



Effective Health Care

Screening and Management of Sepsis

Results of Topic Selection Process & Next Steps

The nominator, the American College of Physicians (ACP), is interested in a new AHRQ evidence review examining screening tools/tests for sepsis, 3 to 6-hour resuscitation bundles, and the effectiveness of crystalloid fluid resuscitation by volume for patients with sepsis and septic shock to inform the creation of a new guideline. Due to limited program resources, the program will not develop a review at this time. No further activity on this topic will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Screening and Management of Sepsis

Topic #: 0714

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary of Key Findings:

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would be somewhat duplicative. We identified 12 completed or in-process reviews pertaining to the 3 Key Questions, which covered much of this nomination. Areas not covered included portions of KQ1. In addition, reviews relevant to KQ2 came to differing conclusions, and reviews identified for KQ3 do not exactly match the proposed review scope.
- Impact: A new review has moderate impact potential. There are recent consensus definitions for sepsis and septic shock by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine (SEPSIS-3), and recent guidelines by the National Institute for Health and Care Excellence (NICE) and the Surviving Sepsis Campaign. However, the specificity of recommendations is variable across guidelines. A review that is scoped to address the ACP's three questions may have a moderate impact by comparing the newly devised qSOFA to other screening tools (KQ1), resolving debate around the effectiveness of resuscitation bundles (KQ2), and looking at a specific cut-off point for fluid resuscitation.

- Feasibility: A new AHRQ evidence review is feasible.
 - *Size/scope of the review*: We identified 13 studies examining screening tests/tools for sepsis (KQ1), 2 studies and 1 protocol examining 3-6 hour resuscitation bundles (KQ2), and 1 study on the volume of fluid administered (KQ3).
 - *Clinicaltrials.gov*: We identified 4 ongoing studies on screening tests/tools for sepsis, including 2 examining the qSOFA (KQ1). We identified no ongoing or recently completed studies on 3 or 6 hour resuscitation bundles (KQ2). We identified 1 ongoing study on a conservative fluid balance approach to resuscitation.
- Value: This nomination has high impact potential as ACP plans to develop a guideline on the topic that could be used by clinicians in multiple fields. The ACP has previously developed high-quality guidelines, and is transparent about its methodology.

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Introduction

According to the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3), sepsis is a life-threatening medical condition caused by a dysregulated host response to infection.¹ Septic shock is a subset of sepsis and consists of circulatory, cellular, and metabolic abnormalities that are associated with an increased risk of mortality.¹ Severe sepsis, a term previously used to describe sepsis that was associated with tissue hypoperfusion or organ dysfunction, was determined by the Sepsis-3 to be redundant with the definitions of sepsis and septic shock.^{1,2} Sepsis and septicemia (bloodstream infection) are present in over 1 million hospitalizations in the U.S. each year, and account for over \$23 billion in annual health care costs.^{3,4} Overall, sepsis accounts for 37% to 56% of inpatient deaths.⁵ The majority of patients who die from sepsis initially had less severe sepsis, suggesting that there is an opportunity to intervene to improve outcomes and a need to standardize care provided to this group of septic patients.⁵

Topic nomination #0714 *Screening and Management of Sepsis* was received on October 28, 2016. It was nominated by the American College of Physicians. After consultation with the nominator, we focused KQ1 on the qSOFA, 2 SIRS [Systemic Inflammatory Response Syndrome] criteria plus suspicion of infection, and procalcitonin. For KQ2, the nominator clarified they are interested in the 2015 Surviving Sepsis definition of a 3 to 6 hour resuscitation bundle.⁶ This intervention is most often referred to as “early goal directed therapy” or “protocolized resuscitation” in the literature. For KQ3, we clarified that the nominator is interested in the effects of different volumes of fluid administration on clinical outcomes, as opposed to the specific type of fluid administered (i.e., balanced or unbalanced crystalloid).

The questions for this nomination are:

Key Question 1. In seriously ill adult patients with suspected or known infection, does screening for sepsis improve clinical outcomes?

- a) What is the accuracy and reliability of screening tests for detecting sepsis?
- b) How does screening for sepsis impact diagnosis and treatment?
- c) What harms are associated with screening for sepsis?

Key Question 2. In adults with severe sepsis or septic shock, what is the effect of complete 3- or 6-hour resuscitation bundle compliance on clinical outcomes?

Key Question 3. In adults with sepsis or septic shock or severe sepsis or septic shock, what is the effect of 30 ml/kg fluid resuscitation (either balanced or unbalanced crystalloids) compared to less fluid on clinical outcomes?

- a) In adults with sepsis, what is the effect of any fluid resuscitation (either balanced or unbalanced crystalloids) compared to no fluids?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, and outcomes (PICO) of interest. See Table 1.

Table 1. Key Questions and PICOTs

Key Questions	<p>1. In seriously ill adult patients with suspected or known infection, does screening for sepsis improve clinical outcomes?</p> <p>a. What is the accuracy and reliability of screening tests for detecting sepsis?</p> <p>b. How does screening for sepsis impact diagnosis and treatment?</p> <p>c. What harms are associated with screening for sepsis?</p>	<p>2. In adults with severe sepsis or septic shock, what is the effect of complete 3- or 6-hour resuscitation bundle compliance on clinical outcomes?</p>	<p>3. In adults with sepsis, severe sepsis, or septic shock, what is the effect of 30 ml/kg fluid resuscitation (either balanced or unbalanced crystalloids) compared to less fluid on clinical outcomes?</p> <p>a. In adults with sepsis, what is the effect of any fluid resuscitation (either balanced or unbalanced crystalloids) compared to no fluids?</p>
Population	Seriously ill adult patients with suspected or known infection	Adults with severe sepsis or septic shock	<p>3. Adults with sepsis, severe sepsis, or septic shock</p> <p>3a. Adults with sepsis</p>
Intervention	<p>Screening tests/tools, including:</p> <p>1) Quick Sepsis Related Organ Failure Assessment (quickSOFA or qSOFA)</p> <p>2) Two SIRS criteria [abnormality in temperature, heart rate, respiration, or white blood count] plus suspicion of or known infection</p> <p>3) Procalcitonin</p>	<p>2015 Surviving Sepsis Campaign-defined 3 or 6 hour resuscitation bundles, described below:</p> <p><u>3-hour resuscitation bundle</u></p> <ol style="list-style-type: none"> 1. Measure Lactate Level 2. Obtain Blood Cultures Prior to Administration of Antibiotics 3. Administer Broad Spectrum Antibiotics 4. Administer 30 mL/kg Crystalloid for Hypotension or Lactate ≥ 4 mmol/L <p><u>6-hour resuscitation bundle</u></p> <ol style="list-style-type: none"> 1. Apply Vasopressors (for Hypotension That Does Not Respond to Initial Fluid Resuscitation) to Maintain a Mean Arterial Pressure (MAP) ≥ 65 mmHg 2. In the Event of Persistent Arterial Hypotension After Initial Fluid Administration (MAP < 65 mmHg) or 	<p>3. 30 ml/kg fluid resuscitation with balanced or unbalanced crystalloids</p> <p>a. Any fluid resuscitation with balanced or unbalanced crystalloids (any dosage)</p>

		if Initial Lactate ≥ 4 mmol/L, re-assess volume status and tissue perfusion and document findings 3. Remeasure Lactate If Initial Lactate Was Elevated	
Comparator	Use of other tests/tools (eg, qSOFA, SIRS criteria with suspicion or known infection, procalcitonin, SOFA, MEWS, other biomarkers)	Less than complete bundle compliance	3. Less than 30 ml/kg fluid resuscitation with balanced or unbalanced crystalloids a. No fluid resuscitation
Outcomes	1. Mortality, length of stay in intensive care, overall hospital length of stay, and use of mechanical ventilation 1a. Accuracy and reliability [eg, likelihood ratios, predictive values, risk reclassification indices] in detecting sepsis 1b. Time to diagnosis; decision to alter treatment; use of appropriate, timely treatment 1c. False positives, unnecessary use of tool, overtreatment, costs, misclassification, mortality, length of hospital stay, length of ICU stay, rehospitalization, antibiotic use, resistance, overuse of resources, fluid overload	Mortality, length of ICU stay, length of hospital stay, use of mechanical ventilation, use of resources, costs]	Mortality, length of ICU stay, length of hospital stay, acute kidney injury, use of mechanical ventilation, other harms [eg, increased risk of hyperchloremic metabolic acidosis]

Abbreviations: ICU= Intensive Care Unit; MAP=Mean Arterial Pressure; MEWS=modified early warning system; qSOFA= quick Sepsis Related Organ Failure assessment; SIRS=Systemic Inflammatory Response Syndrome

Methods

To assess topic nomination #0714 *Screening and Management of Sepsis* for priority for a systematic review or other AHRQ EHC report, we used a modified process based on established criteria. Our assessment is hierarchical in nature, with the findings of our assessment determining the need for further evaluation. Details related to our assessment are provided in Appendix A.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance (see Appendix A).

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews pertaining to the key questions of the nomination. Table 2 includes the citations for the reviews that were determined to address the key questions.

Impact of a New Evidence Review

The impact of a new evidence review was assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether a new review could influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.). See Appendix A.

Feasibility of New Evidence Review

We conducted a literature search in PubMed from December 2011 to December 2016. Because a large number of articles (n=982) were identified, we reviewed a random sample of 200 titles and abstracts for inclusion and classified identified studies by study design, to assess the size and scope of a potential evidence review. We then calculated the projected total number of included studies based on the proportion of studies included from the random sample. See Table 2, Feasibility Column, Size/Scope of Review Section for the citations of included studies.

We also searched Clinicaltrials.gov for recently completed or in-process unpublished studies. See Appendix B for the PubMed search strategy and links to the ClinicalTrials.gov search.

Value

We assessed the nomination for value (see Appendix A). We considered whether a partner organization could use the information from the proposed evidence review to facilitate evidence-based change; or the presence of clinical, consumer, or policymaking context that is amenable to evidence-based change.

Compilation of Findings

We constructed a table outlining the selection criteria as they pertain to this nomination (see Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. Sepsis and septicemia (a bloodstream infection) are present in 1 million hospitalizations in the U.S. each year, and account for over \$23 billion in annual health care costs.^{3,4} Sepsis accounts for 37% to 56% of inpatient deaths.⁵

Desirability of New Review/Duplication

A new review would be somewhat duplicative of existing products. We identified 12 completed or in-process reviews pertaining to the 3 Key Questions, which covered much of this nomination. Areas not covered included portions of KQ1. In addition, reviews relevant to KQ2 came to differing conclusions, and reviews identified for KQ3 do not exactly match the proposed review scope.

For KQ1, we identified 1 completed reviews⁷ and 3 review protocols.⁸⁻¹⁰ The most relevant were a 2015 systematic review⁷ on procalcitonin testing for guiding sepsis treatment and a 2014 Cochrane protocol⁸ on the effectiveness and safety of procalcitonin evaluation in sepsis, severe sepsis and septic shock. Although not considered for duplication, we also identified an archived 2012 AHRQ review¹¹ on procalcitonin testing for guiding sepsis treatment. We did not identify any systematic reviews on SIRS criteria or qSOFA.

For KQ2, we identified 3 completed reviews¹²⁻¹⁴ and 2 review protocols.^{15,16} These included: a 2016 systematic review¹² on early goal-directed resuscitation for patients with severe sepsis and septic shock, a 2015 systematic review¹⁴ on early goal directed therapy for septic shock, a 2016 meta-analysis¹³ on protocol-based resuscitation for patients with septic shock, a 2014 NIH-funded protocol¹⁵ on early goal directed therapy for sepsis, severe sepsis, and septic shock and a 2014 protocol¹⁶ on bundles for sepsis, severe sepsis, and septic shock. The completed reviews came to slightly different conclusions on the effectiveness of resuscitation bundles, but this may be due to the different populations and interventions examined in each.

For KQ3, we identified a 2014 meta-analysis¹⁷ (KQ 3) on conservative fluid therapy for patients with septic shock, a 2014 systematic review¹⁸ (KQ 3a) on fluid bolus therapy for patients with sepsis, and a 2015 protocol for a review¹⁹ (KQ 3) on fluid strategies for patients with acute respiratory distress syndrome, sepsis and systemic inflammatory response syndrome. Although these reviews include studies that are potentially relevant to the KQ, the scope of the review's questions are slightly different than the nominator's.

See Table 2, Duplication column for the systematic review citations that were determined to address the key questions.

Impact of a New Evidence Review

A new systematic review may have moderate impact.

In January 2017, the Surviving Sepsis Campaign released guidelines for managing sepsis which included recommendations on screening for sepsis, resuscitation bundles, and volume of initial fluid resuscitation.²⁰ We contacted the ACP to see if these recommendations changed either the scope or their enthusiasm for the nomination. They stated they would still like to move forward with the nomination as discussed.

In 2016, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine (SEPSIS-3)¹ created consensus definitions for sepsis and sepsis shock, and recommended the qSOFA for sepsis screening. Also in 2016, the National Institute for Health and Care Excellence (NICE) released recommendations on the recognition, assessment and early management of sepsis, which discussed screening tools, early goal-directed therapy, and

volume of fluid administered.²¹ Although there is a considerable amount of recent guidance on the management of sepsis, the guidance varies in the degree of specificity. For example, in terms of screening, SEPSIS-3 recommends the qSOFA, NICE recommends early warning scores, and Surviving Sepsis recommends that sepsis screening be incorporated as part of performance improvement programs.

An AHRQ review would likely not uncover any new literature that was not incorporated in these guidelines. However, a review that is scoped to address the ACP's three questions may have a moderate impact by comparing the newly devised qSOFA to other screening tools (KQ1), resolving debate around the effectiveness of resuscitation bundles (KQ2), and looking at a specific cut-off point for fluid resuscitation.

Feasibility of a New Evidence Review

A new evidence review is feasible.

From our PubMed search, we identified 13 studies²²⁻³⁴ examining screening tests/tools for sepsis. We identified two studies^{35,36} and one protocol³⁷ examining 3-6 hour resuscitation bundles (KQ2), and one study³⁸ on the volume of fluid administered (KQ3). We project there may be 83 studies relevant to this nomination.

From our search of Clinicaltrials.gov, we identified four ongoing studies³⁹⁻⁴² on screening tests/tools for sepsis, including two^{40,42} examining the qSOFA (KQ1). We identified no ongoing or recently completed studies on 3 or 6 hour resuscitation bundles (KQ2). We identified one ongoing study⁴³ on a conservative fluid balance approach to resuscitation.

See Table 2, Feasibility column for the citations that were determined to address the key questions.

Table 2. Key questions with the identified corresponding evidence reviews and original research

Key Question	Duplication (Completed or In-Process Evidence Reviews, 12/2011-12/2016)	Feasibility (Published and Ongoing Research, 12/2011-12/2016; Yield=982)
KQ 1: Does screening for sepsis improve clinical outcomes?	Total number of identified systematic reviews: 1 <ul style="list-style-type: none"> Other: 1⁷ In process (Cochrane) 1⁸ 	<u>Size/scope of review</u> Relevant Studies Identified: 1 <ul style="list-style-type: none"> qSOFA: 0 SIRS: 0 Procalcitonin <ul style="list-style-type: none"> Prospective cohort: 1²⁵ Projected Total: 5 <u>Clinicaltrials.gov</u> Relevant Trials: 1 <ul style="list-style-type: none"> qSOFA: 0 SIRS: 0 Procalcitonin <ul style="list-style-type: none"> Recruiting: 1⁴⁰
KQ 1a. What is the accuracy and reliability of sepsis screening tests?	Total number of identified systematic reviews: 2 <ul style="list-style-type: none"> In process (other): 2^{9,10} 	<u>Size/scope of review</u> Relevant Studies Identified: 12 <ul style="list-style-type: none"> qSOFA: <ul style="list-style-type: none"> Retrospective observational: 1³⁴ SIRS <ul style="list-style-type: none"> Prospective observational: 1²⁴ Retrospective observational: 1^{23,34} Procalcitonin <ul style="list-style-type: none"> Prospective observational: 5^{22,25,26,29,30} Retrospective observational: 5^{27,28,31-33}

Key Question	Duplication (Completed or In-Process Evidence Reviews, 12/2011-12/2016)	Feasibility (Published and Ongoing Research, 12/2011-12/2016; Yield=982)
		<p>Projected Total: 59</p> <p>Clinicaltrials.gov Relevant Trials: 5</p> <ul style="list-style-type: none"> • qSOFA <ul style="list-style-type: none"> ○ Recruiting: 2^{41,42} • SIRS: 0 • Procalcitonin <ul style="list-style-type: none"> ○ Recruiting: 2^{39,40}
KQ 1b. How does screening for sepsis impact diagnosis and treatment?	<p>Total number of identified systematic reviews: 1</p> <ul style="list-style-type: none"> • Other: 1^{7*} 	<p><u>Size/scope of review</u> Relevant Studies Identified: 1</p> <ul style="list-style-type: none"> • qSOFA: 0 • SIRS: 0 • Procalcitonin <ul style="list-style-type: none"> ○ Prospective cohort: 2⁵ <p>Projected Total: 5</p> <p>Clinicaltrials.gov Relevant Trials: 1</p> <ul style="list-style-type: none"> • Procalcitonin <ul style="list-style-type: none"> ○ Recruiting: 1⁴⁰
KQ 1c. What harms are associated with screening for sepsis?	<p>Total number of identified systematic reviews: 1</p> <ul style="list-style-type: none"> • Other: 1⁷ • In process (Cochrane) 1⁸ 	<p><u>Size/scope of review</u> Relevant Studies Identified: 1</p> <ul style="list-style-type: none"> • qSOFA: 0 • SIRS: 0 • Procalcitonin: <ul style="list-style-type: none"> ○ Prospective cohort: 1²⁵ <p>Projected Total: 5</p> <p>Clinicaltrials.gov Relevant Trials: 1</p> <ul style="list-style-type: none"> • Procalcitonin <ul style="list-style-type: none"> ○ Recruiting: 1⁴⁰
KQ 2. What is the effect of complete 3 or 6 hour resuscitation bundle compliance on clinical outcomes?	<p>Total number of identified systematic reviews: 2</p> <ul style="list-style-type: none"> • Other: 2¹²⁻¹⁴ • In process (NIH-funded): 2¹⁵ • In process (other): 1¹⁶ 	<p><u>Size/scope of review</u> Relevant Studies Identified: 3</p> <ul style="list-style-type: none"> • RCT: 1³⁶ • Retrospective observational: 1³⁵ • Protocol: 1³⁷ <p>Projected Total: 15</p> <p>Clinicaltrials.gov None identified</p>
KQ3. What is the effect of 30 ml/kg fluid resuscitation (either balanced or unbalanced crystalloids) compared to less fluid?	<p>Total number of identified systematic reviews: 2</p> <ul style="list-style-type: none"> • Other: 1¹⁷ • Protocol: 1¹⁹ 	<p><u>Size/scope of review</u> Relevant Studies Identified: 1</p> <ul style="list-style-type: none"> • Prospective observational: 1³⁸ <p>Projected Total: 5</p> <p>Clinicaltrials.gov Relevant Trials: 1</p> <ul style="list-style-type: none"> • Recruiting: 1⁴³
KQ 3a. What is the effect of any fluid resuscitation (either balanced or	<p>Total number of identified systematic reviews: 2</p> <ul style="list-style-type: none"> • Other: 1¹⁸ 	<p><u>Size/scope of review</u> None identified</p> <p>Clinicaltrials.gov</p>

Key Question	Duplication (Completed or In-Process Evidence Reviews, 12/2011-12/2016)	Feasibility (Published and Ongoing Research, 12/2011-12/2016; Yield=982)
unbalanced crystalloids) compared to no fluids?		None identified

Abbreviations: RCT=Randomized Controlled Trial; qSOFA= quick Sepsis Related Organ Failure assessment; SIRS=Systemic Inflammatory Response Syndrome

*Although this review doesn't address the use of procalcitonin as a screening tool per se, it does discuss the use of procalcitonin for medical decision making, which we felt addressed the nominator's question.

Value

This nomination has high impact potential as ACP plans to develop a guideline on the topic that could be used by clinicians in multiple fields. The ACP has previously developed high-quality guidelines, and is transparent about its methodology.

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would be somewhat duplicative. We identified 12 completed or in-process reviews pertaining to the 3 Key Questions, which covered much of this nomination. Areas not covered included portions of KQ1. In addition, reviews relevant to KQ2 came to differing conclusions, and reviews identified for KQ3 do not exactly match the proposed review scope.
- Impact: A new review has moderate impact potential. There are recent consensus definitions for sepsis and septic shock by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine (SEPSIS-3), and recent guidelines by the National Institute for Health and Care Excellence (NICE) and the Surviving Sepsis Campaign. However, the specificity of recommendations is variable across guidelines. A review that is scoped to address the ACP's three questions may have a moderate impact by comparing the newly devised qSOFA to other screening tools (KQ1), resolving debate around the effectiveness of resuscitation bundles (KQ2), and looking at a specific cut-off point for fluid resuscitation.
- Feasibility: A new AHRQ evidence review is feasible.
 - *Size/scope of the review:* We identified 13 studies examining screening tests/tools for sepsis (KQ1), 2 studies and 1 protocol examining 3-6 hour resuscitation bundles (KQ2), and 1 study on the volume of fluid administered (KQ3).
 - *Clinicaltrials.gov:* We identified 4 ongoing studies on screening tests/tools for sepsis, including 2 examining the qSOFA (KQ1). We identified no ongoing or recently completed studies on 3 or 6 hour resuscitation bundles (KQ2). We identified 1 ongoing study on a conservative fluid balance approach to resuscitation.
- Value: This nomination has high impact potential as ACP plans to develop a guideline on the topic that could be used by clinicians in multiple fields. The ACP has previously developed high-quality guidelines, and is transparent about its methodology.

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Appendices

Appendix A: Selection Criteria Summary

Appendix B: Search Strategy & Results (Feasibility)

Appendix A. Selection Criteria Summary

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents a health care drug and intervention available in the U.S.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes, the focus of this review is on effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, this topic represents a significant burden. Sepsis and septicemia (a bloodstream infection) are present in 1 million hospitalizations in the U.S. each year, and account for over \$23 billion in annual health care costs. ^{3,4}
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic is of high public interest. Overall, sepsis accounts for 37% to 56% of inpatient deaths. ⁵
2c. Represents important uncertainty for decision makers	Yes, this topic represents important uncertainty for decision makers.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination addresses both benefits and potential harms.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, this topic represents a high cost. Sepsis and septicemia account for over \$23 billion in annual health care costs. ^{3,4}
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	<p>A new review would be somewhat duplicative of existing products. We identified 12 completed or in-process reviews^{7-10,12-19} pertaining to the 3 Key Questions, which covered much of this nomination. Areas not covered included portions of KQ1. In addition, reviews relevant to KQ2 came to differing conclusions, and reviews identified for KQ3 do not exactly match the proposed review scope.</p> <p>For KQ1, we identified 1 completed reviews⁷ and 3 review protocols.⁸⁻¹⁰ The most relevant were a 2015 systematic review⁷ on procalcitonin testing for guiding sepsis treatment and a 2014 Cochrane protocol⁸ on the effectiveness and safety of procalcitonin evaluation in sepsis, severe sepsis and septic shock. Although not considered for duplication, we also identified an archived 2012 AHRQ review¹¹ on procalcitonin testing for</p>

	<p>guiding sepsis treatment. We did not identify any systematic reviews on SIRS criteria or qSOFA.</p> <p>For KQ2, we identified 3 completed reviews¹²⁻¹⁴ and 2 review protocols.^{15,16} These included: a 2016 systematic review¹² on early goal-directed resuscitation for patients with severe sepsis and septic shock, a 2015 systematic review¹⁴ on early goal directed therapy for septic shock, a 2016 meta-analysis¹³ on protocol-based resuscitation for patients with septic shock, a 2014 NIH-funded protocol¹⁵ on early goal directed therapy for sepsis, severe sepsis, and septic shock and a 2014 protocol¹⁶ on bundles for sepsis, severe sepsis, and septic shock. The completed reviews came to slightly different conclusions on the effectiveness of resuscitation bundles, but this may be due to the different populations and interventions examined in each.</p> <p>For KQ3, we identified a 2014 meta-analysis¹⁷ (KQ 3) on conservative fluid therapy for patients with septic shock, a 2014 systematic review¹⁸ (KQ 3a) on fluid bolus therapy for patients with sepsis, and a 2015 protocol for a review¹⁹ (KQ 3) on fluid strategies for patients with acute respiratory distress syndrome, sepsis and systemic inflammatory response syndrome. Although these reviews include studies that are potentially relevant to the KQ, the scope of the review's questions are slightly different than the nominator's.</p>
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	<p>In January 2017, the Surviving Sepsis Campaign released guidelines for managing sepsis which included recommendations on screening for sepsis, resuscitation bundles, and volume of initial fluid resuscitation.²⁰ In 2016, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine (SEPSIS-3)¹ created consensus definitions for sepsis and sepsis shock, and recommended the qSOFA for sepsis screening. Also in 2016, the National Institute for Health and Care Excellence (NICE) released recommendations on the recognition, assessment and early management of sepsis, which discussed screening tools, early goal-directed therapy, and volume of fluid administered.²¹ Although there is a considerable amount of recent guidance on the management of sepsis, the guidance varies in the degree of specificity.</p> <p>An AHRQ review would likely not uncover any new literature that was not incorporated in these guidelines. However, a review that is scoped to address the ACP's three questions may have a moderate impact by</p>

	comparing the newly devised qSOFA to other screening tools (KQ1), resolving debate around the effectiveness of resuscitation bundles (KQ2), and looking at a specific cut-off point for fluid resuscitation.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, there is practice variation due to the controversies surrounding the definition and optimal treatment of sepsis.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	<p>An AHRQ evidence review is feasible.</p> <p><i>Size/scope of the review:</i> We identified 13 studies²²⁻³⁴ examining screening tests/tools for sepsis. We identified two studies^{35,36} and one protocol³⁷ examining 3-6 hour resuscitation bundles (KQ2), and one study³⁸ on the volume of fluid administered (KQ3). We project there may be 83 studies relevant to this nomination.</p> <p><i>Clinicaltrials.gov:</i> We identified four ongoing studies³⁹⁻⁴² on screening tests/tools for sepsis, including two^{40,42} examining the qSOFA (KQ1). We identified no ongoing or recently completed studies on 3 or 6 hour resuscitation bundles (KQ2). We identified one ongoing study⁴³ on a conservative fluid balance approach to resuscitation.</p>
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes, the proposed topic exists within a clinical context that is amenable to evidence-based change.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, the ACP will develop evidence-based guidelines based on the results of an AHRQ evidence review.

Appendix B. Search Strategy & Results (Feasibility)

Topic: Sepsis Diagnosis Date: December 21, 2016 Database Searched: MEDLINE (PubMed)	
Concept	Search String
Sepsis	((("Systemic Inflammatory Response Syndrome"[Majr:NoExp]) OR "Sepsis"[Majr:NoExp]) OR "Shock, Septic"[Majr:NoExp] OR (Sepsis[Title] OR "septic shock"[Title]))
AND	
[Diagnosis/Screening/Classification (general)]	((("diagnosis" [Subheading]) OR "classification" [Subheading]) OR "Organ Dysfunction Scores"[Majr])
OR	
Named Tests: quick Sepsis Related Organ Failure assessment (quickSOFA) SIRS criteria]	((("Sepsis related organ failure assessment"[Title]) OR (quickSOFA[Title] OR SOFA[Title])) OR "SIRS criteria"[Title])
AND	
[Accuracy and reliability of tests]	((("Predictive Value of Tests"[Mesh]) OR "Validation Studies" [Publication Type])
OR	
Treatment and patient outcomes	(((((("Outcome Assessment (Health Care)"[Mesh:NoExp]) OR "Patient Outcome Assessment"[Mesh]) OR "Treatment Outcome"[Mesh]) OR "therapy" [Subheading]) OR "Prognosis"[Mesh:NoExp])
OR	
Harms, adverse events or contraindications]	((("adverse effects" [Subheading]) OR "Patient Harm"[Mesh]) OR "contraindications" [Subheading])
NOT	
Not Editorials, etc.	(((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type])
Limit to last 5 years ; human ; English ; adult	Filters activated: published in the last 5 years, Humans, English, Adult: 19+ years
N=764	
Systematic Review N=15	PubMed subsection "Systematic [sb]"
Randomized Controlled Trials N=310	Cochrane Sensitive Search Strategy for RCT's "(((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt]))"
Other N=439	

Clinicaltrials.gov

61 studies found for: diagnosis | Recruiting | sepsis | Adult, Senior | Studies received from 12/22/2011 to 12/22/2016

https://clinicaltrials.gov/ct2/results?term=diagnosis&type=&rslt=&recr=Recruiting&age_v=&age=1&age=2&gndr=&cond=sepsis&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=12%2F22%2F2011&rcv_e=12%2F22%2F2016&lup_s=&lup_e=

11 studies found for: diagnosis | Active, not recruiting | sepsis | Adult, Senior | Studies received from 12/22/2011 to 12/22/2016

https://clinicaltrials.gov/ct2/results?term=diagnosis&type=&rslt=&recr=Active%2C+not+recruiting&age_v=&age=1&age=2&gndr=&cond=sepsis&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=12%2F22%2F2011&rcv_e=12%2F22%2F2016&lup_s=&lup_e=

=

41 studies found for: diagnosis | Completed | sepsis | Adult, Senior | Studies received from 12/22/2011 to 12/22/2016

https://clinicaltrials.gov/ct2/results?term=diagnosis&type=&rslt=&recr=Completed&age_v=&age=1&age=2&gndr=&cond=sepsis&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=12%2F22%2F2011&rcv_e=12%2F22%2F2016&lup_s=&lup_e=

Topic: Sepsis Fluid Resuscitation Date: December 21, 2016 Database Searched: MEDLINE (PubMed)	
Concept	Search String
Sepsis	("Sepsis/drug therapy"[Mesh]) OR ((sepsis[Title] OR "septic shock"[Title]))
AND	
Fluid Resuscitation	("Fluid Therapy"[Mesh]) OR ((fluid[Title] OR resuscitation[Title]))
NOT	
Not Editorials, etc.	(((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type]
Limit to last 5 years ; human ; English ; adult	Filters activated:
N=254	
Systematic Review N=35	PubMed subsection "Systematic [sb]"
Randomized Controlled Trials N=108	Cochrane Sensitive Search Strategy for RCT's "(((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt])"
Other N=111	

Clinicaltrials.gov

26 studies found for: Recruiting | sepsis | fluid | Adult, Senior | Studies received from 12/21/2011 to 12/21/2016

https://clinicaltrials.gov/ct2/results?term=&type=&rslt=&recr=Recruiting&age_v=&age=1&age=2&gndr=&cond=sepsis&intr=fluid&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=12%2F21%2F2011&rcv_e=12%2F21%2F2016&lup_s=&lup_e=

8 studies found for: Active, not recruiting | sepsis | fluid | Adult, Senior | Studies received from 12/21/2011 to 12/21/2016

https://clinicaltrials.gov/ct2/results?term=&type=&rslt=&recr=Active%2C+not+recruiting&age_v=&age=1&age=2&gndr=&cond=sepsis&intr=fluid&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=12%2F21%2F2011&rcv_e=12%2F21%2F2016&lup_s=&lup_e=

19 studies found for: Completed | sepsis | fluid | Adult, Senior | Studies received from 12/21/2011 to 12/21/2016

https://clinicaltrials.gov/ct2/results?term=&type=&rslt=&recr=Completed&age_v=&age=1&age=2&gndr=&cond=sepsis&intr=fluid&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=12%2F21%2F2011&rcv_e=12%2F21%2F2016&lup_s=&lup_e=