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Procalcitonin-Guided Antibiotic Therapy

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

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Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

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We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Procalcitonin-Guided Antibiotic Therapy

Structured Abstract

Objectives: To systematically review comparative studies of the use of procalcitonin in the clinical management of adult and pediatric patients with suspected local or systemic infection.

Data Sources: MEDLINE®, EMBASE®, the Cochrane Database of Systematic Reviews, National Institute for Clinical Excellence, the National Guideline Clearinghouse, and the Health Technology Assessment Programme were searched from January 1, 1990, to August 6, 2010**.** A search of the gray literature included databases with regulatory information, clinical trial registries, abstracts and conference papers, grants and federally funded research, and information from manufacturers.

Review methods: We sought studies that compared procalcitonin-guided versus clinical-criteria-guided initiation, discontinuation, or change of antibiotic therapy. Outcomes were antibiotic usage, mortality, morbidity, and adverse drug events of antibiotic therapy. Data were abstracted by a single reviewer and fact-checked by a second reviewer. Study quality was assessed using the U.S. Preventive Services Task Force framework. A meta-analysis on short-term mortality in intensive care unit (ICU) patients was performed using a random-effects model. Strength of the body of evidence was assessed according to the *AHRQ Methods Guide*.

Results: There were 18 randomized, controlled trials that addressed five patient populations. Procalcitonin guidance reduces antibiotic usage when used to discontinue antibiotics in adult ICU patients and to initiate or discontinue antibiotics in patients with respiratory tract infections (high evidence), without increasing morbidity and mortality (moderate evidence). In contrast, procalcitonin-guided intensification of antibiotics in adult ICU patients increases morbidity (moderate evidence). There is moderate evidence from a single good quality study that procalcitonin guidance reduces antibiotic usage for suspected early neonatal sepsis, but insufficient evidence on morbidity and mortality outcomes. Evidence is insufficient to draw conclusions on outcomes of procalcitonin guidance for: 1) fever of unknown source in children 1-36 months of age; or 2) preemptive antibiotics after surgery.

High-risk populations were generally excluded from procalcitonin guidance studies. Thus, findings from this review should not be extrapolated to patients with the following conditions: pregnancy; absolute neutropenia; immunocompromised states; chronic infections and infections where prolonged antibiotic therapy is standard of care (e.g., infective endocarditis).

Conclusions: Procalcitonin guidance reduces antibiotic usage when used to discontinue antibiotic in adult ICU patients and to initiate or discontinue antibiotic in patients with respiratory tract infections. Populations for future research include: immunocompromised patients; patients with other conditions (e.g., pregnancy, cystic fibrosis), and pediatric patients. Future research should compare procalcitonin guidance to antibiotic stewardship programs and to implementation of guidelines. Outcomes of high interest for future research are consequences of reduction in antibiotic usage on antibiotic resistance and adverse events of antibiotic therapy.

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Executive Summary

Background

Sepsis is a serious condition with high morbidity and mortality for which clinical diagnostic criteria lack sensitivity and specificity. Early initiation of appropriate antibiotics and goal-directed therapies reduce mortality. Conversely, overuse and misuse of antibiotics, including continuing antibiotics longer than necessary for cure can result in adverse events and add to the increasing problem of antibiotic resistance. Although critically ill patients in the intensive care units (ICU) have higher morbidity and mortality, the same issues are also true for clinical criteria for the diagnosis of neonatal sepsis, pneumonia, and other respiratory tract infections for the initiation, duration or change in antibiotic therapy. Again, the duration of antibiotic therapy is often undefined, and clinical features are of limited help in guiding discontinuation of therapy.[1]

Several serum biomarkers have been identified in recent years that have the potential to help diagnose local and systemic infections, differentiate bacterial and fungal infections from viral syndromes or noninfectious conditions, prognosticate, and ultimately guide management, particularly antibiotic therapy. Among these, procalcitonin is the most extensively studied biomarker.[2, 3]

Numerous studies have investigated the potential roles of procalcitonin in diagnosing and managing of local and systemic infections.[4-6] There is some evidence that procalcitonin is more specific for bacterial infections, with serum levels rising at the onset of infection and falling rapidly as the infection resolves compared to other markers.[7, 8] However, its clinical utility in diagnosing and managing patients with suspected infections remains unclear.

In healthy people, procalcitonin levels are very low. In systemic infections, including sepsis, procalcitonin levels are generally greater than 0.5–2 ng/mL, but often reach level greater than 10 ng/mL. Higher levels correlate with the severity of illness and prognosis. In patients with suspected respiratory tract infection, the levels of procalcitonin are not necessarily as elevated, and a cutoff of greater than 0.25 ng/mL seems to be most predictive of a bacterial respiratory tract infection requiring antibiotic therapy, while a level less than 0.25 ng/mL signals resolution of the infection.[9, 10]

The cutoffs for other clinical situations may be quite different. For example, neonates normally show a characteristic increase in procalcitonin after birth, with a rapid return to normal by 48 to 72 hours. In neonates, a nomogram for procalcitonin cutoffs that accounts for the time from birth in hours must be used.[11] Likewise, the stress of surgery may increase procalcitonin levels, but again, there is an incremental increase in patients with infection, including subclinical or high risk of infection. The cutoff level of procalcitonin to identify postoperative patients with infection or at risk of infection may be higher than that used for other patient groups. Although procalcitonin may have a role in diagnosis and identification of patients who need initiation of systemic antibiotics, it may have greater applicability in guiding decisions about when to discontinue antibiotic therapy as procalcitonin levels quickly return to less than 0.25 ng/mL as infection resolves.[12]

Objectives

The objective of this systematic review was to synthesize comparative studies examining the various uses of procalcitonin in the clinical management of patients with suspected local or systemic infection.

The patient populations included those with suspected sepsis or other serious bacterial infections in critically ill adults, neonates with suspected early neonatal sepsis, patients with upper and lower respiratory tract infections, children with fever of unknown source, and postoperative patients of infection. Initial review of the literature during topic development and topic refinement suggested that the most common use for procalcitonin-guided management was in decision making related to the initiation or discontinuation of antibiotic therapy in these various populations. This led us to construct an analytical framework that focused on the following key question.

Key Question

In selected populations of patients with suspected local or systemic infection, what are the effects of using procalcitonin measurement plus clinical criteria for infection to guide initiation, discontinuation or a change of antibiotic therapy, when compared to clinical criteria for infection alone on:

- Intermediate outcomes, such as initiation, discontinuation or change of antibiotic therapy, antibiotic usage, and length of stay?
- Health outcomes, such as morbidity, mortality, function, quality of life, and adverse events of antibiotic therapy (persistent or recurrent infection, and antibiotic resistance)?

The PICOTS (Patient, Intervention, Comparator, Outcome, Timing, and Setting) for the Key Question follows:

Patients	Adult and pediatric patients with known or suspected local or systemic infection, including critically ill patients with sepsis syndromes or ventilator-associated pneumonia, adults with respiratory tract infections, neonates with sepsis, children with fever of unknown source, and postoperative patients at risk of infection.

Intervention	Initiation, discontinuation, and intensification of antibiotic therapy guided by procalcitonin plus clinical criteria for infection
Comparator	Initiation, discontinuation, or intensification of antibiotic therapy guided by clinical criteria for infection alone
Outcomes	Antibiotic usage (duration of antibiotic therapy, prescription rate[*] and total antibiotic exposure[†]), mortality, morbidity (length of stay, severity of illness score), and adverse events of antibiotic therapy (persistent or recurrent infection, and antibiotic resistance)
Timing	3 months
Setting	ICUs (medical and surgical), inpatient acute care hospitals, emergency departments, and outpatient clinics

A comprehensive review evaluating different patient populations and all the potential uses of procalcitonin will identify the areas that require further prospective investigation and will serve as a roadmap for future research.

As we proceeded to synthesize the evidence, it was apparent that the evidence on initiation, discontinuation or change of antibiotic therapy was not easily separated. Many studies reported on both discontinuation and change of antibiotic therapy. For example, studies in the ICU population addressed discontinuation only, while studies of respiratory tract infection patients addressed both initiation and discontinuation. Moreover, serum procalcitonin level cut-offs differ for different patient populations, so it could be misleading to synthesize results across rather than within populations. Therefore, the results of our systematic review are reported by patient population, rather than in accordance with key questions originally framed in our topic refinement.

Analytic Framework

Following is an analytic framework (see Figure ES-1) depicting the potential impact of using procalcitonin on both intermediate outcomes and health outcomes. Direct evidence of the impact of testing on health outcomes is shown by link A (morbidity, function, quality of life, and/or mortality) and links G and H (adverse events of testing/therapy). Indirect evidence would have to be assembled in the absence of randomized, controlled trials (RCTs) of the effects of testing on health outcomes. An early link in an indirect chain of evidence concerns the diagnostic accuracy of testing (B). Link C addresses whether test results influence decisions about therapy, which may have an impact on health outcomes (link D) or intermediate outcomes (link E). Intermediate outcomes—such as antibiotic exposure, duration of antibiotic therapy, length of stay, and response to therapy—may have an association with health outcomes (link F).

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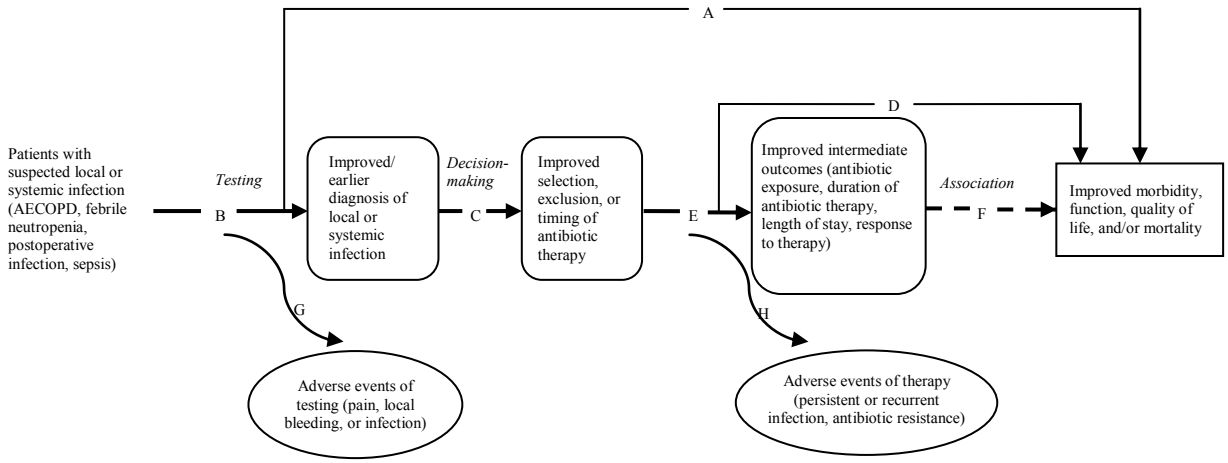
[*] Defined as the percentage of patients that are initiated on antibiotic therapy, either during initial presentation or subsequent follow-up

[†] Calculated by multiplying the total number of antibiotics by the number of days the patient is receiving each of antibiotic divided by total duration of antibiotic therapy.

Figure ES-1. Analytic framework for procalcitonin as a diagnostic indicator for infection and as an indicator of response to therapy



Methods

Input from Stakeholders

This systematic review was developed and written by the Evidence-based Practice Center (EPC) with input from stakeholders. Stakeholders were broadly defined as anyone involved with making health care decisions, including patients, clinicians, professional and consumer organizations, and purchasers of health care. Individuals from various stakeholder groups were invited as Key Informants, Technical Experts, and/or Peer Reviewers to guide this systematic review.

Key informants are end-users of research. A Key Informant panel refined the Key Questions to focus on the most important aspects of procalcitonin to inform health care decisions in various clinical settings. The Key Questions were then posted on the AHRQ website for public commentary. Input from the Key Informants panel and public were incorporated into the final Key Questions.

The Technical Expert Panel (TEP) reviewed the research protocol in two phases: 1) initial draft protocol; 2) revised protocol that incorporated the Panel's comments on the draft and findings of a preliminary literature search.

All potential Key Informants, Technical Experts, and Peer Reviewers were required to disclose any potential conflicts of interest in accordance with AHRQ policy. The AHRQ Task Order Officer and the EPC worked to balance, manage, or mitigate any potential conflicts of interest identified. Individuals who had conflicts of interest that precluded participation as informants, experts or reviewers were able to submit comments through the public comment mechanism. Writing and editing the report was solely the responsibility of the EPC.

Data Sources and Selection

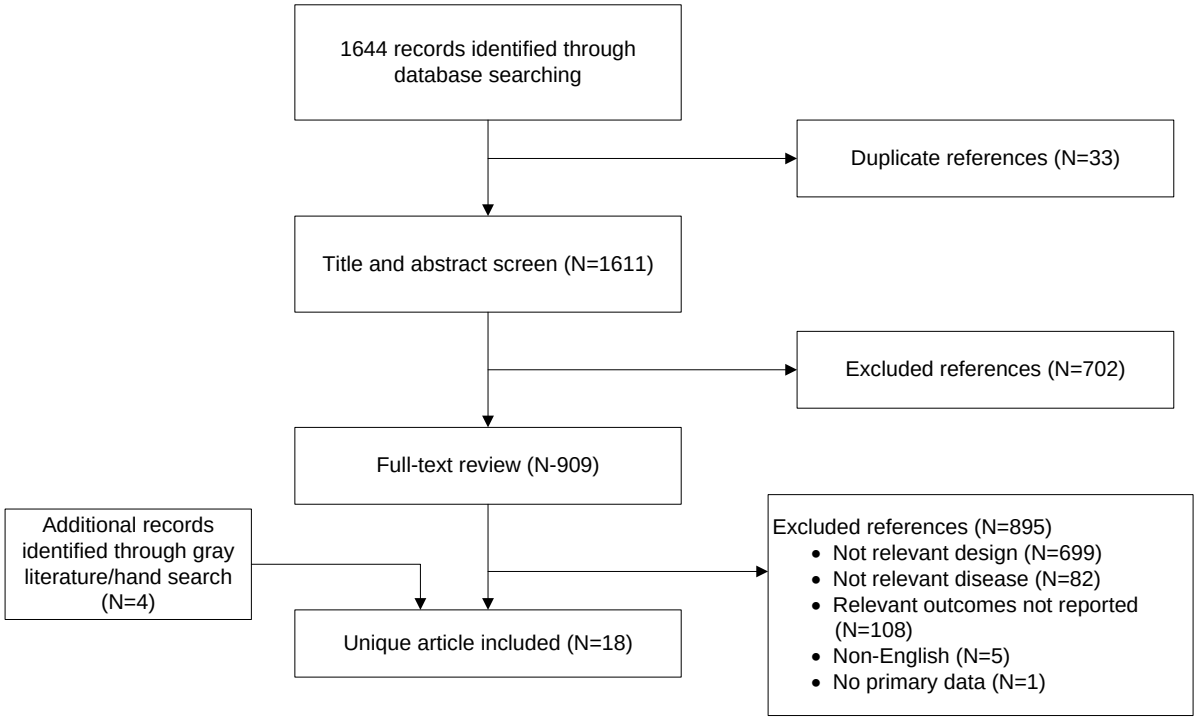
MEDLINE®, EMBASE® and the Cochrane Controlled Trials Register were searched from 1990 through August 6, 2010 for randomized and nonrandomized comparative studies using the

following search terms: procalcitonin AND systemic inflammatory response syndrome, chronic obstructive pulmonary disease, COPD, surgical wound infection, critical illness, intensive care, postoperative infection(s), postoperative complication(s), postsurgical infection(s), intensive care units, febrile neutropenia, sepsis, septic, systematic inflammatory response syndrome, ICU, critically ill, intensive care unit, OR postoperative infection. Searches were limited to English-language and human studies.

The Cochrane Controlled Trials register was also searched with no date restriction. In addition, a search for systematic reviews was conducted in MEDLINE®, the Cochrane Database of Systematic Reviews, and the websites of the National Institute for Clinical Excellence, the National Guideline Clearinghouse, and the Health Technology Assessment Programme**.** A search of the gray literature included in databases with regulatory information, clinical trial registries, abstracts and conference papers, grants and federally funded research, and manufacturing information.

The titles and abstracts were screened for studies that looked at antibiotic usage, morbidity, and mortality with procalcitonin-guided initiation and/or discontinuation of antibiotic therapy compared to use of clinical criteria in adult and pediatric patients with suspected infections. A single reviewer made decision about a full text review. Citations marked as uncertain were reviewed by a second reviewer for full text review. A third reviewer was consulted if necessary. We included randomized, controlled trials. We also sought, but did not find, nonrandomized comparative studies. The PRISMA diagram (see Figure ES-2) depicts the flow of search screening and study selection.

Figure ES-2. PRISMA diagram for identified trials—Key Questions



Data Extraction and Quality Assessment

Data were abstracted by a single reviewer, and fact checked by another reviewer. If there were disagreements they were resolved through discussion among the review team. Categories of data elements were abstracted as follows: quality assessment (number of participants and flow of participants, treatment allocation methods, blinding, and independent outcome assessor), applicability and clinical diversity assessment (patient, diagnostic, and treatment characteristics), outcome assessment (primary and secondary outcomes, response criteria, followup frequency and duration, data analysis details).

Quality of included studies was assessed using the U.S. Preventive Services Task Force framework[13] based on the following criteria: assembly and maintenance of comparable groups, loss to followup, measurements (equal, reliable, and valid), clear definition of interventions, all important outcomes considered, and analysis (adjustment for potential confounders and intention-to-treat analysis). Three quality categories were used: good, fair, and poor. Quality of the abstracted studies was assessed by at least two independent reviewers, and the final quality rating was assigned by consensus adjudication.

Data Synthesis and Analysis

We anticipated that the decision to incorporate formal data synthesis into this evidence review would be made after completing the formal literature search. Similarly we also anticipated that the decision to pool studies would be based if there were sufficient number of studies available that were designed to ask similar questions and reported similarly defined outcomes. If a meta-analysis could be performed, subgroup and sensitivity analyses would be based on assessment of clinical diversity in available studies. The pooling method would involve inverse variance weighting and a random effects model.

The overall strength of evidence grade was determined in compliance with the *Methods Guide*[19] and is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[20] This system explicitly addressed the following domains: risk of bias, consistency, directness, and precision. The grade of evidence strength was classified into the following four categories: high, moderate, low, and insufficient. Specific outcomes and comparisons were rated depending on the evidence found in the literature review. The grade rating was made by independent reviewers, and disagreements were resolved by consensus adjudication.

Results

Overview

There were 18 randomized, controlled trials (Table ES1) that compared procalcitonin guidance with use of clinical criteria to manage antibiotic therapy in patients with known or suspected infection, or at risk of infection. The evidence addressed five patient populations that were reviewed separately because of different clinical characteristics and predicted outcomes: 1) critically ill adult patients in the ICU, including patients with ventilator-associated pneumonia (VAP) and those critically ill with suspected bacterial infections, severe sepsis, and septic shock; 2) patients with symptoms and signs of various respiratory tract infections; 3) neonates with suspected sepsis; 4) children between 1-36 months of age with fever of unknown source; and 5) postoperative patients at risk of infection. Additionally, we separately reviewed two studies in

Table ES-1. Summary Characteristics of the Included Studies

Characteristic	Critically Ill/VAP (*Antibiotic discontinuation)*	Critically Ill/VAP (*Antibiotic Intensification)*	Respiratory Tract Infections	Neonatal Sepsis	Fever of Unknown Source (children aged 1-36 months)	Preemptive Postoperative Antibiotic Therapy
Study design	RCT=5	RCT=2	RCT=7 Cluster RCT=1	RCT=1	RCT=1	RCT=1
Number of studies	5	2	8	1	1	1
Total N	938	1272	3492	121	384	250
Funding	Not reported=3 Mixed=2	Non industry=1 Mixed=1	Non industry=2 Not reported=1 Mixed=5	Industry=1	Industry= 1	Not reported=1
Study quality	Fair=2 Good=3	Fair=1 Good=1	Poor=4 Good=4	Good=1	Poor=1	Good=1
Conflict of interest	Yes=5	Yes=1 NR=1	Yes=6 No=1 NR=1	NR=1	No=1	NR=1
References	14-18	21-22	23-30	31	32	33

RCT: Randomized controlled trial; NR: Not reported; VAP: Ventilator associated pneumonia.

seriously adult ill ICU patients where the procalcitonin-guidance was used for intensification of antibiotic therapy rather than initiation or discontinuation of therapy, a very different approach.

Conducting meta-analysis was precluded in all but one instance due to heterogeneity of outcome definitions, sparseness of commonly defined outcomes and lack of sufficient detail in outcome reporting. A meta-analysis was performed on short-term mortality (28-day or in-hospital mortality) in a group of five studies[14-18] that included critically ill patients and those with ventilator-associated pneumonia. The pool of studies was too small to permit meaningful subgroup and sensitivity analyses.

Intensive Care Unit Patients

Procalcitonin-Guided Discontinuation of Antibiotic Therapy

Five trials[14-18] (N=938) addressed procalcitonin-guided discontinuation of antibiotic therapy in critically ill patients. Strength of evidence (Table ES-2) was judged to be high that procalcitonin guidance reduces antibiotic usage. The absolute difference in duration of antibiotic use in these five studies [14-18] ranged from -1.7 to -5 days, with relative reductions ranging from 21 to 38 percent. There is moderate evidence that procalcitonin-guided antibiotic discontinuation does not increase mortality or morbidity as indicated by ICU length of stay (LOS). However, a limitation of the evidence is the very large number of study participants that would be required to narrow the confidence interval for estimated mortality. Only one study[18] reported on multidrug resistant organisms and superinfections.

Procalcitonin-Guided Intensification of Antibiotic Therapy

There is moderate evidence that procalcitonin-guided intensification of antibiotic therapy that broadens the spectrum of bacterial coverage does not improve outcomes in critically ill patients, and in fact, may have adverse consequences. The large (n=1,200) high-quality trial by Jensen et al.,[21] found greater duration and increased total exposure to antibiotics with procalcitonin guidance. There was also increased morbidity, including a 1-day increase (p=0.004) in ICU LOS, a significant increase in days on mechanical ventilation, and increased days with abnormal renal function. A second study[22] (n=72) was judged too small to be informative.

Respiratory Tract Infection

Eight trials[23-30] (N=3,492) addressed initiation and/or discontinuation of antibiotics in patients with acute upper and lower respiratory tract infection. Settings included primary care clinics, emergency department (ED), and hospital wards. There is high strength of evidence that procalcitonin guidance reduces antibiotic duration and prescription rates; and moderate evidence of reduction in total antibiotic exposure. Absolute reduction in duration of antibiotic therapy ranged from 1 to 7 days, with relative reductions ranging from -13 to -55 percent. Absolute reduction in prescription rates ranged from -2 to -7 percent with relative reductions ranging from -1.8 to -72 percent. There was moderate evidence that procalcitonin guidance did not increase mortality, hospital LOS, or ICU admission rates. However, a limitation of the evidence is the very large number of study participants that would be required to narrow the confidence interval for estimated mortality. There was insufficient evidence to judge effects on days of restricted

Table ES-2. Summary of Outcomes Measures and Strength of Evidence

Patient Group	Outcome	Unit	No of Studies	Ref	No of subjects	B	C	D	P	Overall Grade	Effect*
Critically ill/VAP patients (antibiotic discontinuation)	Antibiotic usage	Duration of use, days	5	14-18	938	L	Y	Y	Y	High	Improve (Range: -1.7 to – 5)
	Mortality	In-hospital, overall or 28- day	5	14-18	938	L	Y	Y	Y	Moderate	No worse
	Morbidity	ICU length of stay, days	5	14-18	837	L	Y	Y	Y	Moderate	No worse
Critically ill/VAP patients (antibiotic intensification)	Morbidity	Percent days in ICU with GFR<60	1	21	1200	L	U	Y	Y	Moderate	Worse (5.0%, 95% CI: 3.0, 6.9)
		Percent days on ventilator	1	21	1200	L	U	Y	Y	Moderate	Worse (4.9%, 95%CI: 3.0, 6.7)
Respiratory tract infection	Antibiotic usage	Duration of use, days	7	23-27,29-30	3284	L	Y	Y	Y	High	Improve (Range:-1 to -7)
		Prescription Rate	7	23-30	3492	L	Y	Y	Y	High	Improve (Range:-2 to -7%)
	Mortality	≤ 6 wks or 6 months	8 (7/1)	23-30	3492	L	Y	Y	Y	Moderate	No worse
	Morbidity	Hospital length of stay	5	25-26, 28-30	2303	M	Y	Y	Y	Moderate	No worse
		ICU admission rates	5	25-26, 28-30	2303	M	Y	Y	Y	Moderate	No worse
		Antibiotic Adverse Events	3	24, 25, 27	2367	L	N	Y	N	Insufficient	Unknown
Neonatal sepsis	Duration of antibiotic use	Hours	1	31	121	L	U	Y	Y	Moderate	Improve (-22.4, p=0.012)
	Morbidity	Recurrence of infection	1	31	121	L	U	Y	N	Insufficient	Unknown
	Mortality	In-hospital	1	31	121	L	U	Y	N	Insufficient	Unknown
Fever of unknown source in children	Antibiotic use	Prescription rate	1	32	384	H	U	Y	N	Insufficient	Unknown
	Morbidity	Hospitalization rate	1	32	384	H	U	Y	N	Insufficient	Unknown
	Mortality	In-hospital	1	32	384	H	U	Y	N	Insufficient	Unknown
Preemptive Postoperative Antibiotic Therapy	Morbidity	Sepsis/SIRS	1	33	20	U	U	Y	N	Insufficient	Unknown
	Mortality	In-hospital	1	33	20	U	U	Y	N	Insufficient	Unknown

B: Risk of bias; C: Consistency; D: Directness; P: Precision, N/A: not applicable; N: No; U: Unknown; Y: Yes.

* Comparison between procalcitonin measurement plus clinical criteria versus clinical criteria alone to guide to guide initiation, discontinuation or a change of antibiotic therapy.

activity or on antibiotic adverse events. Three studies[24, 25, 27] reported on adverse antibiotic effects, and there was a statistically significant reduction in the procalcitonin-guided arm versus the control arm that was associated with reduced antibiotic usage. There was no consistency, however, on how adverse effects were defined and details on the types of adverse reactions were lacking.

Neonatal Sepsis

One good quality[31] study (n=121) provided moderate evidence that procalcitonin guidance reduces the use of antibiotic therapy for suspected early neonatal sepsis. The duration of antibiotic use was overall reduced by 22.4 hours (22.0 percent). Further, the proportion of neonates on antibiotics for longer than 72 hours was reduced by 27 percent. Greatest reductions were seen among neonates who were judged according to clinical criteria to have possible infection or unlikely to have infection as compared to those with proven or probable infection. Strength of evidence was judged insufficient to make conclusions on mortality and morbidity due to small study size.

Fever of Unknown Source in Children Ages 1-36 Months

The strength of evidence was judged insufficient to draw conclusions on outcomes of procalcitonin-guided antibiotic therapy for fever of unknown source in children 1-36 months of age. One good quality RCT[32] (n=384) reported no significant results.

Postoperative Patients at Risk of Infection

The strength of evidence was judged insufficient to draw conclusions on outcomes of procalcitonin-guidance to determine preemptive antibiotic therapy for patients after colorectal surgery. The evidence consisted of one small (n=20) trial.[33]

Discussion

The diagnosis of sepsis is challenging because the clinical criteria for the diagnosis overlap with noninfectious causes of systemic inflammation such as the systemic inflammatory response syndrome. Initiation of antibiotic therapy for sepsis is necessary even while the diagnostic evaluation is ongoing since delayed antibiotic therapy is associated with increased mortality.[34-36] A biomarker, such as procalcitonin, that improves decisions about initiating, discontinuing or changing antibiotic therapy, could have substantial clinical benefits. Our systematic review found that procalcitonin guidance reduces antibiotic usage for adult patients in both medical and surgical ICUs. Studies included patients who had comorbidities that are common in ICU patients (e.g., cardiac disease, diabetes, chronic lung disease, cirrhosis, chronic renal failure, cancer), and thus, the evidence from these studies is applicable to clinical practice in the ICU setting.

Respiratory tract infections contribute significantly to the problem of antibiotic misuse. Approximately 75 percent of all antibiotics prescribed in the ambulatory setting are for acute respiratory tract infections, but the vast majority of these infections are viral and do not benefit from antibiotic treatment.[37] Clinical and microbiological evaluations are neither sensitive nor specific to differentiate bacterial from viral respiratory tract infections. Our systematic review found that procalcitonin guidance for initiation and discontinuation of antibiotic therapy significantly reduced antibiotic prescription rates and duration in patients with acute respiratory

tract infections, including acute exacerbations of chronic obstructive pulmonary disease (COPD), community acquired pneumonia (CAP), and acute bronchitis.

Certain populations, however, were excluded from one or more studies of procalcitonin guidance reviewed in this report. Thus, findings from this review should not be extrapolated to these high-risk groups which include: pregnant patients; patients with absolute neutropenia; and other immunocompromised populations (solid organ and stem-cell transplant recipients, patients with advanced HIV infection/AIDS). Patients with chronic infections and infections where a longer duration of antibiotic therapy is standard of care, such as infective endocarditis, were also appropriately excluded from these studies.

Although such patients were excluded in these studies, future studies may help to determine if procalcitonin-guided antibiotic therapy is beneficial in these groups as well. For example, febrile neutropenic patients are usually continued on antibiotics until the neutropenia resolves; the most recent guidelines suggest that patients can be switched to an oral fluoroquinolone when an infection has been adequately treated, and procalcitonin guidance could potentially be used in this context.[38]

Applicability to pediatric settings is a significant gap in the present evidence. Only two randomized, controlled trials[31, 32] reported on procalcitonin guidance in pediatric populations. One study[31] included neonates with suspected early sepsis. While antibiotic use was reduced, the trial was underpowered for morbidity and mortality outcomes. The second study[32] evaluated procalcitonin-guided antibiotic therapy in children ages 1-36 months presenting to the ED with fever of unknown source. No significant differences were observed for measures of antibiotic use, morbidity, or mortality with procalcitonin guidance. The evidence from this single study was judged insufficient to reach conclusions about the use of procalcitonin guidance in this setting. There were no studies of procalcitonin guidance in children ages 3 to 18 years.

Ultimately, the value of procalcitonin-guided antibiotic therapy depends on the clinical benefits of reduced antibiotic use, which is difficult to quantify. Immediate consequences may include decrease in allergic reactions, drug toxicities, and frequency of *Clostridium difficile* infection. A major downstream effect of reducing antibiotic usage may be a lower probability of emergence of antibiotic-resistant strains. Antimicrobial resistance contributes to morbidity, mortality, and health care costs. There are several studies and indirect lines of evidence that suggest that control of antibiotic usage can reduce emergence of resistance, but the data is limited.[39]

Reductions in antibiotic course duration have been associated with significant reductions in antibiotic adverse effects, *C. difficile* colitis, and superinfection with multidrug resistant (MDR) Gram-negative rods.[34, 39, 40] In our systematic review, few studies reported on allergic and adverse events of antibiotic usage,[24, 25, 27] and only one reported on antibiotic resistance.[14]

The durability in reduction of antibiotic usage is not addressed in these trials, which limits their applicability to clinical practice. The setting of a clinical trial, or highly visible introduction of a new practice, can have a halo effect on physician behavior so the present evidence does not address long-term impact of using procalcitonin guidance in a real-world clinical setting. Antibiotic stewardship programs are now recommended for all institutions and there are guidelines for how they should function.[41] Antibiotic stewardship programs are associated with reduced antibiotic usage and also decreased adverse effects of antibiotic therapy. The evidence in this review does not compare outcomes of using procalcitonin guidance versus antibiotic stewardship programs, nor does it address whether addition of procalcitonin to an antibiotic stewardship program improves outcomes.

Antibiotic stewardship activities are usually limited to the acute care hospital setting. Although it would be difficult or impractical for antibiotic stewardship programs to have active intervention in the outpatient setting, the use of procalcitonin might complement other types of outpatient programs, such as educational programs for physicians and patients aimed at reducing the use of antibiotics for respiratory tract infections.[37]

Discussion of Present Findings in Context of Other Systematic Reviews

We are aware of four systematic reviews[4, 42-44] that were published prior to our present review; the findings of our review are discussed in the context of these prior reviews. All of the previous reviews (including the present review) came to similar conclusions: procalcitonin-guided antibiotic decision making compared to clinical criteria-guided antibiotic decision making reduces antibiotic usage and is not associated with increased mortality or morbidity.

We reviewed all published randomized, controlled trials of the use of procalcitonin-guided initiation or discontinuation of antibiotic therapy, as well as studies that used procalcitonin for other interventions in patients with infection and/or sepsis. A total of 18 randomized, controlled trials[14-18, 21-33] were included in our systematic review. Our systematic review differs from previous systematic reviews in terms of number of studies included, scope of indications addressed, and how populations were grouped for clinical relevance. The number of trials included in previous systematic reviews ranged from seven trials[4, 42, 44] to 14 trials.[43] Our review addresses pediatric populations separately from adult patients, and also recognizes that there are distinct patient groups within the pediatric population stratified by age.

As the most recent systematic review, ours is the only one that includes the Jensen trial.[21] This trial was unique in showing that procalcitonin-guided intensification of antibiotic therapy to broaden the spectrum of bacterial coverage does not improve outcomes in critically ill patients, and in fact, may have adverse consequences.

Summary of Weaknesses or Gaps in the Evidence

We identified five gaps in the evidence related to specific populations or comparators. We also identified methodologic weaknesses that were common across the studies and bodies of evidence reviewed in this report.

Research Gap #1: What are the outcomes of procalcitonin guidance in subgroups of patients who are immunocompromised?

Patients with certain conditions were excluded from these studies, including neutropenia, and immunocompromised states (solid organ and stem cell transplant recipients, and patients with advanced HIV infection). Immunocompromised patients often comprise a significant portion of the ICU population. In the large PRORATA[18] study, immunocompromised patients comprised of 16.6 percent of the study population and were included in the trial. In the PROVAP[16] study of ventilator-associated pneumonia, 27.9 percent of the eligible patients were excluded because of immunosuppression.

Even in community respiratory tract infections, such as CAP (7.6 percent excluded) and even in other RTIs (2.5 percent excluded), there is a significant subpopulation of patients who are immunocompromised or have condition such as cystic fibrosis where the efficacy and safety of procalcitonin-guided therapy is unknown.[29, 30]

While severely immunocompromised patients presenting with clinical signs of infection are most likely treated empirically with antibiotics, patients with mild to moderate immunosuppression, such as patients on low-dose corticosteroids for chronic inflammatory conditions, may not benefit from antibiotic therapy, even though they are often treated empirically. Procalcitonin guidance may have a potential role in reducing antibiotic usage in the ambulatory patients with mild to moderate immunosuppression compared to standard therapy.

Research Gap #2: What are the outcomes of procalcitonin guidance in pediatric patients?

Only two studies[31, 32]reported on procalcitonin guidance in pediatric populations, and both were underpowered to assess morbidity and mortality outcomes. Both studies were limited to the acute care hospital setting. The overuse of antibiotics in pediatrics, in both the inpatient and outpatient setting, is as important among children as it is in adults.

Research Gap #3: What are the outcomes of procalcitonin guidance in identifying patients at risk of infection who might benefit from pre-emptive antibiotic therapy?

The study by Chromik et al.,[33] reported that procalcitonin levels could accurately identify a subpopulation, 8 percent of patients who underwent elective colorectal surgery, who were at risk of a local or systemic infection. Although this was a small study, it suggests that this approach might identify a group who would benefit from pre-emptive antibiotic therapy given before any infection is clinically evident. Larger studies are needed to confirm that pre-emptive antibiotic therapy can reduce infectious complications. Other patient populations who are at risk for infectious complications include burn patients, ICU patients and post-operative patients who have undergone procedures other than colorectal surgery.

Research Gap #4: Does the use of procalcitonin guidance reduce antibiotic resistance and antibiotic adverse events?

Although the importance of reducing antibiotic use is recognized, there was insufficient evidence from the RCTs we reviewed that the observed reduction in antibiotic use had benefits with respect to antibiotic adverse reactions, superinfections, or the development of resistance. When designing future studies, there should be consideration for standardized reporting of adverse events from antibiotics, the incidence of *C. difficile*, and active surveillance for colonization with drug-resistant pathogens.

Research Gap #5: How does procalcitonin-guided antibiotic therapy compare to other approaches to reducing unnecessary antibiotic use, such as antibiotic stewardship programs and implementation of practice guidelines?

In view of the present emphasis on the overuse of antibiotics, other interventions to reduce antibiotic use, such as institution of antibiotic stewardship programs and structured implementation of practice guidelines, may be more robust comparators by which to assess the outcomes of procalcitonin-guided decisions on initiation and discontinuation of antibiotic therapy.

Methodological Weaknesses

In addition to the research gaps above, we also identified four important methodological weaknesses that were common across the studies and bodies of evidence reviewed in this report.

1. Measurement of total antibiotic exposure

Total antibiotic exposure is used to capture the patient's total exposure to all antibiotics and is conventionally reported as mean days per 1,000 days of followup. However, some of the studies in this review only reported relative or absolute differences. Consistent use of the conventional measure would improve accumulation of evidence on the outcomes of procalcitonin guidance.

2. Measurement of morbidity

There were various measures of morbidity across these studies. Although admission rates, LOS, and ICU LOS were easy to compare, other measures were not. In the ICU populations, for example, the need for mechanical ventilation was often reported differently and studies used a variety of severity of illness scores (SOFA, SAP II, SAP III, and APACHE II). This makes it difficult to compare or pool data across studies.

3. Rationale for noninferiority margins for studies of mortality

Mortality rates in trials of procalcitonin-guided therapy implicitly or explicitly pose a question of noninferiority. That is, can reduction in antibiotic use be achieved without a deleterious impact on survival? The choice of a noninferiority margin incorporates clinical and statistical judgments.[45] Studies should provide an explicit rationale for the choice of noninferiority margin in specific patient populations.

4. Reporting and interpretation of nonsignificant differences

A common statistical error in the medical literature is the conclusion that nonsignificant differences ($p>0.05$) are "similar."[46] Clearly stating in the abstract that the study was not powered to detect a difference in mortality would provide a more accurate reporting of the results.

Limitations of the Review Process

A challenging aspect of this review was appraising the strength of evidence that procalcitonin-guided therapy did not result in any increased morbidity or mortality in the ICU and respiratory tract infection populations. We adopted a qualitative noninferiority approach that incorporated assumptions about the likelihood that larger numbers of subjects would show a greater adverse effect given the baseline mortality risk in the relevant populations. Presently there are studies of 4,000 additional patients in progress. We performed calculations in which simulated data from an additional 4,000 patients was added to the meta-analysis of short-term mortality for Critically Ill/VAP, assuming the same results as the largest existing study, to assess the impact on the point estimate and 95% confidence interval.

Another limitation of our review is that we did not systematically seek evidence comparing procalcitonin guidance to antibiotic stewardship programs or other programs aimed at reducing antibiotic use. Nor did we seek studies that implemented procalcitonin-guided antibiotic therapy into an antibiotic stewardship program.

Implications for Future Research

We identified gaps in the available evidence and opportunities for improving the methods of studies comparing procalcitonin guidance with use of clinical criteria to guide antibiotic therapy.

Populations of interest for future research on procalcitonin guidance are:

- Immunocompromised patient subgroups
- Other conditions for which patients were excluded from the study (e.g., pregnancy
- Pediatric populations, stratified by age (neonates; younger than 3 years of age; older than 3 years of age)
- Patients at high risk of infection who may benefit from preemptive antibiotic therapy

Comparators of interest for future research are:

- Procalcitonin guidance compared to antibiotic stewardship programs
- Antibiotic stewardship programs compared with and without procalcitonin guidance
- Procalcitonin guidance compared with implementation of guidelines

Outcomes of interest for future research are:

- Consequences of reduction in antibiotic usage on antibiotic resistance
- Consequences of reduction in antibiotic usage on antibiotic adverse events

Opportunities for Improving Study Methods

1. Consistent measurement of total antibiotic exposure: mean days total exposure to all antibiotics per 1,000 days of followup
2. Use of consistent measurements of morbidity, for example: need mechanical ventilation; severity of illness scores
3. Studies should provide an explicit rationale for noninferiority margins for mortality in specific patient populations
4. Transparent reporting and interpretation of nonsignificant differences: Clearly stating in the abstract if the study was not powered to detect a difference in mortality or morbidity

Glossary

Procalcitonin: Procalcitonin is a precursor of the hormone calcitonin which is produced by parafollicular cells (C cells) of the thyroid and other tissues, such as the neuroendocrine cells of the lung and the intestine. Its levels are low in healthy individuals but rises in a response to a proinflammatory stimulus, especially of bacterial origin.
Sepsis: Clinical syndrome due to the presence of microbe or microbial products in the blood or other tissue resulting in systemic inflammatory state.
Infection: Invasion and multiplication of microorganisms or parasites in body tissues.

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Introduction

Background and Objectives

Sepsis is a condition with high morbidity and mortality for which clinical diagnostic criteria lack sensitivity and specificity. Rapid diagnosis of sepsis and early initiation of antibiotic and goal-directed therapies have demonstrated a reduction in mortality. Conversely, overuse and misuse of antibiotics can result in adverse events and add to the increasing problem of antibiotic resistance. Several serum biomarkers have been identified in recent years with potential uses to help diagnose local and systemic infections, differentiate bacterial and fungal infections from viral syndromes or noninfectious conditions, prognosticate, and ultimately guide management, particularly antibiotic therapy. Among these potential uses of serum biomarkers, there is particular interest in finding a biomarker for diagnosis of sepsis. Currently, there are at least 178 serum biomarkers that have potential roles in the management of patients with infections, and 34 have been studied specifically as a diagnostic tool for sepsis. Among these, procalcitonin is the most extensively studied biomarker.[1, 2]

Serum levels of procalcitonin were recognized to be elevated in patients with infections during the early 1990s, and since that time, numerous studies have investigated the potential roles of procalcitonin in diagnosing and managing of local and systemic infections.[3-5] Procalcitonin is the prohormone precursor of calcitonin that is expressed primarily in C-cells of the thyroid gland and to a smaller extent in neuroendocrine tissue of other organs, such as the lungs and intestines. The final step in conversion of procalcitonin to calcitonin is inhibited by various cytokines and bacterial endotoxins and, therefore, high levels of cytokines and/or bacterial endotoxins cause procalcitonin levels to rise. Cytokines are released nonspecifically in response to inflammation and infection, but endotoxins are released specifically during bacterial infections because they are derived primarily from the Gram-negative bacterial cell wall. There is some evidence that procalcitonin is more specific for bacterial infections, with serum levels rising and falling more rapidly in bacterial infection.[6, 7]

Although viruses, parasites, and fungi can increase procalcitonin levels due to systemic inflammation, procalcitonin's primary diagnostic utility is thought to be in establishing the presence of local or systemic bacterial infections particularly in bacterial sepsis. In case of fungal infection, the diagnostic utility of procalcitonin is limited because the levels do not rise until 1 to 2 days after the onset of infection. A greater increase in procalcitonin levels would be anticipated in Gram-negative versus Gram-positive bacterial infections due to the release of endotoxin from the Gram-negative bacterial cell wall; however, only few studies have demonstrated higher levels of procalcitonin with Gram-negative bacterial infections when compared to Gram-positive bacterial infections.[5] Procalcitonin appears to be a promising serum biomarker for infection, but its exact utility in diagnosing and managing patients with suspected infections remains unclear.

The U.S. Food and Drug Administration (FDA) has cleared for marketing at least three procalcitonin quantitative assays that are commercially available (see Table 1), but the optimal approach to laboratory testing of procalcitonin has yet to be clarified. The labeled indication is the same for all three assays. According to the approved labels, these assays are intended for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of intensive care unit (ICU) admission, for progression to severe sepsis and septic shock.[8-10] Quantitative and qualitative (semi-quantitative) assays for measuring procalcitonin are currently available. The qualitative tests use test strips,

are rapid (results available in less than 30 minutes), and are designed for point-of-care testing. The quantitative tests utilize a luminescence immunoassay platform, are slower (results available in a few hours), and are designed for once or twice daily batch testing. Most studies supporting the use of procalcitonin have used the quantitative test, which is neither rapid nor available at the bedside. Whether or not the semi-quantitative test will yield similar results to the quantitative test is unknown.[4, 11]

Table 1. FDA-cleared procalcitonin assays

Test Name	Device type	Manufacturer	FDA marketing clearance approval date
BRAHMS PCT LIA[8]	Immunoluminometric assay (ILMA)	BRAHMS Aktiengelsellschaft	January 7, 2005
VIDAS BRAHMS PCT LIA Assay[9]	Enzyme-linked fluorescent immunoassay (ELFA)	bioMerieux, Inc.	October 11, 2007
BRAHMS PCT sensitive KRYPTOR®[10]	Immunofluorescent test based on Time-Resolved Amplified Cryptate Emission (TRACE®)	BRAHMS Aktiengelsellschaft	March 31, 2008

PCT: procalcitonin

The purpose of this systematic review is to synthesize comparative studies examining the use of procalcitonin in the management of patients with presumed local or systemic infection. Although important, the analytic validity of quantitative and qualitative procalcitonin testing is beyond the scope of this comparative effectiveness review. However, diagnostic accuracy studies that look at the use of procalcitonin in determining the cause of fever or other symptoms and signs of systemic or localized infections will be discussed briefly, since these studies are the basis for the cutoff procalcitonin levels used in the randomized, controlled trials. The comparator in the diagnostic accuracy studies is usually clinical criteria for the diagnosis of the particular infection, such as the criteria for the diagnosis of systemic inflammatory response syndrome (SIRS) and sepsis, which were developed at a 1992 consensus conference.[12] Unfortunately, clinical criteria for sepsis require identifying a source of infection, which may be difficult. Microbiological evaluation may be helpful, but insensitivity of cultures is problematic. These same issues are also true for clinical criteria for the diagnosis of neonatal sepsis, pneumonia, and other respiratory tract infections.[13]

In healthy people, procalcitonin levels are very low. In systemic infections, including sepsis, procalcitonin levels are generally greater than 0.5–2 ng/mL, but often reach levels of greater than 10 ng/mL, and higher levels correlate with the severity of illness and prognosis. Studies indicate procalcitonin is superior to C-reactive protein (CRP), interleukin-6 (IL-6), and interleukin-8 (IL-8) for diagnosis of sepsis.[14] Lower respiratory tract infections (LRTI) are often less serious, although patients with severe community-acquired pneumonia (CAP) may have life-threatening disease. Procalcitonin levels in patients with suspected respiratory tract infection (RTI) may be useful in determining if patients require antibiotic therapy. In RTIs, the levels of procalcitonin are not necessarily as elevated, and a cutoff of greater than 0.25 ng/mL seems to be most predictive of a bacterial respiratory tract infection requiring antibiotic therapy, while a level less than 0.25 ng/mL signals resolution of the infection.[15, 16]

The cutoffs for other clinical situations may be quite different. For example, neonates normally show a characteristic increase in procalcitonin after birth, with a rapid return to normal by 48 to 72 hours. In this circumstance, the elevated procalcitonin levels are an acute phase

reactant in response to the stress of the birth process, yet an incremental increase is still detectable in infants with neonatal sepsis. Unlike adults with systemic bacterial or fungal infection, sepsis, or RTIs that require antibiotic therapy, a nomogram for procalcitonin cutoffs that accounts for the time from birth in hours must be used.[17] Likewise, the stress of surgery may increase procalcitonin levels, but again, there is an incremental increase in patients with infection, including subclinical or high risk of infection. Postoperatively, the procalcitonin cutoff level to identify patients with infection or at risk of infection may be higher than that used for other patient groups. Although procalcitonin may have a role in diagnosis and identification of patients who need initiation of systemic antibiotics, it may have greater applicability in guiding decisions about when to discontinue antibiotic therapy as procalcitonin levels quickly return to less than 0.25 ng/mL as infection resolves.[18]

Most of the randomized, controlled trials of procalcitonin-guided diagnosis or management utilize one of the BRAHMS assays cleared for use in the United States and currently being marketed by bioMerieux. The recommendations for clinical cutoffs being marketed are in consensus with the cutoff used and evaluated in the randomized, controlled trials looking at the use of procalcitonin in patient management. Most of these randomized, controlled trials of procalcitonin-guided diagnosis or management involve two clinical entities: sepsis/systemic bacterial infections and LRTIs. As a result, two different cutoffs for interpretation of results are being marketed for these two clinical entities. A nomogram for neonates is also recommended.

Although the utility of procalcitonin in clinical management has been reviewed in other meta-analyses and systematic reviews, this Report will afford valuable new information. Some of the previous reviews have been limited to selected populations, or have evaluated studies of distinct populations or different procalcitonin-guided therapies together. When this systematic review was initiated, the most recent meta-analysis of the effects of procalcitonin-guided therapy in patients with infections included seven randomized trials published through November 2008.[3] Since that time, the number of trials, including randomized, controlled trials, studying procalcitonin-guided therapy has more than doubled. Further, there have also been several comprehensive literature reviews and two very recent systematic reviews of the use of procalcitonin to guide duration of antibiotic therapy in the ICU.[19-21] Even though our understanding of the potential clinical benefits of procalcitonin assays is still evolving, clinicians have already begun to request that laboratories perform procalcitonin measurements and, therefore, another systematic review of the use of procalcitonin is needed at the present time. Furthermore, a comprehensive review evaluating different patient populations and all the potential uses of procalcitonin will identify the areas that require further prospective investigation and will serve as a roadmap for future research. The following Key Questions and Analytic Framework outline the approach and key issues to be addressed in this review.

Key Questions

During the period the Key Questions were posted for public comment on the Effective Health Care Program Web site (www.effectivehealthcare.ahrq.gov), four general comments were received. The comments varied greatly from being supportive to being skeptical of procalcitonin's utility in diagnosing and managing infections. The contrasting opinions about procalcitonin's utility underscore the importance of performing a formal comparative effectiveness review. One comment questioned whether or not pediatric populations will be included in this review; in response, we note that pediatric populations have not been excluded from this review. Some studies have explored the use of procalcitonin in children with suspected

infections, such as neonatal sepsis, urinary tract infections, and meningitis. The utility of procalcitonin as a screening tool for bacterial skin colonization or as a diagnostic tool for heat stroke is beyond the scope of this review and will not be included. No changes were made to the key clinical questions based on the public comments.

Key Question

In selected populations of patients with suspected local or systemic infection, what are the effects of using procalcitonin measurement plus clinical criteria for infection to guide initiation, discontinuation or a change of antibiotic therapy, when compared to clinical criteria for infection alone on:

- Intermediate outcomes, such as initiation, discontinuation or change of antibiotic therapy, antibiotic usage, and length of stay?
- Health outcomes, such as morbidity, mortality, function, quality of life, and adverse events of antibiotic therapy (persistent or recurrent infection, and antibiotic resistance)?

The PICOTS (Patient, Intervention, Comparator, Outcome, Timing, and Setting) for the Key Question follows:

Population(s)

- Adult patients with suspected infection including, but not limited to, the following:
  - Local infections
    - Acute exacerbation of chronic obstructive pulmonary disease
    - Pneumonia
    - Surgical site infection
    - Osteomyelitis
  - Systemic infections
    - Neutropenic fever
    - Bacteremia
    - Sepsis
    - Septic shock
- Pediatric patients with suspected infection, including, but not limited to, the following:
  - Local infections
    - Pneumonia
    - Urinary tract infection
    - Meningitis
  - Systemic infections
    - Neutropenic fever
    - Bacteremia
    - Sepsis
    - Septic shock

Interventions

- Initiation, discontinuation, and intensification of antibiotics therapy guided by procalcitonin plus clinical criteria for infection

Comparators

- Initiation, discontinuation, or intensification of antibiotic therapy guided by clinical criteria for infection alone

Outcomes

- Intermediate outcomes
  - Antibiotic exposure
  - Duration of antibiotic therapy
  - Length of stay
- Health outcomes
  - Morbidity
  - Mortality
  - Function
  - Quality of life as measured by validated scales
- Adverse events
  - Persistent or recurrent infection
  - Antibiotic resistance

Timing

- 3 months

Settings

- Outpatient: ambulatory clinics, urgent care centers
- Inpatient: hospital wards, intensive care units, emergency departments

Methods

Methodological practices followed in this review were derived from the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews[22] (hereafter referred to as the "Methods Guide") and its subsequent updates.

Topic Development and Refinement

Key questions were reviewed and refined as needed by the Evidence-based Practice Center (EPC) with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions were specific and explicit about what information was being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

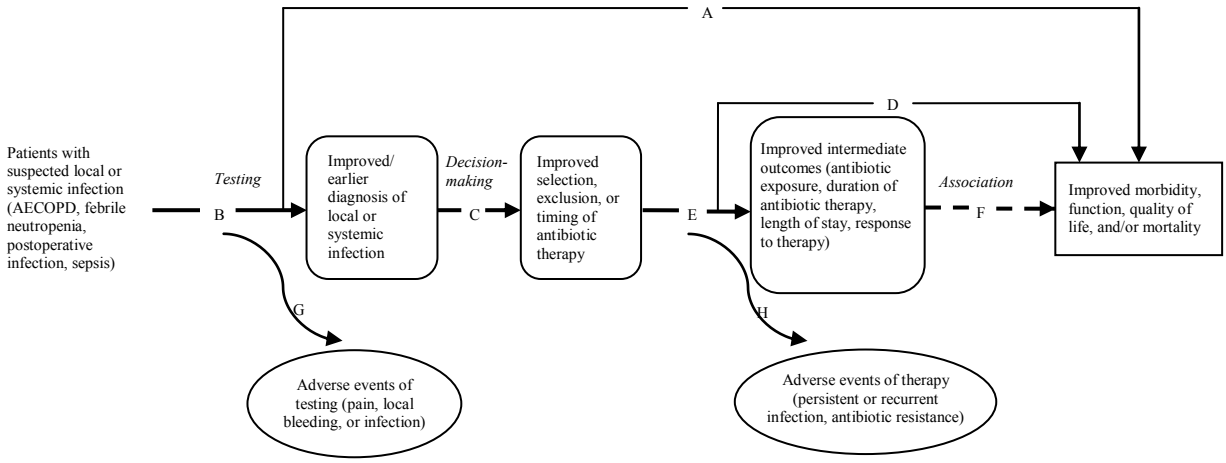
Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants had to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals were invited to serve as Key Informants and those who presented without potential conflicts were retained. The AHRQ Task Order Officer (TOO) and the EPC worked to balance, manage, or mitigate any potential conflicts of interest identified.

Analytic Framework

Following is an analytic framework (see Figure 1) depicting the potential impact of using procalcitonin on both intermediate outcomes and health outcomes. Direct evidence of the impact of testing on health outcomes is shown by link A (morbidity, function, quality of life, and/or mortality) and links G and H (adverse events of testing/therapy). Indirect evidence would have to be assembled in the absence of randomized, controlled trials (RCTs) of the effects of testing on health outcomes. An early link in an indirect chain of evidence concerns the diagnostic accuracy of testing (B). Link C addresses whether test results influence decisions about therapy, which may have an impact on health outcomes (link D) or intermediate outcomes (link E). Intermediate outcomes—such as antibiotic exposure, duration of antibiotic therapy, length of stay, and response to therapy—may have an association with health outcomes (link F).

Figure 1. Analytic framework for procalcitonin as a diagnostic indicator for infection and as an indicator of response to therapy



AECOPD: acute exacerbation of chronic obstructive pulmonary disease

Literature Search Strategy

The databases listed below were searched for citations. The full search strings and strategies can be found in Appendix A. The search was limited to English-language references because our EPC's experience in past projects that included non-English references did not yield high-quality information that justified the resources required for translation. Furthermore, the search was limited to literature published after 1990, which is approximately 10 years before reports of the use of modern serum biomarkers began to appear in the medical literature in the late 1990s.

- MEDLINE® (January 1, 1990, to August 6, 2010)
- EMBASE® (January 1, 1990, to August 6, 2010)
- Cochrane Controlled Trials Register (no date restriction)

To identify systematic reviews, we searched MEDLINE®, the Cochrane Database of Systematic Reviews, and the websites of the National Institute for Clinical Excellence (www.nice.org.uk), the National Guideline Clearinghouse (www.guidelines.gov), and the Health Technology Assessment Programme (www.hta.ac.uk) from January 1, 1990, to August 6, 2010**.** We used results from previously conducted meta-analyses and systematic reviews when appropriate.

The TEP and individuals and organizations providing peer review were asked to inform the project team of any studies relevant to the key questions that were not included in the draft list of selected studies.

Search results were stored in EndNote9® and ProCite® databases. Using the study selection criteria for screening titles and abstracts, a single reviewer marked each citation as: 1) eligible for

review as full-text articles; 2) ineligible for full-text review; or 3) uncertain. Citations marked as uncertain were reviewed by a second reviewer and inclusion and exclusion were decided by consensus opinion; a third reviewer was consulted if necessary. Using the final study selection criteria, full-text articles were reviewed in the same fashion to determine their inclusion in the systematic review. Records of the reason for exclusion for each paper retrieved in full-text, but excluded from the review, were kept in the EndNote9® and ProCite® databases. A listing of excluded studies with reasons for exclusion can be found in Appendix B.

Study Selection

Inclusion criteria: Studies were included if they fulfilled all of the following criteria.

- Study was a randomized controlled trial or a nonrandomized comparative study (observational, case-control, and cohort studies).
- Study included adult and/or pediatric patients with known or suspected local or systemic infection, including critically ill patients with sepsis syndromes or ventilator-associated pneumonia, adults with respiratory tract infections, neonates with sepsis, children with fever of unknown source, and postoperative patients at risk of infection.
- Study intervention included initiation, discontinuation, and/or intensification of antibiotic therapy guided by procalcitonin plus clinical criteria for infection
- Study outcomes included related to antibiotic usage, mortality, morbidity and adverse events of antibiotic therapy

Exclusion criteria: Studies were excluded if they fulfilled at least one of the following criteria.

- Published in non-English language
- Did not report primary data
- Did not use a relevant design
- Did not study relevant disease
- Did not report relevant outcomes

Search Strategies for Gray Literature

The EPC staff conducted a systematic search of the following gray literature sources to identify unpublished studies or studies published in journals that are not indexed in major bibliographic citation database in accordance with guidance from Effective Health Care Scientific Resource Center. The search strategies can be found in Appendix A.

1. Regulatory Information
    a. FDA
2. Clinical Trial Registries
    a. ClinicalTrials.gov
    b. Current Controlled Trials
    c. Clinical Study Results
    d. World Health Organization (WHO) Clinical Trials
3. Abstracts and Conference Papers
    a. Conference Papers Index
    b. Scopus

    c. Annual meeting of Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)
    d. Annual meeting of Infectious Diseases Society of America (IDSA)
    e. Annual meeting of American College of Chest Physicians (ACCP)
    f. Annual meeting of Pediatric Academic Societies (PAS)
4. Grants and Federally Funded Research
    a. NIH RePORTER (a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions)
    b. HSRPROJ (a database providing access to ongoing grants and contracts in health services research)
    c. AHRQ GOLD (an online searchable database of AHRQ grants, working papers and HHS recovery act projects)
5. Manufacturer database: Industry stakeholders were invited to submit the following types of information for possible inclusion as evidence:
    - A current product label;
    - Published randomized controlled trials and observational studies relevant to the clinical outcomes; and
    - Unpublished randomized controlled trials and observational studies relevant to the clinical outcomes.

These sources were searched using sensitive searches similar to the searches in bibliographic databases, except for the following:

- Regulatory information: The FDA website was searched for only 510(k) decision summary documents related to procalcitonin assays.
- For clinical registries, NIH RePORTER, HSRPROJ, and AHRQ GOLD searches were limited to completed studies only.
- For abstracts and conferences, studies published prior to 2006 were excluded.

Data Extraction and Data Management

Data Elements

The following data elements from the intervention studies were abstracted, or recorded as not reported. The data elements to be abstracted were defined in consultation with the TEP and included the following:

- Quality Assessment
    - Number of participants and flow of participants through steps of study
    - Treatment-allocation methods (including concealment)
    - Use of blinding
    - Prospective versus retrospective
    - Use of an independent outcome assessor
    - Additional elements are described below under Assessment of Methodological Quality of Individual Studies

- Study funding sponsorship source acknowledgement
- Assessment of Applicability and Clinical Diversity
  - Patient characteristics, including:
    - Age
    - Sex
    - Race/ethnicity
    - Disease and type
    - Disease duration
    - Other prognostic characteristics (e.g., comorbidities and other potential confounders and/or effect modifiers)
    - Setting
      - Outpatient
      - Inpatient

  - Diagnostic and Treatment characteristics, including:
    - Procalcitonin assay type
    - Other measured indicators of sepsis or of response to treatment (e.g., fever, white blood cell count)
    - Decision making for diagnosis and/or treatment (e.g., when to administer antibiotic therapy)
    - Antibiotic usage during study period
    - Duration of observation
    - Other treatment modalities

- Outcome Assessment

  - Identified primary outcome
  - Identified secondary outcomes
  - Response criteria
  - Followup frequency and duration
  - Data analysis details, including:

    - Statistical analyses (statistical test/estimation results)
      - Test used
      - Summary measures
      - Sample variability measures
      - Precision of estimate
      - p values

Evidence Tables

Templates for evidence tables were created in Microsoft Word®. One reviewer performed primary data abstraction of all data elements into the evidence tables, and a second reviewer reviewed the articles and evidence tables for accuracy. Disagreements were resolved by

discussion, and if necessary, by consultation with a third reviewer. When small differences occurred in quantitative estimates of data from published figures, the values were calculated by averaging the estimates of the first two reviewers. Data abstraction tables can be found in Appendix C.

Individual Study Quality Assessment

Definition of Ratings Based on Criteria

In adherence with the Methods Guide,[22] the general approach to grading individual comparative studies was performed by using a method used by the U.S. Preventive Services Task Force.[23] The quality of the abstracted studies and the body of evidence were assessed by two independent reviewers. Discordant quality assessments were resolved with input from a third reviewer, if necessary.

- The quality of studies was assessed on the basis of the following criteria:
    - Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders (e.g., other concomitant care) were distributed equally among groups.
    - Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination).
    - Important differential loss to followup or overall high loss to followup.
    - Measurements: equal, reliable, and valid (includes masking of outcome assessment).
    - Clear definition of interventions.
    - All important outcomes considered.
    - Analysis: adjustment for potential confounders and intention-to-treat analysis.
        - Intention-to-treat analysis was defined as no more than 5 percent loss in the analysis or use of a missing data handling procedure.

The rating of intervention studies encompasses these three quality categories:

- **Good.** Meets all criteria; comparable groups were assembled initially and maintained throughout the study (followup at least 80 percent); reliable and valid measurement instruments were used and applied equally to the groups; interventions were spelled out clearly; all important outcomes were considered; and appropriate attention was given to confounders in analysis. In addition, intention-to-treat analysis was used for randomized, controlled trials.

- **Fair.** Studies were graded “fair” if any or all of the following problems occurred, without the fatal flaws noted in the “poor” category below: In general, comparable groups were assembled initially, but some questions remained about whether some (although not major) differences occurred with followup; measurement instruments were acceptable (although not the best) and were generally applied equally; some but not all important outcomes were considered; and some but not all potential confounders were accounted for. Intention-to-treat analysis was done for randomized, controlled trials.

- **Poor.** Studies were graded "poor" if any of the following fatal flaws existed: Groups assembled initially were not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments were used or not applied at all equally among groups; and key confounders were given little or no attention. Generally, lack of masked outcome assessment is considered a fatal flaw, but due to the nature of the interventions and comparators in this systematic review, it was not considered a fatal flaw. For randomized, controlled trials, intention-to-treat analysis was lacking

Data Synthesis

We anticipated that the decision to incorporate formal data synthesis into this evidence review would be made after completing the formal literature search. Similarly we also anticipated that the decision to pool studies would be based if there were sufficient number of studies available that were designed to ask similar questions and reported similarly defined outcomes. If a meta-analysis could be performed, subgroup and sensitivity analyses would be based on assessment of clinical diversity in available studies. The pooling method would involve inverse variance weighting and a random effects model.

Assessment of Applicability

Applicability of findings in this review was assessed within the EPICOT framework (Evidence, Population, Intervention, Comparison, Outcome, Timestamp).[24] Selected studies were assessed for relevance against target populations, interventions of interest, and outcomes of interest.

Grading the Body of Evidence for Each Key Question

The system used for rating the strength of the overall body of evidence is outlined in the *Methods Guide*[22] and is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[25] This system explicitly addressed the following domains: risk of bias, consistency, directness, and precision. The grade of evidence strength was classified into the following four categories:

- **High.** High confidence that the evidence reflected the true effect. Further research was very unlikely to change our confidence in the estimate of effect.

- **Moderate.** Moderate confidence that the evidence reflected the true effect. Further research may have changed our confidence in the estimate of effect and may have changed the estimate.

- **Low.** Low confidence that the evidence reflected the true effect. Further research was likely to change our confidence in the estimate of effect and was likely to change the estimate.

- **Insufficient.** Evidence was either unavailable or did not permit estimation of an effect.

- Additional domains including strength of association, publication bias, coherence, dose-response relationship, and residual confounding were addressed if appropriate.

Specific outcomes and comparisons were rated depending on the evidence found in the literature review. The grade rating was made by independent reviewers, and disagreements were resolved by consensus adjudication.

Peer Review and Public Commentary

Peer reviewers will be invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report will be considered by the EPC in preparation of the final draft of the report. Peer reviewers have not participated in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report will not necessarily represent the views of individual reviewers. The dispositions of the peer review comments will be documented and published three months after the publication of the evidence report.

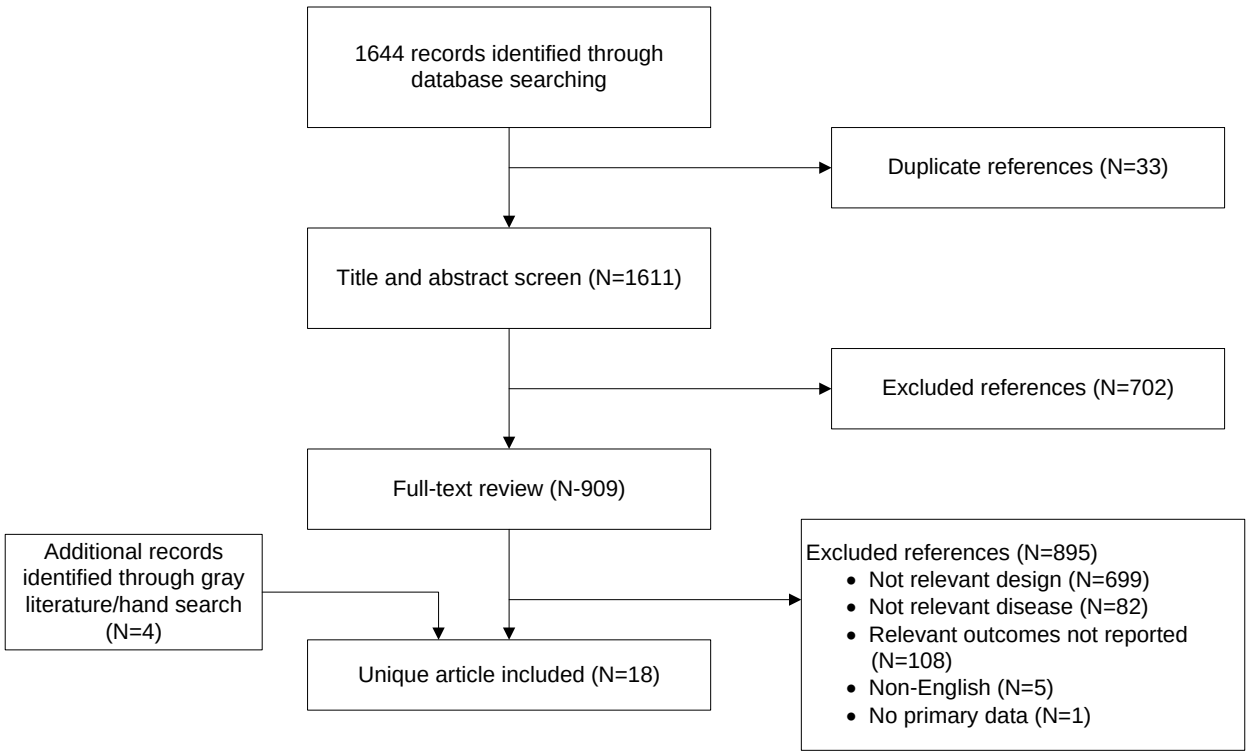
Potential reviewers will have to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers cannot have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest will be able to submit comments on draft reports through the public comment mechanism.

Results

Literature Search

Of the 1644 records identified through the literature search, 1630 were excluded at various stages of screening and 14 records were included. The PRISMA diagram (Figure 2) depicts the flow of search screening and study selection. We sought, but did not find, nonrandomized comparative studies (observational, case-control, and cohort studies) of populations, comparisons, interventions, and outcomes that were not adequately studied in the randomized, controlled trials.

Figure 2. PRISMA diagram for identified trials—Key Questions



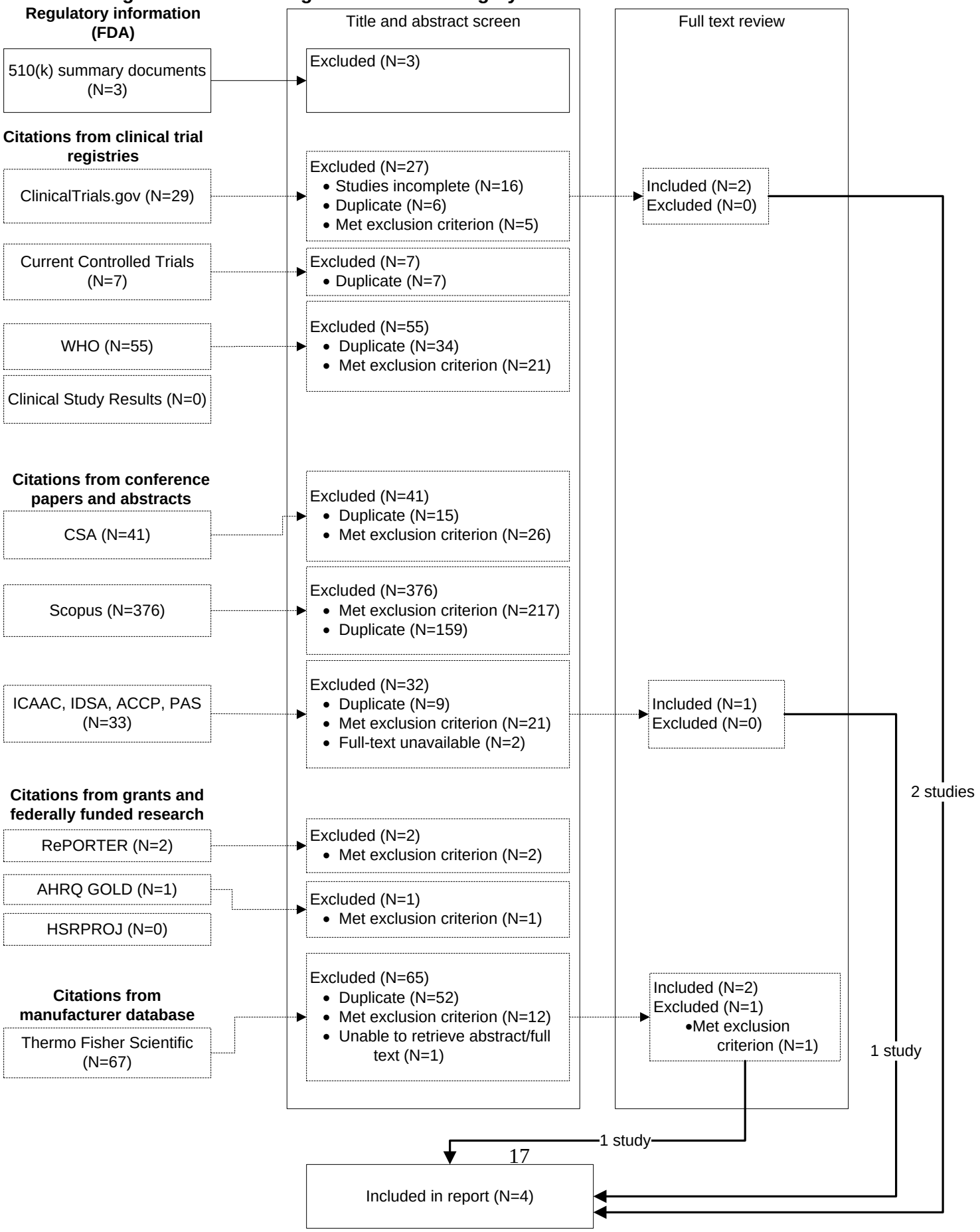
Gray Literature Search

We evaluated the results of the gray literature search with results summarized in Figure 3.

- **Regulatory Information:** The search yielded three 510(k) summaries for procalcitonin assay; BRAHMS PCT LIA,[8] VIDAS® BRAHMS PCT,[9] and BRAHMS PCT sensitive KRYPTOR® Test System.[10] Citations in the summary documents were screened against the main bibliographic databases. No new studies were identified from this source.

- **Clinical trial registries:** Citations for published articles linked to trials registered at ClinicalTrials.gov were included. The search yielded 91 clinical trials of which 89 were excluded during the title and abstract screen: 47 were duplicate (literature

Figure 3. PRISMA diagram for identified gray literature



- citations already included in our reference database), 16 were ongoing studies and 26 met the exclusion criterion (study did not compare procalcitonin-guided antibiotic therapy to an alternative). Two references (Manzano et al., 2010[26] and Burkhardt et al., 2010[27]) were reviewed in full-text and were included according to the study protocol.
- **Abstracts and Conference Papers:** The search yielded 450 citations of which 447 were excluded during the title and abstract screen: 183 references were duplicates and 264 met the exclusion criterion. The three remaining references (Jensen et al., 2011[28]; Rho 2010[29]; Sanches et al., 2010[30]) were randomized studies comparing procalcitonin-guided antibiotic therapy to an alternative. Two of these studies (Rho 2010[29] and Sanches et al., 2010[30]) were published only as abstracts at international meetings and were, therefore, excluded. The remaining study (Jensen et al., 2011[28]) was included in the Report.
- **Grants and federally funded research:** The search yielded three citations and all three were excluded as they met the exclusion criterion.
- **Manufacturer database (SIPs):** In response, scientific information packets (SIPs) were received from Thermo Fisher Scientific. The submissions consisted of 67 published references or listings of clinical trials with abstracts; no unpublished data were provided by the company. Of the 67 references, 65 were excluded during abstract and title screen: 52 were duplicate and 12 met the exclusion criterion and one study could not be retrieved. The remaining two references were reviewed in full-text and one was excluded as it met the exclusion criterion. The remaining study (Long et al., 2011[31]) was included in the report.

Overall, search of gray literature yielded 4 published studies[26-28, 31] that were included in the present evidence review.

We reviewed all published randomized, controlled trials (RCTs) of the use of procalcitonin-guided initiation or discontinuation of antibiotic therapy, as well as studies that used procalcitonin for other interventions in patients with infection and/or sepsis. A total of 18 RCTs were identified for the review. Data abstraction tables can be found in Appendix C. There was a distinct pattern in the patient populations included in these studies and therefore, we grouped these 18 studies into 5 patient populations. These were 1) critically ill adult patients in intensive care unit (ICU), including patients with ventilator-associated pneumonia (VAP) and those critically ill with suspected bacterial infections, severe sepsis, and septic shock; 2) patients with symptoms and signs of various respiratory tract infections; 3) neonates with suspected sepsis; 4) children between 1 to 36 months of age with fever of unknown source; and 5) postoperative patients at risk of infection (pre-emptive antibiotic therapy). In addition to being different patient populations with respect to age, underlying diseases, and morbidity and mortality, some studies also differed with respect to the specific algorithms for procalcitonin-guided management. Among these different strategies, one strategy used procalcitonin measurements to discontinue antibiotic therapy, while other strategies used procalcitonin levels to intensify or initiate antibiotic therapy. Sixteen studies used a BRAHMS® quantitative procalcitonin assay, one study used the BRAHMS® semi-quantitative assay, and one study did quantitative procalcitonin measurements, but did not specify the testing kit. The cutoffs for initiation and discontinuation of therapy were for the most part similar in each group, and many of the studies used similar measures for the outcomes of interest.

We also reviewed ongoing clinical trials that utilize procalcitonin-guided antibiotic therapy listed at ClinicalTrials.gov. The details of these ongoing trials including sample size, presenting condition, primary and secondary outcomes and expected date of completion are summarized in Appendix D.

Critically Ill/Ventilator-Associated Pneumonia

There were a total of seven RCTs[28, 32-37] comparing procalcitonin-guided therapy with standard antibiotic therapy in this population. Five studies[32-36] addressed procalcitonin-guided discontinuation of antibiotics. Two studies[28, 37] addressed procalcitonin-guided intensification of antibiotic therapy.

Procalcitonin-Guided Antibiotic Discontinuation

Study Characteristics

There were five RCTs[32-36] comparing procalcitonin-guided therapy with standard antibiotic therapy (Table 2). Analyses of outcomes tested superiority of procalcitonin-guided therapy in all but one case: one study[32] conducted a noninferiority analysis for mortality. Sample sizes ranged from 27 to 621, with three studies[32, 34, 36] greater than 100. Overall, 938 patients were enrolled into these trials.

Procalcitonin criteria for discontinuation of antibiotic varied somewhat. Absolute values that prompted antibiotic discontinuation included 0.25, 0.5 and 1 ng/mL. Relative values included 25 to 35 percent of baseline or 80 and 90 percent reductions from baseline. Physicians in the control groups administered antibiotics according to their standard practice. In the largest study by Bouadma et al.,[32] local and international guidelines on duration of antibiotic therapy were available on a website. While the lack of specificity about what constituted antibiotic could be viewed as a limitation in study designs, it could also be viewed as a strength regarding applicability to actual practice. Study duration varied, but was for the duration of hospitalization, at least 28 days in three studies,[32, 34, 35] and at 60 days in one study.[32]

Three studies[32, 34, 35] identified antibiotic use as a primary outcome and two studies[33, 36] did not mention a primary endpoint. One study[32] looked at mortality as a primary outcome, and mortality was a predefined secondary outcome in one other study.[35] Mortality data were available from all five studies.

Table 2. Summary of characteristics for five trials included in the analysis of procalcitonin-guided antibiotic discontinuation in the critically ill/ventilator-associated pneumonia patients

Author, year, country	Disease state	N	PCT for ABT discontinuation	Control interventions	Study duration	Predefined endpoints
Bouadma, 2010, France[32]	Critically ill, suspected bacterial infection	PCT 307 Ctrl 314	PCT <0.5ng/mL or >/= 80% decrease from peak	Broad-spectrum ABTs started ASAP; de-escalation based on cultures if possible; ABT duration by local and international guidelines	60 days	Primary outcome mortality, number of days without ABT Secondary ABT exposure, morbidity
Schroeder, 2009, Germany[33]	Severe sepsis	PCT 14 Ctrl 13	PCT ≤1 ng/mL or 25-35% of baseline	Dx of severe sepsis by ACCP guidelines; standard ABT therapy	Not defined	Not defined
Stolz, 2009, Switzerland & USA[34]	ICU, VAP	PCT 51 Ctrl 50	PCT <0.5 ng/mL or decrease of > /= 80% from baseline	VAP Dx by ATS guidelines; standard ABT therapy	28 days	Primary outcome ABT-free days at day 28
Nobre, 2008, Switzerland[35]	Severe sepsis	PCT 39 Ctrl 40	PCT <0.25 ng/mL or decreased by 90% from baseline	Sepsis, septic shock Dx by ACCP criteria; standard broad-spectrum ABT therapy	28 days	Primary outcome ABT exposure Secondary outcomes 28 day mortality, ICU LOS, other
Hochreiter, 2009, Germany[36]	ICU, sepsis	PCT 57 Ctrl 53	PCT <1 ng/mL or 25-35% of baseline over 3 days	SIRS Dx by ACCP criteria; standard ABT therapy for 8 days	Not defined	Not defined

ABT: antibiotic; ACCP: American College of Chest Physicians; ASAP: as soon as possible; ATS: American Thoracic Society, Ctrl: control, Dx: diagnosis; ICU: intensive care unit; LOS: length of stay; PCT: procalcitonin; SIRS: systemic inflammatory response syndrome; VAP: ventilator associated pneumonia

Study Quality

The overall rating for three studies[32, 34, 35] was good and fair for the remaining two studies[33, 36] (Table 3). All studies assembled groups appearing to have similarly distributed potential confounders with no obvious imbalances. Two studies[33, 36] did not describe their procedure for allocation concealment.

Judgments of whether outcome measurements were equal, valid and reliable usually depend in part on the requirement for blinded outcome assessor. However, in these studies, it was not feasible to blind the treating physicians to the patient's assigned treatment. Decisions on antibiotic use were made by unblinded physicians who could take other clinical information into account and override the algorithm based on their clinical judgment. Procalcitonin guidance is intended as an adjunct to, not a replacement for, clinical criteria for assessing and managing infection. In this setting, we did not require use of a blinded outcome assessor as a dimension of study quality.

Intention-to-treat analyses were consistently performed. One study[35] reported both intention-to-treat and per-protocol analyses. The study designed to test noninferiority of mortality in the procalcitonin-guided group was powered to exclude a 10 percent between-group mortality difference. No other studies were powered to detect differences in mortality or morbidity outcomes. The explicit reasoning behind the choice of the margin for mortality was not discussed.

Antibiotic Use

Outcomes related to antibiotic usage are summarized in Table 4. The duration of antibiotic therapy was reduced in the procalcitonin-guided arm of all five studies.[32-36] The absolute difference ranged from -1.7 to -5 days, with a percent reduction of 21 to 38 percent. Three studies reported the reduction in antibiotic use in terms of days without antibiotic therapy. Again, this favored procalcitonin-guided therapy, with an additional 2.3 to 3.8 days without antibiotics, an 18 to 37 percent reduction. Three studies[32, 34, 35] reported total antibiotic exposure, which also accounted for the use of multiple agents (intensity), as well as duration of therapy. Total exposure per 1,000 patient-days ranged from 644 to 1,341 for the control groups, with a longer duration seen for VAP, but in all 3 studies total exposure in the procalcitonin-guided arm was reduced by 16 to 20 percent. The study[35] that reported both intention-to-treat and per-protocol analyses found statistically significant reductions only with the latter for antibiotic duration, days without antibiotic and total antibiotic exposure. In summary, procalcitonin-guided therapy resulted in consistent reductions in antibiotic usage by all measures. The range of reduction in antibiotic usage was also similar across studies.

Table 3. Procalcitonin-guided antibiotic discontinuation in the critically ill/ventilator-associated pneumonia patients, study quality

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal followup loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Bouadma, 2010[32]	Y	Y	Y	Y	Y	Y	Y	Good
Schroeder, 2009[33]	Y*	Y	Y	Y	Y	Y	Y	Fair
Stolz, 2009[34]	Y	Y	Y	Y	Y	Y	Y	Good
Nobre, 2008[35]	Y	Y	Y	Y	Y	Y	Y	Good
Hochreiter, 2009[36]	Y*	Y	Y	Y	Y	Y	Y	Fair

Y= Yes
*No details on allocation concealment but groups were comparable

Table 4. Procalcitonin-guided antibiotic discontinuation in the critically ill/ventilator-associated pneumonia patients—outcomes related to antibiotic usage

Outcome	Author, year	n	PCT-guided therapy	Control	Difference PCT-CTRL (95% CI)	p value
ABT Duration (days)	Hochreiter, 2009[36]	110	5.9	7.9	-2.0 (-2.5, -1.5)	< 0.001
	Nobre, 2008[35]	79	6 6	9.5 (ITT) 10 (PP)	-2.6 (-0.3, 5.5), -3.2 (-1.1,- 5.4)	0.15 0.003
	Schroeder, 2009[33]	27	6.6	8.3	-1.7 (-2.4, -1.0)	<0.001
	Stolz, 2009[34]	101	10	15	-5	0.049
	Bouadma, 2010[32]	621	6.1	9.9	-3.8 (-4.8, -2.7),	<0.0001
Days without ABTs (day 28)	Nobre, 2008[35]	79	15.3 17.4	13 13.6	2.3 (-5.9, 1.8) 3.8 (0.1, 7.5) §	0.28 0.04
	Stolz, 2009[34]	101	13	9.5	3.5	0.049
	Bouadma, 2010[32]	621	14.3	11.6	2.7 (1.4, 4.1)	<0.001
Total ABT exposure*	Nobre, 2008[35]	79	541 504	644 655	1.1** (0.9, 1.3) 1.3** (1.1, 1,5) §	0.07 0.0002
	Stolz, 2009[34]	101	1077	1341		
	Bouadma*, 2010[32]	621	653	812	-159 (-185, -131)	<0.001

ABT: antibiotic; CI: confidence interval; CTRL: control; ITT: intention to treat; PCT: procalcitonin; PP: per protocol
*Per 1000 inpatient days, **Rate ratios, §Per protocol analysis

Mortality

Three studies[32, 34, 35] reported 28-day mortality, one study[32] reported both 28- and 60-day mortality, two studies[34, 35] reported in-hospital mortality, and two studies[33, 36] reported overall mortality (Table 5). Mortality rates at 28 days in control arms ranged from 20 to 24 percent. In one study,[33] the reduction in 28-day mortality with procalcitonin-guided therapy was 8.3 percent, and in two studies, mortality increased by 0.5 percent[35] and 0.8 percent.[32] None of these differences was statistically significant.

Only one study[32] reported 60-day mortality. There was a 3.9 percent increase in mortality in the procalcitonin-guided group that was not statistically significant, but procalcitonin-guided therapy met the predefined criteria for noninferiority with respect to 60-day mortality. Additionally, deaths between 28 and 60 days were analyzed, and none was related to relapse of infection. In-hospital mortality was higher in the procalcitonin-guided group by 0.6 percent in one study[35] and reduced by 8.4 percent in one study,[34] but neither difference reached statistical significance. Overall mortality was slightly reduced in the two studies from 0.1[36] to 1.7[33] percent reduction, but the differences were not significant.

Most studies were powered to determine if there was a difference in antibiotic usage, and not powered to detect differences in morbidity and mortality. Only the study by Bouadma et al.,[32] the largest RCT looking at procalcitonin-guided therapy to date, was powered to determine noninferiority of procalcitonin-guided therapy versus standard care. The study was powered to have an 80 percent power to exclude a 10 percent difference in mortality between groups. Noninferiority was met for 28-day and 60-day mortality in this study, but there is concern that the 10 percent margin chosen was not sufficiently narrow to exclude excess mortality.

Table 5. Procalcitonin-guided antibiotic discontinuation in the critically ill/ventilator-associated pneumonia patients—mortality

Outcome	Author, year	N	Mortality PCT-guided therapy	Mortality Control	Difference PCT-CTRL (95% CI)	p value
28-day mortality	Nobre, 2008[35]	79	8/39 (20.5%) 5/31 (16.1%)	8/40 (20.0%) 6/37 (16.2%)	0.5 (-17.2, 18.2), -0.1 (-17.7, 17.5) [§]	0.95 0.99
	Stolz, 2009[34]	101	8/51 (15.7%)	12/50 (24.0%)	-8.3 (-23.8, 7.2)	0.29
	Bouadma, 2010[32]	621	65/307 (21.2%)	64/314 (20.4%)	0.8 (-5.6, 7.2)	0.81
60-day mortality	Bouadma, 2010[32]	621	92/307 (30.0%)	82/314 (26.1%)	3.9 (-3.2, 10.9)	0.29
In-hospital	Nobre, 2008[35]	79	9/39 (23.1%) 6/31 (19.4%)	9/40 (22.5%) 7/37 (18.9%)	0.6 (-17.9, 19.1) 0.4+ (-18.3, 19.2)	0.95 0.96
	Stolz, 2009[34]	101	10/51 (19.6%)	14/50 (28.0%)	-8.4, (-24.9, 8.1)	0.32
Mortality	Hochreiter, 2009[36]	110	15/57 (26.3%)	14/53 (26.4%)	-0.1, (-16.6, 16.4)	0.99
	Schroeder, 2009[33]	27	3/14 (21.4%)	3/13 (23.1%)	-1.7, (-33.1, 29.8)	0.92

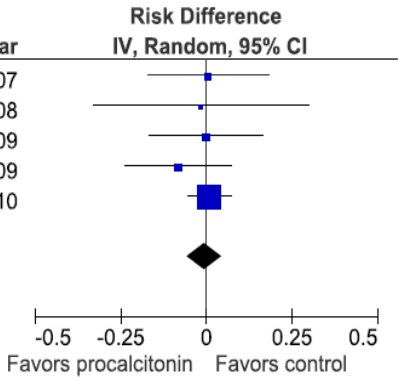
CI: confidence interval; CTRL: control; PCT: procalcitonin
[§]Per protocol analysis

A meta-analysis was performed to pool mortality data from all five studies[32-36] in order to increase the probability of detecting a significant difference in between-group mortality. Pooling was performed for studies reporting short-term (28-day or in-hospital) mortality. Results show a pooled point estimate of 0.4 percentage point reduction in mortality favoring the procalcitonin-guided therapy group (Figure 4). The 95 percent confidence interval indicates that benefit greater than 6 percentage point decrease in mortality with procalcitonin is unlikely, and also that greater than a 5 percentage point increase in mortality with procalcitonin is unlikely.

Figure 4. Meta-analysis of risk differences, short-term mortality (in-hospital or 28-day)

Study or Subgroup	Procalcitonin Events	Procalcitonin Total	Control Events	Control Total	Weight	Risk Difference IV, Random, 95% CI	Year
Nobre 2007	8	39	8	40	8.7%	0.01 [-0.17, 0.18]	2007
Schroeder 2008	3	14	3	13	2.8%	-0.02 [-0.33, 0.30]	2008
Hochreiter 2009	15	57	14	53	10.1%	-0.00 [-0.17, 0.16]	2009
Stolz 2009	8	51	12	50	11.4%	-0.08 [-0.24, 0.07]	2009
Bouadma 2010	65	307	64	314	67.1%	0.01 [-0.06, 0.07]	2010
Total (95% CI)		**468**		**470**	**100.0%**	**-0.00 [-0.06, 0.05]**	
Total events	99		101				

Heterogeneity: Tau² = 0.00; Chi² = 1.15, df = 4 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)



Morbidity

Three studies[32, 34, 35] evaluated hospital length of stay (LOS), four studies[32, 33, 35, 36] evaluated ICU LOS, one study[34] evaluated ICU-free days alive, three studies[32, 33, 36] evaluated some type of severity of illness score, and three studies[32, 34] reported on days without mechanical ventilation (Table 6). Hospital LOS was reduced by 0 to 2.5 days in the procalcitonin-guided arms. This represents a 0 to 11 percent reduction in LOS, but the difference was not statistically significant in any of the studies. ICU LOS similarly was reduced by 0.3 to 4.6 days in three studies, and increased by 1.5 days in another study. The only study reporting a significant decrease in ICU LOS was the Nobre study[35] of severe sepsis and septic shock, where ICU LOS was reduced by 43 percent. Among studies reporting severity of illness scales, there was a small difference in severity that favored procalcitonin-guided therapy in two[33, 36] out of three[32, 33, 36] studies, but the differences were not significant. Only one study[32] showed a significant increase in the severity of illness at 28 days, but the difference was minimal and the absolute severity scores were extremely low for both groups. One study[32] reported a reduction in mechanical ventilation and one study[34] reported an increase in mechanical ventilation, but none of the differences was significant.

Because ICU LOS was reported by four studies,[32, 33, 35, 36] we considered conducting meta-analysis on this outcome. However, one study[36] did not report data necessary for calculation, so the decision was made to not proceed with pooling, as only three studies would be represented in the meta-analysis.

Table 6. Procalcitonin-guided antibiotic discontinuation in the critically ill/ventilator-associated pneumonia patients—morbidity

Outcome	Author, year	N	PCT	Control	Difference, PCT-CTRL (95% CI)	p value
LOS (days)	Nobre, 2008[35]	79	17	23.5	-2.5 (-6.5, 1.5)	0.85
	Stolz, 2009[34]	101	26	26	0	0.15
	Bouadma, 2010[32]	621	26.1	26.4	-0.3 (-3.2, 2.7)	0.87
ICU LOS (days)	Hochreiter, 2009[36]	110	15.5	17.7	-2.2	0.046
	Nobre, 2008[35]	79	4	7	-4.6 (-8.2, -1.0)	0.02
	Schroeder, 2009[33]	27	16.4	16.7	-0.3,(-5.6, 5.0)	NSS
	Bouadma, 2010[32]	621	15.9	14.4	1.5 (-0.9, 3.1)	0.23
ICU-free days alive, 1-28	Stolz, 2009[34]	101	10 (0-18)	8.5 (0-18)	1.5	0.53
SOFA day 28	Bouadma, 2010[32]	621	1.5	0.9	0.6 (0.0, 1.1)	0.037
SOFA score max	Schroeder, 2009[33]	27	7.3	8.3	-8.1 (-4.1, 1.7)	NSS
SAPS II score	Hochreiter, 2009[36]	110	40.1	40.5	-0.4 (-6.4, 5.6)	> 0.05
Days without MV	Stolz, 2009[34]	101	21	19	2.0	0.46
	Bouadma, 2010[32]	621	16.2	16.9	-0.7 (-2.4, 1.1)	0.47

CI: confidence interval; CTRL: control; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; PCT: procalcitonin; SAPS: Simplified Acute Physiology Score; SOFA: Sepsis-related Organ Failure Assessment

Adverse Events of Antibiotic Therapy

Only one study[32] reported on adverse effects of antibiotic therapy. Bouadma et al., reported on emergence of multi-drug resistant (MDR) organisms (17.9 % versus 16.6 % in the procalcitonin versus the control group respectively, difference 1.3 %, 95% CI: -4.6, 7.2, p = 0.67) and superinfection (34.5 % versus 30.9 % in the procalcitonin versus the control group respectively, difference 3.6 %, 95% CI: -3.8, 11, p = 0.29).

GRADE Evidence

Methods for grading strength of evidence[25] developed for the AHRQ Effective Health Care Program were applied to this body of literature (Table 7). The quality of studies reviewed was an important consideration. Three of the five studies[32, 34, 35] received a good quality rating and two studies[33, 36] received a fair rating.

For the body of evidence reviewed here, the strength of evidence was graded high for a reduction in antibiotic usage. The three studies[32, 34, 35] judged as good quality included 85 percent of the total patient population (801 of 938) and also reported on all three antibiotic usage measures. The results consistently favored procalcitonin-guided therapy, and differences were generally highly statistically significant and were of a magnitude that has been associated with clinical benefits using other approaches to reduction of antibiotic use, such as active interventions of antibiotic stewardship programs and implementation of practice guidelines.[38-40] The absolute difference in antibiotic use duration, the measure that was reported by all five studies, ranged from -1.7 to -5 days, with a percent reduction of 21 to 38 percent.

The strength of evidence that there was no difference in mortality with procalcitonin-guided discontinuation of antibiotic therapy in the critically ill/VAP patients was graded as moderate. The results of all five studies[32-36] were consistent in finding no significant difference in short-term (28-day or in-hospital) mortality between procalcitonin-guided therapy and control groups. Four of the studies[33-36] were not sufficiently powered to assess mortality. The largest study by Bouadma et al.,[32] was a noninferiority study that had 80 percent power to exclude a 10 percent

difference in mortality between groups. Meta-analysis was performed to increase the probability of detecting a significant difference in between-group mortality. Results show a pooled point estimate of 0.4 percentage point reduction in mortality favoring the procalcitonin-guided therapy group. The 95 percent confidence interval indicates that benefit greater than 6 percentage point decrease in mortality with procalcitonin is unlikely, and also that greater than a 5 percentage point increase in mortality with procalcitonin is unlikely.

The writing team considered whether the confidence interval was sufficiently precise to merit a grade of moderate, rather than low. At present, two large trials[41, 42] of procalcitonin-guided antibiotic therapy in ICU patients (Total N=3,946) are in progress. We hypothesized that if the mortality events in these two trials was same as the Bouadma study,[32] the resulting pooled estimate by adding expected mortality data from an additional 4,000 patients was 0.6 percent (95 percent CI: -1.7, 2.8 percent). Thus, we judged that the confidence that the present evidence reflects the true effect was moderate.

All five studies[32, 33, 35, 36] reported on ICU LOS as a measure of morbidity. Risk of bias was rated low due to the preponderance of patients in good quality studies. Evidence was judged consistent as four of five studies[33, 35, 36] reported shorter ICU LOS for procalcitonin arm. Evidence was considered direct and sufficiently precise to support the judgment that procalcitonin guidance does not increase morbidity as indicated by ICU LOS. The strength of evidence that procalcitonin does not increase ICU LOS was graded moderate.

Table 7. Procalcitonin-guided antibiotic discontinuation in the critically ill/ventilator-associated pneumonia patients—GRADE evidence table

	Outcome	No of Studies (subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Antibiotic use	Duration	5 RCTs (n=938)[32-36]	Low	Consistent	Direct	Precise	High
	Days without ABTs (day 28)	3 RCTs (n=801)[32, 34, 35]	Low	Consistent	Direct	Precise	High
	Total exposure	3 RCTs (n=801) [32, 34, 35]	Low	Consistent	Direct	Precise	High
Mortality	In-hospital, overall or 28 day	5 RCTs (n=938) [32-36]	Low	Consistent	Direct	Precise	Moderate
Morbidity	ICU length of stay	5 RCTs (n=837) [32-36]	Low	Consistent	Direct	Precise	Moderate

ABT: antibiotic; ICU: intensive care unit; RCT: randomized controlled trial

Procalcitonin-Guided Antibiotic Intensification

Study Characteristics

There were two RCTs[28, 37] of procalcitonin-guided antibiotic intensification (Table 8). Both studies evaluated critically ill patients in the ICU. The Svoboda study[37] was limited to patients in the surgical ICU, while surgical patients were only a portion, but well represented, subgroup in the Jensen study.[28] One study[37] followed the patients for the duration of hospitalization, while the other study[28] looked at outcomes at 28 days. Both studies reported intention-to-treat to treat analysis. Svoboda et al.,[37] enrolled 72 patients and Jensen[28] enrolled 1,200 patients. In the Svoboda study[37] an elevated procalcitonin level prompted IV catheter changes and changes in the antibiotic regimen. In the Jensen study,[28] an algorithm for expanded radiographic evaluation and broadening the spectrum of antimicrobial therapy was used for patients with elevated procalcitonin. In the Svoboda study,[37] the only description of antibiotic therapy in the control

group was that it was standard of care. Jensen,[28] in contrast, had a very detailed approach to antibiotic therapy and physicians were educated as to the approach to be taken for empiric therapy and intensification of antibiotic therapy. Mortality was the primary outcome for the large study by Jensen.[28] The other study[37] did not predetermine outcomes to be assessed.

Table 8. Summary of characteristics for two trials included in the analysis of procalcitonin-guided antibiotic intensification in the critically ill/ventilator-associated pneumonia patients

Author, year	Disease state	N	PCT for ABT discontinuation	Other PCT-guided interventions	Control interventions	Study duration	Predefined endpoints
Svoboda, 2007, Czech[37]	Severe sepsis, septic shock	PCT 38 Ctrl 34	NA	PCT >2, change catheters and ABTs, PCT <2, US or CT and repeat surgery	Standard supportive care; broad-spectrum ABTs; catheter changes as indicated by guidelines	Not defined	Not defined
Jensen, 2011, Denmark[28]	Critically ill in the ICU	PCT 604 Ctrl 596	NA	PCT ≥1.0 or less than 10% lower than previous day, enhanced radiographic evaluation and broadened spectrum of ABT therapy	Standard microbiological and radiographic evaluation, ABT therapy	28 days	Primary 28-day mortality Secondary Duration of organ failure; duration of stay in the ICU

ABT: antibiotic; CI: confidence interval; CT: computed tomography; CTRL: control; ICU: intensive care unit; PCT: procalcitonin; US: ultrasound

Study Quality

The quality ratings for the two studies[28, 37] are described in Table 9. Both studies[28, 37] assembled comparable groups and described randomization concealment. The study by Jensen[28] clearly outlined the specific interventions for intensification, while the other study[37] only vaguely described a push to change IV catheter and change antibiotics. One study[37] broadly described an initiative to change antibiotics and IV catheters, pursue radiographic imaging, and reoperation if a local infection was confirmed, but did not give any details regarding these interventions. The outcomes were strictly defined, and in the higher quality study by Jensen,[28] there was assurance that physicians, investigators, and coordinators were unaware of outcomes during the study or procalcitonin levels in the control group.

Antibiotic Use

In the study by Jensen,[28] procalcitonin-guided intensification resulted in a 2 day (50 percent) increase in the duration of antibiotic therapy (Table 10). It also resulted in greater antibiotic exposure with a 7.9 percent increase in number of days on 3 or more antibiotics in the ICU.

Table 9. Procalcitonin-guided antibiotic intensification in the critically ill/ventilator-associated pneumonia patients–study quality

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal followup loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Svoboda, 2007[37]	Y	Y	Y	Y	N	Y	Y	Fair
Jensen, 2011[28]	Y	Y	Y	Y	Y	Y	Y	Good

Y= yes, N= no

Table 10. Procalcitonin-guided antibiotic intensification in the critically ill/ventilator-associated pneumonia patients–outcomes related to antibiotic usage

Author, year	Outcome	n	PCT	Control	Difference PCT-CTRL (95%)	p value
Jensen, 2011[28]	ABT Duration (days)	1200	6 (3-11)	4 (3-10)	Not reported	NR
Jensen, 2011[28]	Days spent in ICU on $\geq$ 3 ABTs	1200	3570/5447 (65.5%)	2721/4717 (57.7%)	7.9% (6.0 to 9.7)	0.002

ABT: antibiotic; CI: confidence interval; CTRL: control; ICU: intensive care unit; NR: not reported; PCT: procalcitonin;

Mortality

The impact of procalcitonin-guided antibiotic intensification on mortality is described in Table 11. There was a statistically insignificant reduction in mortality in the Svoboda[37] study, which was not powered to show differences in mortality. Jensen[28] was a superiority trial powered to test a 7.5 percent decrease in 28-day mortality, but no significant difference in mortality was observed with procalcitonin-guided intensification. Jensen[28] showed no beneficial or adverse effect on mortality with procalcitonin-guided intensification.

Table 11. Procalcitonin-guided antibiotic intensification in the critically ill/ventilator-associated pneumonia patients—28-day mortality

Author, year	N	PCT	Control	Difference PCT-CTRL (95% CI)	p value
Svoboda, 2007[37]	72	10/38 (26.3%)	13/34 (38.2%)	-11.9 (-33.4, 9.6)	0.28
Jensen, 2011[28]	1200	190/604 (31.5%)	191/596 (32.0%)	-0.6 (-4.7 to 5.9)	0.83

CI: confidence interval; CTRL: control; PCT: procalcitonin

Morbidity

The Svoboda[37] showed a 3.3 day reduction in ICU stay, which was not statistically significant. Jensen[28] study showed a significant 1 day increase in ICU LOS (Table 12). Furthermore, this larger, good quality study demonstrated a significant increase in organ dysfunction, specifically an extra 5 days of mechanical ventilation and an additional 5 days of abnormal renal function, both of which were statistically significant.

Table 12. Procalcitonin-guided antibiotic intensification in the critically ill/ventilator-associated pneumonia patients—morbidity

Outcome	Author, year	N	PCT	Control	Difference, PCT-CTRL (95% CI)	p value
ICU LOS (days)	Svoboda, 2007[37]	72	16.1	19.4	-3.3 (-7.0, 0.4)	0.09
	Jensen, 2011 [28]	1200	6 (3-12)	5 (3-11)	1	0.004
SOFA score	Svoboda, 2007[37]	72	7.9	9.3	-1.4. (-2.8, 0.0)	0.06
Days on MV	Svoboda, 2007[37]	72	10.3	13.9	-3.6 (-7.6, 0.4)	0.08
	Jensen, 2011[28]	1200	3569 (65.5%)	2861 (60.7%)	4.9% (3 to 6.7)	< 0.0001
Percent days in ICU with GFR <60	Jensen, 2011[28]	1200	2796 (51.3%)	2187 (46.4%)	5.0 % (3.0 to 6.9)	<0.0001

CI: confidence interval; CTRL: control; GFR: glomerular filtration rate; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; PCT: procalcitonin;

Adverse Events of Antibiotic Therapy

None of the studies in this patient group reported the adverse events of antibiotic therapy.

GRADE Evidence

The strength of evidence is moderate that procalcitonin-guided intensification of antibiotic therapy increases morbidity. The large (n=1,200) good quality study by Jensen[28] was judged to have low risk of bias. This study was notable for its specificity in describing study interventions, especially treatment algorithms. Consistency was rated as unknown (single study). The evidence

is direct and sufficiently precise to judge that procalcitonin-guided intensification does not improve outcomes in critically ill patients. A second study (n=72)[37] was too small to be informative.

Respiratory Tract Infections

There were eight studies[27, 31, 43-48] in total, seven randomized, controlled trials[27, 31, 43-47] and one cluster-randomized controlled trial.[48] All studies compared procalcitonin-guided initiation and/or discontinuation of antibiotics in patients with respiratory tract infections to standard therapy. The sample size in these studies ranged from 162 to 1,359, with all studies having populations larger than 100. Overall, 3,492 patients were enrolled in these trials.

Study Characteristics

The populations in this study consisted of patients with acute upper and lower respiratory tract infections in the community, including community-acquired pneumonia (CAP), acute exacerbation of chronic obstructive pulmonary disease (COPD), and acute bronchitis (Table 13). The study populations and settings varied between studies. Three studies[31, 44, 47] looked only at CAP, but the settings varied in these studies. One study[31] included patients from the outpatient setting, one study[47] included patients from the emergency department, and one study[44] included patients admitted to the hospital. Two studies[27, 45] included patient populations that had upper or lower respiratory tract infections. Both of these studies looked at patients in the outpatient setting (primary care clinics). Two studies[43, 48] included patients with lower respiratory tract infections only, and both of these studies enrolled patients that presented to emergency departments. One study[46] looked only at patients with acute exacerbation of COPD in the emergency department.

All studies[27, 31, 43-48] evaluated the use of procalcitonin for the initiation of antibiotics. All studies encouraged initiation of antibiotics with procalcitonin levels greater than 0.25 ng/mL, and four studies[43, 44, 47, 48] strongly encouraged antibiotics with procalcitonin levels greater than 0.5 ng/mL. Seven studies[27, 31, 43-45, 47, 48] used procalcitonin measurement to recommend discontinuation of antibiotics. Five studies [27, 31, 44, 45, 48] recommended discontinuing antibiotics if procalcitonin level was less than 0.25 ng/mL, and one of these studies[31] strongly recommended discontinuation if level was less than 0.1 ng/mL. One study[43] recommended discontinuation if the procalcitonin level was less than 20 percent of the baseline level, and strongly recommended discontinuation if the level was less than 10 percent. One study [47] recommended discontinuation of antibiotics if the procalcitonin level was 10 percent of baseline, if the baseline level was greater than 10 ng/mL.

Physicians in the control groups administered antibiotics according to their own standard practices and/or evidence-based guidelines. Two studies[31, 47] used international guidelines on standard therapy that were cited in the references. One study[43] used evidence-based, international guidelines which were stated in the methods section but not cited in the references.

The study durations ranged from 14 days to 30 days in five studies,[27, 31, 43 45, 48] 6 weeks in one study,[47] and 6 months in one study.[46] Study duration was not defined in one study.[44]

Table 13. Summary of characteristics for eight trials included in the analysis of procalcitonin-guided antibiotic initiation and/or discontinuation in patients with respiratory tract infections

Author, year, country	Disease state	N	PCT for ABT initiation	PCT for ABT discontinuation	Study duration	Predefined endpoints
Long, 2011, China[31]	Suspected CAP outpatient	PCT 81 Ctrl 81	PCT >0.25 ng/mL	PCT< 0.1ng/mL strongly discouraged PCT 0.1-0.25 ng/mL antibiotics discouraged	28 days	Primary : Total antibiotic use and duration of antibiotic treatment, antibiotic prescription rate Secondary outcomes: Treatment failure, treatment success, death, recurrence, relapse, patients lost to followup
Burkhardt, 2010, Germany[27]	Acute respiratory tract infection	PCT 275 Ctrl 275	PCT ≥0.25 ng/ml	PCT <0.25 ng/mL	28 days	Primary: Number of days with significant health impairment due to RTI at day 14 Secondary: Prescription rate, duration of abts, days with abt-associated SEs, symptoms on day 14 and 28, revisit within 28 days, change of abts within 28 days, hospitalization within 28 days, 28 day mortality
Schuetz, 2009, Switzerland[43]	LRTI; (CAP, AECOPD, acute bronchitis)	PCT 671 Ctrl 688	PCT <0.1 ng/mL, strongly discouraged; PCT ≤0.25 ng/mL, discouraged; PCT > 0.25 ng/mL, encouraged; PCT >0.5 ng/mL, strongly encouraged	PCT <10% of baseline, stopping strongly encouraged; PCT <20% of baseline, stopping discouraged	30 days	Primary: (Noninferiority) Total adverse event rate at 30 days (composite outcome of death, ICU admission, disease-specific complications, and recurrent LRTI in need of antibiotics with or without hospital readmission) Secondary: ABT exposure, duration, adverse effects, LOS
Kristoffersen, 2009, Denmark[44]	LRTI (CAP)	PCT 103 Ctrl 107	PCT <0.25 ng/mL, discouraged PCT 0.25-5.0 ng/mL, encouraged PCT >0.5 ng/mL, strongly encouraged	PCT <0.25 ng/mL, discontinued	Not defined	Primary: ABT duration, LOS Secondary: Proportion of patients for whom physicians disregarded treatment guidelines
Briel, 2008, Switzerland[45]	URTI (cold, sinusitis, pharyngitis, tonsillitis), LRTI (CAP, AECOPD, tracheobronchitis)	PCT 232 Ctrl 226	PCT >0.25 ng/mL, recommended PCT 0.1-0.25 ng/mL, not recommended, PCT increase 50% with worse symptoms, ABTs, recommended	PCT ≤0.25	28 days	Primary: (Noninferiority) Number of days of restricted activity due to respiratory infection Secondary: ABT prescription rate and duration, discomfort scale, days work missed, days with adverse effects of medication, relapse of infection, serious adverse events

Table 13. Summary of characteristics for eight trials included in the analysis of procalcitonin-guided antibiotic initiation and/or discontinuation in patients with respiratory tract infections (continued)

Author, year, country	Disease state	N	PCT for ABT initiation	PCT for ABT discontinuation	Study duration	Predefined endpoints
Stolz, 2007, Switzerland[46]	Acute exacerbation of COPD	PCT 102 Ctrl 106	PCT <0.1 ng/mL strongly discouraged; PCT ≥1.0 ≤0.25 ng/mL, ABTs based on clinical condition; PCT >0.25 ng/mL, encouraged	NA	6 months	Primary: ABT use at index AECOPD ABT use up to 6 months Secondary: Success, LOS, ICU need, CRP, PCT, PFTs on admission, short- and long-term F/U, exacerbation rate, time to next exacerbation
Christ-Crain, 2006, Switzerland[47]	CAP admitted to ED, single center	PCT 151 Ctrl 151	PCT <0.1 strongly discouraged PCT ≥0.1, <0.25, discouraged PCT ≥0.25, ≤0.5 ng/mL, encouraged PCT >0.5 ng/mL, strongly encouraged	If baseline >10 ng/mL, ABTs discontinued if less than 10% of initial value	6 weeks	Primary: Total ABT use (prescription) and duration Secondary: Laboratory, clinical outcomes
Christ-Crain, 2004, Switzerland[48]	LRTI (CAP, AECOPD, acute bronchitis, asthma)	PCT 124 Ctrl 119	PCT ≤0.1 ng/mL, strongly discouraged PCT 0.1-0.25 ng/mL, discouraged PCT 0.25-0.5 ng/mL, encouraged PCT ≥0.5 ng/mL, strongly encouraged	PCT <0.25 ng/mL	14 days	Primary: ABT prescription rate, ABT exposure, costs Secondary: QOL, Temp, WBC count, CRP, PCT, Admission rates, LOS, ICU, death for LRTIs, Re-exacerbation, readmission for AECOPD

ABT: antibiotic; AECOPD: acute exacerbation of chronic obstructive pulmonary disease; CAP: community acquired pneumonia; CRP: C-reactive protein; Ctrl: control; ED: emergency department; F/U: followup; ICU: intensive care unit; LOS: length of stay; LRTI: lower tract infections; NA: not applicable; PCT: procalcitonin; PFT: pulmonary function test; QOL: quality of life; RTI: respiratory tract infection; URTI: upper respiratory tract Infection; WBC: white blood cells

The primary endpoints varied by the study. Prescription rate[*], antibiotic duration and total antibiotic exposure[†] were primary endpoints in four studies.[31, 46-48] Number of days of restricted activity was the primary endpoint in two studies.[27, 45] LOS was a primary endpoint in one study,[44] and cost was a primary endpoint in another study.[48] The 2009 study by Schuetz et al.,[43] was a noninferiority trial that calculated a composite outcome of total adverse events as the primary endpoint.

Study Quality

The overall study rating was good for four studies[27, 43, 45, 47] and poor for the other four studies[31, 44, 46, 48] (Table 14). Four of the studies were given a poor rating because of lack of intention-to-treat analysis. The studies rated poor because of percentages of excluded patients are: Christ-Crain et al., (2004)[48] (8.6 percent), Kristoffersen et al., (2009)[44] (5.8 percent), Long et al., (2011)[31] (5.8 percent), and Stolz et al., (2007)[46] (8.0 percent). All studies assembled groups appearing to have similarly distributed potential confounders with no obvious imbalances. Allocation concealment was not explicitly stated in two studies,[31, 46] and concealment was not applicable in the one cluster-randomized trial.[48] All studies had clearly defined interventions.

Judgments of whether outcome measurements were equal, valid and reliable usually depend in part on the requirement for blinded outcome assessor. For studies comparing procalcitonin-guided therapy and standard therapy, this requirement was not applied. In these studies, it was not feasible to blind treating physicians to which group participants were allocated. Decisions on antibiotic use were made by unblinded physicians who could take other clinical information into account and override the algorithm based on their clinical judgment. Procalcitonin guidance is intended as an adjunct to, not a replacement for, clinical criteria for assessing and managing infection. In this setting, we did not require use of a blinded outcome assessor as a dimension of study quality.

Five of the trials[27, 31, 44, 46, 47] were superiority trials with intention-to-treat analyses, and two trials[43, 45] were noninferiority trials with both intention-to-treat and per-protocol analyses. One study[43] tested for noninferiority of the composite adverse event rate, including death, ICU admission, disease-specific complications, or recurrent infection requiring antibiotic treatment within 30 days. A predefined noninferiority boundary of 7.5 percent was used, and based on this noninferiority boundary, a sample size of 1,002 patients was determined to allow for an adverse outcome rate in the control group of 20 percent or less with a power of 90 percent. A second study[45] used noninferiority design to compare the number of days of restricted activity due to respiratory infection. Noninferiority was defined as a difference between the procalcitonin-guided therapy and control groups of no more than one day.

[*]defined as the percentage of patients that are initiated on antibiotic therapy, either during initial presentation or subsequent followup

[†]calculated by multiplying the total number of antibiotics by the number of days the patient is receiving each of antibiotic divided by total duration of antibiotic therapy.

Table 14. Procalcitonin-guided antibiotic initiation and/or discontinuation in patients with respiratory tract infections—study quality

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal followup loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Schuetz, 2009[43]	Y-balanced Y-concealment	Y	Y	Y	Y	Y	Y	Good
Christ-Crain, 2004[48] (cluster-randomized trial)	Y-balanced N/A-concealment	Y	Y	Y	Y	Y	N	Poor*
Kristoffersen, 2009[44]	Y- balanced Y-concealment	Y	Y	Y	Y	Y	N	Poor*
Briel, 2008[45]	Y- balanced Y-concealment	Y	Y	Y	Y	Y	Y	Good
Long, 2011[31]	Y- balanced U-concealment	Y	Y	Y	Y	Y	N	Poor*
Burkhardt, 2010[27]	Y balanced Y-concealment	Y	Y	Y	Y	Y	Y	Good
Stolz, 2007[46]	Y- balanced U-concealment	Y	Y	Y	Y	Y	N	Poor*
Christ-Crain, 2006[47]	Y- balanced Y-concealment	Y	Y	Y	Y	Y	Y	Good

Y: Yes; N: No; U: Unknown

*Overall study rating was poor due to >5% of patients excluded from analyses as detailed below.

Antibiotic Use

The results consistently demonstrated reduction in antibiotic usage, with regard to duration, prescription rates, and total exposure (Table 15).

Antibiotic duration was reported in all studies except for one.[46] The duration of antibiotic therapy was reduced with procalcitonin-guided therapy in six of the seven studies, and the absolute reduction ranged from -1.0 to -7.1 days, with a relative reduction of -12.7 to -55 percent. Only one study[27] reported an absolute increase in antibiotic duration of 0.1 days with a relative increase of 1.3 percent. The absolute reduction was statistically significant in four of the five studies in which p values were either reported or calculated.

Antibiotic prescription rate was reported in all eight studies.[27, 31, 43-48] An absolute reduction in antibiotic prescription rate was demonstrated with procalcitonin-guided therapy in seven of the eight studies. The absolute reduction in prescription rates ranged from -1.8 to -72 percent, and the reductions were statistically significant in all seven studies, with five being highly statistically significant. Only one study[44] reported an absolute increase in prescription rate by 6.0 percent, which was not statistically significant.

Four studies[31, 46-48] reported on total antibiotic exposure, which accounted for the use of multiple agents, as well as duration of therapy. Two studies[47, 48] reported total exposure per 1,000 patient-days with relative reductions of 0.52 and 0.49, which were both highly statistically significant. One study[46] reported an absolute reduction of -31.5 percent, which was highly statistically significant. One study[31] reported a statistically significant relative risk of 0.55, but no additional details were given.

Mortality

Overall, mortality results were consistent and did not suggest higher mortality rates with procalcitonin-guided therapy as compared to the control arm (Table 16). Mortality rates in patients in the control arm ranged from 0 to 13.2 percent. The absolute differences between the procalcitonin and control arms ranged from -3.6 to 1.0 percent. One study[47] reported higher mortality rates in both the procalcitonin-guided therapy and control groups which appear to be due to disease-related mortality.

Six studies[27, 31, 43-45, 48] reported 28-day mortality, and only one study[48] reported a reduction in mortality with procalcitonin-guided therapy by -0.1 percent. The other five studies[27, 31, 43-45] reported absolute differences ranging from 0 to 1.0 percent. None of the differences in 28-day mortality were statistically significant.

One study[47] reported 6-week mortality with an absolute reduction in mortality of 1.3 percent. One study [46]reported 6-month mortality with an absolute reduction in mortality of 3.6 percent. None of the 6-week or 6-month absolute reductions in mortality rate were statistically significant.

Table 15. Procalcitonin-guided antibiotic initiation and/or discontinuation in patients with respiratory tract infections—outcomes related to antibiotic usage

	Author, year	n	PCT	Control	Absolute Difference PCT-CTRL (95% CI)	p value	Relative Difference PCT-CTRL (95% CI)	p value
ABT Duration (days)	Schuetz, 2009[43]	1359	5.7	8.7	-3.0	--	-34.8% (-40.3 to -28.7)	--
	Christ-Crain, 2004[48]	243	10.9	12.8	-1.9 (-3.1 to -0.7)	0.002	-14.8%	--
	Kristoffersen, 2009[44]	210	5.1	6.8	-1.7	--	-25%	0.007
	Briel, 2008[45]	458	6.2	7.1	-1.0 (-1.7 to -0.4)	<0.05	-12.7%	--
	Long, 2011[31]	162	5[†]	7[†]	-2.0	<0.001	-28.6%	--
	Burkhardt, 2010[27]	550	7.8	7.7	0.1 (-0.7 to 0.9)	0.8	1.3%	--
	Christ-Crain, 2006[47]	302	5.8	12.9	-7.1(-8.4 to -5.8)	<0.0001	-55.0%	--
Antibiotic Prescription Rate (%)	Schuetz, 2009[43]	1359	506/671 (75.4%)	603/688 (87.6%)	-12.2% (-16.3 to -8.1)	<0.05	--	--
	Christ-Crain, 2004[48]	243	55/124 (44.4%)	99/119 (83.2%)	-38.8% (-49.9 to -27.8)	<0.0001	--	--
	Kristoffersen, 2009[44]	210	88/103 (85.4%)	85/107 (79.4%)	6.0% (-4.3 to 16.2)	0.25	--	--
	Briel, 2008[45]	458	58/232 (25.0%)	219/226 (96.9%)	-72% (-78 to -66)	<0.05	--	--
	Long, 2011[31]	162	NR (84.4%)	NR (97.5%)	-13.1%	0.004	--	--
	Stolz, 2007[46]	208	41/102 (40.2%)	76/106 (71.7%)	-31.5% (-44.3 to -18.7)	<0.0001	--	--
	Christ-Crain, 2006[47]	302	128/151 (84.8%)	149/151 (98.79%)	-13.9% (-19.9 to -7.9)	<0.0001	--	--
	Burkhardt, 2010[27]	550	84/275 (30.5%)	89/275 (32.4%)	-1.8% (-9.6 to 5.9)	0.701	--	--
Total ABT exposure	Stolz, 2007[46]	208	NR	NR	-31.5% (18.7 to 44.3)	<0.0001	44% (0.27 to 0.57)	<0.0001
	Long, 2011[31]	162	NR	NR	NR	--	0.55[*] (0.51 to 0.60)	0.003
	Christ-Crain, 2006[47]	302	136**	323**	--	--	0.52 (0.48 to 0.55)[∞]	<0.001
	Christ-Crain, 2004[48]	243	332**	661**	--	--	0.49 (0.44 to 0.55)[‡∞]	<0.0001

ABT: antibiotic; CI: confidence interval; CTRL: control; PCT: procalcitonin; NR: not reported
*Relative Risk; **mean per 1,000 days of followup; [†]median values; [‡]adjusted for potential confounding and possible cluster effects; [∞]rate ratios

Table 16. Procalcitonin-guided antibiotic initiation and/or discontinuation in patients with respiratory tract infections—mortality

Outcome	Author, year	N	PCT	Control	Absolute Difference PCT-CTRL (95% CI)	p value
6-month mortality	Stolz, 2007[46]	208	5/102 (4.9%)	9/106 (8.5%)	-3.6% (-10.3 to 3.2%)	0.30
6-week mortality	Christ-Crain, 2006[47]	302	18/151 (11.9%)	20/151 (13.2%)	-1.3% (-8.8 to 6.2)	0.73
≤28-day mortality	Christ-Crain, 2004[48]	243	4/124(3.2%)	4/119 (3.4%)	-0.1% (-4.6 to 4.4)	0.95
	Schuetz, 2009 (30-day)[43]	1359	34/671(5.1%)	33/688(4.8%)	0.3% (-2.1 to 2.5)	0.82
	Briel, 2008[45]	458	0/231(0%)	1/224 (0.4%)	-0.4% (-1.3 to 0.4)	0.31
	Burkhardt, 2010[27]	550	0/275(0%)	0/275 (0%)	0	--
	Kristoffersen, 2009[44]	210	2/103(1.9%)	1/107 (0.9%)	1.0% (-2.2 to 4.2)	0.54
	Long, 2011[31]	162	0/81 (0%)	0/81 (0%)	0	--

CI: confidence interval; CTRL: control; PCT: procalcitonin
All studies performed intention-to-treat analyses

Morbidity

Overall, studies did not suggest an increase in-hospital LOS, ICU admission rates, antibiotic adverse events, or days of restricted activity with procalcitonin-guided therapy (Table 17).

Five studies[43-47] reported hospital LOS. Hospital LOS was reduced with procalcitonin-guided therapy in four of five studies with an absolute reduction in days ranging from -0.5 to -1. The differences were not statistically significant in any of the studies. One study[43] reported an absolute increase in LOS by 0.2 days.

Five studies[43-47] reported need for ICU admission. ICU admission rates were reduced with procalcitonin-guided therapy with absolute reductions ranging from -0.7 to -2.5 percent. None of the reductions in ICU admissions was statistically significant.

Three studies[27, 43, 45] evaluated antibiotic adverse events. The definition of antibiotic adverse events differed with each study. One study[27] reported, but did not define, antibiotic adverse events. A second study[43] included diarrhea, nausea, and rash, and the third study[45] included abdominal pain, nausea, vomiting, diarrhea, and skin rash as adverse antibiotic events. Two studies[27, 43] reported absolute differences in adverse event rates of 2.8 and -8.2 percent, but neither of these differences was statistically significant. A third study[45] reported mean number of days with adverse events as 2.3 days in the control group and 3.6 days in the procalcitonin-guided therapy group. The absolute difference between the groups was -1.1 days, which was statistically significant.

Two studies[27, 45] evaluated days of restricted activity. It was defined as number of self assessed impaired days of daily work and/or leisure activities within the first 14 days of illness. The absolute differences were -0.25 and 0.2 days and none were statistically significant.

Adverse Events of Antibiotic Therapy

For the respiratory tract infection studies, three studies[27, 43, 45] reported on adverse antibiotic effects. Schuetz et al.,[43] reported a significant difference in the proportion of patients with an antibiotic adverse events (19.8 % versus 28.1 %, difference – 8.2 %, 95% CI: -12.7, -3.7) that favored PCT-guided therapy. Briel et al.,[45] reported that there was a decrease in the days with adverse antibiotic effects in the PCT guided arm (2.3±4.6 versus 3.6±6.1, difference -1.1, 95% CI: -2.1, -0.1) that was mainly due to a lower incidence of antibiotic-associated diarrhea. Burkhardt et al.,[27] reported a lower incidence of antibiotic adverse effects (11/275 versus 16/275, $p = 0.331$) and fewer days with antibiotic adverse effects (5.6±2.2 versus 6.1±3.7, $p = 0.94$), but neither difference was statistically significant.

GRADE Evidence

Methods for grading strength of evidence developed for the AHRQ Effective Health Care Program[25] were applied to this body of literature. An important consideration in grading the literature was the quality ratings of the studies. Four[27, 43, 45, 47] of the eight studies[27, 31, 43-48] received a good quality rating, but the other four studies[31, 44, 46, 48] received a poor quality rating due to lack of intention-to-treat analysis (Table 18). The studies receiving a poor rating represent 23.6 percent of the total patients in these studies (823 of 3,492 patients).

Overall, the grade of the strength of evidence was high, and the data demonstrate a reduction in antibiotic duration and prescription rates which were reported in the majority of studies. The risk of bias was low and the evidence was consistent, direct, and precise for these antibiotic

outcomes. The reduction in antibiotic duration ranged from -1.0 to -7.1 days and from -1.8 to -72 percent for antibiotic prescription rates.

The overall grade of the evidence for total antibiotic exposure was moderate. Total antibiotic exposure was only reported by four studies,[31, 46-48] but three of these studies[31, 46, 48] were given a poor quality rating. In general, total antibiotic exposure is difficult to calculate, and the data for this outcome was reported differently in these studies. Two studies[31, 34] reported relative risk ratios without providing additional details, and two studies[47, 48] reported means per 1,000 days of followup. Because the majority of these studies were poor quality and the reporting differed, the data was graded to have a moderate risk of bias. The evidence was graded to be consistent, direct, and precise. All of the absolute or relative reductions reported in total antibiotic exposure were statistically significant, and overall, the data suggest a reduction in total antibiotic exposure.

Table 17. Procalcitonin-guided antibiotic initiation and/or discontinuation in patients with respiratory tract infections–morbidity

Outcome	Author, year	N	PCT	Control	Absolute Difference PCT-CTRL (95% CI)	p value
LOS (days)	Schuetz, 2009[43]	1359	9.4	9.2	0.2	--
	Christ-Crain, 2004[48]	224	10.7 ± 8.9	11.2 ± 10.6	-0.5 (-3.0 to 2.0)	0.69
	Kristoffersen, 2009[44]	210	5.9	6.7	-0.8	0.22
	Stolz, 2007[46]	208	9	10	-1	0.96
	Christ-Crain, 2006[47]	302	12.0 ± 9.1	13.0 ±9.0	-1 (-3.0 to 1.0)	0.34
ICU Admission (%)	Schuetz, 2009[43]	1359	43/671 (6.4%)	60/688 (8.7%)	-2.3% (-5.2 to 0.4)	0.12
	Christ-Crain, 2004[48]	224	5/124 (4.0%)	6/119 (5.0%)	-1.0% (-6.2 to 4.2)	0.71
	Kristoffersen, 2009[44]	210	7/103 (6.8%)	5/107 (4.7%)	-2.1% (-4.2 to 8.4)	0.51
	Stolz, 2007[46]	208	8/102 (7.8%)	11/106 (10.4%)	-2.5% (-10.3 to 5.3)	0.53
	Christ-Crain, 2006[47]	302	20/151 (13.2%)	21/151 (13.94%)	-0.7% (-8.4 to 7.1)	0.87
Antibiotic Adverse Events	Schuetz, 2009[43]†	1359	133/671 (19.8%)	193/688 (28.1%)	-8.2% (-12.7 to -3.7)	--
	Briel, 2008[45]‡	458	2.3 days	3.6 days	-1.1 days(-2.1 to -0.1)	<0.05
	Burkhardt, 2010[27]∞	550	11 /59 (18.6%)	16/101 (15.8%)	2.8% (-9.4 to 15.0)	0.65
Restricted Activity (days)*	Briel, 2008[45]	458	8.7±3.9	8.6±3.9	0.2 (-0.4 to 0.9)	>0.05
	Burkhardt, 2010[27]	550	9.1	8.8	0.25 (-0.52 to 1.03)	>0.05

CI: confidence interval; CTRL: control; ICU: intensive care unit; LOS: length of stay; PCT: procalcitonin
†Nausea, diarrhea, and rash; ‡Abdominal pain, diarrhea, nausea, vomiting, and rash; ∞Antibiotic adverse events not defined;
*Days during the first 14 days of illness that work and leisure activities were restricted

Table 18. Procalcitonin-guided antibiotic initiation and/or discontinuation in patients with respiratory tract infections–GRADE evidence table

Outcome	No of Studies (subjects)	Risk of Bias	Consistency	Directness	Precision	Overall GRADE
Antibiotic duration	7 RCTs (n=3284)[27, 31, 43-45, 47, 48]	Low	Consistent	Direct	Precise	High
Antibiotic Prescription Rate	8 RCTs (n=3492) [27, 31, 43-48]	Low	Consistent	Direct	Precise	High
Total Antibiotic Exposure	4 RCTs (n=915)[31, 46-48]	Medium	Consistent	Direct	Precise	Moderate
Mortality	8 RCTs (n=3492) [27, 31, 43-48]	Low	Consistent	Direct	Precise	Moderate
Hospital length of stay	5 RCTs (n=2303)[43, 44, 46-48]	Medium	Consistent	Direct	Precise	Moderate
ICU admission rates	5 RCTs (n=2303) [43, 44, 46-48]	Medium	Consistent	Direct	Precise	Moderate
Antibiotic Adverse Events	3 RCTs (n=2367) [27, 43, 45]	Low	Inconsistent	Direct	Imprecise	Insufficient

ICU: intensive care unit; RCT: randomized controlled trial

The mortality data was given a moderate overall grade. All eight studies[27, 31, 43-48] reported mortality rates. The absolute difference in 28-day mortality rates ranged from -0.3 to 0.4 percent, but none of these differences was statistically significant. The data were graded to have a low risk of bias and be consistent, direct, and precise. Overall grade was moderate, largely due to the low baseline mortality rates in patients with respiratory tract infections; additional evidence would be unlikely to change the results.

The overall grade of the evidence for hospital LOS and ICU admission rates was moderate. Five studies[43-47] reported these outcomes. The data were graded to have a M risk of bias because three[44, 46, 48] of the five studies[43-47] were given a poor quality rating. The absolute differences in LOS and ICU admission rates ranged from -1 to 0.2 days and -2.5 to -0.7 percent, respectively, but none of these differences was statistically significant. Thus, the present evidence does not suggest an increase in hospital LOS or ICU admission rates.

The current data does not permit a conclusion regarding the effects of procalcitonin-guided therapy on antibiotic adverse events, and the overall grade was insufficient. Three studies[27, 43, 45] with a low risk of bias reported this outcome; however, the data were inconsistent and imprecise. Two studies reported percentages with absolute differences of -8.2 percent[43] and 2.8 percent,[27] and one study[45] reported an absolute difference of -1.1 days that was statistically significant. The data for this outcome are limited, and therefore, no conclusions can be drawn on the impact of procalcitonin-guided therapy on antibiotic adverse events.

Neonatal Sepsis

Study Characteristics

There was only one RCT[49] of procalcitonin-guided antibiotic therapy for suspected early onset neonatal sepsis that included 101 neonates, both arms stratified by the likelihood of infection (Table 19). Neonatal sepsis was suspected on the basis of risk factors, as well as clinical signs and symptoms including apnea, tachycardia or bradycardia, hypotension, seizures, “floppiness,” irritability, or ileus, and standard laboratory tests, including C-reactive protein and immature leukocyte ratio. Procalcitonin values used to decide on antibiotic initiation and discontinuation were based on a nomogram based on the time since birth, since procalcitonin is elevated in the first three days of life due to birth stress. Antibiotic therapy in the standard group was based on the attending physician’s assessment. The trial was designed to have 90 percent power to detect a 30 percent difference in antibiotic duration. The primary outcomes for this study were the duration of antibiotics and the proportion of neonates on antibiotics longer than 72 hours. Secondary outcomes were recurrence of infection and mortality, but the study was not powered to detect differences in these outcomes. Followup duration was 21 days.

Study Quality

The quality rating for the one study is described in Table 20. In this study[49] of neonatal sepsis, neonates in the two arms were comparable at baseline. Details of allocation concealment were described. Analysis was appropriate, but again, this study was not powered to detect differences in morbidity or mortality.

Table 19. Summary of characteristics for one trial included in the analysis of procalcitonin-guided antibiotic therapy in neonatal sepsis

Author, year, country	Disease state	N	PCT for ABT initiation	PCT for ABT discontinuation	Other PCT-guided interventions	Study duration	Predefined endpoints
Stocker, 2010, Switzerland[49]	Suspected early onset neonatal sepsis	PCT 60 Ctrl 61	PCT according to nomogram based on age since birth, hours	PCT according to nomogram based on age since birth, hours	NA	30 days	Primary outcome ABTs ≥72 hours, duration of ABTs Secondary outcomes, Survival, recurrence of infection

ABT: antibiotic; CI: confidence interval; PCT: procalcitonin; NA: not applicable

Table 20. Procalcitonin-guided antibiotic therapy in neonatal sepsis–study quality

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal followup loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Stocker, 2010[49]	Y	Y	Y	Y	Y	Y	Y	Good

Antibiotic Use

Outcomes related to antibiotic usage are summarized in Table 21. The duration of antibiotic use was significantly decreased overall by 22.4 hours (24 percent reduction), with the greatest differences seen for the 80 to 85 percent of neonates who had possible infection or were unlikely to have infection and little difference for the small proportion of neonates with proven of probable infection. The proportion of neonates on antibiotics for 72 or more hours was significantly reduced overall by 27 percent, again with the difference seen only for neonates with possible sepsis (38 percent reduction) or neonates unlikely to have infection (27 percent reduction).

Table 21. Procalcitonin-guided antibiotic therapy in neonatal sepsis in the study by Stocker et al., 2010[49] (n=121)–outcomes related to antibiotic usage

Outcome	Patient subgroup	PCT	Control	Difference PCT-CTRL (95%)	p value
ABTs ≥72 hours (%)	All neonates	33/60 (55%)	50/61 (82%)	-27.0 (-42.8 to -11.1)	0.002
	Infection proven/probably	9/9 (100%)	12/12 (100%)	0% (0 to 0)	NA
	Infection possible	13/21 (61.9%)	19/19 (100%)	-38.1 (-58.9 to -17.3)	0.003
	Infection unlikely	11/30 (36.7%)	19/30 (63.3%)	-26.6 (-51.1 to -2.3)	0.038
ABT Duration, hours	All neonates	79.1	101.5	-22.4	0.012
	Infection proven/probably	177.8	170.8	-7	NSS
	Infection possible	83.4	111.5	-28.1	< 0.001
	Infection unlikely	46.5	67.4	-20.9	0.001

ABT: antibiotic; CI: confidence interval; CTRL: control; PCT: procalcitonin; NA: not applicable

Mortality

Only in-hospital mortality was reported by Stocker et al.,[49] No deaths occurred in either study arm (Table 22).

Morbidity

There was a small but statistically insignificant reduction in the rate of recurrence of infection in the study by Stocker et al.,[49] i.e., the neonates treated with antibiotics for 120 or more hours (Table 22).

Table 22. Mortality and morbidity data for early onset neonatal sepsis for Stocker et al., 2010[49] (n=121)

Outcome	PCT	Control	Difference PCT-CTRL (95% CI)	p value
Mortality (in-hospital)	0%	0%	0 (0 to 0)	NA
Morbidity (recurrence of infection)	32%	39%	- 7	0.45

CI: confidence interval; CTRL: control; PCT: procalcitonin; NA: not applicable

Adverse Events of Antibiotic Therapy

The study by Stocker et al.,[49] did not report adverse events of antibiotic therapy.

GRADE Evidence

The strength of evidence was judged to be moderate that use of procalcitonin guidance reduces the use of antibiotic therapy for suspected neonatal sepsis. This good quality study was judged to have low risk of bias. That finding that significant reduction in duration of antibiotic therapy was observed in the subgroups with possible or unlikely infection, rather than those with probable infection, lends face validity to the results. Consistency was rated as unknown (single study). The evidence was direct and sufficiently precise to conclude that procalcitonin guidance reduces antibiotic use. This small study[49] (n=121) was not powered to detect mortality or morbidity outcomes, and strength of evidence was judged insufficient to make conclusions on mortality and morbidity.

Fever of Unknown Source (children aged 1-36 months)

Study Characteristics

There was only one RCT[26] of procalcitonin-guided antibiotic therapy for fever of unknown source in children 1-36 months of age (Table 23). Three-hundred and eighty-four children were enrolled. Sixty-two (16 percent) were subsequently diagnosed with a serious bacterial infection and 10 (2.6 percent) were found to be neutropenic. Procalcitonin values used to decide on antibiotic initiation and discontinuation were based on a nomogram based on the time since birth, since procalcitonin is elevated in the first three days of life due to birth stress. Antibiotic therapy in the standard group was based on the attending physician's assessment. The primary outcome for this study[26] was the antibiotic prescription rate. The secondary outcome was difference in hospitalization rate. Sample size needed was calculated based on rates of antibiotic prescription. Followup duration for this study was 30 days.

Table 23. Summary of characteristics for one trial included in the analysis of procalcitonin-guided antibiotic therapy in children (aged 1-36 months) with fever of unknown source

Author, year, country	Disease state	N	PCT for ABT initiation	PCT for ABT discontinuation	Other PCT-guided interventions	Study duration	Predefined endpoints
Manzano, 2010, Canada[26]	Fever without a source, children 1-36 months of age	PCT 192 Ctrl 192	PCT < 0.5, infection unlikely; PCT ≥ 0.5, moderate risk; PCT ≥ 2.0, high-risk			30 days	Primary outcome ABT prescription rate Secondary outcomes, Hospitalization, additional studies

ABT: antibiotic; PCT: procalcitonin

Study Quality

The quality rating for the one study is described in Table 24. The two study arms were comparable, but more than 10 percent of patients in each arm were excluded from the analysis

Table 24. Procalcitonin-guided antibiotic therapy in children (aged 1-36 months) with fever of unknown source–study quality

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal followup loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Manzano, 2010[26]	Y	Y	Y	Y	Y	Y	N	Poor

(insufficient blood for assay) and no strategy to adjust for missing data was performed. Details of allocation concealment were described. This study was not powered to detect differences for the morbidity and mortality outcomes.

Antibiotic Use

There were no differences in the antibiotic prescription rates or hospitalization rate, although rates were low for both arms with only one-quarter of children being hospitalized and receiving antibiotics[26] (Table 25).

Table 25. Procalcitonin-guided antibiotic therapy in children (aged 1-36 months) with fever of unknown source–outcomes related to antibiotic usage in the study by Manzano et al., 2010[26] (n=384)

Outcome	Subgroups	PCT	Control	Difference PCT-CTRL (95% CI)	p value
Antibiotic prescription rate (%)	All children	48/192 (25%)	54/192 (28.0%)	-3.1 (-12.0 to 5.7)	0.49
	No SBI or neutropenia	14/158 (9%)	16/154 (10%)	-1.5 (-8.1 to -5.0)	0.65

CI: confidence interval; CTRL: control; PCT: procalcitonin

Mortality

Only in-hospital mortality was reported, and mortality was 0 percent in both arms (Table 26).

Morbidity

In this single RCT,[26] overall rates of hospitalization were relatively low, with only one quarter of the children being admitted (Table 26). This rate was even lower for those children who did not have a serious bacterial infection or neutropenia. There were no significant differences in the proportion of infants who were started on empiric antibiotic therapy, all children, and the subgroup of children without a serious blood infection or neutropenia. Overall, procalcitonin measurement had no impact on antibiotic use or hospitalization in this population.

Table 26. Mortality and morbidity data for fever of unknown source in children 1-36 months of age for Manzano et al., 2010[26] (n=384)

Outcome	Sub group	PCT	Control	Difference PCT-CTRL (95% CI)	p value
Mortality	All children	0%	0%	0 (0 to 0)	NA
Morbidity (hospitalization rate)	All children	50/192 (26%)	48/192 (25%)	1 (-8 to 10)	0.81
	No SBI or neutropenia	16/158 (10%)	11/154 (7%)	3 (-3 to 10)	0.34

CI: confidence interval; CTRL: control; PCT: procalcitonin; NA: not applicable; SBI: serious blood infection

Adverse Events of Antibiotic Therapy

The study by Manzano et al.,[26] did not report adverse events of antibiotic therapy.

GRADE Evidence

The strength of evidence was judged insufficient to draw conclusions on outcome of procalcitonin-guided antibiotic therapy for fever of unknown source in children 1-36 months of age. This RCT[26] (n=384) reported no significant results.

Preemptive Postoperative Antibiotic Therapy

There was only one study[50] that evaluated the value of monitoring procalcitonin post-operatively in 250 consecutive patients undergoing colorectal surgery (Table 27). Procalcitonin levels were used to identify patients at risk for local and systemic infectious complications who might benefit from antibiotic therapy (ceftriaxone) given as a prophylaxis or preemptive therapy in patients without other clinical evidence of infection. Of 230 patients with low postoperative procalcitonin, only 16 local wound infections (7.0 percent) not requiring surgery or antibiotics occurred and systemic infection occurred in only 4 patients (1.7 percent). The negative predictive value of procalcitonin for systemic infections requiring antibiotics was 98.3 percent and 93.0 percent for local wound infections that resolved without antibiotics or re-operation.

The other 20 patients had two or more procalcitonin measurements greater than 1.5 ng/mL in the first three postoperative days, and these patients were randomized to receive IV ceftriaxone or standard management. The 10 patients in the control arm of the randomized portion of this study were treated when signs of infection became evident. Patients were followed for the duration of their hospitalization.

Table 27. Summary of characteristics for one trial[50] included in the analysis of procalcitonin-guided preemptive postoperative antibiotic therapy

Author, year, country	Disease state	N	PCT for ABT initiation	PCT for ABT discontinuation	Other PCT-guided interventions	Study duration	Predefined endpoints
Chromik, 2005, Germany[50]	Colorectal surgery patients	250 patients overall 230 patients with low 20 with elevated PCT post-op;	PCT > 1.5 post-op randomized to receive pre-emptive ABTs or standard care			Not defined	Primary outcome Local and systemic infectious complications Secondary outcomes, Mortality, LOS, duration of ABTs

ABT: antibiotic; LOS: length of stay; PCT: procalcitonin; Postop: postoperative

Study Quality

The quality rating for the one study is described in Table 28. The patients in the two arms of the interventional part of this trial[50] were comparable at baseline. Details of allocation concealment were described. Analysis was appropriate, but again, this study was not powered to detect differences in morbidity or mortality.

Table 28. Procalcitonin-guided preemptive postoperative antibiotic therapy–study quality

Author, year	Assembled comparable groups	Maintained comparable groups	Minimal followup loss	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Chromik, 2005[50]	Y	Y	Y	Y	Y	Y	Y	Good

Antibiotic Use

Although all patients in the preemptive ceftriaxone arm received this antibiotic for a period of time (range: 4-11 days), the duration of antibiotic therapy was lower by 3.5 days in this group compared to the control group[50] (Table 29). This difference, however, did not reach statistical significance.

Table 29. Procalcitonin-guided preemptive postoperative antibiotic therapy–outcomes related to antibiotic usage in the study by Chromik et al., 2005.[50]

N	Outcome	PCT	Control	Difference PCT-CTRL (95% CI)	p value
20	ABT duration (days)	5.5	9	-3.5	0.27

ABT: antibiotic; CI: confidence interval; CTRL: control; PCT: procalcitonin

Mortality

Mortality was 20 percent higher in the control arm (Table 30). This was not statistically significant.

Morbidity

Patients in the control arm of the study had a more prolonged LOS (12 days longer), and the difference approached statistical significance (Table 30). The control arm also had a higher incidence of local and systemic infection. Patients in the control arm were significantly more likely to have SIRS or sepsis and require vasopressors for shock.

Table 30. Procalcitonin-guided preemptive postoperative antibiotic therapy–mortality and morbidity data for Chromik et al., 2005[50] (n=20)

	Outcome	PCT	Control	Difference PCT-CTRL (95% CI)	p value
Mortality		1/10 (10%)	3/10 (30%)	-20 (-54.0 to 14.0)	0.07
Morbidity	Hospital LOS (days)	18	30	-12	0.057
	Local wound infection (%)	1/10	2/10	-10 (-41.0 TO 21.0)	0.53
	Systemic infection (%)	3/10	7/10	-40.0 (-80.2 to 0.2)	0.07
	Sepsis/SIRS (%)	2/10	8/10	-60.0 (-95.1 to -24.9)	0.007

CI: confidence interval; CTRL: control; LOS: length of stay; PCT: procalcitonin; SIRS: Systemic Inflammatory Response Syndrome

Adverse Events of Antibiotic Therapy

The study by Chromik et al.,[50] did not report adverse events of antibiotic therapy.

GRADE Evidence

This single RCT[50] suggests procalcitonin levels can identify postoperative patients who are at risk for wound and systemic infection who will benefit from prophylaxis or preemptive antibiotic therapy. Not only did procalcitonin identify a group of patient for whom antibiotics can prevent significant morbidity and mortality, but low procalcitonin levels accurately identified a low-risk

group for whom antibiotics were unnecessary. The use of procalcitonin helped limit the use of antibiotic prophylaxis to 8 percent of the entire postsurgical population. Further studies of this strategy are needed to confirm this result. The evidence on procalcitonin-guided preemptive post operative antibiotic therapy was deemed insufficient to be graded as only one small study (n=20) was available for peer review.

Summary and Discussion

Summary of the Main Findings

There were 18 randomized, controlled trials that compared procalcitonin guidance to use of clinical criteria to manage antibiotic therapy in patients with known or suspected infection, or at risk of infection. The evidence addressed five patient populations: 1) seriously ill adult patients in the intensive care unit (ICU), including patients with ventilator-associated pneumonia (VAP) and those critically ill with suspected bacterial infections, severe sepsis, and septic shock; 2) patients with symptoms and signs of various respiratory tract infections; 3) neonates with suspected sepsis; 4) children between 1-36 months of age with fever of unknown etiology; and 5) postoperative patients without clinical evidence of infection.

Intensive Care Unit Patients

Five trials[32-36] (N=938) addressed procalcitonin-guided discontinuation of antibiotic therapy. Strength of evidence was judged to be high that procalcitonin guidance reduces antibiotic usage. The absolute difference in duration of antibiotic use, the measure that was reported by all five studies,[32-36] ranged from -1.7 to -5 days, with relative reductions that ranged from 21 to 38 percent. There is moderate evidence that procalcitonin-guided antibiotic discontinuation does not increase mortality or morbidity as indicated by ICU length of stay. However, a limitation of the evidence is the very large number of study participants that would be required to narrow the confidence interval for estimated mortality.

There is moderate evidence that procalcitonin-guided intensification of antibiotic therapy that broadens the spectrum of bacterial coverage does not improve outcomes in critically ill patients, and in fact, may have adverse consequences. The large (n=1,200), high-quality trial by Jensen et al.,[28] found greater duration and increased total exposure to antibiotics with procalcitonin guidance. There was also increased morbidity, including a 1 day increase (p=0.004) in ICU length of stay (LOS), a significant increase in days on mechanical ventilation, and increased days with abnormal renal function. A second fair quality study[37] (n=72) was judged to be too small to be informative.

Reduced antibiotic usage should decrease the number of allergic reactions, antibiotic-related side effects and toxicities, and superinfections, including the emergence of multi-drug resistant (MDR) organism and *Clostridium difficile*. Only 1 study[32] reported on the emergence of MDR organisms and superinfections.

Respiratory Tract Infection

Eight trials[27, 31, 43-48] (N=3,492) addressed initiation and/or discontinuation of antibiotics in patients with acute upper and lower respiratory tract infection. Settings included primary care clinics, emergency department (ED), and hospital wards. There is high strength of evidence that procalcitonin guidance reduces antibiotic duration and prescription rates; and moderate evidence of reduction in total antibiotic exposure. Absolute reduction in duration of antibiotic therapy ranged from 1 to 7 days with relative reductions ranging from -13 to -55 percent. Absolute reduction in prescription rates ranged from -2 to -7 percent with relative reductions ranging from

-1.8 to -72 percent. There was moderate evidence that procalcitonin guidance did not increase mortality, hospital length of stay, or ICU admission rates. However, a limitation of the evidence is the very large number of study participants that would be required to narrow the confidence interval for estimated mortality. There was insufficient evidence to judge effects on days of restricted activity or on antibiotic adverse events. Three studies[27, 43, 45] reported on adverse antibiotic effects, and there was a statistically significant reduction in the PCT-guided arm versus the control arm that was associated with reduced antibiotic usage. There was no consistency, however, on how adverse effects were defined and details on the types of adverse reactions were lacking. Only one study[45] reported that the reduction in adverse antibiotic adverse effects was mainly due to a reduction in diarrhea. A more uniform approach to evaluating and reporting adverse effects related to antibiotic usage would be useful in future studies.

Neonatal Sepsis

One good quality[49] study (n=121) provided moderate evidence that procalcitonin guidance reduces the use of antibiotic therapy for suspected early neonatal sepsis. The duration of antibiotic use was overall reduced by 22.4 hours (22.0 percent). Further, the proportion of neonates on antibiotics for longer than 72 hours was reduced by 27 percent. Greatest reductions were seen among neonates who were judged according to clinical criteria to have possible infection or unlikely to have infection as compared to those with proven or probable infection. Strength of evidence was judged insufficient to make conclusions on mortality and morbidity due to small study size.

Fever of Unknown Source in Children ages 1-36 Months

The strength of evidence was judged insufficient to draw conclusions on outcomes of procalcitonin-guided antibiotic therapy for fever of unknown source in children 1-36 months of age. One good quality randomized, controlled trial[26] (n=384) reported no significant results.

Postoperative Patients at Risk of Infection

The strength of evidence was judged insufficient to draw conclusions on outcomes of procalcitonin-guidance to determine preemptive antibiotic therapy for patients after colorectal surgery. The evidence consisted of one small (n=20) trial.[50]

Clinical Context and Applicability of Evidence for Decision Making

The diagnosis of sepsis is challenging because the clinical criteria for the diagnosis overlap with noninfectious causes of systemic inflammation, such as the systemic inflammatory response syndrome. Initiation of antibiotic therapy for sepsis is necessary even while the diagnostic evaluation is ongoing since delayed antibiotic therapy is associated with increased mortality.[14, 40, 51] A biomarker, such as procalcitonin, that improves decisions about initiating, discontinuing, or changing antibiotic therapy, could have substantial clinical benefits. This systematic review found that procalcitonin guidance reduces antibiotic usage for adult patients in both medical and surgical ICUs. Studies included patients who had comorbidities that are common in the ICU patients (e.g., cardiac disease, diabetes, chronic lung disease, cirrhosis,

chronic renal failure, cancer), and thus, the evidence from these studies are applicable to clinical practice in the ICU setting.

Respiratory tract infections contribute significantly to the problem of antibiotic misuse. Approximately 75 percent of all antibiotics prescribed in the ambulatory setting are for acute respiratory tract infections, but the vast majority of these infections are viral and do not benefit from antibiotic treatment.[52] Clinical and microbiological evaluations are neither sensitive nor specific to differentiate bacterial from viral respiratory tract infections. Because procalcitonin levels rise soon after the onset of a bacterial infection, procalcitonin can help to differentiate bacterial from viral infections. Our systematic review found that procalcitonin guidance for initiation and discontinuation of antibiotic therapy significantly reduced antibiotic prescription rates and duration in patients with acute respiratory tract infections, including acute exacerbations of chronic obstructive pulmonary disease (COPD), community acquired pneumonia (CAP) and acute bronchitis. In most of these studies, antibiotic therapy was encouraged if the procalcitonin level was greater than 0.25 ng/mL, because a bacterial infection was likely. Similarly antibiotic therapy was discouraged if procalcitonin level were less than 0.25 ng/mL because a bacterial infection was unlikely.

Certain populations, however, were excluded from one or more studies of procalcitonin guidance reviewed in this report. These groups might be considered high risk for increased morbidity and/or mortality with delayed initiation or shorter courses of antibiotic therapy, or may not have the same procalcitonin rise in response to infection due to their comorbidities. Thus, findings from this review should not be extrapolated to these high-risk groups, which include pregnant patients; patients with absolute neutropenia; and other immunocompromised populations (solid organ and stem-cell transplant recipients, patients with advanced HIV infection/AIDS). Although such patients were excluded in these studies, future studies may help to determine if procalcitonin-guided antibiotic therapy is beneficial in these groups, as well. Although febrile neutropenic patients are usually continued on antibiotics until the neutropenia resolves, the most recent guidelines suggest that patients can be switched to an oral fluoroquinolone when an infection has been adequately treated, and procalcitonin guidance could potentially be used in this context.[53] Of note, patients with chronic infections and infections where a longer duration of antibiotic therapy is standard of care, such as infective endocarditis, were also appropriately excluded from these studies.

Applicability to pediatric settings is a significant gap in the present evidence. Only two randomized, controlled trials[26, 49] reported on procalcitonin guidance in pediatric populations. One study[49] included neonates with suspected early sepsis. While antibiotic use was reduced, the trial was underpowered for morbidity and mortality outcomes. In fact, there were no mortality events in either arm of the study and only 21 of 121 neonates in the study had a probable or proven infection.[49] The second study[26] evaluated procalcitonin-guided antibiotic therapy in children ages 1-36 months presenting to the ED with fever of unknown etiology. No significant differences were observed for measures of antibiotic use, morbidity, or mortality with procalcitonin guidance. The evidence from this single study was judged insufficient to reach conclusions about the use of procalcitonin guidance in this setting. It is important to note that bacterial infections were uncommon in the study population. Only 25 percent of children were admitted to the hospital and about 27 percent received antibiotics overall. This rate was even lower, 10 and 9 percent respectively, if the children with neutropenia or a serious bacterial infection were excluded. There were no studies in children ages 3 to 18 years.

Ultimately, the value of procalcitonin-guided antibiotic therapy depends on the clinical benefits of reduced antibiotic use, which is difficult to quantify. Immediate consequences may include decrease in allergic reactions, drug toxicities, and frequency of *Clostridium difficile* infection. A major downstream effect of reducing antibiotic usage may be a lower probability of emergence of antibiotic-resistant strains. Antimicrobial resistance contributes to morbidity, mortality, and health care costs. Though infection control programs reduce transmission of resistant bacteria between patients, they do not affect development of resistance which occurs, in part, due to antibiotic overuse. There is some evidence that the development of resistance is more related to antibiotic treatment than transmission from patient to patient.[54, 55] There are several studies and indirect lines of evidence that suggest that control of antibiotic usage can reduce emergence of resistance, but the data are limited.[38] Reductions in antibiotic course duration have been associated with significant reductions in antibiotic adverse effects, *C. difficile* colitis, and superinfection with multidrug-resistant Gram-negative rods.[38-40]

In our systematic review, few studies reported on allergic and adverse events of antibiotic usage [27, 43, 45] and only one[35] reported on antibiotic resistance. The durability in reduction of antibiotic usage is not addressed in these trials which limits their applicability to clinical practice. The setting of a clinical trial, or highly visible introduction of a new practice, can have a halo effect on physician behavior so the present evidence does not address long-term impact of using procalcitonin guidance a in real-world clinical setting. Antibiotic stewardship programs are now recommended for all institutions and there are guidelines for how they should function.[56] Antibiotic stewardship programs are associated with reduced antibiotic usage and also decreased adverse effects of antibiotic therapy. The evidence in this review does not compare outcomes of using procalcitonin guidance versus antibiotic stewardship programs nor does it address whether addition of procalcitonin to an antibiotic stewardship programs improves outcomes. There is at least one report[57] that indicates the use of procalcitonin measurements may be used as part of an antibiotic stewardship program to decrease the duration of antibiotic therapy. Antibiotic stewardship activities are usually limited to the acute care hospital setting. Although it would be difficult or impractical for antibiotic stewardship programs to have active intervention in the outpatient setting, the use of procalcitonin might complement other types of outpatient programs, such as educational programs for physicians and patients aimed at reducing the use of antibiotics for respiratory tract infections.[52]

Discussion of Present Findings in Context of Other Systematic Reviews

We are aware of four systematic reviews[3, 19-21] that were published prior to our present review; the findings of our review are discussed in the context of these prior reviews. All of the previous reviews (including the present review) came to similar conclusions: procalcitonin-guided antibiotic decision making compared to clinical criteria-guided antibiotic decision making reduces antibiotic usage and is not associated with increased mortality or morbidity. We reviewed all published randomized, controlled trials of the use of procalcitonin-guided initiation or discontinuation of antibiotic therapy, as well as studies that used procalcitonin for other interventions in patients with infection and/or sepsis. A total of 18 randomized, controlled trials were included in our systematic review. As the most recent systematic review, ours is the only one that includes the large (n=1,200) high quality trial by Jensen et al.[28] The Jensen trial[28] is unique in showing that procalcitonin-guided intensification of antibiotic therapy to broaden the spectrum of bacterial coverage does not improve outcomes in critically ill patients, and in fact,

may have adverse consequences. Among all the systematic reviews, only ours distinguished between procalcitonin-guided antibiotic intensification therapy, in contrast to procalcitonin-guided antibiotic initiation or discontinuation therapy.

As Table 31 shows, our systematic review differs from previous systematic reviews in terms of number of studies included, scope of indications addressed, and how populations were

Table 31. Summary of systematic reviews

Author, year	Studies	N	Pediatric Patients?	Pooled Patient Groups (number of studies)	Boudama, 2010	Schroeder, 2009	Stolz, 2009	Nobre, 2008	Hochreiter, 2009	Svoboda, 2007	Jensen, 2011	Long, 2011	Burkhardt, 2010	Schuetz, 2009	Kristoffersen, 2009	Briel, 2008	Stolz, 2007	Christ-Crain, 2004	Christ-Crain, 2006	Stocker, 2010	Manzano, 2010	Chromik, 2005	Laiyos, 2009†	Long, 2009
Tang, 2008[3]	7	1,458	No	Adult ICU (3) and RTI (4)				X	X	X						X	X	X	X					
Kopterides, 2010[21]	7	1,131	Yes	ICU [adult (6) and neonates(1)]	X	X	X	X	X	X										X				
Agarwal, 2011[20]	6	1,476	No	Adult ICU (6)	X	X	X	X	X														X	
Scheutz, 2011[19]	14	4,467	No	Primary care (2)									X			X								
				ED (6)										X	X		X	X	X					X
				ICU (6)	X	X	X	X	X	X														
Current Review	18	4,955	Yes	Adult ICU discontinuation	X	X	X	X	X															
				Adult ICU intensification						X	X													
				Adult RTI								X	X	X	X	X	X	X	X					
				Neonates																X				
				Children, 1-36 months																	X			
				Postop patients																		X		

ICU: intensive care unit; ED: emergency department; RTI: respiratory tract infection
† Published only as an abstract

grouped for clinical relevance. The number of trials included in previous systematic reviews ranged from seven trials[3, 20, 21] to 14 trials.[19] While the three systematic reviews[3, 20, 21] that each included seven studies overlapped to a large degree, none included the same studies. Agarwal and Schwartz included one published abstract[58] not included in any other systematic review. We did not include the published abstract by Layios[58] in our review, since it was not possible to assess study quality from an abstract. Tang[3] included patients in ICUs and patients with respiratory tract infections, but did not analyze the data from each population separately. Kopterides[21] focused on studies in the ICU population but their meta-analysis of antibiotic usage outcomes pooled data from neonatal population with the adult population. A strength of the Scheutz review[19] was separate meta-analyses of mortality based on acuity of illness (primary care, ED, and ICU patients), as well as a meta-analysis for the total population. The authors concluded that procalcitonin guidance reduces antibiotic duration in primary care, ED, and ICU patients, and reduces prescription rates only in lower acuity primary care and ED patients. The Scheutz review included the 2009 study by Long,[59] whereas we had access to an overlapping, but more recent report of this study.[31]

A strength of the present review is that it addresses pediatric populations separately from adult patients. In addition, it also recognizes that there are distinct patient groups within the pediatric population stratified by age. In our review, we separately grouped neonates and children ages 1-36 months, each represented by a single study. There were no studies in children ages 3 years to 18 years.

Limitations of Present Review

A challenging aspect of this review was appraising the strength of evidence that procalcitonin-guided therapy did not result in any increased morbidity or mortality in the ICU and respiratory tract infection populations. A limitation of the available evidence is that a very large sample size would be required to narrow the confidence interval for estimated mortality. In grading the strength of evidence on mortality outcomes, we adopted a qualitative noninferiority approach that incorporated assumptions about the likelihood that larger numbers of subjects would show a greater adverse effect given the baseline mortality risk in the relevant populations.

Our systematic review compared procalcitonin guidance to antibiotic therapy based on usual clinical criteria, algorithms, or guidelines. In view of the present emphasis on the overuse of antibiotics, other interventions to reduce antibiotic use, such as institution of antibiotic stewardship programs and implementation of practice guidelines in institutional settings, may have been more robust comparators by which to assess the outcomes of procalcitonin guidance. A limitation of our review is that we did not systematically seek evidence comparing procalcitonin guidance to antibiotic stewardship programs or other programs aimed at reducing antibiotic use. We also did not assess studies that have implemented procalcitonin-guided antibiotic therapy into an antibiotic stewardship program.

Future Research

Summary of Weaknesses or Gaps in the Evidence

This systematic review compared outcomes of procalcitonin guidance compared to clinical criteria alone to initiate, discontinue or intensify antibiotic therapy. We identified five gaps in the

evidence related to specific populations or comparators. We also identified methodologic weaknesses that were common across the studies and bodies of evidence reviewed in this report.

Research Gap #1: What are the outcomes of procalcitonin guidance in subgroups of patients who are immunocompromised?

Patients with certain conditions were excluded from these studies, including neutropenia and immunocompromised states (solid organ and stem-cell transplant recipients, and patients with advanced HIV infection). The reasons for excluding such patients were not specifically stated. Because procalcitonin levels are affected by the host cytokine response to infection, the procalcitonin cut-off levels are most likely to differ in these populations. These populations are often excluded from clinical trials because these groups may be at higher risk of adverse outcomes. Finally, for some groups, such as neutropenic patients, antibiotics are continued until the neutropenia resolves, rather than until there is a clinical resolution.

Immunocompromised patients often comprise a significant portion of the ICU population, and in the large PRORATA[32] study, where immunocompromised patients were included, they accounted for 16.6 percent of the population. In the PROVAP[34] study of ventilator-associated pneumonia, 27.9 percent of the eligible patients were excluded because of immunosuppression. Even in community respiratory tract infections, such as CAP (7.6 percent excluded) and even in other respiratory tract infections (2.5 percent excluded), there is a significant subpopulation of patients who are immunocompromised or have condition such as cystic fibrosis where the efficacy and safety of procalcitonin-guided therapy is unknown.[47, 48]

Six[31, 43, 45-48] of the eight[27, 31, 43-48] studies evaluating procalcitonin guidance in patients with acute respiratory tract infections specifically excluded immunocompromised patients. While severely immunocompromised patients presenting with clinical signs of infection are most likely treated empirically with antibiotics, patients with mild to moderate immunosuppression, such as patients on low-dose corticosteroids for chronic inflammatory conditions, may not benefit from antibiotic therapy, even though they are often treated empirically. Procalcitonin guidance may have a potential role in reducing antibiotic usage in the ambulatory patients with mild to moderate immunosuppression compared to standard therapy.

Exclusion of immunocompromised patients was common across all five patient populations in this review. Immunocompromised patients are considered high risk for increased morbidity and/or mortality with delayed initiation or shorter courses of antibiotic therapy, or may not have the same procalcitonin rise in response to infection due to their comorbidities. However, immunocompromised patients may also gain significant clinical benefits if their antibiotic usage can be safely reduced, because they are vulnerable to mortality and morbidity from antibiotic resistance and adverse effects of antibiotics.

Research Gap #2: What are the outcomes of procalcitonin guidance in pediatric patients?

Only two studies[26, 49]reported on procalcitonin guidance in pediatric populations, and both were underpowered to assess morbidity and mortality outcomes. Both studies were limited to the acute care hospital setting. In our review, we grouped separately neonates[49] and children[26] ages 1-36 months, each represented by a single study. There were no studies in children ages 3 years to 18 years. Future studies of procalcitonin-guided initiation and discontinuation of antibiotics in the pediatric population will be extremely important. The overuse of antibiotics in pediatrics, in both the inpatient and outpatient setting, is as important among children, as it is in adults.

Research Gap #3: What are the outcomes of procalcitonin guidance in identifying patients at risk of infection who might benefit from preemptive antibiotic therapy?

The study by Chromik et al.[50] reported that procalcitonin levels could accurately identify a subpopulation, 8 percent of patients who underwent elective colorectal surgery, who were at risk of a local or systemic infection. Although this was a small study, the evidence suggests that this approach might identify a group who would benefit from preemptive antibiotic therapy given before any infection is clinically evident. Larger studies are needed to confirm that preemptive antibiotic therapy can reduce infectious complications. Other patient populations who are at risk for infectious complications include burn patients, ICU patients, and postoperative patients who have undergone procedures other than colorectal surgery.

Research Gap #4: Does the use of procalcitonin guidance reduce antibiotic resistance and antibiotic adverse events?

Although the importance of reducing antibiotic use is recognized and accepted, there was insufficient evidence from the randomized, controlled trials we reviewed that the observed reduction in antibiotic use had any benefits with respect to antibiotic adverse reactions, superinfections, or the development of resistance. Adverse antibiotic effects were reported in only three studies[27, 43, 45] and the findings were reported in different ways. Only one study[32] reported on the emergence of multidrug resistant bacteria, with no differences found between procalcitonin-guided and standard antibiotic therapy, and none reported on the incidence of *C. difficile*. When designing future studies, there should be consideration for standardized reporting of adverse events from antibiotics, the incidence of *C. difficile*, and active surveillance for colonization with drug-resistant pathogens.

Research Gap #5: How does procalcitonin-guided antibiotic therapy compare to other approaches to reducing unnecessary antibiotic use, such as antibiotic stewardship programs and implementation of practice guidelines?

In view of the present emphasis on the overuse of antibiotics, other interventions to reduce antibiotic use, such as institution of antibiotic stewardship programs and structured implementation of practice guidelines, may have been more robust comparators by which to assess the outcomes of procalcitonin-guided decisions on initiation and discontinuation of antibiotic therapy. Our review did not systematically seek evidence comparing procalcitonin guidance to other interventions to reduce antibiotic use, or evidence assessing whether addition of procalcitonin guidance to other interventions improves outcomes. So a systematic review that addresses a broader range of comparators is likely an initial step to determine whether there is an evidence gap and the nature of any gap or gaps. Given the urgency of reducing unnecessary use of antibiotics, there may be promising opportunities for future research that can inform clinical practice.

In addition to the research gaps above, we also identified four important methodologic weaknesses that were common across the studies and bodies of evidence reviewed in this report.

1. Measurement of total antibiotic exposure

Total antibiotic exposure is used to capture the patient's total exposure to all antibiotics, and it is calculated by multiplying the total number of antibiotics by the number of days the patient is receiving each of the antibiotics. Total antibiotic exposure is conventionally reported as mean days per 1,000 days of followup, but some of the studies in this review only reported relative or absolute differences. The differences in reporting limited our ability to pool the total antibiotic exposure data in this review. Consistent use of the conventional measure of mean days per 1,000 days of followup would improve accumulation of a robust body of evidence on the outcomes of procalcitonin guidance.

2. Measurement of morbidity

There were various measures of morbidity across these studies, and that was true even between studies that were grouped together because of their similarities. Although admission rates, LOS, and ICU LOS were easy to compare, other measures were not. In the ICU populations, for example, the need for mechanical ventilation was often reported differently and studies used a variety of severity of illness scores (SOFA, SAP II, SAP III, and APACHE II). This makes it difficult to compare or pool data across studies.

3. Rationale for noninferiority margins for studies of mortality

Mortality rates in trials of procalcitonin-guided therapy implicitly or explicitly pose a question of noninferiority, that is, can reduction in antibiotic use be achieved without a deleterious impact on survival? Is mortality no worse than with usual care? The choice of a noninferiority margin incorporates clinical and statistical judgments.[60] The PRORATA[32] trial, which was the largest trial (n=621) of procalcitonin used to discontinue antibiotic in the ICU populations, was designed to have an 80 percent power to exclude a 10 percent difference in mortality between groups. However, there is concern that the 10 percent noninferiority margin chosen was not sufficiently narrow to exclude excess mortality.[61-63] Studies where mortality is an outcome of interest should provide an explicit rationale for the choice of noninferiority margin in specific patient populations. Moreover, "the choice of margin should be independent of considerations of power as the size of the clinically important difference is not altered by the size of the study."[64]

4. Reporting and interpretation of non-significant differences

A common statistical error in the medical literature is the conclusion that nonsignificant differences ($p>0.05$) are "similar."[65] Most studies included in our systematic review were insufficiently powered to address mortality outcomes. Of the five studies[32-36] of antibiotic discontinuation in ICU patients, only the Bouadma et al., study[32] was powered to show noninferiority in mortality between procalcitonin-guided and control group antibiotic therapy. However, three[33-35] of the four[33-36] remaining studies have erroneously concluded that mortality was similar between procalcitonin and control group guided antibiotic therapy based on observed nonsignificant differences in mortality. These three studies reported results as follows: "…without any adverse effects on outcome…"[33] "…a similar mortality were observed in procalcitonin and control groups…"[35] and "…absence of differences in overall mortality suggest that procalcitonin guided antibiotic reduction is not associated with a worse outcome in

VAP…”[34] Clearly stating in the abstract that the study was not powered to detect a difference in mortality would provide a more accurate reporting of the results.

Abbreviations

ABT	antibiotic
ACCP	American College of Chest Physicians
AECOPD	acute exacerbations of chronic obstructive pulmonary disease
AIDS	acquired immunodeficiency syndrome
ANC	absolute neutrophil count
APACHE	acute physiology and chronic health evaluation
APGAR	appearance, pulse, grimace, activity, respiration
ARDS	acute respiratory distress syndrome
ATS	American Thoracic Society
CAP	community acquired pneumonia
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CRF	chronic renal failure
CRP	C-reactive protein
CVC	central venous catheter
CXR	chest x ray
ED	emergency department
EPC	evidence practice center
EPICOT	evidence, population, intervention, comparison, outcome, timestamp
FDA	food and drug administration
FEV	forced expiratory volume
GOLD	global initiative for chronic obstructive pulmonary diseases
GRADE	grading of recommendations assessment, development and evaluation
HAP	hospital-acquired pneumonia
HIV	human immunodeficiency virus
HR	hazard ratio
ICAAC	Annual Meeting of Interscience Conference on Antimicrobial Agents and Chemotherapy
ICU	intensive care unit
IDSA	Annual Meeting of Infectious Diseases Society of America
IL	interleukin
IQR	inter quartile range
LOS	length of stay
LRTI	Lower respiratory tract infection
LTFU	lost to followup
MICU	medical intensive care unit
NR	not reported
NSS	not statistically significant
NYHA	New York Heart Association
ODIN	organ dysfunction and/or infection score
PAS	annual meeting of pediatric academic societies
PCT	procalcitonin
PFT	pulmonary function test
PICOTS	patient, intervention, comparator, outcome, timing, and setting
PROM	premature rupture of membranes
PRORATA	Procalcitonin to Reduce Antibiotic Treatments In Acutely Ill Patients
PSI	pneumonia severity index
QOL	quality of life
RCCM	Respiratory and Critical Care Medicine
RCT	randomized controlled trial
RR	relative risk
RRR	relative risk reduction
RTI	respiratory tract infection
SAEs	serious adverse events
SAPS	simplified acute physiology score

SBI	serious blood infections
SCT	stem cell transplantation
SD	standard deviation
SICU	surgical intensive care unit
SIPs	scientific information package
SIRS	systemic inflammatory response syndrome
SOFA	Sepsis-Related Organ Failure Assessment
SSI	surgical site infection
TB	tuberculosis
TEP	technical expert panel
TNF	tumor necrosis factor
TOO	Task Order Officer
URTI	upper respiratory tract infection
UTI	urinary tract infection
VAP	ventilator-associated pneumonia
VAS	visual analog scale
WBC	white blood cells

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