REVIEW ARTICLE

Procalcitonin Algorithms for Antibiotic Therapy Decisions

A Systematic Review of Randomized Controlled Trials and Recommendations for Clinical Algorithms

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Previous randomized controlled trials suggest that using clinical algorithms based on procalcitonin levels, a marker of bacterial infections, results in reduced antibiotic use without a deleterious effect on clinical outcomes. However, algorithms differed among trials and were embedded primarily within the European health care setting. Herein, we summarize the design, efficacy, and safety of previous randomized controlled trials and propose adapted algorithms for US settings. We performed a systematic search and included all 14 randomized controlled trials (N=4467 patients) that investigated procalcitonin algorithms for antibiotic treatment decisions in adult patients with respiratory tract infections and sepsis from primary care, emergency department (ED), and intensive care unit settings. We found no significant difference in mortality between procalcitonin-treated and control patients overall (odds ratio, 0.91; 95% confidence interval, 0.73-1.14) or in primary care (0.13; 0-6.64), ED (0.95; 0.67-1.36), and intensive care unit (0.89; 0.66-1.20) settings individually. A consistent reduction was observed in antibiotic prescription and/or duration of therapy, mainly owing to lower prescribing rates in low-acuity primary care and ED patients, and shorter duration of therapy in moderate- and high-acuity ED and intensive care unit patients. Measurement of procalcitonin levels for antibiotic decisions in patients with respiratory tract infections and sepsis appears to reduce antibiotic exposure without worsening the mortality rate. We propose specific procalcitonin algorithms for low-, moderate-, and high-acuity patients as a basis for future trials aiming at reducing antibiotic overconsumption.

Arch Intern Med. 2011;171(15):1322-1331

The advent of antibiotic therapy led to dramatic reductions in mortality and morbidity rates due to bacterial infections and sepsis.[1] However, overuse of antibiotics to fight infections may cause considerable harm by exposing individual patients to adverse events resulting from antibiotic use and by increasing the development of bacterial resistance. Combating the emergence of bacterial resistance to antimicrobial agents requires more effective efforts to reduce the inappropriate or unnecessarily prolonged use of antibiotics.[2]

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Patients and physicians share the common goals of improving the patient's health and resolving infections as quickly as possible; they often believe use of antibiotics to be the most expeditious intervention to address these goals. This one-size-fits-all approach fails to consider the following basic questions: (1) Who truly benefits from antibiotic therapy? and (2) If treated, what is the optimal treatment duration?[1]

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Considerable interest has been expressed in antibiotic stewardship programs aiming at reducing antibiotic over-

use and the associated emergence of multiresistant pathogens.[3,4] A previous cohort study[3] of hospitalized adult patients illustrated the effect of antimicrobial-resistant infections on hospitalization duration, mortality rate, and cost. In this study, the 188 patients with antimicrobial-resistant infections stayed 6.4 to 12.7 days longer in the hospital, had attributable mortality of 6.5%, and incurred societal costs ranging from $18 588 to $29 069 (2008 dollars) per patient.

A novel approach for determining the necessity and optimal duration of antibiotic therapy is the use of biomarkers, such as procalcitonin (PCT) levels, which become upregulated during bacterial infections and appear to mirror the severity of infections.[5,6] A growing body of literature supports the measurement of PCT levels to improve the ability to differentiate bacterial from nonbacterial infections because nonbacterial infections and nonspecific inflammatory reactions do not result in elevated PCT levels.[7] Also, an initial study[8] has shown that a decrease in PCT levels indicates a favorable patient response to antimicrobial therapy. Thus, PCT is a promising candidate marker to help physicians more rationally decide on prescription and duration of antibiotic therapy in patients with infections.

Procalcitonin, the precursor peptide of the hormone calcitonin, is released ubiquitously in response to primarily bacterial toxins and bacteria-specific proinflammatory mediators, particularly interleukin 1b, tumor necrosis factor, and interleukin 6.[5] In previous studies,[9,10] a strong correlation was observed between the concentration of PCT and the extent and severity of bacterial infections. Of particular interest, PCT levels are attenuated by the cytokines typically released in response to viral infections, namely, interferon-γ.[10] Levels of PCT have been shown to increase within 6 to 12 hours of the initial bacterial infection, and circulating PCT levels are expected to decrease by half daily when the infection is controlled by the host immune system and antibiotics (Abx).[11] A previous study[12] has shown that the production of PCT, in contrast to other blood markers, is not attenuated by nonsteroidal and steroidal anti-inflammatory drugs. Based on these promising preclinical data, many studies have investigated the clinical usefulness of measuring PCT levels for different clinical settings and infections.[7] However, owing to the diagnostic uncertainty associated with sepsis and other infectious diseases and the lack of a diagnostic criterion standard, the results of many observational studies have been inconclusive.[7]

To circumvent the limitations of observational studies, including observer bias, selection bias, sample availability, coinfection, colonization, and difficulty of pathogen identification owing to time constraints, several randomized controlled trials (RCTs) have been conducted focusing primarily on the outcomes of patients with or without the use of PCT-guided algorithms for antibiotic therapy. The clinical harm and benefit of using PCT thereby were measured by clinical outcomes, assuming that if the patient recovers without antibiotics, no relevant bacterial illness had existed, and if the patient recovers with fewer days taking antibiotics, the bacterial illness was adequately controlled with shorter antibiotic exposure.

The aim of this systemic review is to summarize the evidence based on previous RCTs for using PCT measurement in respiratory infections and sepsis from the clinical settings for which the most RCT data are available, namely, primary care, the emergency department (ED), the medical intensive care unit (MICU), and the surgical intensive care unit (SICU). Because most published studies were conducted in Europe, we also aim to propose clinical algorithms for use in future United States trials.

METHODS

LITERATURE SEARCH

We searched EMBASE (from 1974 to the present), MEDLINE via PubMED and Ovid (from 1948 to the present), and the Cochrane Central Register of Controlled Trials (from 1991 to 2011) for articles regarding PCT levels taken into account when making decisions regarding Abx. The following search terms were included: *procalcitonin* (mp [multiple posting, in which the term appears in the title, abstract, or subject heading]) and *calcitonin* AND *pneumonia* (exp [explode, a search term that automatically includes closely related MeSH terms]), *sepsis* (exp), *chronic obstructive pulmonary disease* (exp), or *respiratory tract infections* (exp). We also included *procalcitonin* (mp) and *calcitonin* AND *intensive care units*, *emergency services, hospital*, or *ambulatory care facilities*. We restricted the search to RCTs performed only in adults. We also identified relevant systematic reviews, meta-analyses, and controlled clinical trials and reviewed their references; in addition, we searched trial registries (http://www.clinicaltrials.gov and http://www.isrctn.org) and contacted experts in the field for additional eligible studies. We included articles in any language and did not exclude articles based on other comorbidities.

ELIGIBILITY CRITERIA AND STUDY SELECTION

Eligible trials had to be RCTs including adults with a diagnosis of respiratory tract infections (ie, pneumonia, acute exacerbations of chronic obstructive pulmonary disease [AECOPD] or other respiratory tract infections) or sepsis. Clinical settings included primary care, the ED, or the ICU. Interventions included measurement of PCT levels to inform decisions regarding antibiotic therapy (ie, regarding its initiation and/or duration). Abstracts or full-text articles for which no abstract was available were reviewed by 2 of us (P.S. and J.L.G.) to ensure topic appropriateness and adherence to inclusion and exclusion criteria. Disagreements were resolved by consensus.

DATA EXTRACTION AND QUALITY ASSESSMENT

Working in teams of 2, 3 investigators (P.S., V.C., and J.L.G.) independently extracted data from the included trials. Disagreements were resolved by consensus. A standardized data abstraction tool was used that included clinical setting, study design, number of study subject individuals, clinical outcomes, and study protocols. Also, an assessment of the methodological study quality was performed, based on the following criteria: adequate sequence generation (eg, computer-generated random numbers, compared with inadequate approaches, which included the use of alternation, case record numbers, or days of the week); adequate allocation concealment (deemed adequate if a central randomization procedure [ie, telephone or Web-based] or the use of sequentially

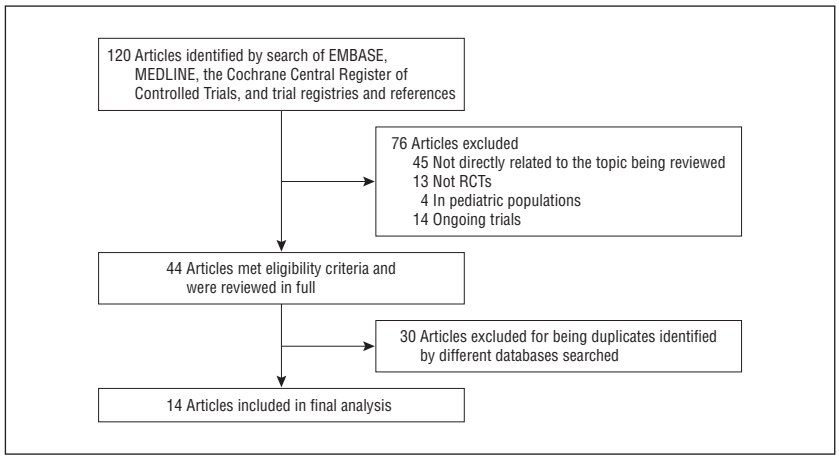

Figure 1. Flowchart depicting the process of article selection. RCT indicates randomized controlled trial.

Table 1. Quality of Studies[a]

Source	Sequence Generation	Allocation Concealment	Masking	Incomplete Outcome Data	Selective Outcome Reporting
Briel et al,[14] 2008	3	3	2	3	3
Burkhardt et al,[21] 2010	2	2	2	3	3
Christ-Crain et al,[22] 2004	2	1	2	3	3
Christ-Crain et al,[23] 2006	3	2	1	3	3
Stolz et al,[24] 2007	2	1	2	3	3
Long et al,[25] 2009	1	1	1	2	3
Kristoffersen et al,[26] 2009	2	1	1	3	3
Schuetz et al,[15] 2009	3	3	1	3	3
Svoboda et al,[27] 2007	3	2	2	2	2
Nobre et al,[28] 2008	3	2	2	2	3
Stolz et al,[29] 2009	2	1	1	3	3
Hochreiter et al,[30] 2009	2	1	1	3	2
Schroeder et al,[31] 2009	3	2	1	3	3
Bouadma et al,[32] 2010	3	3	2	3	3

[a] Evaluated using the methods of Higgins and Green.[13] No other bias was applicable. 1, poor quality or not reporting; 2, unclear reporting; 3, excellent performance and reporting.

numbered, opaque, sealed envelopes was reported); adequate masking of physicians, patients, and outcome assessors; low risk of attrition bias (ie, minimal loss to follow-up and performance of adequate sensitivity analyses); and freedom from selective outcome reporting (eg, if all stated outcomes were reported).[13] Two of us (P.S. and M.B.) who were coauthors of eligible studies[14,15] were excluded from reviewing our own work.

DATA SYNTHESIS

For all included RCTs, we report summary data, including antibiotic prescription rate, duration of antibiotic treatment, mortality rate, and adverse event rate, as defined in the individual studies. We pooled results and calculated odds ratios (ORs) with 95% confidence intervals (CIs) for overall mortality rate using the Peto method.[16] The Peto ORs are appropriate when intervention effects are small (ie, when ORs are close to 1), events are not particularly common, and studies have balanced numbers in intervention and control groups.[17] We tested for heterogeneity with the Cochran Q test and measured the inconsistency (I^2 [the percentage of total variance across studies that is due to heterogeneity rather than chance]) of intervention effects across trials.[18] Also, we performed sensitivity analyses comparing trials with low risk of bias (ie, adequate sequence generation, allocation concealment, and unlikely attrition bias) vs trials at higher risk. We investigated the presence of publication bias by means of funnel plots.[19] Concerning antibiotic treatment, the different studies were too few in number and lacked adequate consistency in reporting across study design and population for a pooled analysis of antibiotic treatment data for different diagnoses and settings. Instead, we summarized antibiotic exposure and outcome data from the different studies grouped by clinical setting. This report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[20] All calculations were performed using commercially available software (STATA, version 9.2 [StataCorp LP, College Station, Texas] and RevMan, version 5.1 [Cochrane Collaboration]).

RESULTS

LITERATURE SEARCH AND QUALITY OF STUDIES

The literature searches of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials and mining of trial registries and references yielded 120 potential results (**Figure 1**). A total of 58 articles were then excluded owing to nonrandomization and/or not focusing on our population of interest. Also, we excluded 4 articles focusing on pediatric populations and 14 ongoing trials, leaving 44 articles that we further assessed for eligibility. After exclusion of 2 duplicate publications in different journals and redundantly identified articles from the different databases, 14 articles remained. Review of the reference lists from the 14 articles and those from selected meta-analyses and reviews regarding the topic yielded no additional trials. Thus, the final quantitative analysis includes 14 RCTs.

Table 1 shows the quality assessment of included trials with regard to sequence generation, allocation concealment, masking, incomplete outcome data, selective outcome reporting, and other biases. The methodological quality varied across included studies; only 3 trials could be considered at low risk for bias, namely, 1 in the primary care,[14] 1 in the ED,[15] and 1 in the ICU setting.[32] The other studies lacked several quality criteria and need to be considered at high risk for bias. None of the studies managed to mask physicians with respect to treatment allocation of patients.

STUDY SETTING, DESIGN, AND PCT ALGORITHMS

Table 2 summarizes clinical design and study setting. It also displays the underlying diagnoses of patients, the study question, the PCT algorithm used, and the outcomes investigated of all included RCTs.

Table 2. Overview of Design and Content of the RCTs Grouped by Study Setting

Source	Study Design[a]	Diagnosis	Research Question	Algorithm by PCT Level, µg/L	Outcome
Primary Care Setting					
Briel et al,[14] 2008	Multicenter, noninferiority	Upper and lower RTI	Safety and reduction of Abx with repeated PCT-level measurement?	<0.10, SRAA; 0.10-0.25, RAA; >0.25, RFA; recheck PCT level at 6-24 h if no Abx initiated	Primary: days with restricted activity in first 14 d Secondary: Abx exposure, adverse events at day 28
Burkhardt et al,[21] 2010	Multicenter, noninferiority	Upper and lower RTI	Safety and reduction of Abx with single PCT-level measurement?	<0.25, RAA; >0.25, RFA	Primary: days with significant health impairment at day 14 Secondary: Abx exposure
ED Settings					
Christ-Crain et al,[22] 2004	ED only, single center	CAP, AECOPD, bronchitis	Reduction of Abx for lower RTI with repeated CAP in ED with single PCT-level measurement?	<0.10, SRAA; 0.10-0.25, RAA; 0.25-0.50, RFA; >0.50, SRFA; recheck PCT level after 6-24 h if no Abx initiated	Primary: Abx prescriptions at day 14 Secondary: readmission, relapse, QOL, cost
Christ-Crain et al,[23] 2006	ED and inpatient, single center	CAP	Reduction of Abx for CAP with repeated PCT-level measurements?	<0.10, SRAA; 0.10-0.25, RAA; 0.25-0.50, RAA; >0.50, SRFA; recheck PCT level every 2 d; discontinue Abx with same cutoffs	Primary: duration of Abx at day 28 Secondary: mortality, adverse outcomes
Stolz et al,[24] 2007	ED and inpatient, single center	AECOPD	Reduction of Abx for AECOPD with repeated PCT-level measurements?	<0.10, SRAA; 0.10-0.25, RAA; 0.25-0.50, RFA; >0.50, SRFA; retest PCT level every 2 d; discontinue Abx with same cutoffs	Primary: Abx use in hospital and first 6 mo Secondary: ICU, death, LOS, AECOPD recurrence rate
Long et al,[25] 2009	ED at 2 centers	CAP	Reduction of Abx for CAP in outpatients with repeated PCT-level measurements?	<0.25, RAA; ≥0.25, RFA; if no Abx, retest PCT at 8-12 h; recheck PCT every 3 d; discontinue Abx with same cutoffs	Primary: Abx use within 28 d Secondary: clinical recovery, treatment failure, cost of Abx
Kristoffersen et al,[26] 2009	ED and inpatient, single center	Lower RTI	Reduction of Abx for lower RTI with single PCT-level measurement?	<0.25, RAA; 0.25-0.50, RFA; >0.50, SRFA	Primary: Abx use Secondary: adherence to algorithm, mortality, ICU
Schuetz et al,[15] 2009	ED and inpatient, multicenter	CAP, AECOPD, bronchitis	Safety, Abx use, and feasibility in CAP, AECOPD, and bronchitis?	<0.10, SRAA; 0.10-0.25, RAA; 0.25-0.50, RFA; >0.50, SRFA; retest PCT level every 2 d; discontinue Abx with same cutoffs	Primary: noninferiority of adverse outcomes at day 28 Secondary: duration of Abx
ICU and Inpatient Settings[b]					
Svoboda et al,[27] 2007	ICU, single center	Postop septic shock	Improvement of outcomes after multiple traumas or major surgery?	>2.00, change in use of Abx and catheters; <2.00, ultrasonography and CT, followed by surgery	Primary: ICU LOS, ICU mortality rate, SOFA score, days using ventilator
Nobre et al,[28] 2008	ICU, single center	Sepsis	Reduction of Abx in ICU patients with sepsis?	Discontinue Abx on day 5 when <0.25 or decrease of ≥90% from peak occurs	Primary: duration of Abx Secondary: mortality rate and LOS at day 28
Stolz et al,[29] 2009	European and US ICU, multicenter	VAP	Reduction of Abx in VAP in different ICUs?	<0.25, discontinue Abx; <0.50 or decrease of >80%, consider discontinuing Abx; >0.50 or decreased <80%, continue Abx; >1, continue Abx	Primary: Abx-free days alive
Hochreiter et al,[30] 2009	ICU, single center	Postop with infection	Reduction of Abx in postop ICU patients with infection?	Discontinue Abx if clinically improvement observed and <1.00 or if decrease to 25%-35% of initial value for 3 d observed	Primary: Abx use Secondary: LOS
Schroeder et al,[31] 2009	ICU, single center	Postop with severe sepsis	Reduction of Abx duration in severe sepsis in postop ICU patients?	Discontinue Abx if decrease to <1.00 or decrease by 25%-35% for 3 d observed	Primary: Abx use Secondary: LOS, mortality rate
Bouadma et al,[32] 2010	ICU, multicenter	Sepsis	Safety and reduction of Abx in ICU patients with sepsis?	<0.25, SRAA; 0.25-0.50, RAA; >0.50-1.00, RFA; >1.00, SRFA; retest PCT level in 6-12 h if Abx not initiated; discontinue Abx when <0.50 or decrease >80% from peak level observed	Primary: mortality rate at days 28 and 60, Abx use at day 28

Abbreviations: Abx, antibiotics; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CAP, community-acquired pneumonia; CT, computed tomography; ED, emergency department; ICU, intensive care unit; LOS, length of stay; PCT, procalcitonin; Postop, postoperative; QOL, quality of life; RAA, recommendation against use of antibiotics; RCT, randomized controlled trial; RFA, recommendation for use of antibiotics; RTI, respiratory tract infection; SICU, surgical ICU; SOFA, sepsis-related organ failure assessment; SRAA, strong recommendation against use of antibiotics; SRFA, strong recommendation for use of antibiotics; VAP, ventilator-associated pneumonia.

[a] All trials test for superiority unless designated noninferiority.

[b] Mostly medical ICU patients, with some SICU and general inpatients.

Primary Care

Two studies in the primary care setting were found.[14,21] Both were noninferiority trials with regard to clinical outcomes, focused on upper and lower respiratory tract infections, and used a similar PCT algorithm (ie, no antibiotics in patients with PCT levels of <0.25 µg/L). However, although the study by Briel et al[14] used repeated PCT measurements and addressed subjects' activity limitations and antibiotic exposure as outcomes, the study by Burkhardt et al[21]

Table 3. Primary and Secondary Outcomes of the Different RCTs, Grouped by Study Setting

Source	Diagnoses	Total No.	Mortality, Control vs PCT Groups, No. Dead/Total (%)	Abx Use, Control vs PCT	Relative Reduction, %	Key Findings
			Primary Care Settings			
Briel et al,[14] 2008[a]	Upper and lower RTI	458	1/226 (0.4) vs 0/232 (0)	Prescription: 97% vs 25% Duration (mean): 7.1 vs 6.2 d	Prescription: –74 Duration: –13	Reduction of Abx without additional days of restricted activity
Burkhardt et al,[21] 2010	Upper and lower RTI	550	0/275 (0) vs 0/275 (0)	Prescription: 36.7% vs 21.5% Duration (mean): 7.7 vs 7.8 d	Prescription: –42 Duration: 1	Reduction of Abx without causing heath impairment
			ED Settings			
Christ-Crain et al,[22] 2004	CAP, AECOPD, bronchitis	243	4/119 (3.4) vs 4/124 (3.2)	Prescription: 83% vs 44% Duration (mean): 12.8 vs 10.9 d	Prescription: –47 Duration: –15	Reduction of Abx prescriptions
Christ-Crain et al,[23] 2006	CAP	302	20/151 (13.2) vs 18/151 (11.9)	Prescription: 99% vs 85% Duration (mean): 12.9 vs 5.8 d	Prescription: –14 Duration: –55	Reduction of initiation and duration of Abx without adverse outcomes
Stolz et al,[24] 2007	AECOPD	208	9/106 (8.5) vs 5/102 (4.9)	Prescription: 72% vs 40%	Prescription: –44	Reduced Abx exposure without adverse outcome
Long et al,[25] 2009	CAP	127	0/64 (0) vs 0/63 (0)	Prescription: 97% vs 86% Duration (median): 10 vs 6 d	Prescription: –11 Duration: –40	Reduction of Abx use and shorter Abx duration
Kristoffersen et al,[26] 2009	Lower RTI	210	1/107 (0.9) vs 2/103 (1.9)	Prescription: 79% vs 85% Duration (mean): 6.8 vs 5.1 d	Prescription: 8 Duration: –25	Reduction of duration of Abx use
Schuetz et al,[15] 2009	CAP, AECOPD, bronchitis	1359	33/688 (4.8) vs 34/671 (5.1)	Prescription: 87.7% vs 75.4% Duration (median): 8.7 vs 5.7 d	Prescription: –14 Duration: –34	Noninferiority for clinical outcomes and decreased Abx use
			Inpatient and ICU Settings			
Svoboda et al,[27] 2007	Postop septic shock	72	13/34 (38.2) vs 10/38 (26.3)	NA	NA	Trend to decrease in SOFA and ventilator/ICU days
Nobre et al,[28] 2008	Sepsis	79	12/40 (30.0) vs 8/39 (20.5)	Duration (median): 9.5 vs 6.0 d	Duration: –37	Reduction in Abx duration and ICU LOS without adverse events
Stolz et al,[29] 2009	VAP	101	12/50 (24.0) vs 8/51 (15.7)	Abx-free days alive: 9.5 vs 13 Duration (median): 15 vs 10 d	Abx-free days alive: 27 Duration: –33	Decreased Abx use without increasing mortality rate
Hochreiter et al,[30] 2009	Postop patients with infection	110	14/53 (26.4) vs 15/57 (26.3)	Duration (mean): 7.9 vs 5.9 d	Duration: –25	Reduction in Abx duration and ICU LOS without adverse events
Schroeder et al,[31] 2009	Postop severe sepsis	27	3/13 (23.1) vs 3/14 (21.4)	Duration (mean): 8.3 vs 6.6 d	Duration: –20	Shorter Abx duration
Bouadma et al,[32] 2010[b]	Sepsis	621	64/314 (20.4) vs 65/307 (21.2)	Abx-free days alive: 11.6 vs 14.3 Duration (mean): 9.9 vs 6.6 d	Abx-free days alive: 19 Duration: –33	Reduction in Abx use without increase in mortality rate

Abbreviations: NA, not available. Other abbreviations: See Table 2.
[a] Indicates intention-to-treat analysis.
[b] Indicates 28-day mortality.

only measured PCT levels once on admission but also measured health impairment and antibiotic exposure.

Emergency Department

A total of 6 studies in the ED setting were identified.[15,22-26] All studies used a similar PCT algorithm (ie, no initiation of Abx or, if already initiated, discontinuation of Abx in patients with PCT levels of <0.25 µg/L). Two studies[22,26] measured PCT levels only on admission, and the remaining 4 studies[15,23-25] used repeated measurements. All studies reported antibiotic exposure and patient outcomes, but only the trial by Schuetz et al[15] was powered for noninferiority with regard to clinical outcomes.

Intensive Care Unit

In the ICU setting, 6 RCTs were identified[27-32] that differed substantially in terms of underlying diagnoses (ie, postoperative infections in the SICU, severe sepsis and/or septic shock, and ventilator-associated pneumonia) and the PCT cutoffs used. All studies based their recommendation primarily on repeated PCT measurements and specified discontinuing Abx when PCT levels dropped to a range of less than 0.25 to less than 1.00 µg/L or by at least 80% to 90%. One study[27] did not focus on de-escalation of antibiotics but specified to change antibiotics or to perform a diagnostic workup if PCT levels did not decrease by an adequate amount. Two studies were multicenter trials,[29,32] and the trial by Bouadma et al[32] was a noninferiority trial in terms of mortality rate and adverse outcomes. Antibiotic exposure, length of stay, and mortality rate were the most commonly reported outcomes.

EFFICACY AND CLINICAL OUTCOMES

Overall, a total of 4467 patients were included in the 14 RCTs (ie, 2240 in the control group and 2227 in the PCT group). **Table 3** displays the detailed results of all RCTs with regard to the number of included patients and underlying diagnoses, mortality rate, absolute and relative antibiotic prescription rates, and duration between the 2 groups. Overall, no sig-

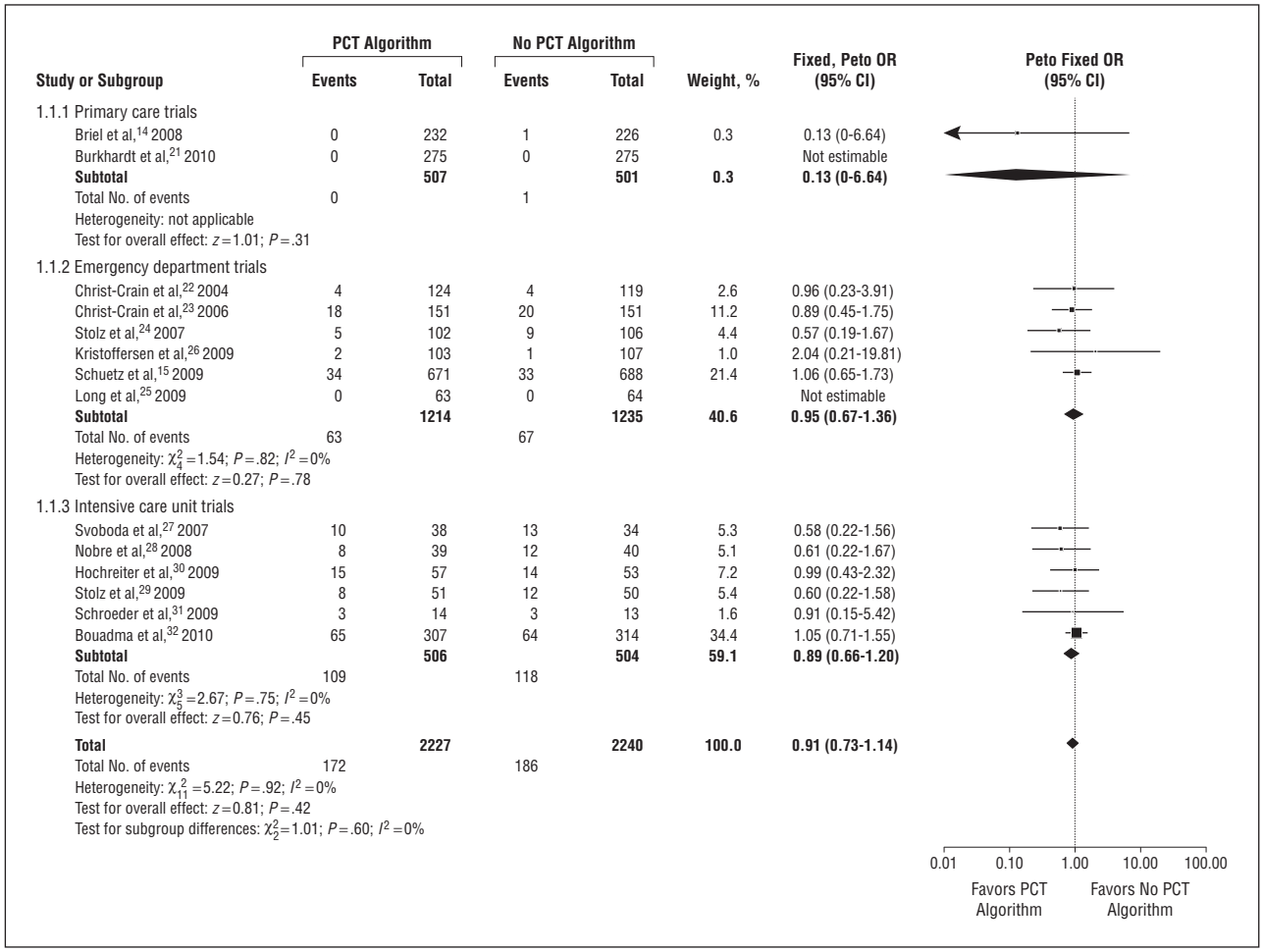

Figure 2. Mortality rate in the procalcitonin (PCT) and control groups. The forest plot depicts the Peto odds ratios (ORs) with 95% confidence intervals (CIs), comparing patients treated in the PCT and control groups in different trials and clinical settings.

nificant difference was observed in mortality in patients in the PCT groups (172 of 2227 [7.7%]) compared with the control group (186 of 2240 [8.3%]), with a summary OR of 0.91 (95% CI, 0.73-1.14) (**Figure 2**). We found no evidence of relevant heterogeneity among trials. The analysis for publication bias indicated no evidence of such bias for mortality rate (eFigure 1; http://www.archinternmed.com).

Primary Care

The 2 primary care trials included a total of 1008 patients with upper and lower respiratory tract infections. The study by Briel et al,[14] which used repeated PCT measurements, found a 74% reduction in antibiotic prescription and a 13% reduction in mean antibiotic duration. However, the study by Burkhardt et al[21] only used a single PCT measurement at admission and found a 42% reduction in antibiotic exposure but not a reduction in treatment duration. In both trials, no differences were observed in the primary safety end points (ie, days with restricted activities and days with health impairment within a 14-day follow-up) between the controls and the PCT-group patients. The mortality rate in both trials was similarly low in both groups (OR, 0.13; 95% CI, 0-6.64) (Figure 2).

Emergency Department

The 6 ED trials[15,22-26] included a total of 2449 patients, mostly with community-acquired pneumonia and AECOPD. For community-acquired pneumonia, the main effect of using PCT was to shorten the duration of antibiotic treatment. Trials using only a single initial PCT measurement had less effect on duration of antibiotic therapy (ie, a 15% reduction in the first study by Christ-Crain et al[22]) compared with those requiring repeated PCT measurements (ie, a 55% reduction in the second study by Christ-Crain et al,[23] a 40% reduction in the study by Long et al,[25] and a 34% reduction in the trial by Schuetz et al[15]). The study by Kristoffersen et al[26] had similar antibiotic prescription rates but a 25% reduction in the duration of antibiotic therapy. Those authors noted, however, that physicians were not asked to wait for PCT results before initiating antimicrobial therapy. Therefore, PCT values were, in most cases, used to motivate cessation or continuation of already-initiated treatments.

For patients with AECOPD, the trial by Stolz et al[24] found a 44% reduction in prescription rates. The patients with COPD guided by a PCT-based algorithm included by Christ-Crain et al[22] and Schuetz et al[15] also had lower prescription rates compared with controls (ie, 87% vs 38% and 70% vs 49%, respectively). In none of the ED trials was an increase in adverse outcomes noted,

although only the trial by Schuetz et al was powered for this end point. Within all ED trials, mortality in PCT groups was 5.2% (63 of 1214) compared with 5.4% (67 of 1235) in control groups (OR, 0.95; 95% CI, 0.67-1.36) (Figure 2).

Intensive Care Unit

The 2 ICU trials that focused on patients with severe sepsis/septic shock (ie, Nobre et al[28] and Bouadma et al[32]) found reductions in antibiotic exposure of 37% and 33%, respectively. The trial by Svoboda et al[27] did not report antibiotic exposure because it only focused on patient outcomes. The trial reported by Stolz et al[29] included only patients with ventilator-associated pneumonia and found a 27% increase in antibiotic-free days alive. Two trials[30,31] focused on patients with postoperative infection and sepsis; they reported reductions of antibiotic exposure by 20% and 25%, respectively. None of the studies reported a difference in mortality rate or adverse outcome, but only the study by Bouadma et al[32] was powered for noninferiority. Within all ICU trials, mortality in the PCT group patients was 21.5% (109 of 506), compared with 23.4% (118 of 504) in standard group patients (OR, 0.89; 95% CI, 0.66-1.20) (Figure 2). A sensitivity analysis contrasting the 3 trials at low risk of bias[14,15,32] with the remaining higher-risk trials yielded similar results (eFigure 2A and B).

COMMENT

Within this systematic review, we address the question of the safety and efficacy of using a PCT-based algorithm for antibiotic therapy decisions in patients with respiratory tract infections and sepsis using data derived from previous RCTs. We found a marked reduction in antibiotic exposure in all settings, levels of disease acuity, and patient populations. This reduction occurred because of lower prescription rates in low-acuity infections such as bronchitis, exacerbation of AECOPD in primary care and ED settings, and shorter duration of antibiotic courses in moderate- and high-acuity patients, such as those with pneumonia and sepsis in the hospital and ICU settings. Critically, none of the trials reported an increase in adverse outcomes, including mortality rate, although only a subset of the included trials were powered to detect changes in clinical outcomes.

Given the limited number of studies included across a breadth of diagnoses and settings in this analysis and the limited methodological quality of many of the included studies (ie, their being at high risk for bias), caution must be used when generalizing these findings. Although it is reassuring to note the uniform absence of adverse events paralleling the similarly uniform presence of antibiotic use reduction across the studies, further data are needed before PCT-based algorithms should be considered the criterion standard of care, especially for diagnoses such as ventilator-associated pneumonia or postoperative infection, in which randomized trial data are limited. Clearly, the most robust data are for pneumonia; in this diagnosis, as with the others, the findings are promising.

Previous meta-analyses have investigated the use of PCT levels for detection of sepsis in adult patients[33-37] and children[38] from observational studies. Also, 3 previous meta-analyses focused on randomized trials only to investigate the measurement of PCT levels for antibiotic decisions in the critical care setting[39,40] and in patients with suspected bacterial infections.[41] Our systematic review included all published RCTs that investigated PCT algorithms for antibiotic treatment decisions concerning escalation and de-escalation of dosage in adult patients with respiratory tract infections and sepsis from primary care, ED, and ICU settings. We focus our analysis on the differences in PCT algorithms used for low-, moderate-, and high-acuity patients; this is a basis for future trials aiming at reducing antibiotic overconsumption and it may be of particular importance for practicing physicians who want to include PCT findings in their hospital protocols. Owing to differences of PCT levels in different clinical settings and patient populations, the correct and safe practical use of this marker will likely vary with the level of disease acuity in patients.

The algorithms in the included studies varied moderately. Nevertheless, a few commonalities can be identified. First, regarding the most severe diseases (eg, sepsis and pneumonia) or the highest-acuity care settings (ie, the ICU and the hospital), PCT levels were not used to determine whether antibiotic therapy should be initiated but when to discontinue it. Second, the decrease of elevated PCT levels appears to correlate adequately with sufficient resolution of bacterial infections to allow for the safe discontinuation of antibiotic therapy, even if this discontinuation occurs before the traditional length of a typical course of antibiotics has elapsed. Third, in lower-acuity settings (eg, the primary care setting) or with clinical entities that are generally less imminently dangerous (eg, bronchitis), PCT values may be used to assist in the initial determination of whether antibiotics should be prescribed at all. However, all patients should undergo reassessment in cases in which Abx are withheld to ensure that the clinical condition improves spontaneously in a clinically appropriate period.

Most of the studies of PCT-based algorithmic approaches to antibiotic management of respiratory tract infections have been conducted in Europe. Despite the recognized importance of antibiotic stewardship and health care cost containment in the United States,[3,4] further studies in a US population may be needed to assuage concerns regarding practice and population differences. Therefore, we recommend the PCT algorithms described herein for use in future US studies. However, algorithms for PCT use, much like those for other biomarkers, should supplement and not supplant clinical impressions.

LOW RISK/LOW ACUITY

For patients with a low pretest probability of contracting a bacterial infection (eg, patients with nonpneumonic upper and lower respiratory tract infection treated in the primary care setting), a single measurement of PCT level and a cutoff ranging from less than 0.10 to less than 0.25 μg/L appears to be an appropriate, safe, and simple approach in

this setting to determine the need for antibiotics. Clinical follow-up with remeasurement of PCT should be performed in all patients in whom Abx were withheld and who show no clinical improvement (**Figure 3**A).

MODERATE RISK/ MODERATE ACUITY

For patients who are clinically stable and are treated at the ED or are hospitalized with pneumonia, the initiation of antibiotic therapy should be based on clinical grounds and a PCT threshold of at least 0.25 µg/L, assuming the PCT results can be obtained expeditiously. In patients with an initial PCT level of no higher than 0.25 µg/L, alternative diagnoses (eg, viral infection and pulmonary embolism) should be considered. Thereafter, repeated measurement of PCT levels every other day should occur, with directions to discontinue antibiotic therapy when PCT levels drop to less than 0.25 µg/L or by at least 80% to 90% of the peak value and when the patient has improved clinically. If Abx are withheld initially, algorithms should suggest retesting PCT levels 6 to 12 hours after the initial measurement (Figure 3B).

HIGH RISK/HIGH ACUITY

In high-risk or ICU patients with suspected sepsis, algorithms should dictate that empirical antibiotic therapy not be delayed for PCT measurement. Periodic monitoring of PCT levels after initiation of antibiotic therapy may be the preferred strategy, and a drop of PCT levels to less than 0.50 µg/L or by at least 80% to 90% from baseline in patients who show a clinical improvement after therapy are reasonable thresholds for cessation of antibiotic therapy in this fragile population (Figure 3C). For postoperative patients in the SICU, a decrease in PCT level to less than 1.0 µg/L may be sufficient to discontinue Abx. As with moderate risk/ moderate acuity algorithms, if Abx is withheld initially based on a low PCT level, a second measurement should be obtained within 6 to 12 hours.

A

Evaluation at time of admission				
PCT result	**<0.10 µg/L**	**<0.25 µg/L**	**≥0.25 µg/L**	**>0.50 µg/L**
Recommendation regarding use of Abx	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged
Overruling the algorithm	Consider use of antibiotics if patients are clinically unstable, have strong evidence of pneumonia, are at high risk (ie, COPD GOLD III-IV), or need hospitalization			
Follow-up/other comments	Follow-up only needed if no symptom resolution after 1 to 2 days; if clinical situation is not improving; consider Abx if PCT level increases to ≥0.25 µg/L		Clinical reevaluation as appropriate	

B

Evaluation at time of admission				
PCT result	**<0.10 µg/L**	**<0.25 µg/L**	**≥0.25 µg/L**	**>0.50 µg/L**
Recommendation regarding use of Abx	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged
Overruling the algorithm	Consider alternative diagnosis, or Abx if patients are clinically unstable, are at high risk for adverse outcome (eg, PSI classes IV-V, immunosupression), or have strong evidence of a bacterial pathogen			
Follow-up/other comments	Reassess patients' condition and recheck PCT level after 6 to 12 hours if no clinical improvement is observed		Recheck PCT level every 2 to 3 days to consider early cessation of Abx	
Follow-up evaluation every 2 to 3 days				
PCT result	**<0.10 µg/L**	**<0.25 µg/L**	**≥0.25 µg/L**	**>0.50 µg/L**
Recommendation regarding use of Abx	Cessation of therapy strongly encouraged	Cessation of therapy encouraged	Cessation of therapy discouraged	Cessation of therapy strongly discouraged
Overruling the algorithm	Consider continuation of Abx if patients are clinically not stable			
Follow-up/other comments	Clinical reevaluation as appropriate		Consider treatment to have failed if PCT level does not decrease adequately	

C

Evaluation at time of admission				
PCT result	**<0.25 µg/L**	**<0.50 µg/L**	**≥0.50 µg/L**	**>1.0 µg/L**
Recommendation regarding use of Abx	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged
Overruling the algorithm	Empirical therapy recommended in all patients with clinical suspicion of infection			
Follow-up/other comments	Consider alternative diagnosis; reassess patients condition and recheck PCT level every 2 days		Reassess patients' condition and recheck PCT level every 2 days to consider cessation of Abx	
Follow-up evaluation every 1 to 2 days				
PCT result	**<0.25 µg/L or drop by >90%**	**<0.50 µg/L or drop by >80%**	**≥0.50 µg/L**	**>1.0 µg/L**
Recommendation regarding use of Abx	Cessation of Abx strongly encouraged	Cessation of Abx encouraged	Cessation of Abx discouraged	Cessation of Abx strongly discouraged
Overruling the algorithm	Consider continuation of Abx if patients are clinically unstable			
Follow-up/other comments	Clinical reevaluation as appropriate		Consider treatment to have failed if PCT level does not decrease adequately	

Figure 3. Proposed algorithms for use of procalcitonin (PCT) values to determine antibiotic treatment of infections. A, An algorithm for low-acuity nonpneumonic infections (ie, low risk) in primary care and emergency department (ED) settings. B, Algorithm for moderate-acuity pneumonic infections (ie, moderate risk) in hospital and ED settings; C, Algorithm for high-acuity infections (ie, high risk; sepsis) in intensive care unit settings. Abx indicates antibiotics; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PSI, pneumonia severity index.

LIMITATIONS

Our review has a number of limitations. First, because it is limited to RCTs in an attempt to minimize bias, it excluded a reasonably large body of literature pertaining to PCT that did not derive from RCTs. This exclusion may have led to the inadvertant omission of relevant findings. Second, although we conducted an extensive literature search for

RCTs on the topic and a funnel plot did not suggest the presence of publication bias, such a bias cannot definitely be ruled out. Third, the methodological quality of most included trials was low to moderate. However, a sensitivity analysis focusing on 3 trials at low risk for bias yielded similar results, and no evidence was observed of heterogeneity among effects on mortality rate.

In conclusion, this systematic review of mostly moderate-quality RCTs suggests that the use of PCT-guided algorithms for antibiotic therapy decisions in patients with respiratory tract infections, including bronchitis, AECOPD, and pneumonia and in patients with sepsis appears to be effective at reducing use of Abx without sacrificing patient safety. These types of algorithms also appear to be useful in different clinical settings. Based on the available evidence, we have proposed PCT algorithms based on clinical acuity levels, which should be used in future large multicenter trials within the United States, powered for patient outcomes and aimed at reducing antibiotic overconsumption.

Accepted for Publication: May 10, 2011.

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Financial Disclosure: Dr Schuetz was supported by research grant PASMP3-127684/1 from the Swiss Foundation for Grants in Biology and Medicine and received support from BRAHMS USA Inc and bioMérieux to attend meetings and to fulfill speaking engagements. Dr Briel is supported by grants from santésuisse and the Gottfried and Julia Bangerter-Rhyner Foundation.

Online-Only Material: The eFigures are available at http://www.archinternmed.com.

Additional Contributions: Qing Wang, PhD, of the Basel Institute for Clinical Epidemiology, University Hospital Basel, Switzerland, helped with the translation of an article published in Chinese. Carole Foxman, MA, MS, Coordinator for Education and Database Services/Research Liaison at the Treadwell Library, Massachusetts General Hospital, assisted with the EMBASE and Cochrane Central Register of Controlled Trials database searches.

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