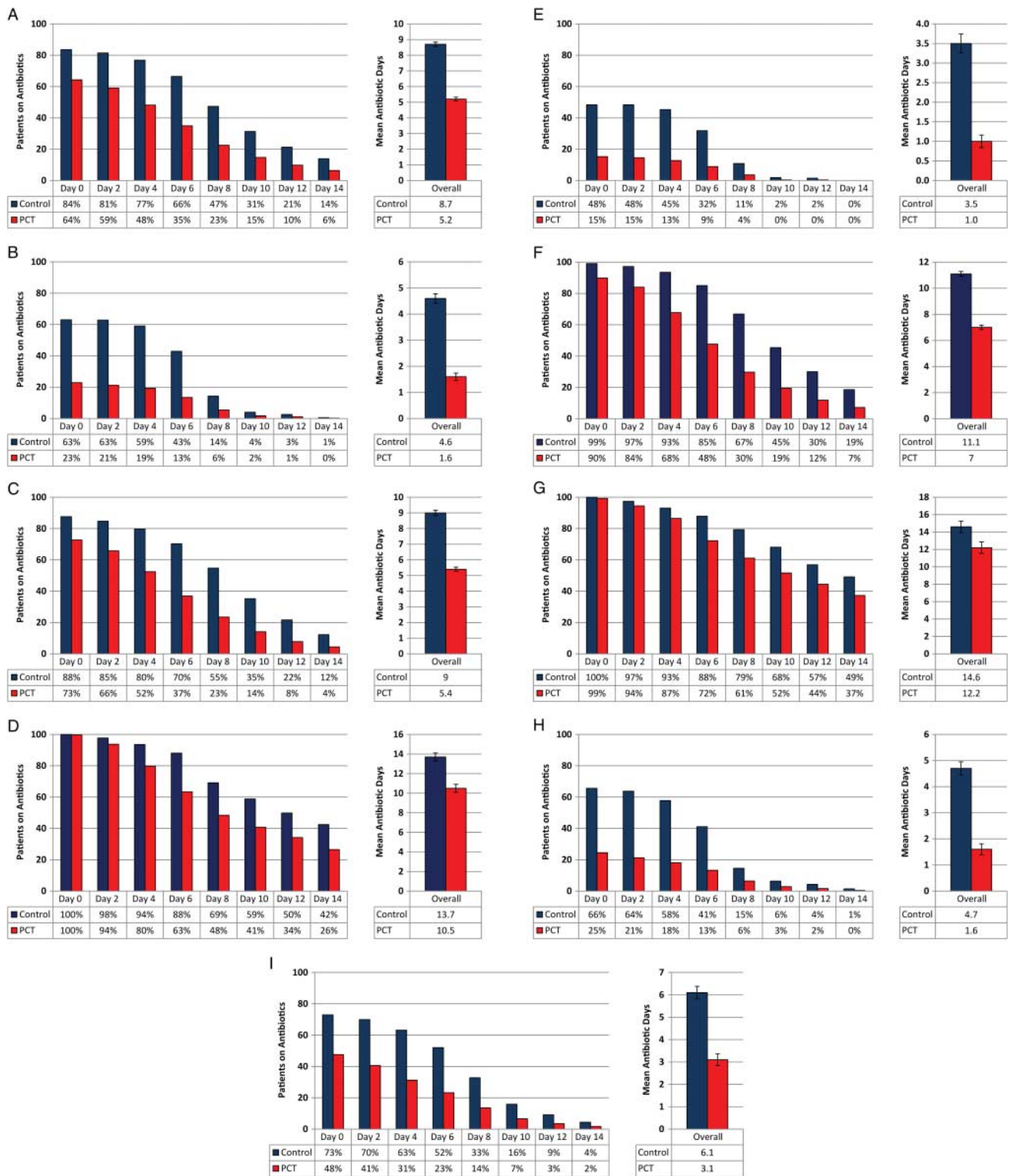


Figure 2. Antibiotic use in all patients ($n = 4221$; *A*), primary-care patients ($n = 1008$; *B*), emergency-department patients ($n = 2605$; *C*), intensive-care patients ($n = 598$; *D*), patients with upper acute respiratory tract infections ($n = 549$; *E*), patients with community-acquired pneumonia ($n = 2027$; *F*), patients with ventilator-associated pneumonia ($n = 242$; *G*), patients with bronchitis ($n = 531$; *H*), and patients with chronic obstructive pulmonary disease exacerbation ($n = 584$; *I*).

Table 5. Antibiotic Treatment Overall and Stratified by Setting and Acute Respiratory Infection Diagnosis

Parameter	PCT Group	Control Group	Adjusted OR or Difference (95% CI) ^c	P Value
Overall	n = 2085	n = 2126		
Initiation of antibiotics, No. (%)	1341 (64)	1778 (84)	0.24 (.20–.29)	<.0001
Duration of antibiotics in days, median (IQR) ^a	7 (4–10)	10 (7–13)	–2.75 (–3.12 to –2.39)	<.0001
Total exposure of antibiotics in days, median (IQR) ^b	4 (0–8)	8 (5–12)	–3.47 (–3.78 to –3.17)	<.0001
Setting specific				
Primary care	n = 507	n = 501		
Initiation of antibiotics, No. (%) ^a	116 (23)	316 (63)	0.10 (.07–.14)	<.0001
Duration of antibiotics in days, median (IQR)	7 (5–8)	7 (6–8)	–0.6 (–1.17 to –.03)	.04
Total exposure of antibiotics in days, median (IQR) ^b	0 (0–0)	6 (0–7)	–3.06 (–3.48 to –2.65)	<.0001
Emergency department	n = 1291	n = 1314		
Initiation of antibiotics, No. (%)	939 (73)	1151 (88)	0.34 (.28–.43)	<.0001
Duration of antibiotics in days, median (IQR) ^a	7 (4–10)	10 (7–12)	–3.7 (–4.09 to –3.31)	<.0001
Total exposure of antibiotics in days, median (IQR) ^b	5 (0–8)	9 (5–12)	–2.96 (–3.38 to –2.54)	<.0001
Intensive care unit	n = 287	n = 311		
Initiation of antibiotics, No. (%)	286 (100)	311 (100)
Duration of antibiotics in days, median (IQR) ^a	8 (5–15)	12 (8–18)	–3.17 (–4.28 to –2.06)	<.0001
Total exposure of antibiotics in days, median (IQR) ^b	8 (5–15)	12 (8–18)	–3.21 (–4.32 to –2.10)	<.0001
Disease specific				
Upper ARI	n = 282	n = 267		
Initiation of antibiotics, No. (%)	43 (15)	129 (48)	0.14 (.09–.22)	<.0001
Duration of antibiotics in days, median (IQR) ^a	7 (5–8)	7 (6–7)	–1.16 (–2.08 to –.24)	.01
Total exposure of antibiotics in days, median (IQR) ^b	0 (0–0)	0 (0–7)	–2.64 (–3.16 to –2.11)	<.0001
Community-acquired pneumonia	n = 999	n = 1028		
Initiation of antibiotics, No. (%)	898 (90)	1019 (99)	0.07 (.03–.14)	<.0001
Duration of antibiotics in days, median (IQR) ^a	7 (5–10)	10 (8–14)	–3.34 (–3.79 to –2.88)	<.0001
Total exposure of antibiotics in days, median (IQR) ^b	6 (4–10)	10 (8–14)	–3.98 (–4.44 to –3.52)	<.0001
Ventilator-associated pneumonia	n = 126	n = 116		
Initiation of antibiotics, No. (%)	125 (99)	116 (100)
Duration of antibiotics in days, median (IQR) ^a	11 (6–17)	14 (9–19.5)	–2.23 (–4.06 to –.39)	.02
Total exposure of antibiotics in days, median (IQR) ^b	11 (6–17)	14 (9–19.5)	–2.34 (–4.18 to –.50)	.01
Acute bronchitis	n = 249	n = 282		
Initiation of antibiotics, No. (%)	61 (24)	185 (66)	0.15 (.10–.23)	<.0001
Duration of antibiotics in days, median (IQR) ^a	7 (4–9)	7 (5–8)	–0.38 (–1.21 to .46)	.38
Total exposure of antibiotics in days, median (IQR) ^b	0 (0–0)	5 (0–7)	–3.06 (–3.69 to –2.43)	<.0001
Exacerbation of COPD	n = 288	n = 296		
Initiation of antibiotics, No. (%)	137 (48)	216 (73)	0.32 (.23–.46)	<.0001
Duration of antibiotics in days, median (IQR) ^a	6 (3–9)	8 (6–10)	–1.58 (–2.33 to –.82)	<.0001
Total exposure of antibiotics in days, median (IQR) ^b	0 (0–6)	7 (0–10)	–3.03 (–3.76 to –2.30)	<.0001

Abbreviations: ARI, acute respiratory infection; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; OR, odds ratio; PCT, procalcitonin.

^a Total days of antibiotic therapy in patients in whom antibiotics were initiated.

^b Total days of antibiotic therapy in all randomized patients.

^c Multivariable hierarchical model adjusted for age and diagnosis and trial as a random effect.

population. Due to the low adherence to PCT protocols in the ICU setting, we performed a number of sensitivity analyses to investigate whether excluding ICU data would affect our overall findings and found similar results in all such analyses. In terms of efficacy, we found a consistent reduction of antibiotic use in PCT groups, mainly due to lower prescription rates

in primary care (predominantly among patients with upper ARI and bronchitis), and lower duration of antibiotic courses in ED and ICU patients (with CAP and VAP).

Because we included a patient population ranging from primary care to ICU, we adapted the definition of treatment failure to clinical settings by including setting-specific and

clinically relevant components in this composite outcome. This may challenge the clinical interpretation in the overall analysis but lead to a better interpretation of patient risk in respective prespecified subgroups. We found lower rates of treatment failure for patients allocated to the PCT group overall, in the ED setting, and in CAP patients. Different sensitivity analyses confirmed this finding. There are 3 potential explanations:

1. PCT appears to provide additional useful information which can influence decision making in areas such as consideration of safe and early discharge [18].

2. In control groups, treatment failures may be related to prolonged antibiotic exposure and risk for secondary complications and rehospitalization [28, 29].

3. The finding turned out to be statistically significant by chance.

Considering the marginally nonsignificant result with the alternate definition, we would like to conservatively interpret this finding (ie, it is unlikely that PCT guidance increases treatment failures).

Similar to other tests [30], the use of PCT cut-offs and test result interpretation need to be reflected in the context of the pretest probability and to be adapted to clinical settings and the risk of patients. In included trials with patients at low risk for severe bacterial infections (eg, primary-care patients), a PCT algorithm was used to determine whether antibiotics should be initiated at all; in trials with higher-risk patients (ICU or ED patients), PCT was mainly used to determine when treatment could be safely discontinued [8]. Importantly, all trials included PCT in clinical algorithms, and physicians could deviate from the PCT algorithm if needed. As a consequence, some trials had low protocol adherence, particularly ICU trials. Although reductions in antibiotic exposure despite this low adherence were impressive, concerns about safety may arise. Clinicians commonly agree that important clinical decisions, such as initiation and continuation of antibiotic therapy, should not be based on a single diagnostic criterion only; PCT should complement but not replace clinical decision making [31]. Accordingly, PCT protocols specified “overruling criteria” whereby the PCT algorithm could be bypassed (eg, if clinical criteria suggest a high-risk situation) [8]. Of note, sensitivity analyses showed no evidence of heterogeneity, and results were similar when only trials with high adherence rates were considered. Poststudy surveys have been published [32, 33] in order to better understand the effects and challenges of PCT protocols in clinical practice, where adherence and confidence will be a crucial factor for the success of this strategy.

Previous meta-analyses of RCTs investigating the effect of PCT algorithms on antibiotic use focused on the critical-care setting [34–36], patients with suspicion of bacterial infections, [37] and patients with sepsis and respiratory infections [38]. However,

these meta-analyses used aggregated data and were not able to investigate the effects of PCT on different ARI diagnoses and on outcomes other than mortality. The strengths of this meta-analysis based on individual patient data from 14 eligible trials include an explicit study protocol, a comprehensive search to retrieve all relevant trials, a network that allowed inclusion of individual patient data from eligible trials, standardized outcome definitions across trials, the possibility to conduct appropriate subgroup and sensitivity analyses, and analyses based on the intention-to-treat principle, thereby overcoming limitations of previous meta-analyses with aggregated data.

Despite these merits, our study has several limitations. Although we included all available evidence in our pooled analysis, we cannot rule out a clinically relevant absolute risk increase of 4% for ICU patients with PCT guidance. In addition, the adherence to the PCT algorithm in the largest ICU trial [20] was relatively low (47%), leaving an even greater uncertainty about the safety of PCT use in ICU patients. There are currently several ongoing trials registered in the Clinical Trials database. Five ongoing trials focus on PCT as a guide to stop antibiotics in ICU patients with sepsis, and 2 of those are enrolling large numbers of patients (>1000 patients each). Hence, these trials may help to further establish the safety of PCT in this vulnerable patient population. However, if one wanted to rule out, for instance, a 10% relative (or 2.3% absolute) mortality increase in ICU patients, a total of 5735 randomized patients would be needed in each group (assuming a mortality rate in control ICU patients with ARI of 23%, an alpha error of 5%, and a power of 80%).

We limited our analysis to adult patients with ARIs that were mostly immunocompetent, thus limiting the generalizability to other populations. Previous RCTs have shown that PCT guidance also reduces antibiotic exposure in a neonatal sepsis population and in children with pneumonia [39, 40], but not in children with fever without a source [41]. We found 7 ongoing pediatric RCTs evaluating PCT algorithms that should shed further light on the benefits and harms of PCT use in pediatric populations.

Finally, included trials were mostly conducted in the European setting, with 2 trials coming from China [15, 16] and 1 multinational trial including US sites [19]. Thus, further validation and adaptation of PCT algorithms to other countries may be needed.

In conclusion, the use of PCT to guide initiation and duration of antibiotic treatment in patients with ARI was not associated with higher mortality rates or treatment failure, but PCT use did significantly reduce antibiotic consumption across different clinical settings and ARI diagnoses. The remaining uncertainty with respect to mortality and the partially low adherence rates to protocols in ICU patients calls for further trials, particularly in the critical-care setting, before

PCT-based algorithms can be considered safe. The use of PCT embedded in clinical algorithms has the potential to improve the antibiotic management of ARI patients and has substantial clinical and public health implications to reduce antibiotic exposure and the associated risk of antibiotic resistance.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Disclaimers. None of these persons received any compensation for their help with this study. P. S. and M. B. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. P. S., M. B., H. C. B., and B. M. conceived of the study and wrote the initial protocol. M. C.-C., D. S. L. B., M. W., C. E. T., J. C., F. T., K. B. B., L. W., O. B., T. W., S. S., V. N., and M. T. 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. N. B. is a research librarian experienced in the design of sensitive search strategies. P. S. and M. B. performed the statistical analyses and drafted the manuscript. All authors amended and commented on the manuscript and approved the final version. P. S., M. B., H. C. B., and B. M. oversaw the study and act as guarantors.

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