Evidence-based Practice Center Rapid Review Protocol

Project Title: *Making Healthcare Safer IV: Sepsis Prediction, Recognition, and Intervention*

Review Questions

1. What is the frequency and severity of harm associated with sepsis?
2. What patient safety measures or indicators have been used to examine the harms associated with sepsis?
3. What patient safety practices (PSPs) have been used to prevent or mitigate harms associated with sepsis and in what settings have they been used?
4. What is the rationale for PSPs used to prevent or mitigate harms associated with sepsis?
5. What are the effectiveness and unintended effects of sepsis-related PSPs and what new evidence has been published since the search was done for the Making Healthcare Safer (MHS) III report in 2019?
6. What are common barriers and facilitators to implementing PSPs targeting sepsis?
7. What resources (e.g., cost, staff, time) are required for implementation?
8. What toolkits are available to support implementation of the PSPs?

Context and Domain Being Studied

The Agency for Healthcare Research and Quality (AHRQ) Making Healthcare Safer (MHS) reports consolidate information for healthcare providers, health system administrators, researchers, and government agencies about practices that can improve patient safety across the healthcare system — from hospitals to primary care practices, long-term care facilities, and other healthcare settings. In Spring of 2023, AHRQ launched its fourth iteration of the MHS Report (MHS IV). Sepsis prediction, recognition, and intervention as a patient safety practice (PSP) was identified as in the MHS IV reports using a modified Delphi technique by a Technical Expert Panel (TEP) that met in December 2022. The TEP included 15 experts in patient safety with representatives of governmental agencies, healthcare stakeholders, clinical specialists, experts in patient safety issues, and a patient/consumer perspective. See the MHS IV Prioritization Report for additional details.[1]

Sepsis is a life-threatening medical emergency involving an extreme immune response to an infection, most commonly bacterial, wherein the body's own immune response causes damage to tissues and organs. Anyone can be affected by sepsis, though certain groups such as neonates, young children, pregnant or recently-pregnant women, older persons and individuals with underlying chronic conditions are at an elevated risk.[2] Overall, sepsis is common, life-threatening, and financially burdensome.[2, 3] The Centers for Disease Control and Prevention (CDC) estimate that at least 1.7 million adults in America develop sepsis every year, and one in three people who die in a hospital had sepsis during their hospital stay.[4] The estimated annual cost of sepsis for Medicare beneficiaries is $41.5 billion, with mortality rates for sepsis ranging from 60% for septic shock diagnoses to 27% for unspecified sepsis diagnoses.[3] Early detection and treatment of sepsis greatly impacts outcomes,[5, 6] so efforts to address sepsis focus heavily on rapid detection and intervention. However, the diagnosis of sepsis is challenging given common sepsis symptoms are nonspecific (e.g., fever, nausea, vomiting, muscle pain), particularly early in its clinical course and sepsis can have highly variable presentations. Realization of the magnitude of human and financial burdens of sepsis spurred the development of the first 'Surviving Sepsis' campaign almost twenty years ago and has driven continued evolution

of sepsis diagnostic criteria, treatment guidelines, and care bundles.[7] In 2018, the Centers for Medicare & Medicaid Services (CMS) launched the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) performance measure. Adherence to this bundle of interventions and tasks varies greatly across institutions, and there are conflicting results from studies assessing the association of the SEP-1 performance measure with clinical outcomes,[8, 9] renewing calls for new types of sepsis interventions[8] and better measures.[10]

Overview of the PSP

PSPs focused on sepsis prediction, recognition, and treatment encompass interventions designed to identify patients with sepsis as early as possible and improve timely adherence to clinical best practice guidelines. The MHS III report included three categories of PSPs intended to improve timely recognition of sepsis and initiation of treatment, with the ultimate goal of improving patient outcomes: manual screening tools, automated alerting systems,[11] and multicomponent sepsis interventions. For manual screening tools, MHS III report found variable sensitivity and specificity across different tools and settings with particularly poor performance in the pre-hospital setting. The MHS III report also found moderate strength of evidence linking manual screening tool use to process measure improvement (e.g., time to treatment), but only sparse evidence supporting an impact on patient outcomes (e.g., mortality, hospital length of stay, intensive care unit transfer). For automated systems, the MHS III report concluded that results across studies were inconsistent but the strength of evidence was moderate, linking use of automated systems to improved process and outcome measures. The multicomponent sepsis interventions included in the MHS III review were multifaceted programs aimed at improving the full spectrum of sepsis recognition and care. All five of the included PSPs had a manual screening tool or patient monitoring system component, however, the other components of each program varied. All the multicomponent sepsis intervention PSPs reported improvement in at least one process measure, however, only two showed improvements in outcome measures. During the prioritization process, the MHS IV TEP reached 100% consensus on inclusion of sepsis prediction, recognition, and treatment in the MHS IV report and did not suggest changes to the definition or scope.

Purpose of the Review

The overall purpose of this review is to determine the effectiveness of sepsis prediction, recognition, and treatment PSPs including the performance of risk assessment tools and automated predictive systems (e.g., sensitivity and specificity), the impact these PSPs have on clinical process measures (e.g., timeliness of diagnosis and treatment, and adherence to clinical best practices), and patient outcomes (e.g., mortality and length of stay) as well as implementation measures (e.g., adherence to predictive system recommendations, and barriers and facilitators to implementation).

Methodologic Approach

For this rapid review, strategic adjustments will be made to streamline traditional systematic review processes and deliver an evidence product in the allotted time. We will follow adjustments and streamlining processes proposed by the AHRQ Evidence-based Practice Center (EPC) Program. Adjustments include being as specific as possible about the questions, limiting the number of databases searched, modifying search strategies to focus on finding the most valuable studies (i.e., being flexible on sensitivity to increase the specificity of the search), and restricting the search to studies published recently (i.e., since 2018 when the search was done for the MHS III report) in English and performed in the United States, and having each study assessed by a single reviewer. Depending on the volume of literature, the EPC team may opt to have a randomly selected 10% sample of articles checked by a second reviewer or use the artificial intelligence (AI) feature of DistillerSR (AI Classifier Manager) as a second reviewer at the title and abstract screening stage, as described below in the section on Data Extraction.

We will search for recent high-quality systematic reviews and will rely primarily on the content of any such systematic review that is found. We will not perform an independent assessment of original studies cited in any such systematic review.

We will ask our content experts to answer Review Questions 1 and 2 by citing selected references that best answer the questions without conducting a systematic search for all evidence on the targeted harms and related patient safety measures or indicators. We will

focus on the harms and patient safety measures or indicators that are addressed in the studies we find for Review Question 5. For Review Question 2, we will also identify relevant measures that are included in the CMS patient safety measures, AHRQ's Patient Safety Indicators, or the National Committee for Quality Assurance (NCQA) patient safety related measures. We will ask our content experts to answer Review Questions 3 and 4 by citing selected references, including PSPs used and explanations of the rationale presented in the studies we find for Review Question 5. For Review Questions 6 and 7, we will focus on the barriers, facilitators, and required resources reported in the studies we find for Review Question 5. For Review Question 8, we will identify publicly available patient safety toolkits developed by AHRQ or other organizations that could help to support implementation of the PSPs. To accomplish that task, we will review AHRQ's Patient Safety Network (PSNet) (https:/psnet.ahrq.gov) and AHRQ's listing of patient safety related toolkits (https://www.ahrq.gov/tools/index.html?search_api_views_fulltext=&field_toolkit_topics=14170&sort_by=title&sort_order=ASC) and we will include any toolkits mentioned in the studies we find for Review Question 5. We will identify toolkits without assessing or endorsing them.

Eligibility Criteria for Studies of Effectiveness

We will search for original studies and systematic reviews on Review Question 5 according to the inclusion and exclusion criteria presented in Table 1.

Table 1. Inclusion and Exclusion Criteria

Study Parameter	Inclusion criteria	Exclusion criteria
Population	Any clinical population (i.e., people receiving care from a health care professional)	None
Intervention	Any intervention designed to predict or recognize the onset of sepsis, and results are used to improve outcomes of interest	Studies of interventions that do not include a prediction or recognition component
Comparator	Usual care or different versions of sepsis PSPs (e.g., comparisons of different risk assessment tools, or comparisons of manual and automated systems)	None
Outcome	*Primary outcomes of interest include*:	Studies that include only secondary outcomes of interest

Study Parameter	Inclusion criteria	Exclusion criteria
	Clinical process outcomes: • Time to diagnosis or treatment • Adherence to clinical guidelines • SEP-I measure Patient outcomes: • Hospital or ICU length of stay • Mortality Implementation outcomes (Review Questions 6 and 7) • Measures of adoption • Barriers and facilitators of implementation Financial measures • Cost *Secondary outcomes of interest include*: Analytic or clinical validity of risk assessment and predictive systems if accompanied by evaluation of clinical utility outcomes: • Sensitivity/specificity • Positive predictive value • AUC	(i.e., no primary outcomes included).
Timing	• Systematic reviews published since 2019 • Original studies published since 2018	•Systematic reviews published before 2019 •Original studies published before 2018
Setting	Healthcare settings in the United States	No site in the United States
Type of studies	Systematic reviews Randomized controlled trials and observational studies with a comparison group, including pre-post studies	• Narrative reviews, scoping reviews, editorials, commentaries, and abstracts • Qualitative studies without quantitative data

AUC = area under the receiver operating characteristic curve; ICU = intensive care unit; PSP = patient safety practice; SEP-1 = Severe Sepsis and Septic Shock Early Management Bundle

Literature Searches for Studies of Effectiveness

Our search strategy will focus on databases expected to have the highest yield of relevant studies, PubMed and the Cochrane Library, supplemented by a narrowly

focused search for reports that are publicly available from governmental agencies or professional societies having a strong interest in the topic.

Data Extraction

To efficiently identify studies that meet the eligibility criteria, we will distribute citations from the literature search to team members, with plans to have the title and abstract of each citation reviewed by a single team member. We will use the artificial intelligence (AI) feature of DistillerSR (AI Classifier Manager) as a semi-automated screening tool to conduct this review efficiently at the title and abstract screening stage. The title and abstract of each citation will be reviewed by a team member, and then the AI Classifier Manager will serve as a second reviewer of each citation. The full text of each remaining potentially eligible article will be reviewed by a single team member to confirm eligibility and extract data. Depending on the results of the literature search, the team will decide whether it has enough time and resources to ask a second team member to check a randomly selected 10% sample of the articles to verify that relevant studies were not excluded and confirm the accuracy of extracted data.

Information will be organized according to the review questions, and will include author, year, study design, frequency and severity of the harms, measures of harm, characteristics of the PSP, rationale for the PSP, outcomes, implementation barriers and facilitators, required resources, and description of toolkits. To streamline data extraction, we will sort eligible studies by specific PSP (if the report covers more than one specific practice), and focus on extracting information about characteristics, outcomes, and barriers/facilitators most pertinent to a specific PSP.

Risk of Bias (Quality) Assessment

For studies that address Review Question 5 about the effectiveness of PSPs, the primary reviewer will use the Cochrane Collaboration's tool for assessing the risk of bias of randomized controlled trials (RCTs) or the ROBINS-I tool for assessing the Risk Of Bias In Non-randomized Studies – of Interventions.[12, 13] When assessing RCTs, we will use the 7 items in the Cochrane Collaboration's tool that cover the domains of selection bias,

performance bias, detection bias, attrition bias, reporting bias, and other bias.[12] When assessing non-randomized studies, we will use specific items in the ROBINS-I tool that assess bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported results.[13] The risk of bias assessments will focus on the main outcome of interest in each study.

If we identify a recent eligible systematic review, the primary reviewer will use the criteria developed by the United States Preventive Services Task Force Methods Workgroup for assessing the quality of systematic reviews.[14]

- **Good** - Recent relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.
- **Fair** - Recent relevant review that is not clearly biased but lacks comprehensive sources and search strategies.
- **Poor** - Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

The Task Leader will review the risk of bias assessments and any disagreements will be resolved through discussion with the team.

Strategy for Data Synthesis

Selected data will be compiled into evidence tables and synthesized narratively. We will not conduct a meta-analysis. For Review Question 5 about the effectiveness of PSPs, we will record information about the context of each study and whether the effectiveness of the PSP differs across patient subgroups (e.g., by age or clinical unit). If any of the PSPs have more than one study of effectiveness, we will grade the strength of evidence for those PSPs using the methods outlined in the AHRQ Effective Health Care Program (EHC) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[15]

Evidence grading would not add value for PSPs that do not have more than one available study.

Analysis of Subgroups or Subsets

We will report if the effectiveness of the PSP differs across patient subgroups for review question 5, but will not conduct subgroup analyses.

Registration

We will submit the protocol to AHRQ and to the PROSPERO international prospective register of systematic reviews.

EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators from participation in the review.

External Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

We will ask at least one clinical content expert and one methodological expert to review the draft report. Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers may not have any financial conflict of interest greater than $5,000.

Role of the Funder

This project is funded under Contract No. 75Q80120D00003/75Q80122F32009 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services. The AHRQ Task Order Officer will review contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by AHRQ or the U.S. Department of Health and Human Services.

Format and Content of Report

The report will follow the most recent template approved by AHRQ at the time of approval of the protocol.

References

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14. U.S. Preventive Services Task Force Procedure Manual. Appendix VI. Criteria for Assessing Internal Validity of Individual Studies. U.S. Preventive Services Task Force. July 2017. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual/procedure-manual-appendix-vi-criteria-assessing-internal-validity-individual-studies.

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