



Effective Health Care Program

Future Research Needs Paper
Number 29

Future Research Needs on Procalcitonin- Guided Antibiotic Therapy



Agency for Healthcare Research and Quality
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Future Research Needs Paper

Number 29

Future Research Needs on Procalcitonin-Guided Antibiotic Therapy

**Identification of Future Research Needs From Comparative Effectiveness Review
No. 78**

Prepared for:

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This report is based on research conducted by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10058-I). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care researchers and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

An important part of evidence reports is not only to synthesize the evidence, but also to identify the research needs in evidence that limited the ability to answer the systematic review questions. AHRQ supports EPCs to work with various stakeholders to identify and prioritize the future research that is needed by decisionmakers. This information is provided for researchers and funders of research in these Future Research Needs papers. These papers are made available for public comment and use and may be revised.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The evidence reports undergo public comment prior to their release as a final report.

We welcome comments on this Future Research Needs document. 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 email to epc@ahrq.hhs.gov.

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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.

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. Numerous studies have investigated the potential roles of procalcitonin in diagnosing and managing local and systemic infections. However, its clinical utility in the diagnosis and management of patients with suspected infections remains unclear.

A Comparative Effectiveness Review (CER) was prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (BCBSA TEC EPC) on Procalcitonin-Guided Antibiotic Therapy.¹ The objective of the CER 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 with infection.

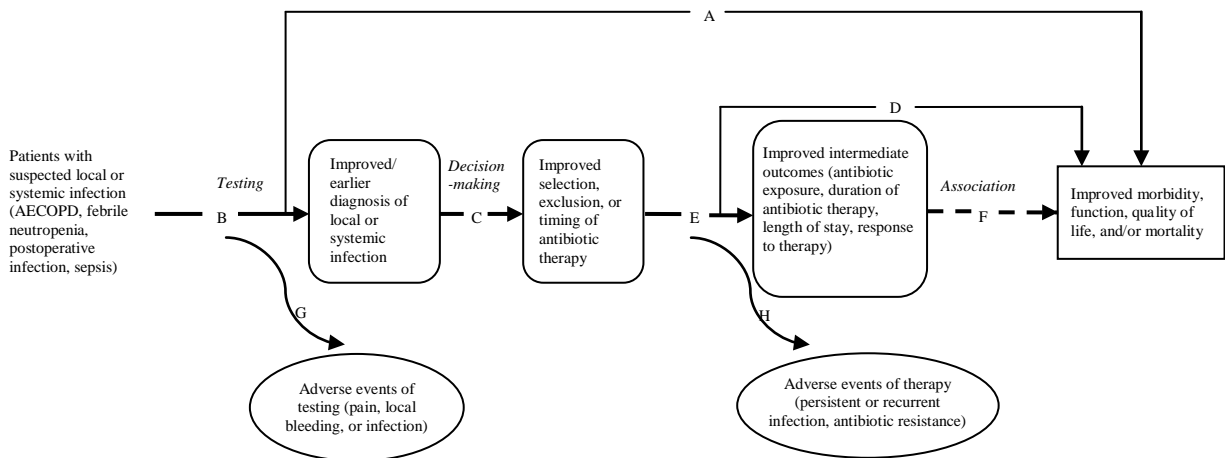
The following Key Question formed the basis for the CER:

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 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 analytical framework that guided the draft CER is provided in Figure A.

Figure A. Analytic framework from draft CER for procalcitonin as a diagnostic indicator for infection and as an indicator of response to therapy



Note: AECOPD, acute exacerbations of chronic obstructive pulmonary disease; CER, Comparative Effectiveness Review.

Five evidence gaps related to specific populations or comparators were identified in the CER. The evidence gaps are as follows:

1. What are the outcomes of procalcitonin guidance in subgroups of patients who are immunocompromised?
2. What are the outcomes of procalcitonin guidance in pediatric patients?
3. What are the outcomes of procalcitonin guidance in identifying patients at risk of infection who might benefit from pre-emptive antibiotic therapy?
4. Does the use of procalcitonin guidance reduce antibiotic resistance and antibiotic adverse events?
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?

Based on these evidence gaps, recommendations for future research targeted priority populations who were excluded explicitly from previous clinical trials or in whom insufficient evidence exists and who represent a high burden to the U.S. health care system (i.e., immunocompromised patients, ambulatory care patients, pediatric subgroups including neonates and young children, patients who are at higher risk of infection). The CER highlighted the importance of using appropriate study comparators and outcome measures that better reflect a real-world health care setting, thereby enhancing their applicability to clinical practice. Thus although the CER did not assess the comparative effectiveness of using procalcitonin guidance versus antibiotic stewardship, this was noted as a recommendation for future research recognizing the potential complementary role of procalcitonin to existing antibiotic stewardship programs and clinical practice guidelines for reducing antibiotic usage and associated adverse events in the acute care setting. Outcome measures should consider the consequences of reduction in antibiotic usage on antibiotic resistance, antibiotic-related adverse events, mortality and morbidity such as length of stay, local wound infection or sepsis. The CER also identified several common methodological weaknesses in the evidence base that should be addressed in

future research (i.e., consistent use of measures of total antibiotic exposure and of morbidity, need for explicit rationale for noninferiority margins for mortality in specific patient populations, transparent reporting and interpretation of nonsignificant differences in outcome measures).

Methods

To identify new research that might address the research needs in the CER, the project team updated literature searches from the CER and clinical trial searches using clinicaltrials.gov. Next, we convened a group of nine stakeholders (Stakeholder Panel or “Panel”), representing diverse perspectives, including methodological/research expertise, clinical experience, and consumer and payer representation. The Stakeholder Panel prioritized each research need and corresponding research questions using an online survey tool called SurveyMonkey[®]. The project team modified the Effective Health Care (EHC) Program Selection Criteria to be applicable to primary research rather than to systematic reviews of original research. The Panel used the modified selection criteria to prioritize both research needs and corresponding research questions. We compiled a final list, taking the Panel members’ comments into consideration and paying particular attention to areas where ongoing efforts might overlap with prioritized research questions. The research questions were characterized using the PICOTS framework using the population(s), interventions, comparators, outcomes, timing, and settings. The project team then evaluated potential study designs to address each of the prioritized research questions in accordance with the recent Future Research Needs methods report authored by the EPCs for the Agency for Healthcare Research and Quality (AHRQ).² The Panel provided insight into how future research agendas and proposed studies to address the research needs fit within these pre-specified criteria.

Results

A total of 10 research needs were identified through a combination of the draft CER findings and discussions with the Stakeholder Panel. These research needs were grouped by specific patient groups addressed in the CER. Through an iterative process, the Panel prioritized the research needs; the EPC generated the final ranking of three research needs taking into account all Panel members’ comments. These three research needs represented the priority populations the Panel determined were most in need of rigorous research, because the burden of illness is high and the information at present is insufficient or imprecise to permit conclusions about the use of procalcitonin for management of:

1. The critically ill patient (all ages) with suspected lower respiratory tract infection (LRTI) or general infection;
2. The patient (all ages) with suspected LRTI in the ambulatory care/emergency department setting in the United States;
3. The immunocompromised patient (all ages).

The Stakeholder Panel then generated and prioritized a list of potential research questions to address these three research needs. The final prioritized list of research needs and research questions accompanied by PICOTS elements are stated in Table A. Suggestions for future study designs are presented in Table B.

Discussion

This Future Research Needs project was developed from the BCBSA TEC EPC CER on Procalcitonin-Guided Antibiotic Therapy.¹ A multidisciplinary Stakeholder Panel of nine participants used an 11-step process to identify and prioritize research needs and key research questions across the selected research needs. The final research questions reflect the deficiency in the evidence related to the key populations identified in the CER. Through this process, we propose a final list of three research needs and six associated research questions.

We used multiple techniques to engage stakeholders, including individual interviews, online surveys and conference calls. The literature search update allowed for more informed decisions in selecting topics that were not duplicative with current ongoing trials and to which further research would add the greatest value.

Future research concerns brought forth for consideration included addressing specific issues related to procalcitonin guidance in pediatrics and immunocompromised patients, as well as addressing both the duration and initiation of antibiotic therapy based on procalcitonin results in specific patient groups. Study design considerations included addressing the appropriate gold standard on which to evaluate the diagnostic properties of procalcitonin, the outcomes to consider for evaluations of procalcitonin, and factors that could influence procalcitonin test results.

One of the major challenges we encountered in our process was the various ways in which to combine/categorize many of the proposed topics; there was crossover and overlap between the various research needs and key underlying research questions across the top-ranked research needs. In addition, it was important to maintain the focus on the research needs in the evidence (and scope) addressed in the CER report. A limitation of this process was that the Stakeholder Panel was presented with the draft results of the CER; the conclusions did change between the draft and the final and thus the impact of these results on the rankings of the research needs is unknown.

Conclusions

Three prioritized research needs and six research questions were identified in this process as important issues to take forward along with recommendations for future research. They are summarized in Table C and presented with the PICOTS framework in Table A.

The focus of the prioritized list of research questions is on the contribution of procalcitonin-guided clinical algorithms aimed at empirically treating suspected or confirmed bacterial infection in non-outbreak settings, including primary care, emergency/ambulatory care and intensive care. To that end, similar study designs may be used to address questions of the contribution of procalcitonin to the decision to initiate, maintain or discontinue antimicrobial therapy across a range of populations; in fact, a single study may sufficiently address all questions within a research need. Table B presents suggestions for the most valid and feasible study designs for future research of procalcitonin that could be considered for each of the prioritized research needs. The CER did not compare outcomes of using procalcitonin guidance versus antibiotic stewardship programs, nor did it address whether addition of procalcitonin to an antibiotic stewardship program improves outcomes. Therefore, a systematic review may be warranted to identify research needs from studies comparing procalcitonin-based strategies to institutional programs aimed at reducing antibiotic use before undertaking new primary research.

Table A. Prioritized list of research needs and research questions with PICOTS information

Research Need	Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
<p>The use of procalcitonin in the management of critically ill patients (all ages) with suspected lower respiratory tract infection (LRTI) or general infection</p> <p>Reason(s) for Research Need:</p> <p>For adults, insufficient evidence on health outcomes (e.g. antibiotic adverse events); Results from available studies are inconsistent (e.g. how adverse effects are defined, lack of details on types of adverse reactions)</p> <p>For pediatrics, insufficient or imprecise information given the limited number of studies</p>	<p><u>1.1</u> For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a PCT-guided strategy used to determine the duration of antimicrobial therapy safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p> <p><u>1.2</u> For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a subsequent decrease in the serial PCT measurement indicate effective empiric treatment of the bacterial infection?</p> <p><u>1.3</u> For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p>	<p>Critically ill adult or pediatric patient with suspected or proven pneumonia/sepsis</p>	<p>Clinical criteria with cultures if available plus PCT thresholds for determining presence/absence of bacterial infection</p>	<ul style="list-style-type: none"> • Clinical criteria with cultures if available • Institutional strategies for reducing antibiotic use (e.g. ASP, educational programs targeting staff in the outpatient setting) 	<ul style="list-style-type: none"> • Hospital or ICU admission rate • Hospital/ICU LOS • Severity of illness • ABT-associated adverse reactions (e.g. allergic reactions) • Emergence of drug resistant pathogens or superinfection • Mortality (e.g. 30-day, hospital) • Antibiotic use (e.g. duration, days without ABT and total ABT exposure in children) 	<p>On admission or suspicion of infection, duration of followup (e.g. ≥ 30 days)</p>	<p>Hospital ICU</p>

Table A. Prioritized list of research needs and research questions with PICOTS information (continued)

Research Need	Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
<p>The use of procalcitonin in the management of patients (all ages) with suspected LRTI in the ambulatory care/emergency department setting in the U.S.</p> <p>Reason(s) for Research Need: For all ages, not the right information as results may not be applicable to U.S. setting;</p> <p>For pediatrics, insufficient or imprecise information given the lack of studies</p>	<p><u>2.1</u> For the otherwise healthy adult or pediatric patient who presents to ambulatory care/ED with fever and/or suspected acute LRTI, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p>	<p>Adult or pediatric patient with no underlying medical conditions who presents with fever/suspected acute LRTI including community-acquired pneumonia, exacerbation of chronic obstructive pulmonary disease, and bronchitis</p>	<p>Clinical criteria with cultures if available plus PCT thresholds for determining presence/absence of bacterial infection</p>	<ul style="list-style-type: none"> • Clinical criteria • Strategies to reduce antibiotic use (e.g. CPGs, education) 	<ul style="list-style-type: none"> • Hospital/ICU admission rate • Hospital/ICU LOS • Severity of illness • ABT-associated adverse reactions (e.g. allergic reactions) • Emergence of drug resistant pathogens or superinfection • Mortality (e.g. 30-day, hospital) • Days of restricted activity with PCT-guided therapy • Relapse of infection • Antibiotic use (e.g. duration, days without ABT and total ABT exposure in children) 	<p>On admission, duration of followup (e.g. ≥ 30 days)</p>	<ul style="list-style-type: none"> • Ambulatory care • Primary care clinic • ED

Table A. Prioritized list of research needs and research questions with PICOTS information (continued)

Research Need	Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
<p>The use of procalcitonin in the management of the immuno-compromised patient (all ages)</p> <p>Reason(s) for Research Need:</p> <p>Insufficient or imprecise information given the limited number of studies;</p> <p>Patients with certain conditions were excluded from these studies, including neutropenia, transplant recipients (stem-cell or solid organ), and other patients on immunosuppressive therapy</p>	<p><u>3.1</u> For the immuno-compromised patient who presents with suspected LRTI/sepsis, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p> <p><u>3.2</u> For the immuno-compromised patient with suspected LRTI/sepsis, does a PCT-guided strategy used to determine the duration of antibacterial therapy safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p>	<p>Immunocompromised patients including patients infected with human immunodeficiency virus and with a CD4 count of < 200 cells/mm³, neutropenic patients, transplant recipients (stem-cell or solid organ), and other patients on immunosuppressive therapy</p>	<p>Clinical criteria with cultures if available plus PCT thresholds for determining presence/absence of bacterial infection</p>	<ul style="list-style-type: none"> • Clinical criteria with cultures if available • Institutional strategies for reducing antibiotic use (e.g. ASP, educational programs targeting staff the outpatient setting) 	<ul style="list-style-type: none"> • Hospital or ICU admission rate • Hospital/ICU LOS • Severity of illness • ABT-associated adverse reactions • Emergence of drug resistant pathogens or superinfection • Mortality (e.g. 30-day, hospital) • Days of restricted activity with PCT-guided therapy • Relapse of infection • Antibiotic use (e.g. duration, days without ABT and total ABT exposure in children) 	<p>On admission or suspicion of infection, duration of followup (e.g. ≥ 30 days)</p>	<ul style="list-style-type: none"> • Outpatient /ED • Hospital ward • ICU

ABT = antibiotic therapy; ASP = antibiotic stewardship program; CPG = clinical practice guideline; ED = emergency department; ICU = intensive care unit; LOS = length of stay

Table B. Study design considerations

Study Design Considerations	Randomized Controlled Trial	Controlled Before-After Study	Modeling
Description of design	<p>Individuals randomly assigned to receive PCT-guided treatment strategy or standard care. Patients are followed during implementation for antibiotic use and health outcomes. Longer followup post implementation may be required if sustainability of outcome is desired (e.g., reduction of antibiotic use).</p> <p>Cluster RCTs that randomize at a hospital or ward level may be more suitable for population-level strategies when outcomes for individuals from a given unit are not independent. If pooling data across institutions is required, consensus on PCT cut-off points, standard care, outcome measures, minimum datasets and followup periods would be needed.</p>	<p>Antibiotic use and other health outcomes are compared in two or more groups of patients at the beginning and end of the study period. The study group receives the PCT-guided antibiotic treatment strategy part way into the study, and the control group receives standard care without use of PCT. Changes in outcomes from the beginning to the end of the study are compared across groups.</p> <p>Investigator controls timing of measurement(s) and variables measured, but not all intervention variables are in the control of the investigator. If pooling data across institutions is required, consensus on standard care, outcome measures, minimum datasets and followup periods would be needed.</p>	<p>Simulation model developed and validated to assess the value of individual strategies or individual components of comprehensive strategies across a range of populations, settings and conditions. Simulation models assume statistical association (e.g. between reduced antibiotic use and antibiotic-associated adverse events) and predict the consequences of the assumption (incidence of drug resistant pathogens).</p> <p>Agent based modeling (i.e., agent is the infectious bacteria) can be used to simulate the process of infectious disease transmission and be used to track drug resistance. This would allow for assessing the impact of a PCT-guided treatment strategy for reducing antibiotic use on rates of drug resistance over time.</p>
Advantages of study design for producing a valid result	<p>Best method to control for selection bias but potentially at the cost of generalizability. It should produce the most internally valid results.</p>	<p>Simple, efficient design with generalizable results. Design offers the ability to assess the temporal relationship between outcomes and 'nonrandomizable' events, e.g., if a hospital or unit has already adopted the use of PCT. Highly susceptible to confounding variables such as other concomitant antimicrobial therapy or dual viral/bacterial infection, regression to the mean and maturation effects. Internal validity may be strengthened by collecting data on confounding variables and matching study and control groups on pre-intervention outcomes of interest (e.g. antibiotic use, infection rates). Adding multiple pre-intervention observations is particularly important for evaluating temporal trends. Adequate statistical methods will be needed to control for confounders and secular trends in resistance and infection rates.</p>	<p>May be the best option to use when questions cannot be addressed using conventional clinical trial methods or existing data analysis, e.g. assessing the impact of various antibiotic treatment strategies on rates of drug resistance over the long term. May inform and help focus future clinical trials and data collection. Models can be tailored to multiple end users and perspectives, conditions and settings to enhance generalizability of findings and to help target interventions (different populations may call for different algorithms). Other forms of modeling (e.g. compartment based, decision tree, etc.) can be informative but will require more assumptions and thus greater variability with less confidence in the results.</p> <p>Its usefulness will be limited by available data and assumptions.</p>

Table B. Study design considerations (continued)

Study Design Considerations	Randomized Controlled Trial	Controlled Before-After Study	Modeling
Resource use, size and duration	Depending on the strategy and desired effect size and outcome (e.g. the acceptability margins used to claim equivalence or noninferiority), costs, sample size and staff time needed for recruitment and implementation could be high. Recruitment of unit “clusters” willing to be randomized may constrain sample size. Duration likely to be a few weeks, which may keep costs down, but longer followup (several years) may be required to account for the lag between change in antibiotic use and rates of nosocomial drug resistance/super-infections.	Generally less resource intensive than an experimental design, but sample size will depend on desired effect and magnitude. Otherwise, size and duration issues would be similar to RCT.	May require substantial personnel time but is generally less resource intensive than primary studies. May require primary data collection to inform components of the model if reliable estimates cannot be obtained from the literature, empiric studies or experts.
Ethical, legal, and social issues	Perception of not receiving efficacious care can pose an ethical issue and barrier to recruitment if standards of clinical equipoise are not met. For cluster RCTs, a waiver of informed consent would be required. Legal mandates or clinical culture may impede randomization to new interventions or supersede trial objectives.	Perception of not receiving efficacious care can pose an ethical issue and barrier to recruitment if standards of clinical equipoise are not met.	Additional data collection may require institutional approvals or informed consent.
Availability of data or ability to recruit	Given the high mortality rates for sepsis, patient or their families may be reluctant to enroll in an RCT. Cluster RCTs require collaborative network of sites willing to participate.	Recruiting is feasible. Design may offer the best way to study interventions where randomization may be unacceptable to patients or providers.	Data would be obtained primarily from published sources, proprietary institutional databases, and expert opinion.

PCT = procalcitonin; RCT = randomized controlled trial.

Table C. Summary of prioritized research needs and research questions

Research Need	Research Question
<p>The use of procalcitonin in the management of critically ill patients (all ages) with suspected lower respiratory tract infection (LRTI) or general infection</p>	<p><u>1.1</u> For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a PCT-guided strategy used to determine the duration of antimicrobial therapy safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p> <p><u>1.2</u> For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a subsequent decrease in the serial PCT measurement indicate effective empiric treatment of the bacterial infection?</p> <p><u>1.3</u> For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p>
<p>The use of procalcitonin in the management of patients (all ages) with suspected LRTI in the ambulatory care/ emergency department setting in the United States</p>	<p><u>2.1</u> For the otherwise healthy adult or pediatric patient who presents to ambulatory care/ED with fever and/or suspected acute LRTI, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p>
<p>The use of procalcitonin in the management of the immunocompromised patient (all ages)</p>	<p><u>3.1</u> For the immunocompromised patient who presents with suspected LRTI/sepsis, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p> <p><u>3.2</u> For the immunocompromised patient with suspected LRTI/sepsis, does a PCT-guided strategy used to determine the duration of antibacterial therapy safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p>

ED = emergency department; ICU = intensive care unit; LRTI = lower respiratory tract infection; PCT = procalcitonin.

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Introduction

Background

Context

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 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 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 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 with other markers.^{7,8} However, its clinical utility in the diagnosis and management of patients with suspected infections remains unclear.

The objective of the Comparative Effectiveness Review (CER) on Procalcitonin-Guided Antibiotic Therapy⁹ prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (BCBSA TEC EPC) 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 with 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. The major impetus of undertaking the CER was that a comprehensive review would determine the benefits and/or risks of procalcitonin-guided initiation and/or discontinuation of antibiotic therapy in different patient populations. In addition, this CER would also identify the major research needs related to procalcitonin-guided antibiotic therapy that require further prospective investigation and would serve as priorities for future research.

The following Key Question formed the basis for the CER:

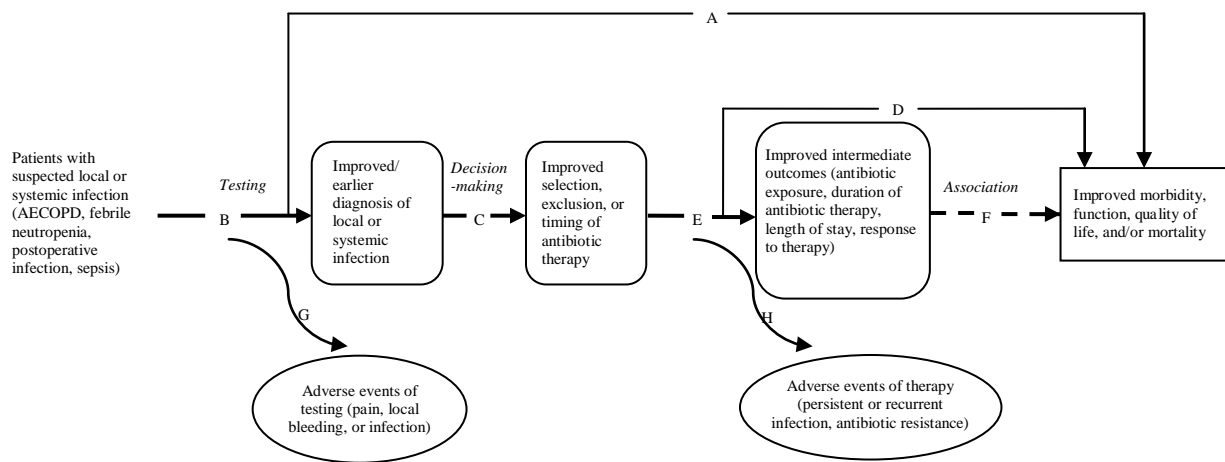
In selected populations of patients with suspected local or systemic infection, what are the effects of using procalcitonin measurement plus clinical criteria for infection to guide initiation, discontinuation or a change of antibiotic therapy, when compared with clinical criteria for infection alone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

- Intermediate outcomes, such as initiation, discontinuation or change of antibiotic therapy, antibiotic 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 CER results were reported separately by patient population because of different clinical characteristics and predicted outcomes. Conducting meta-analysis was precluded in most instances 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 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. Additional meta-analyses were performed on antibiotic duration, ICU length of stay and hospital length of stay.

The findings from the draft CER revealed that 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, without increasing morbidity and mortality. In contrast, procalcitonin-guided intensification of antibiotics in adult ICU patients increases morbidity. There was also evidence that procalcitonin guidance reduces antibiotic usage for suspected early neonatal sepsis, but insufficient evidence on morbidity and mortality outcomes. Evidence was 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. The analytical framework that guided the draft CER is provided in Figure 1. Appendix A provides the draft findings from the CER report.

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



Note: AECOPD, acute exacerbations of chronic obstructive pulmonary disease.

Evidence Gaps

Five evidence gaps related to specific populations or comparators were identified in the CER. They are as follows:

1. What are the outcomes of procalcitonin guidance in subgroups of patients who are immunocompromised?
2. What are the outcomes of procalcitonin guidance in pediatric patients?
3. What are the outcomes of procalcitonin guidance in identifying patients at risk of infection who might benefit from pre-emptive antibiotic therapy?
4. Does the use of procalcitonin guidance reduce antibiotic resistance and antibiotic adverse events?
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?

Based on these evidence gaps, recommendations for future research targeted priority populations who were excluded explicitly from previous clinical trials or in whom insufficient evidence exists and who represent a high burden of illness. Immunocompromised patients with neutropenia or advanced HIV infection and transplant recipients would be important to study, as they often comprise a significant portion of the ICU population. Likewise, ambulatory care patients with mild to moderate immunosuppression on low-dose corticosteroids for chronic inflammatory conditions represent a significant portion of ambulatory care patients who may benefit from procalcitonin-guided antibiotic therapy instead of empiric coverage. The overuse of antibiotics in pediatric subpopulations (neonates; younger than 3 years of age; older than 3 years of age) is an understudied area in both inpatient and outpatient settings. Patients who are at higher risk of infection may benefit from pre-emptive antibiotic therapy given before any infection is clinically evident. These include patients undergoing elective colorectal surgery or other post-operative procedures, burn patients, and ICU patients.

The CER highlighted the importance of using appropriate study comparators and outcome measures that better reflect a real-world health care setting, thereby enhancing their applicability to clinical practice. So, although the CER did not assess the comparative effectiveness of using procalcitonin guidance versus antibiotic stewardship, this was noted as a recommendation for future research in recognition of the potential complementary role of procalcitonin to existing antibiotic stewardship programs and clinical practice guidelines for reducing antibiotic usage and associated adverse events in the acute care setting. Outcome measures should consider the consequences of reduction in antibiotic usage on antibiotic resistance, antibiotic-related adverse events, mortality and morbidity such as length of stay, local wound infection or sepsis.

The CER identified several common methodological weaknesses in the evidence base that should be addressed in future research. Consistent use of measures of total antibiotic exposure (e.g. mean days total exposure to all antibiotics per 1,000 days of followup) and of morbidity (e.g. need mechanical ventilation; severity of illness scores) would assist in comparing or pooling data across studies. Studies should provide an explicit rationale for noninferiority margins for mortality in specific patient populations, as the choice of a noninferiority margin incorporates clinical and statistical judgments. Transparent reporting and interpretation of nonsignificant differences should include clearly stating in the report if the study was powered to detect a difference in mortality or morbidity.

Methods

Identification of Research Needs

Figure 2 outlines the process steps of this Future Research Needs project. The details are described in the text. First, an initial set of evidence gaps was identified through the BCBCA TEC EPC CER. The literature search was updated and clinicaltrials.gov was searched to identify any ongoing or newly completed research studies that might address the research needs. Next, a group of nine stakeholders (Stakeholder Panel) representing diverse perspectives was formed. Through an iterative process the stakeholders prioritized and refined the research needs and research questions (see section on engagement of stakeholders, researchers and funders) using the SurveyMonkey™ Web site. Finally, the exploration of various research designs was conducted by the (Evidence-based Practice Center) EPC. Details of these steps follow.

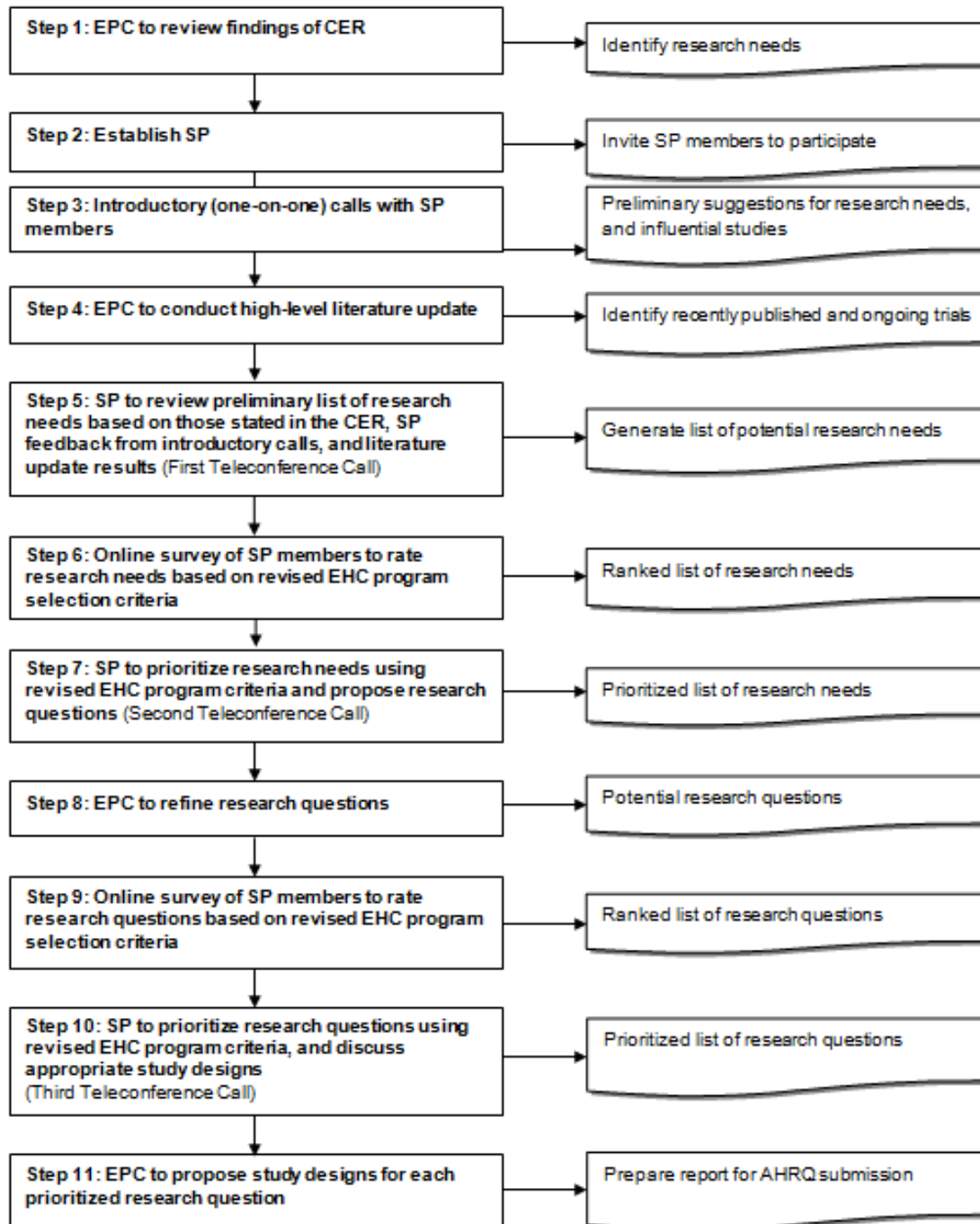
Literature Search Update

To identify recently published and ongoing studies, we conducted an updated search on April 22, 2012 using MEDLINE® (via PubMed®), Embase.com, The Cochrane Library, and the ClinicalTrials.gov databases (see Appendix B). The update captured 96 citations published since March 20, 2012. Searches gathered 88 comparative studies, randomized and nonrandomized, as well as eight clinical trials currently under way. The purpose was to identify important studies addressing research needs that ought to be taken into account when developing potential research questions, rather than to fully update the CER. Given the recent search time period as well as the fact that MEDLINE® and Embase.com contain many “in process” citations with only titles and/or abstracts, searches relied heavily on a “free text” search approach to retrieve the most current procalcitonin citations. Citations were then individually reviewed for inclusion by study type and relevance.

Criteria for Prioritization

To establish criteria for prioritizing research needs and research questions, we modified the Effective Health Care (EHC) Program Selection Criteria to be applicable to primary research rather than to systematic reviews of original research.¹⁰ These criteria are presented in Table 1. The modified EHC Program Selection Criteria were distributed to Panel members each time they were asked to prioritize research needs or research questions. Study design considerations was handled by the EPC in accordance with the recent Future Research Needs methods report by the Research Triangle Institute International-University of North Carolina at Chapel Hill (RTI-UNC) EPC on behalf of the Agency for Healthcare Research and Quality (AHRQ).¹¹ The Stakeholder Panel provided insight into how future research agendas and proposed studies to address research needs fit within these prespecified criteria.

Figure 2. Process flow diagram



AHRQ = Agency for Healthcare Research and Quality; CER = Comparative Effectiveness Review; EHC = Effective Health Care; EPC = Evidence-based Practice Center; SP = Stakeholder Panel

Table 1. Prioritization criteria for research needs and proposed research studies

Category	Criteria
Current importance	<ul style="list-style-type: none"> ● Incorporates both clinical benefits and harms ● Represents important variation in clinical care due to controversy/uncertainty regarding appropriate care ● Addresses high costs to consumers, patients, health-care systems, or payers ● Utility of available evidence limited by changes in practice, for example disease detection
Potential for significant health impact	<ul style="list-style-type: none"> ● Potential for significant health impact: <ul style="list-style-type: none"> ○ To improve <u>health outcomes</u> ○ To reduce <u>significant variation</u> related to quality of care ○ To reduce <u>unnecessary burden</u> on those with health-care problems ● Potential for significant economic impact, reducing unnecessary or excessive costs ● Potential for evidence-based change ● Potential risk from inaction, for example lack of evidence for decision-making produces unintended harms ● Addresses inequities, vulnerable populations, patient subgroups with differential impact (e.g., by age)
Incremental value	<ul style="list-style-type: none"> ● Adds useful new information to existing portfolio of research on topic, or ● Validates existing research when body of evidence is scant
Feasibility	Factors to be considered: <ul style="list-style-type: none"> ● Interest among researchers ● Duration ● Cost ● Methodological complexity (e.g., do existing methods need to be refined?) ● Implementation difficulty ● Facilitating factors ● Potential funders

Methods for Ranking Research Needs

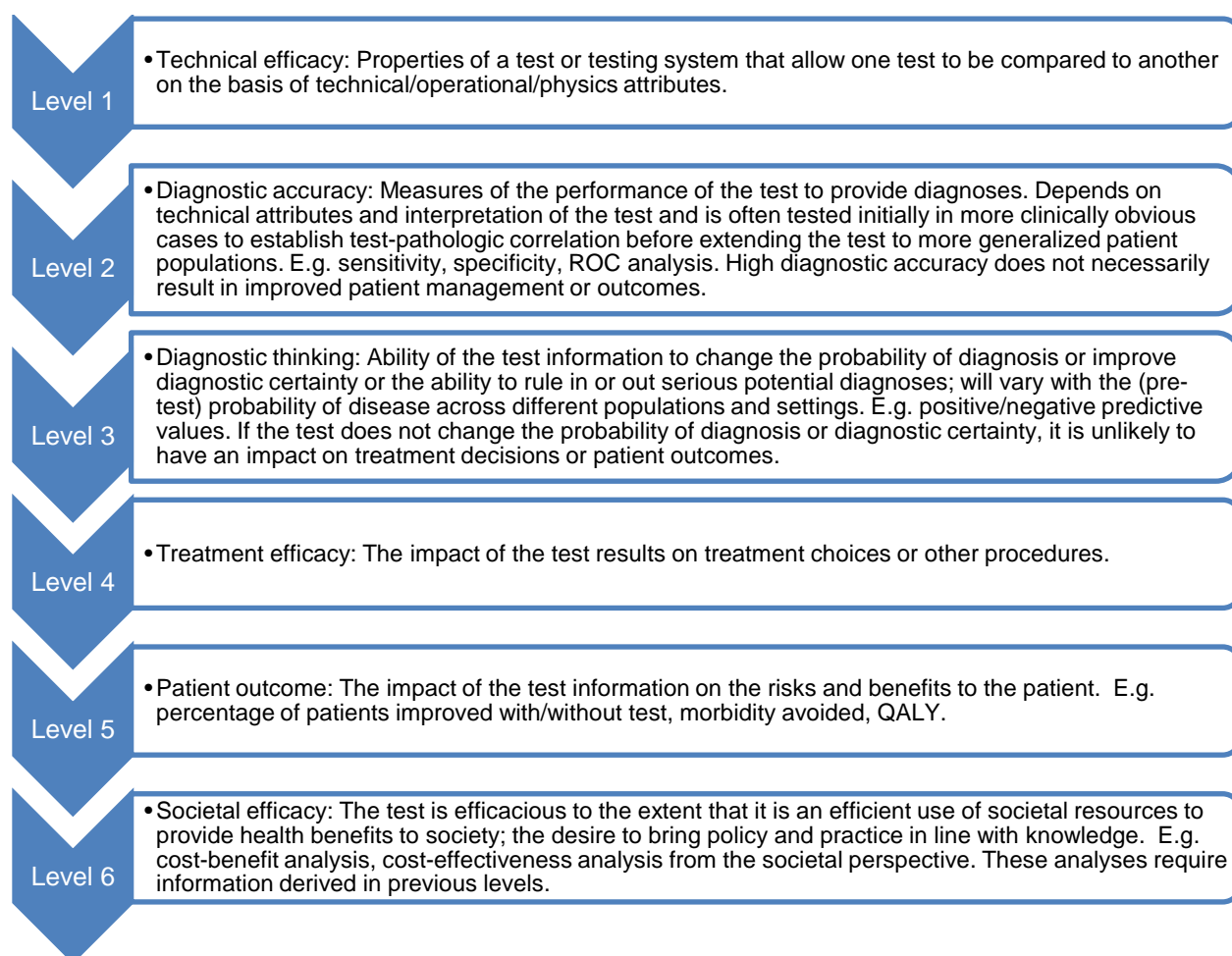
Research needs were ranked via the SurveyMonkey™ Web site. The Stakeholder Panel was sent a link to the Web site where they ranked the research needs from 1 to 5 and generated research questions for each need. The survey allowed each rank to be used only once. Points were assigned to each need: 1 point for a ranking of fifth, up to 5 points for a ranking of first. The research need with the largest number of points was assigned the highest priority. The research needs were presented in a random order for the survey.

For each research need multiple research questions may be needed that encompass the basic science of how procalcitonin fits into the innate response, as well as the properties and use of procalcitonin in diagnosis, prognosis, and treatment planning. Discussions held during the introductory calls and the first teleconference with the Stakeholder Panel revealed considerable uncertainty about the reliability of procalcitonin measured with newer testing platforms and about the predictive values and outcomes associated with its use in lesser studied populations such as pediatrics.

The properties of a diagnostic test (e.g. sensitivity, specificity, predictive values) may vary across testing platforms and populations; they may be well-defined in some populations and not in others. Gauging the progression of knowledge of a test’s diagnostic properties across patient populations may help refine the research in need of further study. To that end, a conceptual

framework for evaluating diagnostic tests was used to assist in discussions of the research needs during the second teleconference with the Stakeholder Panel.¹² This framework recognizes that a new test goes through several stages of evaluation before its usefulness in clinical practice is established. It extends from basic testing principles (Level 1) through clinical applications in diagnosis (Levels 2 and 3) and treatment decisions (Level 4) to patient and societal outcomes (Levels 5 and 6). The study designs and expectations are different for earlier levels than for later levels used in specific clinical problems. If sufficient evidence for earlier levels exists, then higher-level questions could be pursued. However, insufficient evidence at lower levels should be addressed before taking on higher-level studies. The framework is presented in Figure 3.

Figure 3. Framework of potential uses for procalcitonin



QALY = quality-adjusted life year; ROC = receiver operating characteristics

The comments received from the Stakeholder Panel during the calls and as part of the survey were reviewed by EPC staff and incorporated where necessary. In addition to the modified EHC Program Selection Criteria, special attention was paid to research needs that overlapped with existing research. The reasons for each research need were categorized based on a classification scheme created by the Johns Hopkins University EPC on behalf of AHRQ.¹³

Engagement of Stakeholders, Researchers, Funders

Central to the methodology of this report was the use of the Stakeholder Panel to identify and prioritize research needs. A single multidisciplinary Stakeholder Panel was convened to provide input on this project. The Panel included individuals interested in comparative effectiveness research and knowledgeable about current research on sepsis and biomarkers. They consisted of nine participants representing diverse perspectives (from infectious diseases, critical care, internal medicine, health policy), methodological expertise (e.g., guidelines development, clinical trials, epidemiology), and consumer and payer representation. Panel members provided specific clinical and research experience on procalcitonin guidance, including intensive care, respiratory tract infections, pediatric care, antimicrobial use, and other diseases and novel interventions.

The Stakeholder Panel was asked to recommend important studies published since the BCBSA TEC EPC completed the CER, revise and prioritize the research needs listed in the CER and gathered throughout this project, and develop and prioritize a list of potential research questions to address those research needs. As required by AHRQ, conflict of interest forms were completed by all Panel members and staff on this project. The Stakeholder Panel was asked to participate in three conference calls (1 hour each) over the project duration, and some interim communications by email. In addition, a brief introductory call (30 minutes) was scheduled separately with each individual member, to provide an overview of the project, to discuss the role of the Stakeholder Panel, and to solicit preliminary suggestions on further research needs. The first call was held on April 23, 2012. During this call, the members were asked to review the preliminary list of research needs. This list was a synthesis of evidence gaps from the CER, those proposed by Panel members during the individual introductory calls, and results of the literature search update. Members reviewed a list of revised following this call. The Stakeholder Panel was then asked to rank, via an online survey, their top 5 research needs from 1 to 5 with 1 having the highest priority and 5 the lowest. Panel members rated these research needs based on revised EHC program selection criteria (Appendix C).

The second call was scheduled on May 8, 2012. During the second call, Stakeholder Panel members were invited to review the prioritized list of research needs and “brainstorm” research questions to address each research need. Members reviewed a list of potential research questions following this call. The Stakeholder Panel was then asked to prioritize the research questions via an online survey instrument (using SurveyMonkey™) similar to that used for selection of research needs. As with the online survey for research needs, members were asked to rank their top 5 research questions from 1 to 5 with 1 having the highest priority and 5 the lowest (Appendix D). The project team collated the “votes” and reported the results at the third call, convened on June 4, 2012, for prioritization of research questions. The meeting participants reviewed the results and further discussed the importance of the research questions to patient and clinical decision making. These discussions formed the basis for the final prioritized list of research questions submitted to AHRQ in this report. All teleconference call materials were distributed a few days prior to scheduled calls.

Research Question Development and Study Design Considerations

Key research questions for each research need were generated through an online survey instrument and discussions by the Stakeholder Panel (discussed previously). The project team

compiled a final list of research questions taking the feedback of the Panel into consideration. The research questions were characterized using the PICOTS framework using the population(s) (P), interventions (I), comparators (C), outcomes (O), timing (T), and settings (S). This approach is consistent with the guidance produced by the Johns Hopkins University EPC on behalf of AHRQ.¹³ The project team later evaluated potential study designs to address each of the key research questions. The appropriateness of any one study design to address a research need was further evaluated using the following criteria:

- Advantages of the study design for producing a valid result
- Resource use, size, and duration
- Ethical, legal, and social issues
- Availability of data or ability to recruit

The project team used the guidance produced by the RTI-UNC EPC on behalf of AHRQ as a guide during discussions of the least biased study design that was likely to be feasible to undertake.¹¹ To enhance public engagement, AHRQ will solicit broader input on this document by making it available for public input, which will be incorporated and reflected in the final report.

Results

Research Needs

Appendix E provides a synthesis of research needs from the CER, those proposed by Panel members during the individual introductory calls, and results of the literature search update. A total of 10 research needs were identified through a combination of the CER findings and conversations with the Stakeholder Panel. These research needs were grouped by specific populations addressed in the CER. The Stakeholder Panel was asked to review this preliminary list of research needs during the first teleconference call. As stated in the Methods section, the Stakeholder Panel then ranked the research needs. The results of the first survey ranking the importance of these research needs are found in Appendix F. The response rate was 100 percent (n=9); 8 (of 10) research needs received votes. The EPC generated the final ranking of research needs taking all Stakeholder Panel comments into account.

The Stakeholder Panel discussed the implications of the published studies and ongoing trials found in the literature search update. The Panel members proposed condensing research needs that addressed similar issues, and they identified three priority patient groups (critically ill/ICU patients, patients presenting to the emergency department [ED], and immunocompromised patients). Furthermore, they noted that while large European trials have been conducted in some patient populations, they have not been studied in the U.S. context where differences in medical culture, regulation and practice exist. This has limited adoption of procalcitonin, for example, in patients who present to ambulatory care/ED settings in the U.S. with suspected lower respiratory tract infections. Finally, the Panel proposed addressing both adult and pediatric populations in each research need rather than treating pediatrics as a separate research need. The final three research needs are stated in Table 2.

Table 2. Prioritized list of research needs

1. The use of procalcitonin in the management of critically ill patients (all ages) with suspected lower respiratory tract infection (LRTI) or general infection.
2. The use of procalcitonin in the management of patients (all ages) with suspected LRTI in the ambulatory care/emergency department setting in the U.S.
3. The use of procalcitonin in the management of the immunocompromised patient (all ages).

Research Questions

A list of preliminary research questions drafted by the EPC across each of the prioritized research needs was submitted for feedback to Panel members via email following the second Stakeholder Panel call. Following this feedback, the second survey of research questions was submitted to Panel members for ranking prior to the third Stakeholder Panel call. The results of the second survey ranking the importance of research questions are found in Appendix G.

As with the research needs, the research questions were presented in a random order for the survey. The response rate was 100 percent (n=9); all questions received votes. There was discussion on the appropriate threshold with respect to a short list of research questions including further condensing the questions. For example, similarities were noted on the three questions related to ICU patients and Panel members were of the opinion that these could be addressed in the same request for application/grant submitted for consideration for future research. The Stakeholder Panel also discussed the importance and usefulness of future studies on the top-ranked questions based on the voting results at the third Panel call. Future research issues brought forth for discussion at this call included:

- Addressing procalcitonin guidance in pediatrics: The “cut points” are likely to vary between adult and pediatric populations; studies that include all age groups should stratify results by age to assess the contribution of procalcitonin in pediatrics independently from adults, as well as sub-groups within pediatric populations. However, rather than formulating specific research questions for pediatrics, it would be beneficial to integrate this segment of the population within the three patient groups prioritized in the research needs (i.e., ICU, outpatient ED, immunocompromised), recognizing that future procalcitonin studies in children will need a separate analysis. For example, in pediatrics, the duration of treatment in someone with suspected sepsis and negative culture is often arbitrary.
- Future studies in immunocompromised patients should address not only those with neutropenia, but also other subgroups that were specifically excluded from the studies reviewed in the CER; these subgroups include solid organ and stem-cell transplant recipients, patients with advanced HIV infection, and patients on potent immunosuppressive therapy.
- Future studies should address both the duration of use of procalcitonin and initiation of antibiotic therapy based on procalcitonin results in various populations (e.g., stopping initiation could be addressed in an urgent care/ED setting and reducing duration in the ICU setting).

These discussions formed the basis for the final prioritized list of six research questions (Table 3, in order of priority).

Table 3. Prioritized list of research questions

1.	For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a PCT-guided strategy used to determine the duration of antimicrobial therapy safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?
2.	For the otherwise healthy adult or pediatric patient who presents to ambulatory care/ED with fever and/or suspected acute LRTI, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?
3.	For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?
4.	For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a subsequent decrease in the serial PCT measurement indicate effective empiric treatment of the bacterial infection?
5.	For the immunocompromised patient who presents with suspected LRTI/sepsis, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?
6.	For the immunocompromised patient with suspected LRTI/sepsis, does a PCT-guided strategy used to determine the duration of antibacterial therapy safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?

ED = emergency department; ICU = intensive care unit; LRTI = lower respiratory tract infection; PCT = procalcitonin

The Stakeholder Panel also discussed potential study designs for the prioritized list of research questions at the third Panel call. Issues brought forth for discussion on this call included:

- One study design has the potential to address multiple research questions, e.g. questions addressing the use of procalcitonin to determine whether to start antibiotics, and other questions addressing whether to do sequential procalcitonin testing each day.

- What is/are the objective(s) of the study? This is a critical step to determine *a priori*, as separate research questions would be required to address what procalcitonin actually measures in certain populations, how it correlates with other diagnostic markers, and how it affects practice or health outcomes.
- What is the appropriate gold standard? Several clinical studies have compared procalcitonin to an imprecise investigator-adjudicated gold standard comprised of culture and clinical examination data to determine presence or absence of bacterial infection. Microbial etiology using modern molecular diagnostics would be an appropriate gold standard and essential to correlating procalcitonin results with infection etiology.
- What outcomes should be considered for evaluations of treatment strategies using procalcitonin? These should include fewer antibiotic adverse events and emergence of drug-resistant pathogens.
- What factors may influence trial outcomes of treatment strategies using procalcitonin? When considering study design options, there is a need to balance issues of equivalence with the practicality of carrying out a randomized controlled trial (RCT) or cluster RCT. For example, noninferiority trials are increasingly used to identify a new treatment strategy that may have approximately the same efficacy as an existing treatment strategy but may offer other benefits such as fewer side effects and reduced drug resistance. With noninferiority trials, the choice of noninferiority margin should be statistically based, clinically relevant, and appropriately conservative to reflect the uncertainties in the evidence. However, the magnitude of the noninferiority margin is inversely proportional to sample size, which could affect the feasibility of carrying out a RCT or cluster RCT.

The final prioritized list of research needs and research questions with PICOTS information are stated in Table 4.

Study Design Considerations

The focus of the prioritized list of research questions is on the contribution of procalcitonin-guided clinical algorithms aimed at empirically treating suspected or confirmed bacterial infection in non-outbreak settings, including primary care, emergency/ambulatory care and intensive care. To that end, similar study designs may be used to address questions of the contribution of procalcitonin to the decision to initiate, maintain or discontinue antimicrobial therapy across a range of populations; in fact, a single study may sufficiently address all questions within a research need. Table 5 presents suggestions for the most valid and feasible study designs for future research of procalcitonin that could be considered for each of the prioritized research needs. The CER did not compare outcomes of using procalcitonin guidance versus antibiotic stewardship programs, nor did it address whether addition of procalcitonin to an antibiotic stewardship program improves outcomes. Therefore, a systematic review may be warranted to identify research needs from studies comparing procalcitonin-based strategies to institutional programs aimed at reducing antibiotic use before undertaking new primary research.

Requirements of study design include defining setting specific cut-off ranges and functional assay sensitivities for procalcitonin, validated prospectively with other approaches aimed at reducing antibiotic use, to address the optimal strategy for safely addressing antibiotic overuse and emerging multidrug resistance. Study populations at institutions or individual practices that do not offer procalcitonin testing may serve as useful controls if baseline characteristics can be balanced. Investigators will need to weigh the study requirements for adequate power, desired outcomes and feasibility.¹⁴

Since cut-ranges are likely to vary between adult and pediatric populations, studies that include all age groups should stratify results by age to assess the contribution of procalcitonin in pediatrics independently from adults, as well as patient groups within pediatric populations. Studies should account for situations where the physician may decide to override the procalcitonin-guided clinical algorithm, e.g., when the procalcitonin value is low but the absolute risk of bacterial infection in a patient is high. To that end, stratification may be needed to assess the contribution of procalcitonin in populations where the uncertainty or absolute risk of bacterial infection may vary. Stratification according to drug class may be needed to account for sustained declines in antibiotic use across drug classes and antibiotic resistant isolates.

New institutional practices aimed at reducing unnecessary antibiotic use may be introduced during the course of the study as a result of new policy decisions, e.g., legislative mandates. To that end, quasi-experimental designs may offer the best approaches to account for factors that may be outside the control of the investigator. Information on barriers to implementation of procalcitonin-guided strategies and durability of results should be obtained. While a comparison of changes in antibiotic use across study arms can be accomplished in the short term, durability of the results and declines in the rates of resistance may not be observed for several years and would require longer followup. The ability to assess temporal trends in resistance and infection rates will be important in interpreting longer-term outcomes to which simulation modeling may be valuable.

Table 4. Prioritized list of research needs and research questions with PICOTS information

Research Need	Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
<p>The use of procalcitonin in the management of critically ill patients (all ages) with suspected LRTI or general infection</p> <p>Reason(s) for Research Need:</p> <p>For adults, insufficient evidence on health outcomes (e.g. antibiotic adverse events); Results from available studies are inconsistent (e.g. how adverse effects are defined, lack of details on types of adverse reactions)</p> <p>For pediatrics, insufficient or imprecise information given the limited number of studies</p>	<p><u>1.1</u> For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a PCT-guided strategy used to determine the duration of antimicrobial therapy safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p> <p><u>1.2</u> For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a subsequent decrease in the serial PCT measurement indicate effective empiric treatment of the bacterial infection?</p> <p><u>1.3</u> For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p>	<p>Critically ill adult or pediatric patient with suspected or proven pneumonia/sepsis</p>	<p>Clinical criteria with cultures if available plus PCT thresholds for determining presence/absence of bacterial infection</p>	<ul style="list-style-type: none"> • Clinical criteria with cultures if available • Institutional strategies for reducing antibiotic use (e.g. ASP, educational programs targeting staff in the outpatient setting) 	<ul style="list-style-type: none"> • Hospital or ICU admission rate • Hospital/ICU LOS • Severity of illness • ABT-associated adverse reactions (e.g. allergic reactions) • Emergence of drug resistant pathogens or superinfection • Mortality (e.g. 30-day, hospital) • Antibiotic use (e.g. duration, days without ABT and total ABT exposure in children) 	<p>On admission or suspicion of infection, duration of follow up (e.g. ≥ 30 days)</p>	<p>Hospital ICU</p>

Table 4. Prioritized list of research needs and research questions with PICOTS information (continued)

Research Need	Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
<p>The use of procalcitonin in the management of patients (all ages) with suspected LRTI in the ambulatory care/emergency department setting in the U.S.</p> <p>Reason(s) for Research Need: For all ages, not the right information as results may not be applicable to U.S. setting;</p> <p>For pediatrics, insufficient or imprecise information given the lack of studies</p>	<p>2.1 For the otherwise healthy adult or pediatric patient who presents to ambulatory care/ED with fever and/or suspected acute LRTI, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p>	<p>Adult or pediatric patient with no underlying medical conditions who presents with fever/suspected acute LRTI including community-acquired pneumonia, exacerbation of chronic obstructive pulmonary disease, and bronchitis</p>	<p>Clinical criteria with cultures if available plus PCT thresholds for determining presence/absence of bacterial infection</p>	<ul style="list-style-type: none"> • Clinical criteria • Strategies to reduce antibiotic use (e.g. CPGs, education) 	<ul style="list-style-type: none"> • Hospital/ICU admission rate • Hospital/ICU LOS • Severity of illness • ABT-associated adverse reactions (e.g. allergic reactions) • Emergence of drug resistant pathogens or superinfection • Mortality (e.g. 30-day, hospital) • Days of restricted activity with PCT-guided therapy • Relapse of infection • Antibiotic use (e.g. duration, days without ABT and total ABT exposure in children) 	<p>On admission, duration of follow up (e.g. ≥ 30 days)</p>	<ul style="list-style-type: none"> • Ambulatory care • Primary care clinic • ED

Table 4. Prioritized list of research needs and research questions with PICOTS information (continued)

Research Need	Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
<p>The use of procalcitonin in the management of the immuno-compromised patient (all ages)</p> <p>Reason(s) for Research Need:</p> <p>Insufficient or imprecise information given the limited number of studies;</p> <p>Patients with certain conditions were excluded from these studies, including neutropenia, transplant recipients (stem-cell or solid organ), and other patients on immunosuppressive therapy</p>	<p><u>3.1</u> For the immuno-compromised patient who presents with suspected LRTI/sepsis, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p> <p><u>3.2</u> For the immuno-compromised patient with suspected LRTI/sepsis, does a PCT-guided strategy used to determine the duration of antibacterial therapy safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p>	<p>Immunocompromised patients including patients infected with human immunodeficiency virus and with a CD4 count of < 200 cells/mm³, neutropenic patients, transplant recipients (stem-cell or solid organ), and other patients on immunosuppressive therapy</p>	<p>Clinical criteria with cultures if available plus PCT thresholds for determining presence/absence of bacterial infection</p>	<ul style="list-style-type: none"> • Clinical criteria with cultures if available • Institutional strategies for reducing antibiotic use (e.g. ASP, educational programs targeting staff the outpatient setting) 	<ul style="list-style-type: none"> • Hospital or ICU admission rate • Hospital/ICU LOS • Severity of illness • ABT-associated adverse reactions • Emergence of drug resistant pathogens or superinfection • Mortality (e.g. 30-day, hospital) • Days of restricted activity with PCT-guided therapy • Relapse of infection • Antibiotic use (e.g. duration, days without ABT and total ABT exposure in children) 	<p>On admission or suspicion of infection, duration of follow up (e.g. ≥ 30 days)</p>	<ul style="list-style-type: none"> • Outpatient/ED • Hospital ward • ICU

ABT = antibiotic therapy; ASP = antibiotic stewardship program; CPG = clinical practice guideline; ED = emergency department; ICU = intensive care unit; LOS = length of stay; LRTI = lower respiratory tract infection; PCT = procalcitonin

Table 5. Study design considerations

Study Design Considerations	Randomized Controlled Trial	Controlled Before-After Study	Modeling
Description of design	<p>Individuals randomly assigned to receive PCT-guided treatment strategy or standard care. Patients are followed during implementation for antibiotic use and health outcomes. Longer followup post implementation may be required if sustainability of outcome is desired (e.g., reduction of antibiotic use).</p> <p>Cluster RCTs that randomize at a hospital or ward level may be more suitable for population-level strategies when outcomes for individuals from a given unit are not independent. If pooling data across institutions is required, consensus on PCT cut-off points, standard care, outcome measures, minimum datasets and followup periods would be needed.</p>	<p>Antibiotic use and other health outcomes are compared in two or more groups of patients at the beginning and end of the study period. The study group receives the PCT-guided antibiotic treatment strategy part way into the study, and the control group receives standard care without use of PCT. Changes in outcomes from the beginning to the end of the study are compared across groups.</p> <p>Investigator controls timing of measurement(s) and variables measured, but not all intervention variables are in the control of the investigator. If pooling data across institutions is required, consensus on standards of care, outcome measures, minimum datasets and followup periods would be needed.</p>	<p>Simulation model developed and validated to assess the value of individual strategies or individual components of comprehensive strategies across a range of populations, settings and conditions. Simulation models assume statistical association (e.g. between reduced antibiotic use and antibiotic-associated adverse events) and predict the consequences of the assumption (incidence of drug resistant pathogens).</p> <p>Agent based modeling (i.e., agent is the infectious bacteria) can be used to simulate the process of infectious disease transmission and be used to track drug resistance. This would allow for assessing the impact of a PCT-guided treatment strategy for reducing antibiotic use on rates of drug resistance over time.</p>
Advantages of study design for producing a valid result	<p>Best method to control for selection bias but potentially at the cost of generalizability. It should produce the most internally valid results.</p>	<p>Simple, efficient design with generalizable results. Design offers the ability to assess the temporal relationship between outcomes and 'nonrandomizable' events, e.g., if a hospital or unit has already adopted the use of PCT. Highly susceptible to confounding variables such as other concomitant antimicrobial therapy or dual viral/bacterial infection, regression to the mean and maturation effects. Internal validity may be strengthened by collecting data on confounding variables and matching study and control groups on pre-intervention outcomes of interest (e.g. antibiotic use, infection rates). Adding multiple pre-intervention observations is particularly important for evaluating temporal trends. Adequate statistical methods will be needed to control for confounders and secular trends in resistance and infection rates.</p>	<p>May be the best option to use when questions cannot be addressed using conventional clinical trial methods or existing data analysis, e.g. assessing the impact of various antibiotic treatment strategies on rates of drug resistance over the long term. May inform and help focus future clinical trials and data collection. Models can be tailored to multiple end users and perspectives, conditions and settings to enhance generalizability of findings and to help target interventions (different populations may call for different algorithms). Other forms of modeling (e.g. compartment based, decision tree, etc.) can be informative but will require more assumptions and thus greater variability with less confidence in the results.</p> <p>Its usefulness will be limited by available data and assumptions.</p>

Table 5. Study design considerations (continued)

Study Design Considerations	Randomized Controlled Trial	Controlled Before-After Study	Modeling
Resource use, size and duration	Depending on the strategy and desired effect size and outcome (e.g. the acceptability margins used to claim equivalence or noninferiority), costs, sample size and staff time needed for recruitment and implementation could be high. Recruitment of unit “clusters” willing to be randomized may constrain sample size. Duration likely to be a few weeks, which may keep costs down, but longer followup (several years) may be required to account for the lag between change in antibiotic use and rates of nosocomial drug resistance/super-infections.	Generally less resource intensive than an experimental design, but sample size will depend on desired effect and magnitude. Otherwise, size and duration issues would be similar to RCT.	May require substantial personnel time but is generally less resource intensive than primary studies. May require primary data collection to inform components of the model if reliable estimates cannot be obtained from the literature, empiric studies or experts.
Ethical, legal, and social issues	Perception of not receiving efficacious care can pose an ethical issue and barrier to recruitment if standards of clinical equipoise are not met. For cluster RCTs, a waiver of informed consent would be required. Legal mandates or clinical culture may impede randomization to new interventions or supersede trial objectives.	Perception of not receiving efficacious care can pose an ethical issue and barrier to recruitment if standards of clinical equipoise are not met.	Additional data collection may require institutional approvals or informed consent.
Availability of data or ability to recruit	Given the high mortality rates for sepsis, patient or their families may be reluctant to enroll in an RCT. Cluster RCTs require collaborative network of sites willing to participate.	Recruiting is feasible. Design may offer the best way to study interventions where randomization may be unacceptable to patients or providers.	Data would be obtained primarily from published sources, proprietary institutional databases, and expert opinion.

PCT = procalcitonin; RCT = randomized controlled trial

Discussion

Using the BCBSA TEC EPC CER on Procalcitonin-Guided Antibiotic Therapy,⁹ we developed an 11-step process for identifying and prioritizing clinically important research needs and research questions, with key input from a diverse group of stakeholders. The final research questions reflect the research needs in the evidence related to the key populations identified in the CER. Through this process, we propose a final list of three research needs and six associated research questions.

Several issues were brought forth for discussion by the Stakeholder Panel. First, Panel members emphasized that the overriding clinical issue in the U.S. is overuse of antibiotics. If the negative predictive value of procalcitonin can be determined to reliably identify patients who would not benefit from either initiating or continuing empiric antibiotic therapy, then procalcitonin may help reduce unnecessary antibiotic use and resistance, and improve health outcomes. Second, the Stakeholder Panel brought forth the need for further study on the ability of procalcitonin to detect bacterial translocation in the critical care setting (i.e., whether procalcitonin elevations are a surrogate marker for bacterial translocation). In patients with symptoms of sepsis but with no clear source of bacterial invasion, translocation may explain elevated procalcitonin levels which would support the need for antibiotic therapy. A further issue brought forth by the Stakeholder Panel was the need for targeted education strategies for health professionals regarding the appropriate use of procalcitonin given the increasing availability of the test; this issue would be important to consider when creating knowledge translation materials based on the research findings of the CER and this Future Research Needs initiative.

Finally, during discussions on potential study designs, the Stakeholder Panel brought forth issues that were not addressed in the CER but would be important to consider in future studies. Given the differences in procalcitonin assays and populations, it may be difficult to compare results across studies when different platforms or cut-off thresholds are used. There is a need to use consistent platforms and associated cut-off thresholds in order to compare results across studies, yet as the technology evolves, using a single platform might limit the generalizability of study results to other settings. At a minimum, the specific assay should be described. The Panel members acknowledged that this will be a challenging but fundamental issue to address in future research. Furthermore, the Panel members noted that there are newly developed antibodies for procalcitonin from a variety of companies that are not currently available for clinical use, but are used for research purposes. Health professionals may choose to use these technologies for convenience or cost purposes in clinical care. Thus, it would be beneficial if future trials are based on clinically-validated platforms in order to compare data that could be readily transferable to the bedside.

There are several strengths to our process. First, it is important that Panel members represented a wide range of relevant disciplines to ensure a balanced and broad perspective on research needs that addressed the research needs from the CER on this topic. Each stakeholder was highly interested and committed. There were high levels of participation at each step. Two Panel members were part of the Technical Expert Panel for the original CER, and one additional member acted as a peer reviewer. The consumer perspective was especially useful in drawing attention to ways in which patients experience care and the impact of sepsis on other aspects of their lives (e.g., work). The consumer representative noted significant practice variation across health care settings in the U.S. given the absence of rigorous clinical practice guidelines that incorporate procalcitonin; while outside the scope of the CER, there is a need to address effective prevention strategies for sepsis.

Second, given the breadth of potential topics, the introductory one-on-one calls with Panelists helped establish the preliminary list of research needs. This made the first conference call with the Stakeholder Panel more productive. Third, the literature search update allowed for more informed decisions in selecting topics that were not duplicative with current ongoing trials and to which further research would add the greatest value. Given the multiple populations under study, it was helpful to the project team to organize the literature search update and stakeholder information according to the research needs identified in the CER that evolved into specific research questions (e.g., initiating antimicrobial therapy, duration). These themes allowed the team to cover more comprehensively aspects of disease management along the continuum of care, care settings, and populations. The project team also sought feedback from the stakeholders to identify key published studies and ongoing trials across the list of research needs.

Finally, the internet surveys were successful in prioritizing issues across a broad range of categories. When provided with information on available research, rankings by the Stakeholder Panel appeared to be based on the amenability to comparative effectiveness research. A number of stakeholders were complimentary of our process. The Panel members agreed that the final list of research needs and research questions covered key topics for future study on this topic.

We encountered several challenges to our process. First, there were several ways to combine/categorize many of the proposed topics. There was crossover and overlap between the various research needs, and the key underlying research questions across the top-ranked three research needs. The categorization was dependent on how the Stakeholder Panel wanted to approach different topic areas. For example, the proposed topics could be categorized either by different segments of the population (adult, pediatric), specific settings (e.g., ICU, urgent care/ED), or different uses of procalcitonin (initiation of antibiotic therapy, duration) in various populations. Second, the Stakeholder Panel noted that studies of diagnostic performance and interventional studies were at different stages in different populations. For example, there have been many studies in target populations of adults presenting with suspected LRTI, and thus future clinical trials could progress toward interventional studies; once the benefits and harms of the test have been established, studies could then evaluate dissemination strategies, and availability and physician acceptance of the test. For other populations, such as in immunocompromised patients or children, data on procalcitonin diagnostic performance may be inadequate at present. The conceptual framework of evaluating the efficacy of procalcitonin (Figure 3) was useful in guiding these discussions with the Stakeholder Panel.

Third, it was important to maintain the focus on the research needs in the evidence (and scope) addressed in the original CER. The research needs were grouped by categories that could be linked to the CER scope, as the team had the evidence reviews and the updated literature search to back the findings. This always presents a challenge as evidenced by some of the topics brought forth by the Stakeholder Panel listed in the previous paragraphs (differences between assays, bacterial translocation, physician education, etc.). The project team reiterated during the teleconference calls with the Stakeholder Panel the focus of the CER and this Future Research Needs initiative; any additional issues of concern and importance raised by the Panel members would be addressed in the discussion section of the report submitted to AHRQ. Finally, one additional challenge or a limitation of this process was that the Stakeholder Panel was presented with the draft results of the CER; the conclusions did change between the draft and the final report and thus the impact of these results on the rankings of the research needs is unknown.

Conclusion

This Future Research Needs project was developed using the findings of the BCBSA TEC EPC CER. We engaged a multidisciplinary Stakeholder Panel of nine participants using an 11-step process to identify and prioritize research needs and key research questions across the selected research needs. The results of this process are the three prioritized research needs and six research questions in Table 6.

Table 6. Prioritized research needs and research questions

Research Need	Research Question
<p>The use of procalcitonin in the management of critically ill patients (all ages) with suspected LRTI or general infection</p>	<p><u>1.1</u> For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a PCT-guided strategy used to determine the duration of antimicrobial therapy safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p> <p><u>1.2</u> For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a subsequent decrease in the serial PCT measurement indicate effective empiric treatment of the bacterial infection?</p> <p><u>1.3</u> For the critically ill/ICU adult or pediatric patient with suspected pneumonia/sepsis, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p>
<p>The use of procalcitonin in the management of patients (all ages) with suspected LRTI in the ambulatory care/emergency department setting in the U.S.</p>	<p><u>2.1</u> For the otherwise healthy adult or pediatric patient who presents to ambulatory care/ED with fever and/or suspected acute LRTI, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p>
<p>The use of procalcitonin in the management of the immunocompromised patient (all ages)</p>	<p><u>3.1</u> For the immunocompromised patient who presents with suspected LRTI/sepsis, does a strategy for initiating (and maintaining) antimicrobial therapy based on PCT safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p> <p><u>3.2</u> For the immunocompromised patient with suspected LRTI/sepsis, does a PCT-guided strategy used to determine the duration of antibacterial therapy safely reduce antibiotic use and improve health outcomes compared with a strategy not based on PCT?</p>

ED = emergency department; ICU = intensive care unit; LRTI = lower respiratory tract infection; PCT = procalcitonin

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Acronyms and Abbreviations

ABT	Antibiotic therapy
AHRQ	Agency for Healthcare Research and Quality
ASP	Antibiotic stewardship program
BCBSA TEC	Blue Cross and Blue Shield Association Technology Evaluation Center
CER	Comparative Effectiveness Review
CPG	Clinical practice guideline
EHC	Effective Health Care
EPC	Evidence-based Practice Center
ED	Emergency department
ICU	Intensive care unit
LOS	Length of stay
LRTI	Lower respiratory tract infection
PICOTS	Population(s), Interventions, Comparators, Outcomes, Timing, Settings
RCT	Randomized controlled trial
RTI-UNC	Research Triangle Institute International-University of North Carolina

Appendix A. Summary of Evidence From Draft Comparative Effectiveness Review

Patient Group	Outcome	Unit	No. of Studies	Reference	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

Note: This table lists the findings from the draft CER report; the conclusions have changed between the draft and the final report.

B, risk of bias; C, consistency; CI, confidence interval; D, directness; GFR, Glomerular filtration rate; ICU, intensive care unit; N/A, not applicable; 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 to guide initiation, discontinuation or a change of antibiotic therapy.

Appendix B. Search Strategy for Ongoing Studies

PubMed Search Strategy

1. procalcitonin[tiab] OR procalcitonin[title] OR PCT[tiab] = 2037
2. 1 AND ("last 60 days"[PDat]) = 65 English = 60 Added to EndNote = 36

EMBASE Search Strategy

1. PCT OR 'procalcitonin'/de OR procalcitonin AND [20-3-2012]/sd NOT [22-4-2012]/sd AND [english]/lim AND [2012-2012]/py = 69
2. Limited to Publication Types: Articles OR in Press OR Conf Abstract OR Review = 52
Added to EndNote

Clinical Trials.Gov

1. Procalcitonin [ALL-FIELDS] OR PCT [ALL-FIELDS] AND First Received: 3/20/2012 to 4/22/2012
2. Procalcitonin [ALL-FIELDS] OR PCT [ALL-FIELDS] AND Last Updated: 3/20/2012 to 4/22/2012
3. 1 OR 2 = 8 Added to EndNote

Cochrane Search Strategy

1. Procalcitoni :ti, ab,kw OR PCT:ti,ab,kw = 291
2. 1 AND 2012-2012 = 1 already in EndNote

Appendix C. Survey Tool Used To Rate Research Needs

Instructions to fill the survey

The objective is to rate the research needs based on pre-specified criteria by using a voting mechanism. Please read the following instructions carefully before proceeding with your voting.

Instructions:

- There are in total 10 research needs
- Each panel member has been allotted a total of 5 votes.
- Choose and rank research needs in the order of your perceived importance with a score of 1 representing the highest importance and 5 representing lower importance.

Please cast your votes based on the following criteria:

- Current importance
- Potential for significant health impact
- Incremental value
- Feasibility

You can review these criteria in detail [below].

Prioritization Criteria for Research Needs

Current importance

- Incorporates both clinical benefits and harms
- Represents important variation in clinical care due to controversy/uncertainty regarding appropriate care
- Addresses high costs to consumers, patients, health-care systems, or payers
- Utility of available evidence limited by changes in practice, e.g., disease detection

Potential for significant health impact

- Potential for significant health impact:
 - o To improve health outcomes
 - o To reduce significant variation related to quality of care
 - o To reduce unnecessary burden on those with health-care problems
- Potential for significant economic impact, reducing unnecessary or excessive costs
- Potential for evidence-based change
- Potential risk from inaction, i.e., lack of evidence for decision-making produces unintended harms
- Addresses inequities, vulnerable populations, patient subgroups with differential impact (e.g., by age)

Incremental value

- Adds useful new information to existing portfolio of research on topic OR
- Validates existing research when body of evidence is scant

Feasibility

- Factors to be considered:
 - o Interest among researchers
 - o Duration
 - o Cost
 - o Methodological complexity (e.g., do existing methods need to be refined?)
 - o Implementation difficulty
 - o Facilitating factors
 - o Potential funders

(Criteria modified for primary research from: Whitlock EP et al. AHRQ Series Paper 3: Identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the Effective Health-Care program. Journal of Clinical Epidemiology 2010; 63: 491-501)

*Please rank your top 5 Research Needs from 1 to 5 with 1 having the highest priority and 5 the lowest.

1. Management of the pediatric patient with chronic illness presenting with suspected bacterial pneumonia (e.g., in cystic fibrosis, sickle cell disease)
2. Management of patients (all ages) with suspected lower respiratory tract infection (LRTI) in the emergency-room setting in the U.S.
3. Management of critically ill patients (all ages) with suspected LRTI or general infection
4. Management of patients (all ages) on immune-modulators (e.g., steroids) and other systemic therapies
5. Management of patients (all ages, including post-op) with fever of unknown source
6. Management of adults with chronic diseases presenting with suspected pneumonia/sepsis
7. Management of the pediatric patient with suspected bone/joint infections
8. Management of the pediatric patient with periodic fever syndrome
9. Management of the high risk pediatric patient (neonate, age 3-36 months) to rule out need for antibiotics
10. Management of the immunocompromised patient (all ages)

If you have any further comments please give them below:

Appendix D. Survey Tool Used To Rate Research Questions

Instructions to fill the survey

The objective is to rate the research questions based on pre-specified criteria by using a voting mechanism. Please read the following instructions carefully before proceeding with your voting.

Instructions:

- There are in total 13 research questions
- Each panel member has been allotted a total of 5 votes.
- Choose and rank questions in the order of your perceived importance with a score of 1 representing the highest importance and 5 representing lower importance.

Please cast your votes based on the following criteria:

- Current importance
- Potential for significant health impact
- Incremental value
- Feasibility

You can review these criteria in detail [below].

Prioritization Criteria for Research Questions

Current importance

- Incorporates both clinical benefits and harms
- Represents important variation in clinical care due to controversy/uncertainty regarding appropriate care
- Addresses high costs to consumers, patients, health-care systems, or payers
- Utility of available evidence limited by changes in practice, e.g., disease detection

Potential for significant health impact

- Potential for significant health impact:
 - o To improve health outcomes
 - o To reduce significant variation related to quality of care
 - o To reduce unnecessary burden on those with health-care problems
- Potential for significant economic impact, reducing unnecessary or excessive costs
- Potential for evidence-based change
- Potential risk from inaction, i.e., lack of evidence for decision-making produces unintended harms
- Addresses inequities, vulnerable populations, patient subgroups with differential impact (e.g., by age)

Incremental value

- Adds useful new information to existing portfolio of research on topic OR
- Validates existing research when body of evidence is scant

Feasibility

- Factors to be considered:
 - o Interest among researchers
 - o Duration
 - o Cost
 - o Methodological complexity (e.g., do existing methods need to be refined?)
 - o Implementation difficulty
 - o Facilitating factors
 - o Potential funders

(Criteria modified for primary research from: Whitlock EP et al. AHRQ Series Paper 3: Identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the Effective Health-Care program. Journal of Clinical Epidemiology 2010; 63: 491-501)

*Please rank your top 5 research questions from 1 to 5 with 1 having the highest priority and 5 the lowest.

1. For the high risk pediatric patient who presents with fever and suspected early sepsis, does a strategy for initiating antimicrobial therapy based on PCT improve health outcomes compared to a strategy not based on PCT?
2. For ICU patients with pneumonia/sepsis, following initiation of empiric antibacterial therapy, does a subsequent decrease in the PCT serum concentration indicate effective treatment of the bacterial infection?
3. For ICU patients with pneumonia/sepsis, does a PCT-guided strategy used to determine the duration of antibacterial therapy improve health outcomes compared to a strategy not based on PCT?
4. For the immunocompromised patient with suspected LRTI/sepsis, can the duration of therapy be safely based on normalization of the serum PCT level?
5. For patients with underlying stable chronic disease (e.g. diabetes, renal disease, but excluding immunocompromised patients) and a high uncertainty of infection, is PCT a reliable indicator of bacterial infection?
6. For critically ill hypotensive patients with no clear focal bacterial infection and negative blood cultures, does an elevated PCT level indicate occult translocation of intestinal bacteria into the bowel wall, portal vein, and/or bloodstream?
7. For ICU patients with a high uncertainty of pneumonia/sepsis, does a strategy for initiating antimicrobial therapy based on PCT improve health outcomes compared to a strategy not based on PCT?
8. For the high risk pediatric patient who presents with fever, is PCT a reliable indicator of early infection/sepsis?

9. For patients with chronic lung disease who present to urgent care/ER with suspected acute LRTI, can the serum PCT level distinguish bacterial from non-bacterial infection and improve health outcomes?

10. For the immunocompromised patient who presents with suspected LRTI/sepsis, does a strategy for initiating antimicrobial therapy based on PCT improve health outcomes compared to a strategy not based on PCT?

11. For the immunocompromised patient who presents with suspected LRTI/sepsis, is PCT a reliable early indicator of bacterial infection?

12. In the pediatric patient with suspected sepsis but an otherwise negative culture, can the duration of therapy be safely based on normalization of the serum PCT level?

13. For the low risk (otherwise healthy) patient who presents to urgent care/ER with fever and suspected acute LRTI, can the serum PCT level distinguish bacterial from non-bacterial infection and improve health outcomes?

If you have any further comments please give them below:

Appendix E. List of Research Needs

Research Needs	Systematic Review Results	Stakeholders	Primary Studies/Reviews	Ongoing Clinical Trials
What are the outcomes of PCT guidance in subgroups of patients who are immunocompromised?	<ul style="list-style-type: none"> • Little evidence available because often excluded from trials. • Represent significant ICU subpopulations and other conditions e.g. CF, pregnancy. • Vulnerable to antibiotic resistance and adverse effects of antibiotics. • Host cytokine response affects PCT levels, so PCT cut-offs may differ in these populations. • Potential role for PCT guidance in reducing antibiotic usage in the ambulatory patients with mild to moderate immunosuppression vs. standard therapy. 	<ul style="list-style-type: none"> • This is a major priority population. • Depends on definition of immunocompromised. PCT expression of genes that control PCT are mediated by innate immunity, not adaptive immunity. (e.g., patients with febrile neutropenia seem to respond similar to non-immunocompromised.) 	None identified	None identified
What are the outcomes of PCT guidance in pediatric patients?	<ul style="list-style-type: none"> • Evidence is limited to two underpowered studies of children ages 1-36 months in the acute care hospital setting. • No evidence for children ages 3 years to 18 years. • Future studies of PCT-guided initiation and discontinuation of antibiotics will be extremely important to address the overuse of antibiotics in both the inpatient and outpatient settings. 	<ul style="list-style-type: none"> • This is a major priority population. • Specifically, how should PCT be used in the febrile infant who presents through the ER? • Many early (albeit) observational studies of PCT were in pediatrics. • In pediatric patients age 3-36 months use PCT to rule out antibiotics. • Specific populations in need of study of PCT-guided antibiotic therapy are <ul style="list-style-type: none"> ○ Critical care patients ○ Severely immunocompromised patients (e.g., leukemia or febrile neutropenia). ○ Patients who present with fever 	<ol style="list-style-type: none"> 1. Esposito S, et al. Procalcitonin measurements for guiding antibiotic treatment in pediatric pneumonia. <i>Respir Med</i> 2011 Dec;105(12): 1939-45. PMID: 21959024. 2. Jordan I, et al. Procalcitonin: A useful biomarker to discriminate infection after cardiopulmonary bypass in children. <i>Pediatr Crit Care Med</i> 2012 Mar 14. PMID: 22422165. 3. Phillips RS, et al. Systematic review and meta-analysis of the value of initial biomarkers in predicting adverse outcome in febrile neutropenic episodes in children and young people with cancer. <i>BMC Med</i> 2012 	<p>NCT Number: NCT00854932</p> <p>Title: Neonatal Procalcitonin Intervention Study</p> <p>Completion date: July 2013</p> <p>URL: ClinicalTrials.gov/show/NCT00854932</p>

Research Needs	Systematic Review Results	Stakeholders	Primary Studies/Reviews	Ongoing Clinical Trials
		<p>without a source, especially 1-3 months of age (even up to 3 years).</p> <ul style="list-style-type: none"> ○ Periodic fever syndromes. ○ Suspected bacterial pneumonia (e.g., in cystic fibrosis). ○ Children with bone and joint infections (in whom inflammatory markers are used to differentiate inflammation from infection). 	<p>Jan 18;10(1): 6. PMID: 22257704.</p> <p>4. Unal S, et al. Procalcitonin is more useful than C-reactive protein in differentiation of fever in patients with sickle cell disease. Journal of pediatric hematology/oncology 2012 Mar;34(2):85-9. PMID: 22367384.</p> <p>5. Yuksel S, et al. The value of procalcitonin measurements in children with familial Mediterranean fever. Rheumatology international 2011 Nov 6. PMID: 22057145</p> <p>6. Louw JJ, et al. Serum procalcitonin is not an early marker of pulmonary exacerbation in children with cystic fibrosis. European journal of pediatrics 2012 Jan;171(1):139-42. PMID: 21630003.</p>	
<p>What are the outcomes of PCT guidance in identifying patients at risk of infection who might benefit from pre-emptive antibiotic therapy?</p>	<ul style="list-style-type: none"> • Limited evidence from one small study in preoperative patients scheduled for colorectal surgery suggests that PCT may identify a high risk group who would benefit from preemptive antibiotic therapy. • Larger studies are needed to confirm results e.g. reduce infectious complications. • Other high risk patient populations include burns, ICU residents, and other postoperative patients 	<ul style="list-style-type: none"> • How to use PCT in the febrile hospital patient (e.g., post trauma or post surgery). The existing research has studied heterogeneous populations. We need to determine cut-offs for these specific populations. • Post-op patients to reduce risk of bacterial translocation from the GI tract. This is just ripe for clinical study because we have two markers that can be correlated for supporting evidence of bacterial translocation. Both are easily available and are generally accepted in critical care medicine. 	<p>Jordan I, et al. Procalcitonin: A useful biomarker to discriminate infection after cardiopulmonary bypass in children. Pediatr Crit Care Med 2012 Mar 14. PMID: 22422165.</p>	<p>NCT Number: NCT01264549 Title: Stroke Adverse Outcome is Associated With Nosocomial Infections: PCTus-Guided Antibacterial Therapy in Severe Ischemic Stroke Patients (STRAWINSKI) Completion Date: July 2012 URL: ClinicalTrials.gov/show/NCT01264549</p>

Research Needs	Systematic Review Results	Stakeholders	Primary Studies/Reviews	Ongoing Clinical Trials
<p>Does the use of PCT guidance reduce antibiotic resistance and antibiotic adverse events?</p>	<ul style="list-style-type: none"> Evidence from RCTs was insufficient to show a correlation between an observed reduction in antibiotic use and effect of antibiotic adverse reactions, super-infections, or drug resistance. Studies lacked standardized reporting of adverse events from antibiotics, especially the incidence of <i>C. difficile</i> and active surveillance for colonization with drug-resistant pathogens. 	<ul style="list-style-type: none"> Need standardized reporting of outcomes 	<ol style="list-style-type: none"> Albrich WC, et al. Procalcitonin-guided antibiotic stewardship in lower respiratory tract infections. A real-life international multicentre quality surveillance (ProREAL). <i>Clinical Microbiology and Infection</i> 2011;17:S9 [ESCMID] Li H, et al. Meta-analysis and systematic review of procalcitonin-guided therapy in respiratory tract infections. <i>Antimicrob Agents Chemother</i> 2011 Dec;55(12):5900-6. PMID: 21947386. Esposito S, et al. Procalcitonin measurements for guiding antibiotic treatment in pediatric pneumonia. <i>Respir Med</i> 2011 Dec;105(12): 1939-45. PMID: 21959024. Jensen JU, et al. Kidney failure related to broad-spectrum antibiotics in critically ill patients: secondary end point results from a 1200 patient randomised trial. <i>BMJ open</i> 2012;2(2):e000635. PMID: 22411933 	<p>NCT01494675 Title: Procalcitonin as a Tool to Shorten Antibiotic Therapy in the ICU Completion Date: Dec 2011 URL: ClinicalTrials.gov/show/NCT01494675</p> <p>NCT00832039 Title: Placebo Controlled Trial of Sodium Selenite and Procalcitonin Guided Antimicrobial Therapy in Severe Sepsis Completion date: Nov 2013 URL: ClinicalTrials.gov/show/NCT00832039</p> <p>NCT01018199 Title: Procalcitonin Versus C-reactive Protein to Guide Therapy in Community Acquired Pneumonia Completion Date: August 2014 URL: ClinicalTrials.gov/show/NCT01018199</p> <p>NCT01264549 Title: Stroke Adverse Outcome is Associated With Nosocomial Infections: PCTus-Guided Antibacterial Therapy in Severe</p>

Research Needs	Systematic Review Results	Stakeholders	Primary Studies/Reviews	Ongoing Clinical Trials
				Ischemic Stroke Patients (STRAWINSKI) Completion Date: July 2012 URL: ClinicalTrials.gov/show/NCT01264549
How does PCT-guided antibiotic therapy compare to other approaches to reducing unnecessary antibiotic use, such as antibiotic stewardship programs and implementation of practice guidelines?	<ul style="list-style-type: none"> Primary studies and systematic reviews are needed to compare the effects of a broad range of interventions (with or without PCT) on the overuse of antibiotics and clinical outcomes Studies are needed to address four important methodologic weaknesses that were common across the studies and bodies of evidence reviewed in this report. 	<ul style="list-style-type: none"> A major priority is impact of antibiotic stewardship programs vs. alternatives e.g., PCT-guided antibiotic therapy or clinical practice guideline (CPG)-guided antibiotic therapy, the latter being a systematic review the societies presented to AHRQ a few years ago. Important area for further study. 	<ol style="list-style-type: none"> Li H, et al. Meta-analysis and systematic review of procalcitonin-guided therapy in respiratory tract infections. <i>Antimicrob Agents Chemother</i> 2011 Dec;55(12):5900-6. PMID: 21947386 Esposito S, et al. Procalcitonin measurements for guiding antibiotic treatment in pediatric pneumonia. <i>Respir Med</i> 2011 Dec;105(12):1939-45. PMID: 21959024 	NCT01379547 Title: Procalcitonin to Shorten Antibiotics Duration in ICU Patients Completion Date: Dec 2012 URL: ClinicalTrials.gov/show/NCT01379547 NCT00832039 Title: Placebo Controlled Trial of Sodium Selenite and Procalcitonin Guided Antimicrobial Therapy in Severe Sepsis Completion Date: Nov 2013 URL: ClinicalTrials.gov/show/NCT00832039

Other priority populations/questions	Stakeholders	References
Is PCT a valid indicator of source control?	<ul style="list-style-type: none"> Jensen study used different endpoints and recommendations of continuing/increasing antibiotics if PCT not decreased; both differ from U.S. practice. 	Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. Journal of clinical microbiology 2010 Jul;48(7):2325-9. PMID: 20421436.
How long should we treat the infection?	<ul style="list-style-type: none"> In U.S., PCT measured every 2-4 days depending on diagnosis until ~.12, which is typically 1-2 days shorter than recommended. How long should we treat the bacteremia, pneumonia, etc. The literature has these very arbitrary re durations of treatment. 	Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. Journal of clinical microbiology 2010 Jul;48(7):2325-9. PMID: 20421436.
Patients admitted to the ED with a lower RTI in the U.S..	<ul style="list-style-type: none"> #1 priority population. This population represents a high burden of illness, but all randomized evidence is solely from European trials, which have shown PCT useful for reducing antibiotic use in this population without reducing outcomes. This has not been studied in U.S. EDs where differences in medical culture, regulation and practice exist. Can these benefits be realized in the U.S. where clinicians may or may not respond to a prompt to obtain PCT levels or obtain them prior to antibiotic prescription? 	Gilbert DN. Procalcitonin as a biomarker in respiratory tract infection. Clin Infect Dis 2011 May;52 Suppl 4:S346-50. PMID: 21460294.
Patients with chronic disease e.g. chronic inflammatory lung disease, CHF, metabolic syndromes	<ul style="list-style-type: none"> These patients make up the bulk of patients we see with suspected pneumonia or sepsis and increasingly the burden of health delivery of patients who are see in ambulatory and urgent care settings. 	[Horie (sp?), 2011 or 2012 in North American Journal of Medical Sciences (not currently indexed in PubMed)]
Patients on immunomodulators (e.g., steroids) and other systemic therapies.	<ul style="list-style-type: none"> How do these therapies impact PCT measurement used for treatment planning? 	Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. Journal of clinical microbiology 2010 Jul;48(7):2325-9. PMID: 20421436.
Unexplained PCT elevation e.g. bacterial translocation from the GI tract.	<ul style="list-style-type: none"> This is just 'ripe' for clinical study because we have two markers that can be correlated for supporting evidence of bacterial translocation. Both are easily available and are generally accepted in the critical care medicine world. 	Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. Journal of clinical microbiology 2010 Jul;48(7):2325-9. PMID: 20421436.
Fever of unknown origin	<ul style="list-style-type: none"> Patients with central venous line or other invasive devices who present with fever with an unknown source. PCT may help identify etiology. 	Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. Journal of clinical microbiology 2010 Jul;48(7):2325-9. PMID: 20421436.
Dual infection	<ul style="list-style-type: none"> PCT levels used to determine viral from bacterial, but need etiology. Need basic science and clinical studies to give physicians more confidence as far as predicting whether a bacterial vs. viral infection is present (help with antibiotic stewardship). 	

Other issues identified by Stakeholders	
Methodological	<ul style="list-style-type: none"> • RCTs are not testing the biomarker, but rather the success of the treatment strategy with versus without PCT. Many systematic reviews have not addressed this point. RCTs should incorporate PCT derived from newer high sensitive assays. The older assays have not been successful as a rule-out test. Systematic reviews often do not address this point. • Need to study the effect of PCT on empiric antibiotic therapy. Most evidence is from Europe, not correlated with etiology. Needs to be confirmed in prospective trials. • For PCT to be useful, need results within 1 hour of specimen collection, but most literature has measured it within 24 hours. A laboratory perspective is essential in planning studies.
General	<ul style="list-style-type: none"> • Major priority issue - Use of PCT is variable because there are no guidelines for using it in practice in U.S. • Overall, need studies that give physicians more confidence in PCT values e.g., viral vs. bacterial, source control, guiding duration of therapy. • Agree with the Research Needs. There have been few RCTs in these areas, the most recent being a Scandinavian trial that found PCT not useful as a rule in test for antibiotic use. Not sure if this trials has yet been published. • Strongest evidence for PCT is in fairly low-risk patients with RTIs. How generalizable are its diagnostic characteristics to other patient populations? • CDC is funding a study of an assay for screening a number of biomarkers, including PCT, for informing the duration of antibiotic treatment for sepsis in the ICU in adults and children. Just started. • Need study of the use of multi-panel assays to differentiate bacterial from viral or fungal infections.

Appendix F. Survey Results of Research Needs

Research Needs and Preliminary Research Questions	Total Votes*	Weighed Total	Technical Efficacy (Level 1)**	Diagnostic Performance (Levels 2 & 3)		Impact on Treatment (Level 4)	Impact on Patient Outcomes (Level 5)	Societal Impact (Level 6)
1. Management of critically ill patients (all ages) with suspected lower respiratory tract infection (LRTI) or general infection	8	33						
1.1.1. Is PCT a valid indicator of bacterial infection in 'non-septic' patients with suspected LRTI or general infection?				√	√			
1.1.2. What is the comparative effectiveness of clinical criteria with vs. without PCT for discontinuing/ changing antibiotic therapy in 'non-septic' persons with suspected LRTI or general infection?						√	√	√
1.2.1. Is PCT a valid indicator of bacterial infection in patients hospitalized with a non-infectious condition who develop delayed fever without signs of sepsis?				√	√			
1.2.2. What is the comparative effectiveness of clinical criteria with vs. without PCT for initiating antibiotic therapy in persons hospitalized with a non-infectious condition who develop delayed fever without signs of sepsis?						√	√	√
2. Management of patients (all ages) with suspected LRTI in the emergency room setting in the U.S.	8	31						
2.1. Is PCT a valid indicator of bacterial infection in patients who present to the emergency room with suspected LRTI?				√	√			
2.2. What is the comparative effectiveness of clinical criteria with PCT vs. without PCT for initiating antibiotic therapy in patients with suspected LRTI?						√	√	√
3. Management of adults with chronic diseases presenting with suspected pneumonia/sepsis	7	22						
3.1. For adults with chronic disease with suspected pneumonia/sepsis, is PCT a valid indicator of bacterial infection?				√	√			
3.2. For adults with chronic disease with suspected pneumonia/sepsis, what is the comparative effectiveness of clinical criteria with PCT vs. without PCT for initiating antibiotic therapy?						√	√	√
3.3. For adults with chronic disease with suspected pneumonia/sepsis, what is the comparative effectiveness of clinical criteria with PCT vs. without PCT for discontinuing/changing antibiotic therapy?						√	√	√

Research Needs and Preliminary Research Questions	Total Votes*	Weighed Total	Technical Efficacy (Level 1)**	Diagnostic Performance (Levels 2 & 3)		Impact on Treatment (Level 4)	Impact on Patient Outcomes (Level 5)	Societal Impact (Level 6)
4. Management of the high risk pediatric patient (neonate, age 3-36 months) [with suspected early sepsis] to rule out need for antibiotics	7	13						
4.1. For high risk pediatric patients who present with suspected early sepsis, is PCT a valid indicator of bacterial infection?				√	√			
4.2. For high risk pediatric patients who present with suspected early sepsis, what is the comparative effectiveness of clinical criteria with PCT vs. without PCT for initiating antibiotic therapy?						√	√	√
5. Management of the immunocompromised patient (all ages)	6	14						
5.1.1. For patients with mild to moderate immunosuppression, is PCT a valid indicator of bacterial infection?				√	√			
5.1.2. For patients with mild to moderate immunosuppression, what is the comparative effectiveness of clinical criteria with PCT vs. without PCT for initiating antibiotic therapy?						√	√	√
5.1.3. For patients with mild to moderate immunosuppression, what is the comparative effectiveness of clinical criteria with PCT vs. without PCT for discontinuing/changing antibiotic therapy?						√	√	√
5.2.1. For patients with severe immunosuppression, is PCT a valid indicator of bacterial infection?				√	√			
5.2.2. For patients with severe immunosuppression, what is the comparative effectiveness of clinical criteria with PCT vs. without PCT for initiating antibiotic therapy?						√	√	√
5.2.3. For patients with severe immunosuppression, what is the comparative effectiveness of clinical criteria with PCT vs. without PCT for discontinuing/changing antibiotic therapy?						√	√	√
6. Management of patients (all ages, including post-op) with fever of unknown source	5	13						
6.1. For patients who present with a fever of unknown source, is PCT a valid indicator of bacterial infection?				√	√			
6.2. For patients who present with a fever of unknown source, what is the comparative effectiveness of clinical criteria with PCT vs. without PCT for initiating antibiotic therapy?						√	√	√

Research Needs and Preliminary Research Questions	Total Votes*	Weighed Total	Technical Efficacy (Level 1)**	Diagnostic Performance (Levels 2 & 3)		Impact on Treatment (Level 4)	Impact on Patient Outcomes (Level 5)	Societal Impact (Level 6)
7. Management of the pediatric patient with chronic illness presenting with suspected bacterial pneumonia (e.g., in cystic fibrosis, sickle cell disease)	3	7						
7.1. For pediatric patients with chronic illness, is PCT a valid indicator of bacterial infection?				√	√			
7.2. For pediatric patients with chronic illness who present with suspected bacterial infection, what is the comparative effectiveness of clinical criteria with PCT vs. without PCT for initiating antibiotic therapy?						√	√	√
7.3. For pediatric patients with chronic illness who present with suspected bacterial infection, what is the comparative effectiveness of clinical criteria with PCT vs. without PCT for discontinuing/changing antibiotic therapy?						√	√	√
8. Management of patients (all ages) on immune-modulators (e.g., steroids) and other systemic therapies [This question could be considered as subset of # 5 on the immunocompromised patient]	1	2						
9. Management of the pediatric patient with suspected bone/joint infections	0	0						
10. Management of the pediatric patient with periodic fever syndrome	0	0						

Note: PCT,procalcitonin.

* Responses from nine (of nine) panel members

** Assumption: This column on Technical efficacy (Level 1) is shaded to indicate that technical feasibility of test has been determined.

Checkmark (√) indicates information needed to address research question

Appendix G. Survey Results of Research Questions

Rank	Research Questions	Total Votes ⁱ	Weighted Score
1	For ICU patients with pneumonia/sepsis, does a PCT-guided strategy used to determine the duration of antibacterial therapy improve health outcomes compared to a strategy not based on PCT?	8	27
2	For the low risk (otherwise healthy) patient who presents to urgent care/ER with fever and suspected acute LRTI, can the serum PCT level distinguish bacterial from non-bacterial infection and improve health outcomes?	5	17
2	For ICU patients with a high uncertainty of pneumonia/sepsis, does a strategy for initiating antimicrobial therapy based on PCT improve health outcomes compared to a strategy not based on PCT?	5	17
4	For ICU patients with pneumonia/sepsis, following initiation of empiric antibacterial therapy, does a subsequent decrease in the PCT serum concentration indicate effective treatment of the bacterial infection?	4	12
5	For the immunocompromised patient who presents with suspected LRTI/sepsis, does a strategy for initiating antimicrobial therapy based on PCT improve health outcomes compared to a strategy not based on PCT?	4	10
6	For the immunocompromised patient who presents with suspected LRTI/sepsis, is PCT a reliable early indicator of bacterial infection?	3	11
7	For patients with underlying stable chronic disease (e.g. diabetes, renal disease, but excluding immunocompromised patients) and a high uncertainty of infection, is PCT a reliable indicator of bacterial infection?	3	9
8	For the high risk pediatric patient who presents with fever, is PCT a reliable indicator of early infection/sepsis?	3	8
8	For the immunocompromised patient with suspected LRTI/sepsis, can the duration of therapy be safely based on normalization of the serum PCT level?	3	8
10	For patients with chronic lung disease who present to urgent care/ER with suspected acute LRTI, can the serum PCT level distinguish bacterial from non-bacterial infection and improve health outcomes?	2	6

Rank	Research Questions	Total Votesⁱ	Weighted Score
11	For critically ill hypotensive patients with no clear focal bacterial infection and negative blood cultures, does an elevated PCT level indicate occult translocation of intestinal bacteria into the bowel wall, portal vein, and/or bloodstream?	2	5
12	For the high risk pediatric patient who presents with fever and suspected early sepsis, does a strategy for initiating antimicrobial therapy based on PCT improve health outcomes compared to a strategy not based on PCT?	2	4
13	In the pediatric patient with suspected sepsis but an otherwise negative culture, can the duration of therapy be safely based on normalization of the serum PCT level?	1	1

Note: ER, emergency room; ICU, intensive care unit; LRTI, lower respiratory tract infection; PCT, procalcitonin.

ⁱ Responses from nine (of nine) panel members.