Effective Health Care Program

Procalcitonin-Guided Antibiotic Therapy

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 reduces 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 (ICUs) have higher morbidity and mortality rates, the same issues are also relevant to other clinical conditions, including neonatal sepsis, febrile illness in children, pneumonia, and other respiratory tract infections with respect to 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 of antibiotic therapy. Among these, procalcitonin is the most extensively studied biomarker.[2,3]

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare. ahrq.gov/reports/final.cfm**.

Numerous studies have investigated the potential roles of procalcitonin in diagnosing and managing 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, as compared with 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 critically ill adults with suspected sepsis or other serious bacterial infections, neonates with suspected early neonatal sepsis, patients with upper and lower respiratory tract infections, children with fever of unknown source, and postoperative patients with infections. Initial review of the literature during topic development and topic refinement suggested that the most common use for procalcitonin-guided management was in decisionmaking 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 with clinical criteria for infection alone on:

- **Intermediate outcomes, such as initiation, discontinuation, or change of antibiotic therapy; antibiotic use; 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, or 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.

Outcome: Antibiotic use (duration of antibiotic therapy, prescription rate,[a] and total antibiotic exposure[b]), mortality, morbidity (length of stay, severity of illness score), and adverse events of antibiotic therapy (persistent or recurrent infection, and antibiotic resistance).

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[a]Defined as the percentage of patients who are initiated on antibiotic therapy, either during initial presentation or subsequent followup.
[b]Calculated by multiplying the total number of antibiotics by the number of days the patient is receiving each antibiotic divided by the total duration of antibiotic therapy.

Timing: Three months.

Settings: ICUs (medical and surgical), inpatient acute care hospitals, emergency departments, and outpatient clinics.

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 cutoffs 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 the Key Questions originally framed in our topic refinement.

Analytic Framework

Following is an analytic framework (Figure A) depicting the potential effects both on intermediate outcomes and on health outcomes from using procalcitonin. Direct evidence of the results of testing on health outcomes is shown by link A (morbidity, function, quality of life, and/or mortality) and link F (adverse events of therapy). Indirect evidence would have to be assembled in the absence of randomized controlled trials (RCTs) of the effects of testing on health outcomes. Link B addresses whether test results influence decisions about therapy, which may affect health outcomes (link C) or intermediate outcomes (link D). 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 E).

Figure A. Analytic framework for procalcitonin as a diagnostic indicator for infection and as an indicator of response to therapy
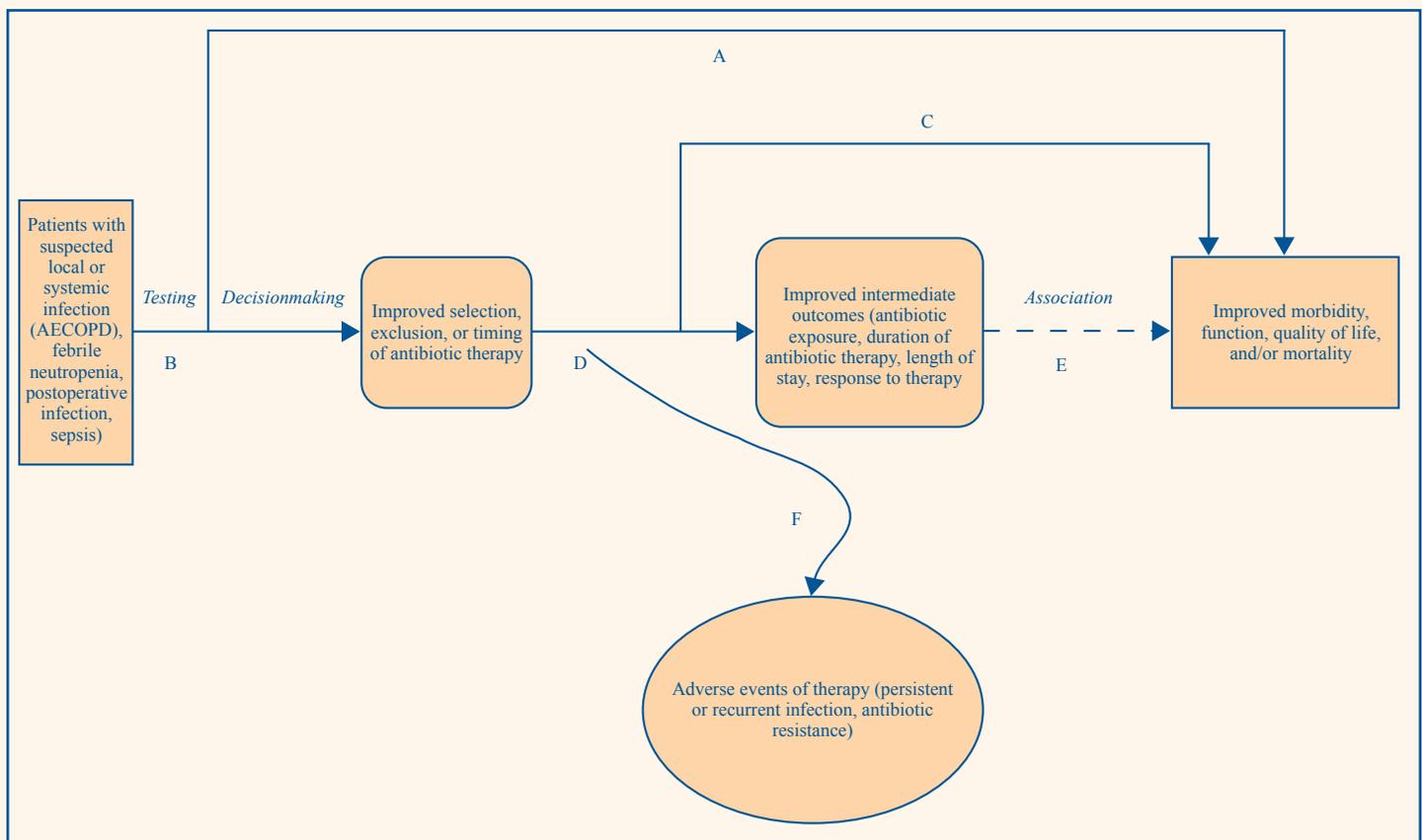
AECOPD = acute exacerbations of chronic obstructive pulmonary disease
Note: A-F show links between test results and outcomes. Please see the text above Figure A for more information

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 provided input to the EPC to help refine the Key Questions and to focus on the most important aspects of procalcitonin to influence health care decisions in various clinical settings. The Key Questions were then posted on the Agency for Healthcare Research and Quality (AHRQ) Web site for public commentary. The Technical Expert Panel provided input on the research protocol in two phases: (1) initial draft protocol; (2) revised protocol that incorporated the panel's comments on the draft protocol and preliminary list of relevant studies.

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 December 16, 2011, for randomized and nonrandomized comparative studies using the following search terms: procalcitonin AND chronic obstructive pulmonary disease; COPD; critical illness; critically ill; febrile neutropenia; ICU; intensive care; intensive care unit; postoperative complication(s); postoperative infection(s); postsurgical infection(s); sepsis; septic; surgical wound infection; systemic inflammatory response syndrome 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 Web sites of the National Institute for Clinical Excellence, the National Guideline Clearinghouse, and the Health Technology Assessment Programme. A search of the gray literature included 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 use, morbidity, and mortality with procalcitonin-guided initiation and/or discontinuation of antibiotic therapy compared with 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 RCTs. We also sought, but did not find, nonrandomized comparative studies. The PRISMA diagram (Figure B) depicts the flow of search screening and study selection.

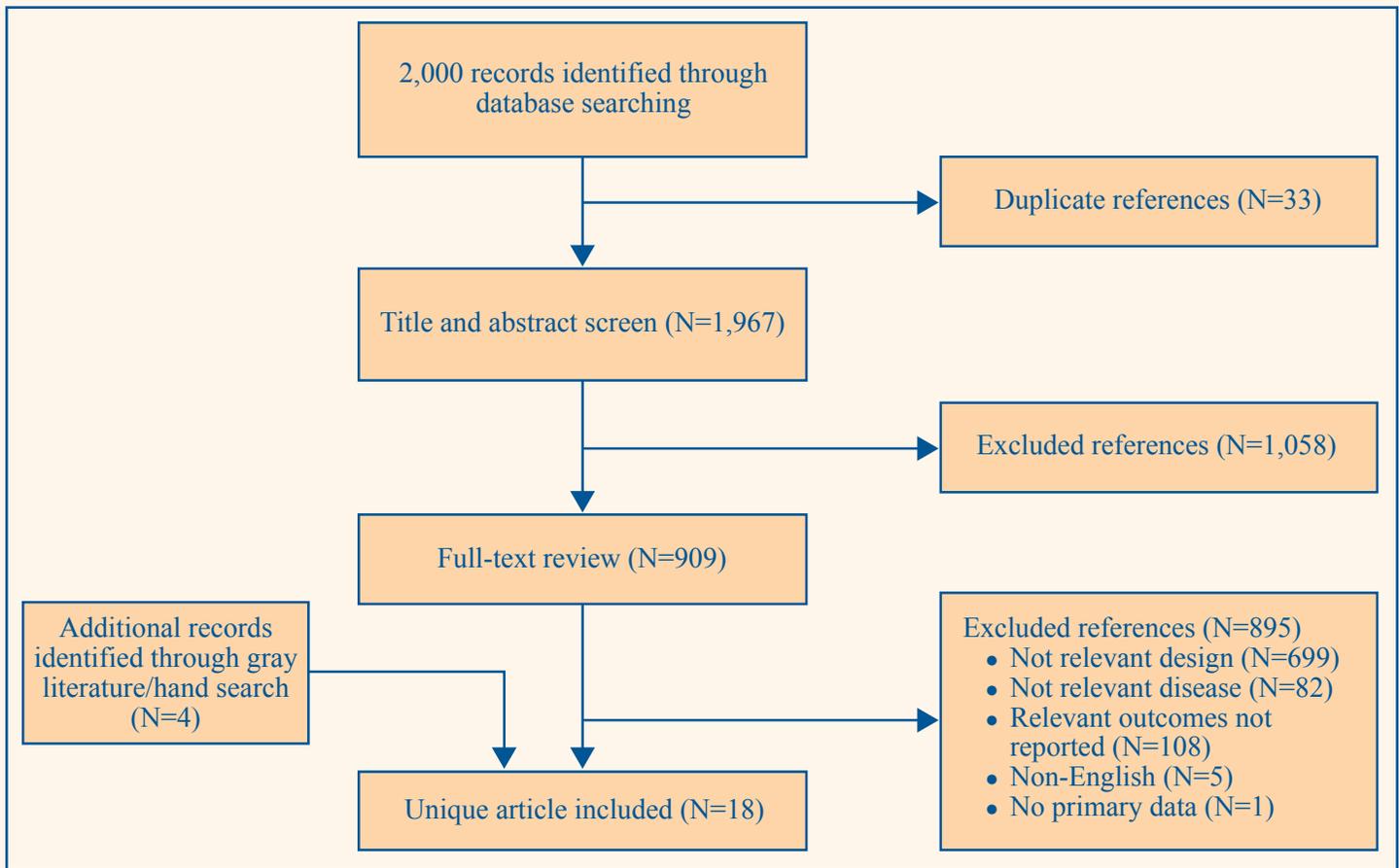### Data Extraction and Quality Assessment

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), and outcome assessment (primary and secondary outcomes, response criteria, followup frequency and duration, and 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

Figure B. PRISMA diagram for identified trials

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┌─────────────────────────────┐
│  2,000 records identified    │
│  through database searching  │────────────► ┌──────────────────────────────┐
└─────────────────────────────┘               │  Duplicate references (N=33)  │
              │                                 └──────────────────────────────┘
              ▼
┌─────────────────────────────┐
│  Title and abstract screen   │
│         (N=1,967)            │────────────► ┌──────────────────────────────┐
└─────────────────────────────┘               │ Excluded references (N=1,058) │
              │                                 └──────────────────────────────┘
              ▼
┌─────────────────────────────┐
│  Full-text review (N=909)    │
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Additional records identified through gray literature/hand search (N=4)

Excluded references (N=895)
- Not relevant design (N=699)
- Not relevant disease (N=82)
- Relevant outcomes not reported (N=108)
- Non-English (N=5)
- No primary data (N=1)

Unique article included (N=18)

also anticipated that the decision to pool studies would be based on whether there were a 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.

Grading the Strength of the Body of Evidence

The overall strength of evidence grade was determined in compliance with AHRQ's Methods Guide for Effectiveness and Comparative Effectiveness Reviews[19] and is based on a system developed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group.[20] This system explicitly addresses the following domains: risk of bias, consistency, directness, and precision. With respect to precision, studies could contribute to a rating of precise if confidence intervals did not overlap the null value or results were statistically significant, regardless of whether studies were powered to detect a particular effect for that outcome. 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

Eighteen RCTs (Table A) compared procalcitonin guidance with the 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 and 36 months of age with fever of unknown

Table A. 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 Ages 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	1,272	3,492	121	384	250
Funding	NR=3 Mixed=2	Nonindustry=1 Mixed=1	Nonindustry=2 NR=1 Mixed=5	Industry=1	Industry=1	NR=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

NR = not reported; RCT = randomized controlled trial; VAP = ventilator-associated pneumonia
*Yes implies published paper reported existence of conflict of interest; No implies published paper reported no existence of conflict of interest; and NR implies published paper did not report whether conflict of interest existed.

source; and (5) postoperative patients at risk of infection. Additionally, we separately reviewed two studies in seriously adult ill ICU patients for whom the procalcitonin-guidance was used to guide intensification of antibiotic therapy rather than use procalcitonin to guide initiation or discontinuation of therapy, a very different approach.

Conducting a meta-analysis was precluded in most instances because of 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 VAP. The pool of studies was too small to permit meaningful subgroup and sensitivity analyses. Additional meta-analyses were performed on antibiotic duration, ICU length of stay and hospital length of stay.

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. There is high strength of evidence (Table B) that procalcitonin guidance reduces antibiotic use. 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 morbidity as indicated by ICU length of stay (LOS). A major concern was uncertainty about the appropriate noninferiority margin for mortality in seriously ill patients in the ICU with sepsis and/or VAP. Although there are potential benefits of reducing antibiotic use, only one study[18] reported on multidrug-resistant organisms and superinfections. There were limited data on other adverse antibiotic effects reported in these studies.

Procalcitonin-Guided Intensification of Antibiotic Therapy. There is moderate evidence 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. The large (n=1,200), high-quality trial by Jensen and colleagues[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 departments (EDs), 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. Evidence was insufficient to judge effects on days of restricted 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. No consistency was found, 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%). 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 with those with proven or probable infection. Strength of evidence was judged insufficient to make conclusions on mortality and morbidity because of the 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 to 36 months of age. One good-quality RCT[32] (n=384) reported no significant results.

Table B. Summary of outcomes measures, and strength of evidence

Patient Group	Outcome	Unit	No. of Studies	References	No. of Subjects	B	C	D	P	Overall Grade	Effect*
Critically ill/VAP patients (antibiotic discontinuation)	Antibiotic use	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	Low**	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	1,200	L	U	Y	Y	Moderate	Worse (5.0%, 95% CI: 3.0, 6.9)
		Percent days on ventilator	1	21	1,200	L	U	Y	Y	Moderate	Worse (4.9%, 95% CI: 3.0, 6.7)
Respiratory tract infection	Antibiotic use	Duration of use, days	7	23-27, 29, 30	3,284	L	Y	Y	Y	High	Improve (Range: −1 to −7)
		Prescription rate	7	23–30	3,492	L	Y	Y	Y	High	Improve (Range: −2 to −7%)
	Mortality	≤ 6 wks or 6 months	8 (7/1)	23–30	3,492	L	Y	Y	Y	Moderate	No worse
	Morbidity	Hospital length of stay	5	25, 26, 28–30	2,303	M	Y	Y	Y	Moderate	No worse
		ICU admission rates	5	25, 26, 28–30	2,303	M	Y	Y	Y	Moderate	No worse
		Antibiotic adverse events	3	24, 25, 27	2,367	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	L	U	Y	N	Insufficient	Unknown
	Mortality	In-hospital	1	33	20	L	U	Y	N	Insufficient	Unknown

B = risk of bias; C = consistency; CI = confidence interval; D = directness; GFR = glomerular filtration rate; ICU = intensive care unit; N = no; P = precision; SIRS = systemic inflammatory response syndrome; U = unknown; VAP = ventilator-associated pneumonia; Y = yes

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

**The overall grade was low based on uncertainty about the appropriate minimum important difference for assessing noninferiority with respect to mortality.

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

Clinical Context and Applicability

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 because 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 use 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 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 for which a longer duration of antibiotic therapy is the standard of care, such as infective endocarditis, were also appropriately excluded from these studies. Patients with these conditions account for a significant proportion of the ICU population.

Although such patients were excluded in these studies, future studies may help to determine whether 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 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 RCTs[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 use may be a lower probability of emergence of antibiotic-resistant strains. Antimicrobial resistance contributes to morbidity, mortality, and health care costs. Several studies and indirect lines of evidence suggest that control of antibiotic use can reduce emergence of resistance, but the data are 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 use,[24,25,27] and only one reported on antibiotic resistance.[14]

The durability in reduction of antibiotic use 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 the long-term outcome of using procalcitonin guidance in a real-world clinical setting. Antibiotic stewardship programs are now recommended for all institutions, and guidelines are available for how they should function.[41] Antibiotic stewardship programs are associated with reduced antibiotic use and also the 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 the 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 interventions 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 viral respiratory tract infections.[37]

Key Findings and Strength of Evidence

Our systematic review concludes that procalcitonin-guided antibiotic therapy can lead to significant reductions in antibiotic use (high strength of evidence [SOE]) without adversely affecting patient outcomes in critically ill patients in the ICU setting (moderate SOE for morbidity, low SOE for mortality). Evidence on mortality was initially rated as stronger but was downgraded to low based on uncertainty about the appropriate noninferiority margin for this outcome. In patients with a variety of respiratory tract infections, procalcitonin-guided antibiotic therapy reduced antibiotic prescription rates and the duration of antibiotic therapy (high SOE) in different clinical settings, again without any increase in morbidity or mortality (moderate SOE). There is insufficient evidence to recommend procalcitonin-guided antibiotic therapy in cases of neonatal sepsis, febrile children, and postoperative patients when procalcitonin has been used to identify patients who may need preemptive antibiotic therapy to prevent local or systemic infections. Use of procalcitonin as an indicator of inappropriate initial antibiotic therapy and the need for intensified antibiotic therapy in the ICU should be discouraged because this approach may lead to increased organ dysfunction (moderate SOE).

Discussion of Present Findings in Context of Other Systematic Reviews

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

We reviewed all published 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. Eighteen RCTs[14-18,21-33] were included in our systematic review. Our systematic review differs from previous systematic reviews in terms of the number of studies included, the 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 it also recognizes that there are distinct patient groups within the pediatric population as 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 Gaps in the Evidence

We identified five gaps in the evidence related to specific populations or comparators.

Research Gap 1: What are the Outcomes of Procalcitonin Guidance in Subgroups of Patients who are Immunocompromised?

Patients with certain conditions, including neutropenia, and those in immunocompromised states (solid organ and stem-cell transplant recipients, and patients with advanced HIV infection) were excluded from this study. Immunocompromised patients often comprise a significant portion of the ICU population. In the large PRORATA[18] study, immunocompromised patients made up 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% excluded), and even in other respiratory tract infections (2.5% excluded), there is a significant subpopulation of patients who are immunocompromised or have condition such as cystic fibrosis for whom the efficacy and safety of procalcitonin-guided antibiotic 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 use in the ambulatory patients with mild to moderate immunosuppression as compared with 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 Preemptive Antibiotic Therapy?

The study by Chromik and colleagues[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 preemptive antibiotic therapy given before any infection is clinically evident. Larger studies are needed to confirm that preemptive antibiotic therapy can reduce infection-related complications. Other patient populations who are at risk for infection-related 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, 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 of patients with drug-resistant pathogens.

Research Gap 5: How Does Procalcitonin-Guided Antibiotic Therapy Compare With Other Approaches for 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 the institution of antibiotic stewardship programs and the structured implementation of practice guidelines, may be more robust comparators by which to assess the outcomes of procalcitonin-guided decisions on the initiation and discontinuation of antibiotic therapy.

Summary of Methodological Weaknesses in the Evidence

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

Weakness 1: Measurement of Total Antibiotic Exposure

Total antibiotic exposure is used to capture a 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.

Weakness 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.

Weakness 3: Rationale for Noninferiority Margins for Studies of Mortality

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

Weakness 4: Reporting and Interpreting 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 antibiotic therapy did not result in any increased morbidity or mortality in critically ill patients and those with respiratory tract infections. In the studies of critically ill patients for whom procalcitonin was used to reduce antibiotic exposure, only the Bouadma study[18] did a power analysis and used a predefined a margin for noninferiority for 28- and 60-day mortality. Meta-analysis was performed looking at early mortality across all five ICU studies. Results show a pooled point estimate of 0.4 percentage point reduction in mortality, and the 95% confidence interval (CI) for the difference in mortality between procalcitonin-guided antibiotic therapy and standard care was between -6 percent and 5 percent, favoring the procalcitonin-guided antibiotic therapy group. There is disagreement, however, over whether this range falls within the appropriate noninferiority margin. The choice of a noninferiority margin only requires sufficient precision to exclude a minimal important difference.[47] Although a 10 percent noninferiority margin for mortality has been recommended by the Infectious Diseases Society of America and American College of Chest Physicians in relevant populations, there is concern, expressed by some of our peer reviewers and in literature, that a 10 percent margin may be too high. Initially, a higher strength of evidence was considered, but because of the uncertainty of the noninferiority margin, the strength of evidence that procalcitonin-guided antibiotic therapy in the ICU does not increase mortality was downgraded to low. Although overall strength of evidence was low, the results were judged to be precise because the pooled point estimate was centered on the null and the 95% CI was narrow (11 percentage points). While only one study was powered for mortality, one purpose for meta-analysis is to overcome insufficient power, and the group of studies was highly consistent: statistical heterogeneity, as expressed by the I^2 statistic, was found to be 0 percent. Sixty-day mortality was reported by one study[18] and was not included in our analysis because late mortality is more likely related to underlying comorbidities. Moreover, there are presently two large trials in progress, which may yield more precise estimates of mortality.

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 changed procalcitonin-guided antibiotic therapy into an antibiotic stewardship program.

Implications for Future Research

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

Populations of interest for future research on procalcitonin guidance are:

- Immunocompromised patient subgroups
- Patients with other conditions who were excluded from the study (e.g., pregnant women)
- 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 with 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 use on antibiotic resistance

- Consequences of reduction in antibiotic use on antibiotic adverse events

- Establishing the appropriate noninferiority margins for mortality and morbidity outcome

Opportunities for Improving Study Methods

1. Studies should use a consistent measurement of total antibiotic exposure: mean days of total exposure to all antibiotics per 1,000 days of followup.

2. Studies should use consistent measurements of morbidity; for example, the need for mechanical ventilation; severity of illness scores.

3. Studies should provide an explicit rationale for noninferiority margins for mortality in specific patient populations.

4. Studies should provide transparent reporting and interpretation of nonsignificant differences: Clearly stating in the abstract whether the study was not powered to detect a difference in mortality or morbidity.

Glossary

Infection: An infection is an invasion and multiplication of microorganisms or parasites in body tissues.

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 they rise in a response to a proinflammatory stimulus, especially of bacterial origin.

Sepsis: Sepsis is a clinical syndrome caused by the presence of a microbe or microbial products in the blood or other tissue resulting in a systemic inflammatory state.

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