

Procalcitonin-Guided Antibiotic Discontinuation and Mortality in Critically Ill Adults

A Systematic Review and Meta-analysis



Dominique J. Pepper, MD; Junfeng Sun, PhD; Chanu Rhee, MD; Judith Welsh, MLS; John H. Powers III, MD; Robert L. Danner, MD; and Sameer S. Kadri, MD

BACKGROUND: Procalcitonin (PCT)-guided antibiotic discontinuation appears to decrease antibiotic use in critically ill patients, but its impact on survival remains less certain.

METHODS: We searched PubMed, Embase, Scopus, Web of Science, and CENTRAL for randomized controlled trials (RCTs) of PCT-guided antibiotic discontinuation in critically ill adults reporting survival or antibiotic duration. Searches were conducted without language restrictions from inception to July 23, 2018. Two reviewers independently conducted all review stages; another adjudicated differences. Data were pooled using random-effects meta-analysis. Study quality was assessed with the Cochrane risk of bias tool, and evidence was graded using GRADEpro.

RESULTS: Among critically ill adults (5,158 randomized; 5,000 analyzed), PCT-guided antibiotic discontinuation was associated with decreased mortality (16 RCTs; risk ratio [RR], 0.89; 95% CI, 0.83-0.97; $I^2 = 0\%$; low certainty). Death was the primary outcome in only one study and a survival benefit was not observed in the subset specified as sepsis (10 RCTs; RR, 0.94; 95% CI, 0.85-1.03; $I^2 = 0\%$), those without industry sponsorship (nine RCTs; RR, 0.98; 95% CI, 0.87-1.10; $I^2 = 0\%$), high PCT-guided algorithm adherence (five RCTs; RR, 0.93; 95% CI, 0.71-1.22; $I^2 = 0\%$), and PCT-guided algorithms without C-reactive protein (eight RCTs; RR, 0.96; 95% CI, 0.87-1.06; $I^2 = 0\%$). PCT-guided antibiotic discontinuation decreased antibiotic duration (mean difference, 1.31 days; 95% CI, -2.27 to -0.35; $I^2 = 93\%$) (low certainty).

CONCLUSIONS: Our findings of increased survival and decreased antibiotic utilization associated with PCT-guided antibiotic discontinuation represent low-certainty evidence with a high risk of bias. This relationship was primarily observed in studies without high protocol adherence and in studies with algorithms combining PCT and C-reactive protein. Properly designed studies with mortality as the primary outcome are needed to address this question.

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FOR EDITORIAL COMMENT, SEE PAGE 1085

ABBREVIATIONS: MD = mean difference; PCT = procalcitonin; RCT = randomized controlled trial; RR = risk ratio

AFFILIATIONS: From the Critical Care Medicine Department (Drs Pepper, Sun, Danner, and Kadri), National Institutes of Health, Bethesda, MD; the

Department of Population Medicine (Dr Rhee), Harvard Medical School/Harvard Pilgrim Health Care Institute, Boston, MA; the National Institutes of Health Library (Ms Welsh), Office of Research Services, National Institutes of Health, Bethesda, MD; and the Clinical Research

Serial procalcitonin (PCT) levels are increasingly used by clinicians to guide antibiotic discontinuation after clinical stabilization, particularly in those with sepsis. Over 1.5 million people develop sepsis each year in the United States, and at least 5% of these patients undergo PCT testing.^{1,2} While PCT-guided antibiotic discontinuation appears to reduce antibiotic duration in this population, nine meta-analyses of randomized clinical trials (RCTs) published before 2017 failed to show any statistically significant survival benefit in those with infection, sepsis, critical illness, or both sepsis and critical illness (e-Table 1).³⁻¹¹ In 2017 and 2018, two meta-analyses reported improved survival with PCT-guided antibiotic discontinuation in critical illness, and two reported no survival benefit in those with sepsis.¹²⁻¹⁵ Only one of these two latter sepsis meta-analyses graded the quality of evidence.¹² One meta-analysis,¹³ which did not focus exclusively on sepsis, concluded their study

provided robust evidence to support and expand the 2016 Surviving Sepsis Campaign (SSC) guidelines that PCT levels be used to shorten the duration of antimicrobial therapy in patients with sepsis.¹⁶

These conflicting findings compelled us to assess the certainty of evidence and plausibility of PCT-guided antibiotic discontinuation to improve survival in critically ill adults. We performed a systematic review and meta-analysis of PCT-guided antibiotic discontinuation RCTs. Using standardized tools, we assessed the risk of bias in individual RCTs and graded the overall certainty of evidence. We sought corroborating evidence within trials that might support the biologic plausibility of any survival advantage. Our main study aim was to estimate the effect of PCT-guided antibiotic discontinuation on survival in critically ill adults and the subset specified as having sepsis.

Methods

Data Sources and Searches

This systematic review was prepared according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement checklist^{17,18} and registered in the PROSPERO (International Prospective Register of Systematic Reviews) database on October 31, 2016 (2016:CRD42016049715) (e-Appendixes 1, 2). We performed comprehensive literature searches (e-Appendix 3) for RCTs of procalcitonin-guided antibiotic discontinuation in critically ill adults in PubMed, Embase, Scopus, Web of Science, and CENTRAL (Cochrane Central Register of Controlled Trials). The searches were conducted without language restrictions from each database's inception to July 23, 2018. Systematic reviews, guidelines, and review articles identified in our search^{3-15,19-34} were searched for additional relevant references.

Study Selection

We included RCTs that exclusively enrolled adults admitted to the ICU; and that also compared mortality rates or antibiotic duration in patients randomized to receive PCT-guided antibiotic discontinuation vs a group of control patients. Exclusion criteria included observational studies and studies that included adults not admitted to the ICU. Two authors (D. J. P., S. S. K.) reviewed search results to identify studies for inclusion. We performed dual review in a two-step process of first

screening titles and abstracts followed by full-text review of selected articles. Author consensus resolved uncertainty regarding study inclusion. Details on data extraction, risk of bias assessment, and certainty assessment using GRADEpro (supplied by GRADEpro GDT) are provided in the online supplement (e-Appendix 4).^{35,36} The primary outcome examined was mortality assessed as the relative risk of death and considered in the following hierarchy: 28-day, 30-day, 60-day, 90-day, hospital, or ICU. Other outcomes examined were hospital length of stay, ICU length of stay, and antibiotic duration or exposure.

Data Synthesis and Analysis

Mortality outcomes between intervention and comparator groups were analyzed as risk ratios (RRs) using random-effects models and the Knapp-Hartung adjustment for small study numbers.³⁷⁻³⁹ Because biologic plausibility would be strengthened if a survival benefit was observed in studies with high (> 80%) algorithm adherence, absence of industry funding, or those with only PCT in the intervention arm, we performed subgroup analyses according to these moderators. An 80% cutoff for high algorithm adherence was chosen as algorithm adherence was clustered in two groups (ie, low adherence: 41%-53% vs high adherence: 81%-97%). Mean differences (MDs) in the length of hospitalization, length of ICU stay, and duration of antibiotic use were analyzed using random-effects models, with conversion from medians (ranges/interquartile ranges) to means (standard deviations) when appropriate (e-Tables 2-4).⁴⁰ Heterogeneity among studies was assessed using the *Q* statistic and *I*² value.⁴¹ Two-sided *P* values < .05 were considered significant. Publication bias was assessed using funnel plots and Egger regression (*P* < .10 considered significant).⁴² All analyses were performed using R (version 3.4.4; R Foundation) with packages meta (version 4.9-1) and metafor (version 2.0-0).⁴³⁻⁴⁵

Directorate/Clinical Monitoring Research Program (Dr Powers), Leidos Biomedical Research, Inc., NCI Campus at Frederick, Frederick, MD.

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CORRESPONDENCE TO: Dominique J. Pepper, MD, Critical Care Medicine Department, National Institutes of Health, 10 Center Dr, Room 2C145, Bethesda, MD 20892; e-mail: dominiquepepper@gmail.com

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Results

Literature Search

The literature search identified 2,576 references (Fig 1). Sixteen RCTs met inclusion criteria; 16 assessed mortality,

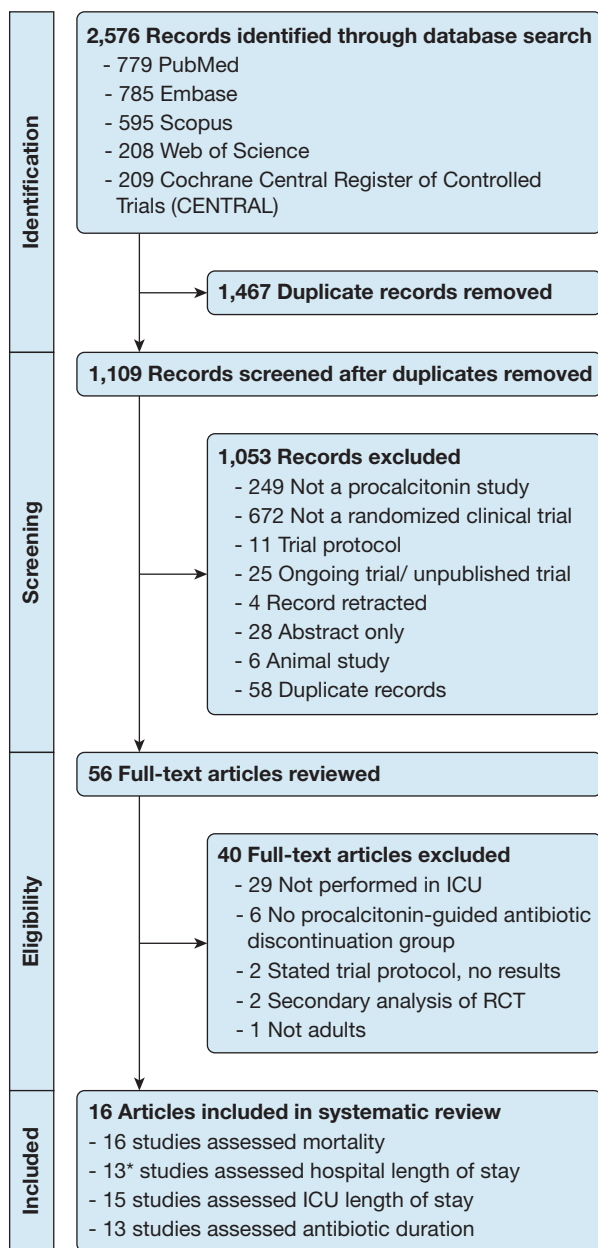


Figure 1 – Search strategy. *In one study results were inconsistent and in another study the data were not normally distributed. Therefore two of these 13 studies were omitted and a total of 11 studies were included in the meta-analysis for hospital length of stay. RCT = randomized controlled trial.

13 assessed hospital length of stay, 15 assessed ICU length of stay, and 13 assessed antibiotic duration or exposure.¹⁹⁻³⁴

Study Characteristics

Sixteen RCTs were conducted in nine countries from 2006 to 2016 (Table 1, e-Table 5). Of these RCTs, nine reported comorbid illnesses, nine reported baseline PCT levels, and three reported the interval from presentation

to randomization (e-Table 6). In 10 RCTs, only patients with sepsis were enrolled. Fourteen RCTs specified the site of infection, predominantly pulmonary, abdominal, and urinary sites (e-Table 7).

Comparison of Interventions

All 16 RCTs described the intervention algorithm, and 15 described the control arm (e-Table 8). In the intervention algorithm, PCT levels were obtained daily in 12 RCTs, and at less frequent intervals in four RCTs. Criteria for antibiotic discontinuation were based on both absolute PCT values and percentage decrease from peak baseline PCT level (13 RCTs), or only on absolute PCT values (three RCTs). In two RCTs, the intervention duration was not specified; in the remaining 14 RCTs, the intervention duration ranged from 2 to 28 days or until ICU discharge or ICU transfer.

PCT algorithm adherence was reported in nine studies (eight in published manuscripts, one personal communication; e-Table 8). Algorithm adherence was clustered in two groups: five RCTs with reported algorithm adherence $\geq 80\%$ (range, 81%-97%; considered high adherence) and four RCTs with reported adherence of 41%-53% (considered low adherence). Seven RCTs were industry funded and nine were not. Eight RCTs had only PCT in the intervention group and the other eight had both PCT and C-reactive protein in the intervention group (e-Tables 5, 8).

Outcomes

Only one RCT reported mortality as a properly powered and designated primary efficacy outcome (e-Table 9). This RCT, a two-by-two factorial trial studying sodium selenite and PCT-guided antimicrobial therapy, found no statistically significant decrease in mortality with PCT-guided antibiotic discontinuation.²⁷ PCT guidance did not affect the frequency of diagnostic or therapeutic procedures, and resulted in a 4.5% reduction in antimicrobial exposure. One RCT, investigating 3-month mortality as the “primary non-inferiority endpoint,” found increased mortality with PCT-guided antibiotic discontinuation, and this increase was within the prespecified 12% noninferiority margin.⁴⁰ Two trials examined mortality as a safety outcome in prospective noninferiority analyses with 80% and 90% power to exclude a 10% and $> 8\%$ mortality difference, respectively.^{32,33} One of these trials showed a significant mortality benefit (19.6% vs 25.0%). Data were not provided to determine whether PCT monitoring resulted in patient management changes that explained

TABLE 1] Evidence Profile Table

Study Characteristic	Data
No. of randomized clinical trials	16
Study years	Conducted, 2006-2016; published, 2008-2018
Date of literature search	1940-July 23, 2018
No. of patients	5,158 randomized; 5,000 analyzed
Race/ethnicity	Unavailable
Age	Adults
Setting	ICUs
Countries	Australia, Brazil, China, France, Germany, Netherlands, Serbia, Switzerland, USA
Comparison	Procalcitonin-guided antibiotic discontinuation vs control group
Primary outcome	Mortality (28-d mortality or hospital mortality)
Secondary outcomes	Antibiotic duration and length of stay

this survival benefit.³³ In the remaining 12 RCTs, 10 defined mortality a priori as a secondary outcome and two did not. None of these 12 RCTs demonstrated any statistically significant mortality benefit with PCT-guided antibiotic discontinuation. A total of 5,158 patients underwent randomization and 5,000 were included in the final analysis (e-Table 10). Ten RCTs

reported an intention-to-treat analysis; six used a modified intention-to-treat analysis.

Meta-analysis of the 16 RCTs showed that PCT-guided antibiotic discontinuation had a statistically significant reduction in mortality compared with control subjects (RR, 0.89; 95% CI, 0.83-0.97; $I^2 = 0\%$) (Fig 2). Influence analysis showed that the omission of only one RCT³⁹ caused these results to no longer be statistically significant (RR, 0.95; 95% CI, 0.88-1.02). This was the only RCT to report a statistically significant survival benefit with PCT-guided antibiotic discontinuation and had a low algorithm adherence of 44% to 53%. This RCT had a fragility index of nine, meaning that if nine cases in the intervention arm changed from “survived” to “died” the survival benefit would no longer be statistically significant. This RCT used a modified intention-to-treat analysis where the number of randomized participants differed from the number in the final analysis by 29 cases. In their discussion, the authors were unable to attribute the observed, unexpected survival benefit to a change in patient management.

PCT-guided antibiotic discontinuation did not significantly improve survival in 10 RCTs that included only critically ill patients with sepsis (RR, 0.94; 95% CI, 0.85-1.03), in nine RCTs that were not industry sponsored (RR, 0.98; 95% CI, 0.87-1.10), in eight RCTs where only PCT was used in the intervention algorithm (RR, 0.96; 95% CI, 0.87-1.06), or in five RCTs where

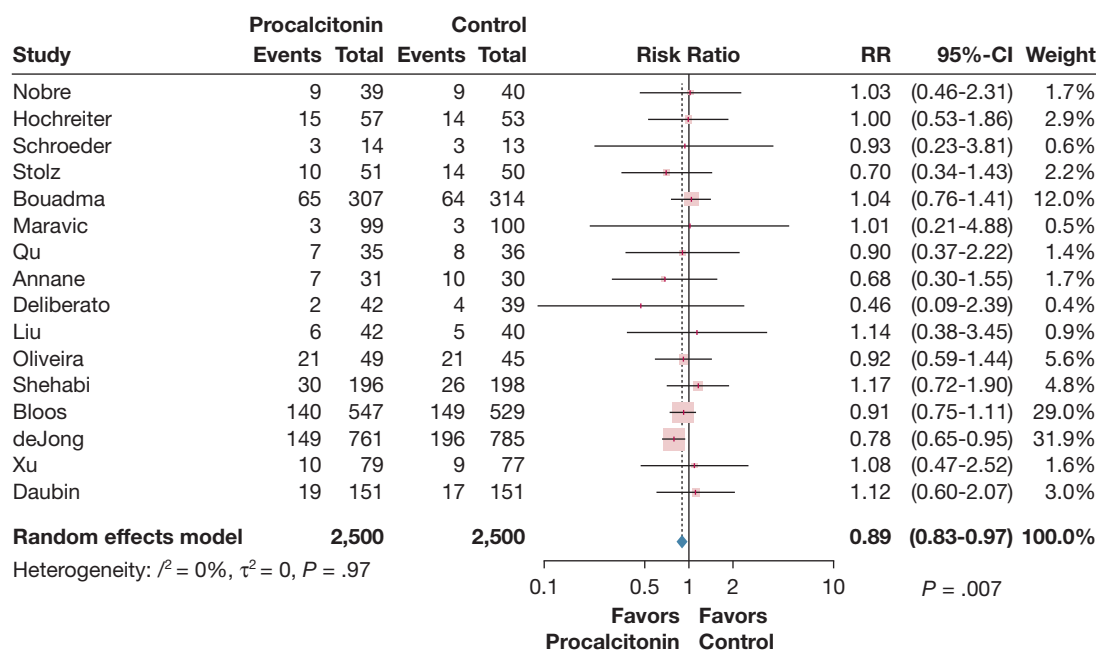


Figure 2 – Survival in 16 randomized clinical trials assessing procalcitonin-guided antibiotic discontinuation in critically ill adults. RR = risk ratio.

adherence to the PCT-guided algorithm exceeded 80% (RR, 0.93; 95% CI, 0.71-1.22) (e-Figs 1-3, 10). A meta-regression using exact compliance rates for each RCT showed that adherence did not affect the relationship between procalcitonin and survival ($P = .30$) (e-Fig 35).

In critically ill adults, PCT-guided antibiotic discontinuation did not decrease hospital length of stay (mean difference [MD], -0.59 days; 95% CI, -3.70 to 2.51; $I^2 = 83%$) or ICU length of stay (MD, -0.48 days; 95% CI, -2.90 to 1.95; $I^2 = 86%$) but decreased antibiotic exposure (MD, -1.31 days; 95% CI, -2.27 to -0.35; $I^2 = 93%$). Similar results were found in critically ill adults with sepsis. All sensitivity analyses for each study outcome (survival, hospital length of stay, ICU length of stay, and antibiotic duration) are provided in e-Figures 1-34.

Study Limitations and Risk of Bias

No studies reported whether antibiotic stewardship programs were used in the control group. Ten RCTs reported adverse events (e-Table 9). Five RCTs documented trial registration before study initiation (e-Table 11). Because of the lack of blinding and the limited data reported for all RCTs, the potential for selection, performance, detection, or attrition bias was present in each RCT. Funnel plots and Egger regression analysis showed no publication bias (e-Figs 10, 11).

Certainty Assessment Using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) Criteria

PCT-guided antibiotic discontinuation in critically ill adults has low certainty to improve survival or decrease antibiotic exposure (Table 2). Evidence does not support decreased hospital or ICU length of stay (low certainty). In critically ill adults with sepsis, evidence does not support improved survival or decreased hospital or ICU length of stay, but supports decreased antibiotic exposure (low certainty for all).

Discussion

This systematic review examined > 2,500 references and identified 16 RCTs of PCT-guided antibiotic discontinuation in critically ill adults. PCT-guided antibiotic discontinuation appears to decrease antibiotic utilization by 1 day and improve mortality. However, these findings are tempered by low-certainty evidence given the substantial risk of bias, indirectness of effect, and the unknown application of antibiotic stewardship programs in control arms. PCT use has no statistically

significant mortality reduction in those with sepsis, in those with > 80% protocol adherence, in those without industry sponsorship, or in those where only PCT is used in the intervention algorithm.

Only one trial showed a mortality benefit, which the authors acknowledge was unexpected as death was examined as a safety outcome using a noninferiority analysis.³³ Influence analysis shows that this one RCT drives any attributed survival benefit to PCT testing. Several features of this RCT raise concern: low algorithm compliance; lack of reporting of differences across baseline comorbidities; and the modified intention-to-treat analysis with a fragility index of nine, substantially less than the number excluded from the final analysis (29 adults). Finally, the speculated reason for the observed decrease in mortality was not tested—the knowledge of PCT concentrations leads to earlier and more adequate diagnoses and treatments.³³ Therefore, how PCT guidance might produce the observed survival benefit remains unexplained. The only trial designed and powered to examine survival as a primary efficacy outcome found no differences in frequency of diagnostic procedures, interventions for source control, readjustment of empirical antimicrobial therapy, or relapses of hospitalization.²⁷

Previous meta-analyses have sought to address whether PCT-guided antibiotic discontinuation improves survival in sepsis, critical illness, and both critical illness and sepsis (e-Table 1). Our search involved a greater number of data sources and articles. We identified and translated additional articles from the Chinese literature^{24,28} and assessed algorithm adherence, industry sponsorship, and the use of cointerventions in the intervention and control arms. Our findings are strengthened by our certainty assessment using GRADEpro (Table 2). We found substantial risk of bias, inconsistency, and indirectness. Therefore, there is low certainty for the use of PCT-guided antibiotic discontinuation to improve survival. The recent patient-level meta-analysis of adults with infection and sepsis by Wirz et al⁴⁶ found improved survival in those with sepsis. Several important differences exist between their meta-analysis and ours. Ours analyzed only those studies with patients ($n = 2,160$) who met a definition of sepsis preceding the 2016 Sepsis-3 definition. Theirs included patients meeting the Sepsis-3 definition ($n = 3,235$). They performed multivariable hierarchical regression analysis and adjusted for treatment arm, age, sex, and type of infection but not adherence to study protocol

TABLE 2] GRADE Assessment of Randomized Clinical Trials

Outcome Examined (No. of Studies)	Certainty Assessment						Summary of Findings					
							No. of Patients		Effect		Certainty	Importance
							Procalcitonin Arm	Control Arm	Estimate (95% CI)	Absolute (95% CI)		
Critical Illness												
Mortality (16)	Randomized trials	Serious ^a	Not serious	Serious ^b	Not serious	None	496/2,500 (19.8%)	552/2,500 (22.1%)	RR, 0.89 (0.83-0.97)	24 fewer per 1,000 (from 10 to 40 fewer)	⊕⊕○○ (low)	Critical
Hospital length of stay (11)	Randomized trials	Serious ^c	Serious ^d	Not serious	Not serious	None			MD, -0.59 d (-3.70 to 2.51)	...	⊕⊕○○ (low)	Important
ICU length of stay (15)	Randomized trials	Serious ^e	Serious ^d	Not serious	Not serious	None			MD, -0.48 d (-2.90 to 1.95)	...	⊕⊕○○ (low)	Important
Antibiotic duration or exposure (13)	Randomized trials	Serious ^f	Serious ^d	Not serious	Not serious	None			MD, -1.31 d (-2.27 to -0.35)	...	⊕⊕○○ (low)	Important
Sepsis and Critical Illness												
Mortality (10)	Randomized trials	Serious ^g	Not serious	Serious ^b	Not serious	None	243/1,096 (22.2%)	250/1,064 (23.5%)	RR, 0.94 (0.85-1.03)	Not estimable	⊕⊕○○ (low)	Critical
Hospital length of stay (7)	Randomized trials	Serious ^h	Serious ^d	Not serious	Not serious	None			MD, -0.27 d (-5.00 to 4.46)	...	⊕⊕○○ (low)	Important
ICU length of stay (10)	Randomized trials	Serious ^g	Serious ^d	Not serious	Not serious	None			MD, -0.69 d (-4.72 to 3.34)	...	⊕⊕○○ (low)	Important

(Continued)

TABLE 2] (Continued)

Outcome Examined (No. of Studies)	Certainty Assessment							Summary of Findings				
	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of Patients		Effect		Importance	
	Randomized trials	Serious ¹	Serious ^d	Not serious	Not serious	None	Procalcitonin Arm	Control Arm	Estimate (95% CI)	Absolute (95% CI)		Certainty
Antibiotic duration or exposure (9)	Randomized trials	Serious ¹	Serious ^d	Not serious	Not serious	None			MD, -0.96 d (-1.82 to -0.10)	...	⊕⊕○○ (low)	Important

GRADE = Grading of Recommendations, Assessment, Development and Evaluation; MD = mean difference; RR = risk ratio.

¹All studies unblinded to participants and personnel; incomplete outcome data (7/15 studies); no data on random sequence generation (4/15 studies); no data on allocation concealment (8/15 studies).

^aA sensitivity analysis showed that studies with higher adherence (> 80%) to procalcitonin-guided algorithm showed no significant benefit whereas studies with lower adherence (< 80%) showed benefit.

^dAll studies unblinded to participants and personnel; incomplete outcome data (7/10 studies); no data on random sequence generation (1/10 studies); no data on allocation concealment (5/10 studies).

^eI² values exceed 75%.

^fAll studies unblinded to participants and personnel; incomplete outcome data (7/14 studies); no data on random sequence generation (5/14 studies); no data on allocation concealment (9/14 studies).

^gAll studies unblinded to participants and personnel; incomplete outcome data (5/12 studies); no data on random sequence generation (4/12 studies); no data on allocation concealment (7/12 studies).

^hAll studies unblinded to participants and personnel; incomplete outcome data (5/10 studies); no data on random sequence generation (3/10 studies); no data on allocation concealment (7/10 studies).

ⁱAll studies unblinded to participants and personnel; incomplete outcome data (5/7 studies); no data on allocation concealment (4/7 studies).

^jAll studies unblinded to participants and personnel; incomplete outcome data (4/9 studies); no data on allocation concealment (2/9 studies); no data on allocation concealment (6/9 studies).

or whether the treatment algorithm specified procalcitonin only in the intervention arm. Also, in the article text, their reported survival benefit of PCT-guided therapy in the subgroup meeting the Sepsis-3 definition (95% CI, 0.76-0.98) differs from the forest plot of 30-day mortality (95% CI crosses 1). Their analysis was supported by industry and used a writing service to draft the manuscript, and they acknowledge that “pathophysiologic mechanisms [for the survival advantage] are incompletely understood.” The validity of their observed survival benefit is not questioned and future studies to investigate this unexpected result are not proposed. In another recent patient-level meta-analysis of 523 bacteremic patients from 13 trials (including six trials of patients with sepsis), PCT-guided antibiotic discontinuation resulted in fewer antibiotic days, and no survival benefit overall.⁴⁷

Although its impact on survival is debatable, many clinicians may conclude that PCT is useful if it can decrease antibiotic exposure without harming patients. Investigators concluded that PCT-based algorithms could potentially save government health systems millions of euros annually,⁴⁸ based on a decision tree analysis of six RCTs.^{19-23,30} However, these six RCTs all had high or unknown risk of bias and do not mention whether an antibiotic stewardship program was used in the control arm. Future studies need to minimize bias and determine the true benefit of PCT-based algorithms on antibiotic exposure using an appropriately rigorous control arm. Among patients with lower respiratory tract infection, a well-designed large multicenter RCT showed that the provision of PCT results to ED- and hospital-based clinicians did not result in less use of antibiotics than did usual care.⁴⁹

We acknowledge several limitations. Baseline characteristics such as comorbidities, site of infection, baseline PCT levels, and the interval from presentation to randomization were not uniformly reported across both study arms for all RCTs. Baseline comparability of illness severity is important as substantial clinical heterogeneity occurs in those admitted to the ICU. Procalcitonin algorithms differed considerably across RCTs and algorithm adherence was either not reported or low. Low algorithm compliance suggests some clinicians disagreed with algorithm-directed changes in care, raising concerns about reproducibility in general practice settings. Our sepsis subgroup only included patients from RCTs that explicitly studied septic

Antibiotics initiated in critical illness for presumed infection or sepsis

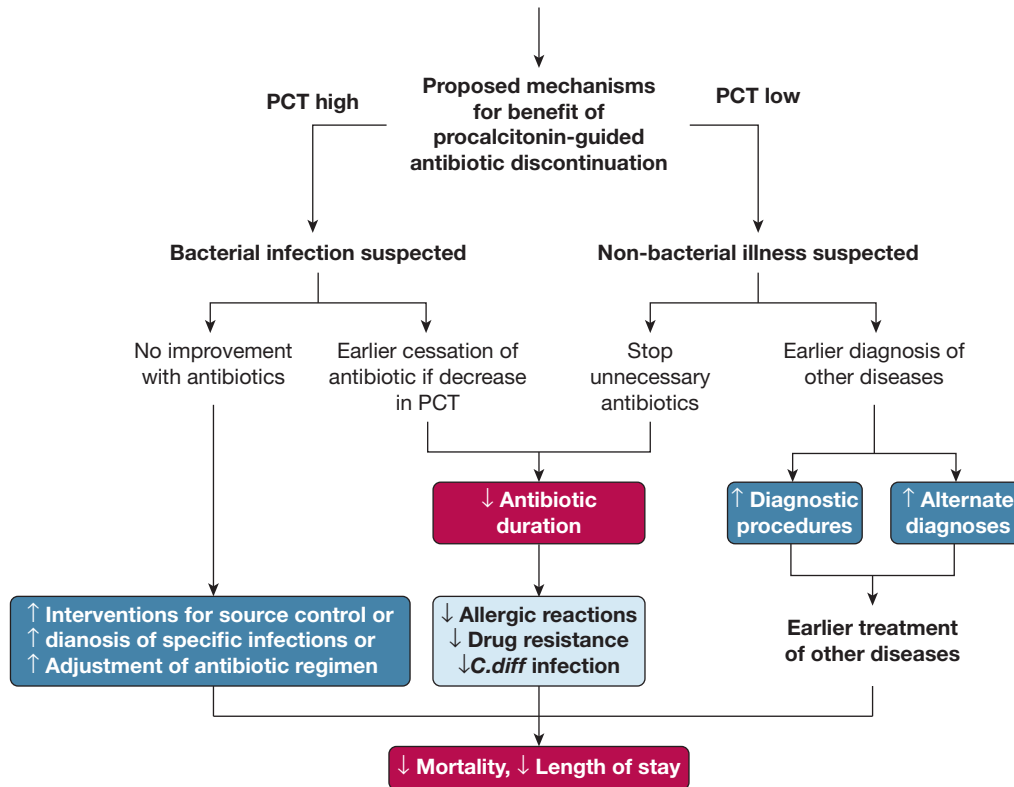


Figure 3 – Testable hypotheses for the potential mechanism of a survival benefit from procalcitonin-guided antibiotic discontinuation. *C.diff* = *Clostridium difficile*; PCT = procalcitonin.

populations. No RCT compared PCT-guided antibiotic discontinuation to control arms compliant with sound principles of antibiotic stewardship. In RCTs that assessed adverse events, data were missing on the development of antibiotic resistance, allergic reactions and *Clostridium difficile* infections. Only 10 RCTs used an intention-to-treat analysis. We excluded observational studies to minimize residual confounding and heterogeneity.

Future studies need to designate survival as the primary outcome and collect data on other potential impactful secondary end points. Knowledge of PCT results might affect other important aspects of care such as antibiotic adequacy, source control, use of diagnostic testing, and diagnosing alternative illnesses that influence survival. Figure 3 summarizes outcomes previously assessed in RCTs (red boxes), as well as putative mechanisms (blue boxes) of potential benefit. In addition to reporting all these outcomes, future RCTs should (1) exclusively use PCT and no other biomarkers in the intervention arm, (2) rigorously report rates and rationales for PCT algorithm nonadherence or overruling, (3) report side effects and complications of

antibiotic administration and antibiotic discontinuation, and (4) test whether these purported mechanisms for improved survival actually decrease mortality. If future RCTs establish proof-of-concept and elucidate mechanisms of benefit,⁵⁰ comparative effectiveness trial designs could assess whether PCT-guided antibiotic discontinuation has generalizable benefits beyond those provided by well-managed antibiotic stewardship programs, which are increasingly the standard of care in hospitals.^{51,52}

We found low-certainty evidence with a high risk of bias to support PCT-guided antibiotic discontinuation to increase survival among critically ill adults. The plausibility of this survival benefit is weakened as this occurred primarily in studies with low protocol adherence (ie, providers frequently overruled PCT guidance) and studies with algorithms combining PCT with other biomarkers (C-reactive protein). Antibiotic discontinuation in recovering critically ill adults remains a challenge for intensivists and administrators, and the routine use of PCT requires ongoing evaluation for biologic plausibility and efficacy.

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Author contributions: D. J. P. and S. S. K. 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, including and especially any adverse effects. D. J. P., J. S., C. R., J. W., J. H. P., R. L. D., and S. S. K. contributed substantially to the study design, data analysis, and interpretation. D. J. P. and S. S. K. drafted the manuscript, and J. S., C. R., J. W., J. H. P., and R. L. D. revised it critically for important intellectual content. D. J. P., J. S., C. R., J. W., J. H. P., R. L. D., and S. S. K. approve the final version to be published.

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Additional information: The e-Appendixes, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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