Making Healthcare Safer IV

# Patient Safety Practices Focused on Sepsis Prediction and Recognition

*Rapid Review*

## Structured Abstract


**Objectives.** Patient safety practices (PSPs) focused on sepsis prediction and recognition, encompass interventions designed to identify patients with sepsis early and improve timely adherence to guidelines. Our objectives were to review the evidence published after the previous Making Healthcare Safer (MHS) report to determine the effectiveness of sepsis prediction and recognition PSPs on patient safety related outcomes.

**Methods.** We searched PubMed and the Cochrane library for systematic reviews and primary studies published from January 2018 through August 2023, supplemented by gray literature searches. We included reviews and primary studies of sepsis prediction and recognition PSPs reporting measures of clinical process (time to diagnosis or treatment, adherence to guidelines, Severe Sepsis and Septic Shock Early Management Bundle), patient outcomes (hospital or intensive care unit (ICU) length of stay, mortality), implementation (use, barriers, and facilitators), or costs.

**Findings.** We focused on 7 systematic reviews and 8 primary studies that were eligible for full review, and briefly summarized 36 pre-post studies that lacked a separate comparison group. All the sepsis prediction and recognition PSPs were multi-component interventions. Across the systematic reviews and primary studies of neonates, the PSPs improved clinical process measures (low strength of evidence), but evidence was insufficient about length of stay or mortality outcomes. Across the systematic reviews and primary studies of adults, the PSPs did not demonstrate an effect on clinical process, length of stay, or mortality outcomes. In primary studies of adults, evidence was insufficient in the prehospital setting for mortality, length of stay, and clinical process measures. In the emergency department setting, strength of evidence was low for mortality and clinical process measures and insufficient for length of stay. In ward or hospitalwide settings, strength of evidence was low across all three outcome types. The secondary outcome of alerting system performance (e.g.,



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positive predictive value) could not be meaningfully compared across studies due to diversity in populations and interventions.

**Conclusions.** This review finds that recent primary studies and systematic reviews do not support that specific PSPs for sepsis prediction and recognition are effective at reducing mortality or length of stay or improve clinical processes in adults in pre-hospital, emergency department, or hospitalwide settings as compared to usual care. Sepsis prediction and recognition PSPs may improve clinical process outcomes in neonates in ICUs.

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# 1. Background and Purpose

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 and recognition PSPs were prioritized for inclusion in the MHS IV series based on a modified Delphi technique used 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 a dysregulated host response to an infection, most commonly bacterial, wherein the host response damages tissues and organs. Anyone can be affected by sepsis, although neonates, young children, pregnant or recently-pregnant women, older persons and individuals with underlying chronic conditions are at an elevated risk.[2] 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 27% for unspecified sepsis diagnoses to 60% for septic shock diagnoses.[3] Early detection and treatment of sepsis greatly impacts outcomes,[5,6] spurring efforts toward rapid detection and intervention. However, diagnosis is challenging because common sepsis symptoms are nonspecific (e.g., fever, nausea, vomiting, muscle pain), particularly early in the course, and sepsis has variable presentations. The human and financial burdens of sepsis spurred the development of the 'Surviving Sepsis' campaign over twenty years ago and have 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, with conflicting results about the association of the SEP-1 performance measure and clinical outcomes.[8,9] Such studies have renewed calls for new sepsis interventions[8,9] and better performance measures.[10]

## 1.1 Overview of the Patient Safety Practice

PSPs that focus on sepsis prediction and recognition seek to identify patients with sepsis early and improve timely adherence to best practice guidelines. The MHS III report included three categories of PSPs with goals of improving patient outcomes: manual screening tools, automated alerting systems, and multicomponent sepsis

interventions.[11] For manual screening tools, the MHS III report found variable sensitivity and specificity across 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, but the other components of each program varied. All studies of the multicomponent sepsis interventions reported improvement in at least one process measure, but only two showed improvements in outcome measures. During the prioritization process, the MHS IV TEP reached 100% consensus on inclusion of sepsis prediction and recognition PSPs in the MHS IV report and did not suggest changes to the definitions or scope.

## 1.2 Purpose of the Rapid Review

The overall purpose of this review is to determine the effectiveness of sepsis prediction and recognition PSPs including the impact these PSPs have on clinical process measures (e.g., timeliness of diagnosis and treatment, and adherence to clinical best practices), patient outcomes (e.g., mortality and length of stay) and implementation measures (e.g., clinician use of predictive system recommendations, and barriers and facilitators to implementation). Additionally, this review describes the performance (e.g., sensitivity and specificity) of risk assessment tools and automated predictive systems. We provide information on other contextual issues to help interpret the results of this review.

## 1.3 Review Questions

1. What is the frequency and severity of harm associated with sepsis?
2. In PSPs designed to improve the prediction or recognition of sepsis, what patient safety measures or indicators have been used to examine the harms associated with sepsis?
3. What PSPs have been used to improve sepsis prediction or recognition and in what settings have they been used?
4. What is the rationale for PSPs used to improve sepsis prediction or recognition?
5. What are the effectiveness and unintended effects of PSPs designed to improve the prediction or recognition of sepsis, and what new evidence has been published since the search was done for the MHS III report in 2019?

6. What are common barriers and facilitators to implementing PSPs targeting the prediction or recognition of sepsis?
7. What resources (e.g., cost, staff, time) are required for implementation?
8. What toolkits are available to support implementation of the PSPs?

# 2. Methods

We followed processes proposed by the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) Program. The final protocol for this rapid review is posted on the AHRQ website at: https://www.ahrq.gov/research/findings/making-healthcare-safer/mhs4/index.html. We registered the protocol for this rapid review in PROSPERO.

For this rapid review, strategic adjustments were made to streamline traditional systematic review processes and deliver an evidence product in the allotted time. Adjustments included being highly specific 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 in English and performed in the United States. For this report, we used the artificial intelligence (AI) feature of DistillerSR (AI Classifier Manager) as a second reviewer at the title and abstract screening stage.

We asked our content experts to help answer Review Questions 1 and 2 by drawing on domain knowledge and 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 focused on the harms and patient safety measures or indicators addressed in the studies included in answering Review Question 5.

For Review Question 2, we focused on identifying 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 asked content experts to help answer Review Questions 3 and 4 by citing selected references, including patient safety practices (PSPs) used and explanations of the rationale presented in the studies we found for Review Question 5. For Review Questions 6 and 7, we focused on the barriers, facilitators, and required resources reported in the studies we found for Review Question 5. For Review Question 8, we identified 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 reviewed AHRQ's Patient Safety Network (PSNet) and AHRQ's listing of patient safety related toolkits and we included any toolkits mentioned in the studies we found for Review Question 5.[12,13] Any identified toolkits are not assessed or endorsed.

## 2.1 Eligibility Criteria for Studies of Effectiveness

We searched for original studies and systematic reviews on Review Question 5 (the question addressing effectiveness studies) 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 healthcare 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*:<br>Clinical process outcomes:<br>• Time to diagnosis or treatment<br>• Adherence to clinical guidelines<br>• SEP-1 measure<br>Patient outcomes:<br>• Hospital or ICU length of stay<br>• Mortality<br>Implementation outcomes (Review Questions 6 and 7):<br>• Measures of adoption<br>• Barriers and facilitators of implementation<br>Financial measures:<br>• Cost<br>*Secondary outcomes of interest include*:<br>Analytic or clinical validity of risk assessment and predictive systems if accompanied by evaluation of clinical utility outcomes:<br>• Sensitivity/specificity<br>• Positive predictive value<br>• AUC | Studies that include only secondary outcomes of interest (i.e., no primary outcomes included). |
| **Timing** | • Systematic reviews published from January 2019 through August 2023<br>• Original studies published from January 2018 through August 2023 | •Systematic reviews published before 2019<br>•Original studies published before 2018 |
| **Setting** | Healthcare settings in the United States | No site in the United States |
| **Type of studies** | Systematic reviews<br>Randomized controlled trials and observational studies with a comparison group, including pre-post studies* | • Narrative reviews, scoping reviews, editorials, commentaries, and abstracts<br>• 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
*We did not include pre-post studies in the main body of the report, but we summarized them briefly in the appendix.

## 2.2 Literature Searches for Studies of Effectiveness

We searched PubMed and Cochrane, supplemented by a narrowly focused search for unpublished reports that are publicly available from governmental agencies or

professional societies having a strong interest in the topic. For details of the search strategy, see Appendix A.

## 2.3 Data Extraction (Selecting and Coding)

We used the 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. A team member screened the title and abstract of each citation based on predefined eligibility criteria (Table 1). The screening responses by team members were used to teach the AI Classifier Manager to serve as a second reviewer of each citation. The AI Classifier Manager generated a ranking score for each citation, based upon a training set of titles and abstracts screened first by team members. The threshold for the AI Classifier Manager to include citations was set at a ranking score of 0.5 or above (scale 0 to 1.0). Discrepancies between team members and the AI Classifier Manager were reviewed and resolved by the team members. The full text of each remaining potentially eligible article was reviewed by a single team investigator to confirm eligibility. Full text articles underwent an additional independent review by a single investigator to determine whether they should be included in the full data abstraction.

We prioritized our efforts by extracting detailed information from the highest quality studies. Given the large number of systematic reviews and studies with strong designs, we focused on extracting detailed information from systematic reviews, randomized controlled trials (RCTs), observational studies with a contemporaneous comparison group, and studies employing time series analyses. We listed otherwise relevant studies having simple pre-post designs in Appendix C, but we did not synthesize them in the text of the results section. If identified primary studies were included in eligible systematic reviews, we made a note of that but did not exclude them from inclusion in the report.

Reviewers extracted available information and organized it according to the review questions and included 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, resources needed for implementation, and description of toolkits. One reviewer completed the data abstraction, and a second reviewer checked all of the first reviewer's abstraction for completeness and accuracy.

## 2.4 Risk of Bias (Quality) Assessment

For studies that addressed Review Question 5 about the effectiveness of PSPs, we used the Cochrane Collaboration's tool for assessing the risk of bias of RCTs or the ROBINS-I tool for assessing the Risk Of Bias In Nonrandomized Studies – of Interventions.[14,15] We did not assess the risk of bias in the pre-post studies, recognizing that they have a high risk of bias because of the lack of a contemporaneous comparison group.

For RCTs, we used the 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.[14] For nonrandomized studies, we used 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. The risk of bias assessment focused on the main outcome of interest in each study.[15]

For recent eligible systematic reviews, the primary reviewer used the criteria developed by the United States Preventive Services Task Force Methods Workgroup for assessing the quality of systematic reviews.[16]

- 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.

## 2.5 Strategy for Data Synthesis

We narratively summarized findings across systematic reviews and across primary studies. We did not conduct a meta-analysis. For Review Question 5 about the effectiveness of PSPs, we recorded information about the context of each primary study and whether the effectiveness of the PSP differed across patient subgroups. We graded the strength of evidence for PSPs with more than one recent primary study of effectiveness using the methods outlined in the AHRQ Effective Health Care Program Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[17] We also noted what the included systematic reviews reported about the strength of evidence.

# 3. Evidence Summary

## 3.1 Benefits and Harms

- For *neonates,* systematic reviews and primary studies, reported that sepsis prediction and recognition PSPs improved clinical process measures (low strength of evidence), but there was insufficient evidence for length of stay or mortality outcomes.
- For *adults,* systematic reviews and primary studies reported that sepsis prediction and recognition PSPs did not demonstrate an effect on clinical process, length of stay, or mortality outcomes. In primary studies of this population, the strength of evidence was insufficient in the pre-hospital setting for mortality, length of stay, and clinical process measures. In the emergency department setting, strength of evidence was low for mortality and clinical process measures and insufficient for length of stay. In ward or hospitalwide settings, strength of evidence was low across all three outcome types.
- The secondary outcome of the performance of the prediction and recognition system (e.g., positive predictive value) could not be meaningfully compared across studies due to diversity in populations.
- Implementation barriers included poor alert system performance, clinician attitudes about clinical interventions and machine learning or artificial intelligence, as well as implementation challenges (e.g., competing sepsis prevention process improvement efforts) and resources required to implement and maintain the system. Facilitators included positive implementation process practices (e.g., using frequent communication, improvement cycles, and clinician engagement throughout the process) and specific sepsis PSP design features (e.g., approaches to training the predictive model, or methods of risk visualization).
- The quality of the sepsis prediction and recognition PSP literature is limited by heterogeneity and inadequate description of intervention details as well as low quality studies employing weak designs.

## 3.2 Future Research Needs

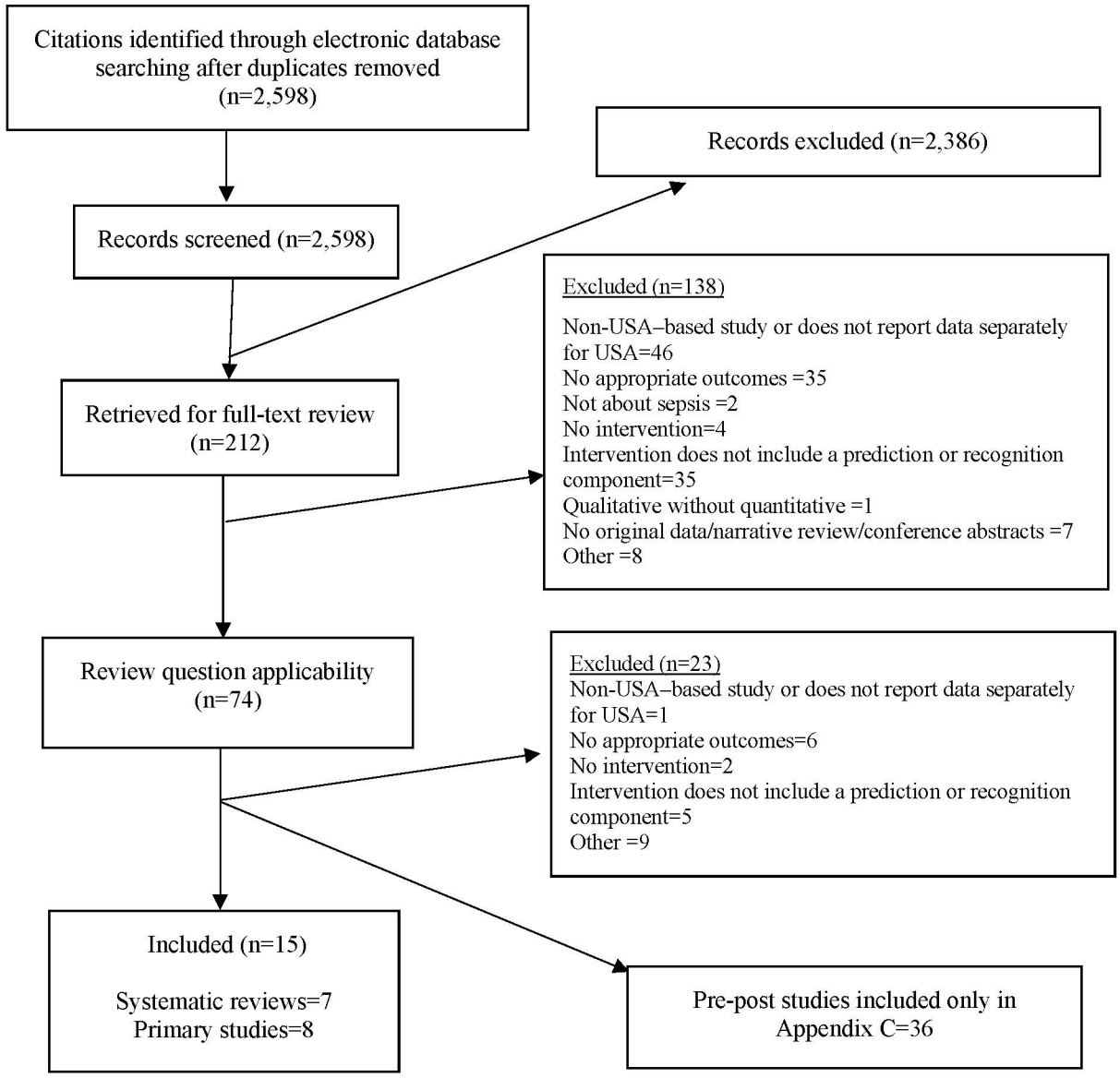
- Future research efforts should focus on higher quality studies (i.e., larger sample sizes, more rigorous designs) of re-designed sepsis prediction and recognition PSPs.

# 4. Evidence Base

## 4.1 Number of Studies

We found 15 studies (7 systematic reviews and 8 primary studies) that met our eligibility criteria (Figure 1). A listing of studies excluded during full-text review is included in Appendix B. Information abstracted from each included study is provided in Appendix C, Evidence Tables.

**Figure 1. Results of the search and screening**



## 4.2 Findings for Review Questions

### 4.2.1 Question 1. What Are the Frequency and Severity of Harm Associated With Sepsis?

According to the Centers for Disease Control and Prevention (CDC), 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] Between 4 and 12 percent of hospital admissions have a sepsis diagnosis.[18-20] Mortality rates for sepsis range from 27% for unspecified sepsis diagnoses to 60% for septic shock diagnoses.[3]

Timely administration of antibiotics is a critical strategy for managing sepsis, but antibiotic therapy carries risks as well (e.g., medication allergy, organ dysfunction, and infections).[21] A recent simulation study estimated that decreasing time to antibiotic treatment did not significantly increase new antibiotic related adverse events.[22]

### 4.2.2 Question 2. In PSPs Designed To Improve the Prediction or Recognition of Sepsis, What Patient Safety Measures or Indicators Have Been Used To Examine the Harms Associated With Sepsis?

In 2018, the Centers for Medicare & Medicaid Services (CMS) launched the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) performance measure. This measure has five elements:

- within three hours of severe sepsis presentation, lactate level was drawn, appropriate antibiotics administered, and blood cultures were drawn;
- within 6 hours of severe sepsis presentation if initial lactate level was elevated, lactate level was redrawn;
- within 3 hours of initial hypotension, appropriate intravenous fluids were given;
- within 6 hours of septic shock presentation if low blood pressure persisted, vasopressors were administered; and
- within 6 hours of septic shock presentation if low blood pressure persisted and lactate was greater than or equal to 4 mmol/l, volume status and tissue perfusion reassessment were performed.

As shown in Table 3, measures used in studies included in this review include the composite SEP-1 measure, its component measures, mortality, and hospital or intensive care unit (ICU) length of stay. In the neonatal population, a different set of clinical measures have been reported in evaluations of sepsis prediction and recognition PSPs. These include outcomes such as reduced overall antibiotic use across all patients (i.e., assessing the positive impact the sepsis prediction and recognition tool can have to reduce unnecessary antibiotics) and reduced lab orders

across all patients. These are stewardship outcomes used to demonstrate the reduction in unnecessary care (and associated risks) for patients who are unlikely to develop sepsis.

### 4.2.3 Question 3. What PSPs Have Been Used To Improve Sepsis Prediction or Recognition and in What Settings Have They Been Used?

Three categories of sepsis prediction and recognition PSPs were included in Making Healthcare Safer (MHS) III: manual screening tools (i.e., electronic or physical checklists to assess a patient's risk of having or developing sepsis), automated alerting systems (i.e., PSPs driven by patient monitoring systems using physiological monitoring or EHR data), and multicomponent sepsis interventions (i.e., PSPs bundling a prediction and recognition tool with additional interventions such as training, or organizational structures like response teams).[11] Sepsis prediction and recognition PSPs included in this report were multicomponent interventions. Individual PSPs included either a manual screening or automated alerting system as well as varying automated communication alerts to different care team members (e.g., physicians, nurses, pharmacists), associated order sets or treatment recommendations, and staff training.

### 4.2.4 Question 4. What Is the Rationale for Psps Used To Improve Sepsis Prediction or Recognition?

Early detection and treatment of sepsis improves outcomes,[5,23,24] so efforts to address sepsis focus heavily on rapid detection and intervention. However, the diagnosis of sepsis is challenging because common sepsis symptoms are nonspecific (e.g., fever, nausea, vomiting, muscle pain), particularly early in the clinical course, and sepsis can have highly variable presentations.

### 4.2.5 Question 5. What Are the Effectiveness and Unintended Effects of PSPs Designed To Improve the Prediction or Recognition of Sepsis, and What New Evidence Has Been Published Since the Search Was Done for the MHS III Report in 2019?

We identified seven recent SRs and eight recent primary studies. Two of the primary studies were evaluated in the included SRs but we included these primary studies separately as well, given heterogeneity in assessment methods across SRs.[25-28] The eight primary studies evaluated PSPs to improve sepsis outcomes.[26,28-34] Two studies were randomized controlled trials (RCTs)[30,34] and the rest were observational studies with comparison groups.[26,28,29,31-33] The study periods varied in length from five months[34] to more than two years.[26,29] One study had data collection overlapping with the Coronavirus Disease 2019 (COVID-19)

pandemic;[29] another two studies terminated early in order to expand the intervention to all patients.[30,34] Characteristics of the included systematic reviews and primary studies are presented in Tables 2 and 3.

**Table 2. Characteristics of the included systematic reviews by population and setting**

| Author, Year<br><br>Population<br><br>Setting | Objective* | Number of Included Studies | Intervention | Primary Outcomes of Interest† |
|---|---|---|---|---|
| Achten, 2019[35]<br><br>Neonatal<br><br>Hospitalwide | To assess the association between management of neonatal EOS guided by the neonatal EOS calculator (compared with conventional management strategies) and reduction in antibiotic therapy for newborns. | 13<br><br>4 before/after studies<br>3 hypothetical database analyses | EOS calculator | • Moderate quality evidence indicated that use of the neonatal EOS calculator was associated with a substantial reduction in the use of empiric antibiotics for suspected EOS compared to the standard of care. There were greater reductions in empiric antibiotic use in studies specifically evaluating the use of the EOS calculator in newborns born to mothers with chorioamnionitis. |
| Deshmukh, 2021[36]<br><br>Neonatal<br><br>Hospitalwide | To compare outcomes of neonatal EOS using sepsis calculator versus conventional approach. | 6 prospective studies | EOS calculator | • Moderate quality evidence indicated that the implementation of a sepsis calculator was associated with reduced use of antibiotics for EOS without a significant change in mortality compared to standard of care. |
| Persad, 2021[37]<br><br>Neonatal<br><br>Hospitalwide | To systematically summarize the current evidence of employing CDSAs using non-invasive parameters for sepsis prediction in neonates. | 36<br><br>2 RCTs<br><br>34 NRS | Clinical decision support algorithms including non-invasive vital sign measurements. | • High quality evidence indicates that clinical decision support algorithms using non-invasive vital sign measurements reduce 30-day mortality compared to standard of care. |
| Warttig, 2019[38]<br><br>Adult<br><br>Medical or surgical ICU | To evaluate whether automated systems for the early detection of sepsis can reduce the time to appropriate treatment (such as initiation of antibiotics, fluids, inotropes, and vasopressors) and improve clinical outcomes in critically ill patients in the ICU. | 3 RCTs | Computerized automated monitoring systems to monitor and alert one or more of the care team when modified SIRS criteria were met | • Very low quality evidence indicated that there were no significant differences in mortality, time to antibiotic therapy, or ICU length of stay with use of automated sepsis monitoring systems compared to standard of care. |
| Hwang, 2020[25]<br><br>Adult<br><br>ED | To determine whether automated electronic sepsis alerts in the ED are accurate and whether they have an impact on quality measures and/or mortality | 10<br><br>7 prospective cohort studies<br>3 retrospective cohort studies | Electronic systems that alert a healthcare provider of sepsis in real or near-real time | • Low quality evidence indicated that electronic sepsis alert systems improved lactate testing, but there was no consistent improvement in mortality, length of stay or antibiotic administration. |

| Author, Year<br><br>Population<br><br>Setting | Objective* | Number of Included Studies | Intervention | Primary Outcomes of Interest† |
|---|---|---|---|---|
| Kausch, 2021[39]<br><br>Adult<br><br>Hospitalwide | To evaluate the modeling approach and statistical methodology of machine learning prediction models for sepsis in the adult hospital population. | 14<br><br>1 RCT<br>13 retrospective cohort studies | Machine learning algorithms for sepsis prediction | • There was no consistent improvement in mortality, ICU length of stay, or hospital length of stay with the use of machine learning sepsis prediction algorithms across studies. SOE was not assessed. |
| van der Vegt, 2023[27]<br><br>Adult<br>Hospital | To retrieve and appraise studies of deployed AI-based sepsis prediction algorithms using systematic methods, identify implementation barriers, enablers, and key decisions and then map these to a novel end-to-end clinical AI implementation framework. | 30<br><br>1 RCT<br>14 retrospective studies<br>2 retrospective observational studies<br>4 prospective observational studies<br>5 before-after studies<br>1 two-arm cohort study<br>1 qualitative study<br>1 DiD study | Machine learning algorithms for sepsis prediction | • There was decreased mortality with the use of machine learning sepsis prediction algorithms across studies. Multiple barriers and facilitators of implementation were identified across studies. SOE was not assessed. |

*As reported in the review
†Additional outcomes assessed in each SR are reported in appendix table C-2
AI = artificial intelligence; CDSA = clinical decision support algorithm; DiD = difference in difference; ED = emergency department; EOS = early-onset sepsis; ICU = intensive care unit; NRS = nonrandomized studies; RCT = randomized controlled trial; SIRS = systemic inflammatory response syndrome; SOE = Strength of evidence

**Table 3. Characteristics of the included primary studies by population and setting***

| Population | Author, Year<br><br>Design<br><br>Setting | Number of Patients, N | Intervention and Comparator Descriptions | Factors Triggering Intervention | Study Results |
|---|---|---|---|---|---|
| Neonatal | Dhudasia, 2023[29]<br><br>Observational<br><br>ICU | 10,112<br><br>Intervention: 5,135<br>Comparison: 4,977 | Intervention is Period 2, 2018-2020: Early onset sepsis risk assessment using the Neonatal Early Onset Sepsis Calculator, which does not require CRP values for decision making<br><br>Comparison is Period 1, 2012-2014: a "categorical approach" to early onset sepsis risk assessment with routine CRP measurement | NR | • No significant difference in length of stay between routine CRP measurement and minimal CRP measurement groups<br>• No significant difference in mortality between comparison groups<br>• Significant reduction in antibiotics initiated, blood cultures obtained, and CSF cultures obtained in the minimal CRP use group without increased mortality rates |
| Adult | Mixon, 2021[32]<br><br>Observational<br><br>Prehospital | 507<br><br>Intervention: 419<br>Comparison: 88 | Field sepsis alert: alert system in place in pre-hospital (emergency response units); a best practice alert notifies the nurse to order a lactate<br><br>ED sepsis alert: same alert system in place in the ED; a best practice alert notifies the nurse to order a lactate level | Two or more SIRS criteria | • No significant difference in length of stay between the study arms.<br>• In-hospital mortality at 60 days was lower among the ED alert group but the difference was not significant.<br>• No significant difference between sepsis alerts initiated in the field *versus* the ED for fluid bolus utilization<br>• Mean time to antibiotic administration was significantly faster in the field alert group. Patients were significantly more likely to receive antibiotics within 60 minutes of ED arrival in the field alert group. |

| Population | Author, Year<br><br>Design<br><br>Setting | Number of Patients, N | Intervention and Comparator Descriptions | Factors Triggering Intervention | Study Results |
|---|---|---|---|---|---|
| | Austrian, 2018[26]<br><br>Observational<br><br>ED | 2,144<br><br>Intervention: 1,306<br>Comparison: 838 | Intervention: ED-based sepsis alert system comprised 3 alerts that fired only while the patient was in the ED: the SIRS advisory alert specifically for ED nurses, and 2 versions of the sepsis advisory alert (one for nurses and the other for physicians, physician assistants, and nurse practitioners)<br><br>Comparison: period prior to sepsis alert system implementation | SIRS advisory alert: required 2 of 4 triggers: temperature > 38°C or < 36°C; heart rate > 90 beats/min (sinus rhythm); respiratory rate > 20 breaths/min or PaCO2 < 32 mm Hg; white blood cell count < $4x10^9$/L, >$12x10^9$/L or >10% bands<br><br>Sepsis advisory alert for nurses or provider: Systolic blood pressure <90 mm Hg or lactate ≥4 mg/dL | • Significant decrease in length of stay between pre- and post-alert periods for both hospital and ICU stay<br>• No significant differences in mortality pre- vs post-alert period.<br>• Time to first lactate showed a significant reduction between pre- and post-alert periods |
| | Tarabichi, 2022[34]<br><br>RCT<br><br>ED | 598<br><br>Intervention: 285<br>Comparison: 313 | Intervention: Early Warning System Alert, which triggered two events:<br>1) displaying an icon on a widely used ED patient tracking tool ("track board") and<br>2) sending a message to an EHR-based messaging pool monitored by ED pharmacists<br><br>Comparison: standard care | No description of threshold for alert | • No significant difference in length of stay, mortality, antibiotic utilization, and fluid bolus administration<br>• Time to antibiotic administration was significantly faster among patients in the standard of care with early warning system *versus* in standard care only |

| Population | Author, Year<br><br>Design<br><br>Setting | Number of Patients, N | Intervention and Comparator Descriptions | Factors Triggering Intervention | Study Results |
|---|---|---|---|---|---|
| | Schertz, 2023[33]<br><br>Observational<br><br>ED | 5278<br><br>Intervention: 1673<br>Comparison 1: 512<br>Comparison 2: 3093 | Intervention: Used a PSS score (a proprietary score based on demographic, comorbidity, vital sign, laboratory, medication, and procedural variables) with an EHR-based navigator bundle with order sets<br><br>Comparison 1 is a historical control site with a SIRS-based alert and Comparison 2 are contemporaneous sites with a SIRS-based alert and order sets | PSS threshold score of 10 to activate the sepsis alert, based on demographic, comorbidity, vital sign, laboratory, medication, and procedural variables | • No significant difference in mortality rates between groups<br>• Time to anti-microbial delivery was significantly lower in the intervention with the PSS score and navigator in comparison to historical data. No significant difference when compared to contemporaneous sites with SIRS alert |
| | Downing, 2019[30]<br><br>RCT<br><br>Ward or Hospitalwide | 1123<br><br>Intervention: 595<br>Comparison: 528 | Intervention: EHR-based alert with text message to intensive care trained nurses<br><br>Comparison: usual care | Co-occurrence of one or more criteria of suspected infection, one or more criteria of organ dysfunction, and three or more criteria of SIRS | • No significant difference between control and intervention groups on length of stay, mortality, or number of blood cultures, lactate level, and anti-infectives ordered |
| | Horton, 2020[31]<br><br>Observational<br><br>Ward or Hospitalwide | 23078<br><br>Intervention: 12681<br>Comparison: 10397 | Intervention: modified Early Warning Score, with scores displayed in the EHR and alerts sent to clinicians<br><br>Comparison: Period before implementation | Modified Early Warning Score alerts when score is 5 or greater | • Hospital length of stay decreased non-significantly post-intervention.<br>• Monthly rate of mortality decreased non-significantly post-intervention.<br>• Pharmacy, supplies, and imaging sub-costs significantly decreased post-intervention |

| Population | Author, Year<br><br>Design<br><br>Setting | Number of Patients, N | Intervention and Comparator Descriptions | Factors Triggering Intervention | Study Results |
|---|---|---|---|---|---|
| | Schootman, 2022[28†]<br><br>Observational<br><br>Ward or Hospitalwide | 7914<br><br>Intervention:<br>Pre: 4862<br>Post: 671<br><br>Comparison:<br>Pre: 2064<br>Post: 317 | Intervention: Investigator-developed alerting tool with an accompanying order set; multicomponent training of staff prior to initiation<br><br>Comparison: Usual care in hospitals without the tool. Within the control and intervention group, authors compared the periods before and after the intervention implementation date | 6% risk of sepsis triggers action | • No significant difference between non-implementation hospitals and implementation hospitals for length of stay, mortality rate, sepsis bundle completion, antibiotic administration |

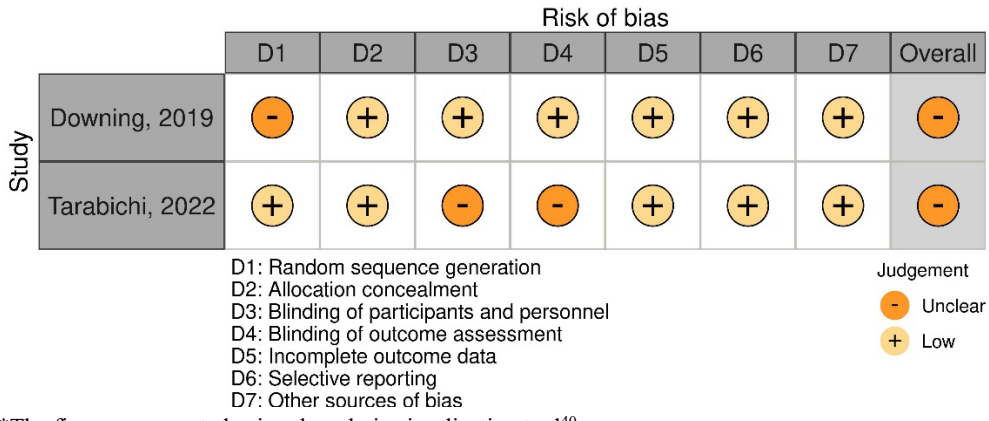
CRP = C-reactive protein; CSF = cerebrospinal fluid; ED = emergency department; EHR = electronic health record; ICU = intensive care unit; N = sample size; PaCO2 = partial pressure of carbon dioxide in arterial blood; PSS = Predicting Sepsis Score; RCT = randomized controlled trial; SIRS = systemic inflammatory response syndrome

*Pre-post studies are not included in this table, but are available in Appendix C

†Schootman, et al. 2022[28] reported data from hospitals that did not implement the predictive model (control) and hospitals that implemented the predictive model (intervention). Within these groups, data was recorded for pre-intervention implementation period and post-implementation periods.

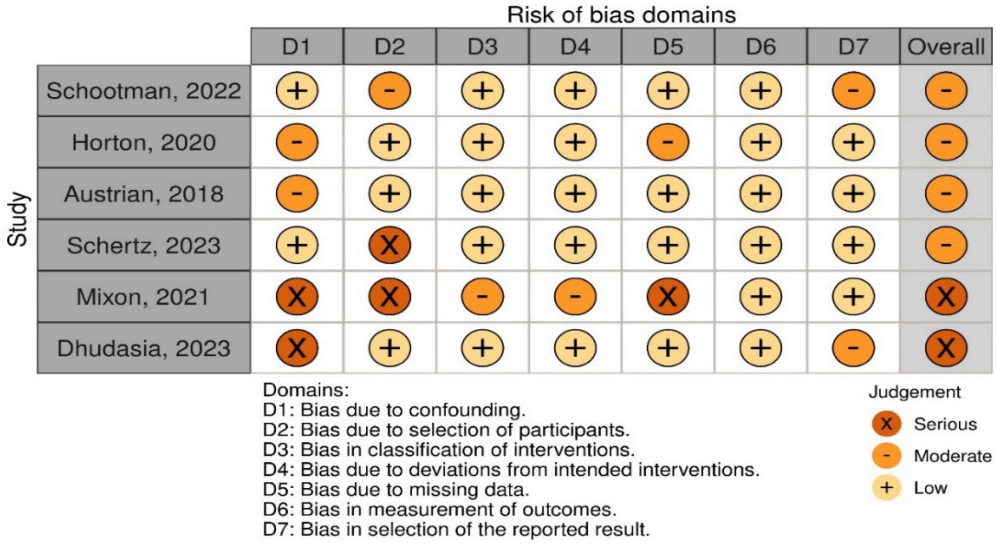
Several types of potential biases were present in the included RCTs and observational studies (Figure 2 and 3). Both RCTs were assessed as having an unclear risk of bias. In one RCT, the randomization technique was unclear;[30] the second RCT had unclear blinding of outcome assessors and participants.[34] For the observational studies, our assessments revealed concerns for bias in confounding, patient selection, and missing data. Two of the six observational studies had critical risks of bias.[29,32]

**Figure 2. Risk of bias assessments for randomized controlled trials included in this review***




*The figure was created using the robvis visualization tool[40]

**Figure 3. Risk of bias assessments for nonrandomized studies included in this review***




*The figure was created using the robvis visualization tool[40]

We present the findings by population. We first discuss the evidence from SRs, followed by evidence from primary studies.

#### 4.2.5.1 Neonates

Three SRs[35-37] evaluated sepsis PSPs in the neonatal population with two of the SRs[35,36] focusing on the use of neonatal early onset sepsis (EOS) calculators versus standard of care. In neonates, sepsis is defined as early- or late-onset based on time of presentation after birth, with cutoffs for EOS that are inconsistent and range between 48 hours and 7 days.[41,42] The other SR[37] evaluated various clinical decision support algorithms that included non-invasive vital sign measurements versus standard of care. The three SRs included 55 studies cumulatively, two of which were RCTs.[35-37]

One primary study was a retrospective cohort study in two neonatal ICUs; it enrolled infants who had been admitted within 3 days after birth.[29] Researchers compared sepsis-related outcomes in two periods: a period from 2012 to 2014 where C-reactive protein (CRP) was *routinely* measured in neonates (4,977 infants) and a period between 2018 and 2020, when it was not routinely measured (5,135 infants). A neonatal EOS calculator was also available in the second period.

##### 4.2.5.1.1 Hospital Mortality

Three of the SRs[27,36,37] reported impacts on mortality. In the SR by Deshmukh et al., one of six included studies evaluated an EOS calculator, which is a risk-based predictive model using a Bayesian approach developed by Kaiser Permanente North California, and found no change in hospital mortality, although there was only one death reported in both the EOS calculator and control groups.[36] Since the only study that reported mortality was not an RCT, Deshmukh et al. concluded that there was low quality evidence for improvement in mortality.[36]

The SR by Persad et al. found two studies that evaluated the use of clinical decision support algorithms that included non-invasive vital sign measurements.[37] One of the included studies showed a decrease in 30-day septicemia-related mortality from 19.6% to 11.8% (p=0.01) and the other showed a decrease from 16.1% to 10%.[37] Both studies included the same sample of patients from an RCT and used the same PSP, the Heart Rate Observation (HeRO) monitoring algorithm, which reports a sepsis risk score based on analysis of heart rate variability and heart rate decelerations.[37] Given the number of participants and the number of events, Persad et al. concluded that there was a high certainty of evidence that the sepsis PSP reduced 30-day septicemia mortality.[37]

The SR by van der Vegt et al, included 9 studies that evaluated the impact of predictive machine learning algorithms on mortality, one of which is the study by Schootman et al.[27,28] All of the studies showed decreased mortality, however, this finding was only statistically significant in five. Notably, only

one study adjusted for differences in characteristics between groups. The SR did not grade the strength of evidence (SOE).

The primary study of neonates compared sepsis-related outcomes in two periods: from 2012 to 2014 where CRP was routinely measured and between 2018 and 2020, when it was not routinely measured.[29] Minimal differences in 7-day mortality (0.5% versus 0.6%) and in mortality before discharge (0.8% versus 0.9%, p=.60) were found between the two time periods.

#### 4.2.5.1.2 Hospital or ICU Length of Stay

One primary study of neonates reported on the impact of sepsis PSPs on length of stay between 2 periods: from 2012 to 2014 where CRP was routinely measured and between 2018 and 2020 when it was not routinely measured.[29] The hospital length of stay was not significantly different between the two periods.

#### 4.2.5.1.3 Adherence to Clinical Guidelines or SEP-1 Measure

Two SRs evaluated the impact of an EOS calculator on antibiotic use. Deshmukh et al. found six studies that evaluated antibiotic use, all of which showed significantly less antibiotic use in the EOS calculator group compared to the standard of care group (1.4% versus 6%; odds ratio (OR) 0.22 [95% confidence interval (CI): 0.14 to 0.36]).[36] Similarly, Achten et al. included thirteen studies, all of which found a lower relative risk of receiving antibiotic therapy in the EOS calculator group.[35] Notably, there were larger reductions antibiotic use in studies limited to newborns born to mothers with chorioamnionitis (a group of infants who are at higher risk for EOS) compared to studies not limited to chorioamnionitis.[35] Both reviews concluded that there was moderate quality evidence indicating EOS calculators reduce antibiotic use.[35,36]

Deshmukh et al. found five studies that evaluated the impact of an EOS calculator on lab testing, all of which showed significant reductions in lab testing in the calculator group compared to standard of care (2.5% versus 15.5%; OR, 0.14; 95% CI, 0.08 to 0.27]).[36] They also found a significant reduction in admissions to the neonatal ICU (5.4% versus 19%; OR, 0.24; 95% CI, 0.11 to 0.51) and no difference in readmissions to the neonatal ICU (OR, 0.87; 95% CI, 0.57 to 1.33]) based on moderate quality evidence.[36]

The primary study of neonates that compared sepsis-related outcomes in two periods (routine versus nonroutine CRP measurement) found that fewer infants met SEP-1 measures in the group that did not use routine CRP measurement: there were fewer antibiotics used within the first 3 days of life (65% versus 57%, $p < 0.001$), fewer blood cultures (75% versus 55%, $p < 0.001$), and fewer cerebrospinal fluid cultures (8.7% versus 1.2%, $p < 0.001$).[29] Yet, there were minimal differences in 7-day mortality and in-hospital mortality across the two time periods.

#### 4.2.5.2 Adults

Four SRs[25,27,38,39] evaluated sepsis PSPs in the adult population. All studies included in the SRs occurred in the hospital setting, but included various sites of implementation (i.e., emergency department [ED], ICU, or acute care floor).[25,27,38,39] Two of the reviews focused on machine learning or artificial intelligence-based sepsis prediction algorithms,[27,39] while the other two evaluated automated sepsis alert systems.[25,38] Only one of ten studies in Kausch et al. SR,[39] one of thirty studies in the van der Vergt et al. SR,[27] and all three studies in the Warttig et al. SR[38] were RCTs.

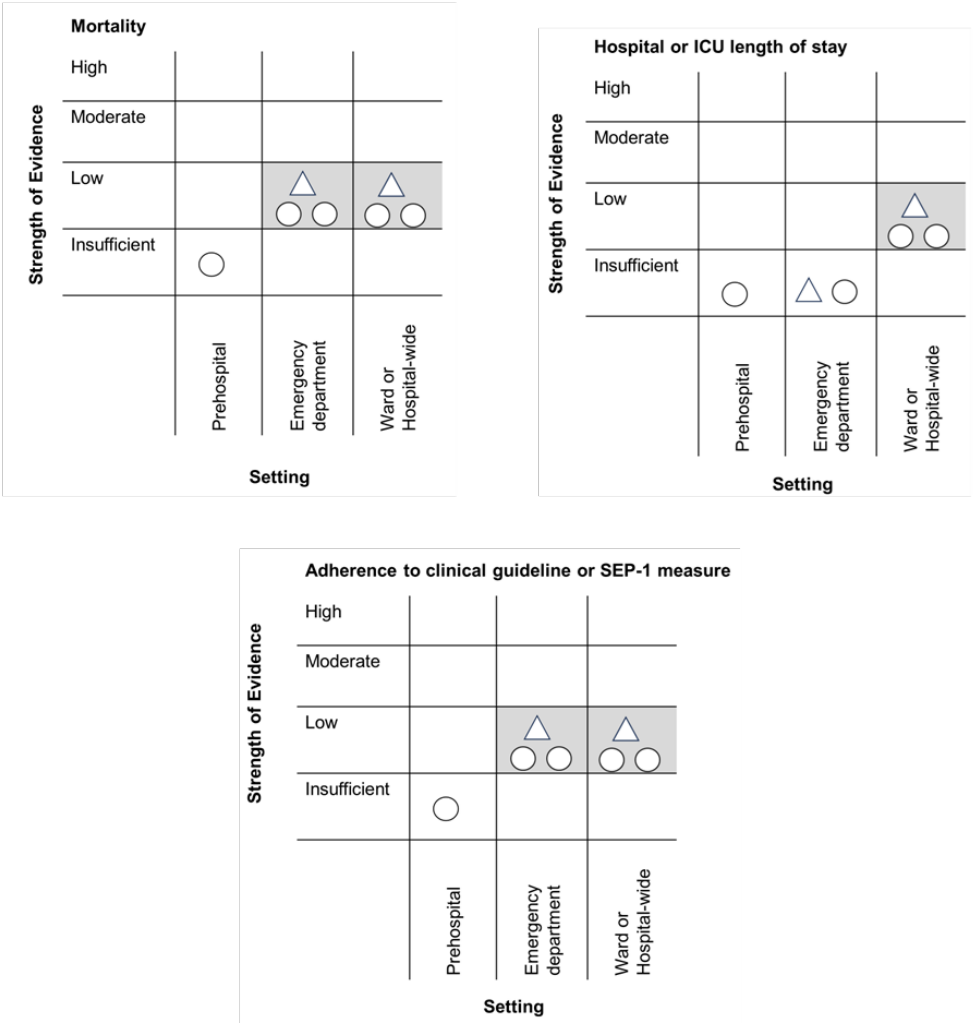
We identified seven primary studies of adults, each evaluating use of an electronic health record (EHR)-based alert system directed at clinicians in combination with a treatment intervention, such as provision of order sets.[26, 28, 30-34] The alert systems, which triggered treatment, varied across studies. Two studies used the Early Warning System (EWS) or a modified EWS where a score was displayed in the EHR and when the score crossed a threshold, an alert was sent to the clinician.[31,34] Three studies used the criteria in the Systemic Inflammatory Response Syndrome (SIRS) definition, where the presence of two or more sepsis criteria elicited a prompt to place a sepsis-related order.[26,30,32] One hospital developed their own predictive model with an alert when the sepsis risk exceeded a threshold;[28] this was also the only study that included patients in ICUs, general medical wards, and EDs. Three of the studies restricted the evaluation to patients in the EDs (Figure 4).[26,33,34]

Of the primary studies, two were RCTs. Patients were randomized to a study arm that generated EHR alerts upon crossing a threshold, or to a study arm that did not generate an alert.[30,34] Five were observational studies. Three compared outcomes during the intervention period to outcomes drawn from historical data before alert systems were in place; the outcomes were evaluated for differences with time-series analyses.[26, 31, 33] Another study compared outcomes in hospitals that implemented an alert system to hospitals that did not, and compared outcomes with a difference-in-difference model.[28] One other observational study evaluated the impact of displaying the alert to pre-hospital clinicians (emergency medical services) compared to displaying the alert to clinicians in the ED.[32]

**Figure 4. Overview of strength of evidence from recent primary studies by outcome and setting for studies of adult populations***

△ = Randomized controlled trial

○ = Observational study




*Shaded areas indicate specific setting for which we concluded there was little to no difference in outcomes

ICU = intensive care unit; SEP-1 = Severe Sepsis and Septic Shock Management Bundle

#### 4.2.5.2.1 Mortality

Three of the SRs reported the impact of sepsis PSPs on mortality. In the SR by Kausch et al., one RCT showed that a machine learning algorithm, the Insight model, reduced mortality in the ICU setting.[39] However, one study evaluating a different machine learning model showed no difference in mortality in the ICU setting.[39] The SR did not grade the SOE.

In the SR by Hwang et al., one low quality study on the use of a sepsis alert system showed a reduction in mortality (26.1% versus 36.3%; incidence

rate ratio (IRR), 0.64; 95% CI, 0.43 to 0.97). However, another low quality study and two high quality studies, one of which was the study by Austrian et al., showed no difference in mortality with the use of a sepsis alert system.[25, 26] The review graded the quality of evidence as low.

In the SR by Warrtig et al., one study found no significant difference in 14-day mortality between groups (20% versus 21%) and another study found no difference in 28-day mortality between groups (14% versus 10%).[38] Due to inadequate reporting of sample sizes for these outcomes in both studies, the 95% CIs could not be estimated.[38] The SR assessed the evidence for this outcome to be of very low quality.

The seven primary studies all reported on mortality; they demonstrated modest impact of the PSPs.[26,28,30-34] Three reported on 30-day (or 28-day) mortality rates.[30,33,34]

We report the findings from the primary studies, by setting, below.

#### 4.2.5.2.1.1 Prehospital Setting

A single, small, observational study compared a field-based (pre-hospital) alert to an ED alert and found lower 60-day mortality among patients who were exposed to the ED alert system (16% versus 9.6%, p = 0.07).[32] We were unable to draw a conclusion due to lack of evidence.(SOE: Insufficient)

#### 4.2.5.2.1.2 Emergency Department Setting

Three studies evaluated a sepsis alert system used in the ED on mortality.[26,33,34] Tarabichi, et al. did not find significantly reduced mortality with display of the alert (mortality rates of 9.9% in the control group versus 6% in the intervention group p = 0.077); this trial included approximately 300 participants per arm.[34] Similarly, in-hospital mortality did not differ significantly (8% versus 4.6%; p = 0.086).

A cohort study evaluated adding a navigator bundle to an alert against both a historical control group without an alert and a contemporaneous control group without the navigator bundle. The study found similar rates of 30-day mortality in all three groups of 9.7%, 8.6%, 9.3%, respectively.[33]

Austrian, et al. conducted a time series study with historical controls and reported the adjusted IRR for death as 0.58 (95% CI, 0.29 to 1.19), which non-significantly favored the intervention period when alerts were in use.[26] This study was also included in the SR by Hwang et al.[25]

Overall, evidence suggests a potentially small benefit, but no statistically significant results were reported in these studies (SOE: Low).

#### 4.2.5.2.1.3 Ward or Hospitalwide Setting

Three studies that tested the intervention in inpatient units or throughout the hospital assessed mortality as an outcome.[28,30,31] The trial conducted by

Downing et al. did not show a mortality benefit associated with display of the alert in the EHR (OR, 0.9; 95% CI, 0.56 to 1.46).[30]

The times series analysis of the EWS system found reduced monthly mortality rates after implementation although the difference was not statistically significant at -3.14% per month (95% CI, -8.76 to 2.48).[31]

One observational study,[23] which was also included in the SR by van der Vegt et al., reported on mortality rates across the observation periods.[27,28] In the adjusted difference-in-difference analysis using control hospitals that did not have the alert intervention, Schootman and colleagues reported a small, and not significant, difference in mortality rates attributable to the intervention (reduction of 1%, p = 0.17).[28]

Overall, there was no difference in mortality outcomes in these studies. (SOE: Low)

#### 4.2.5.2.2 Hospital or Intensive Care Unit Length of Stay

Three SRs reported the impact of sepsis prediction and recognition PSPs on length of stay. In the review by Kausch et al., one RCT showed that the use of a machine learning model, the Insight model, reduced overall length of stay.[39] However, one study showed no difference in length of stay.[39] The review did not grade the SOE.

In the SR by Hwang et al., one high quality study, which is the study by Austrian et al., showed both a decrease in ICU length of stay as well as overall hospital length of stay.[25,28] Additionally, a low quality study showed improvement in overall hospital length of stay (OR, 0.66; 95% CI, 0.53 to 0.82).[25] The review graded evidence as low quality.

The SR by Warrtig et al. included a study with 560 patients which showed no difference in median length of stay with the use of a sepsis alert system (3.0 days versus 3.0 days, p = 0.22).[38] This review assessed the quality of the evidence for this outcome to be low.

There were seven primary studies that reported on hospital or ICU length of stay outcomes.[26,28,30-34]

We report the results from the primary studies, by settings, below.

##### 4.2.5.2.2.1 Prehospital Setting

In the study comparing the field alert (pre-hospital) to the ED alert, there was no significant difference between groups on hospital length of stay.[32] We were unable to draw a conclusion due to lack of evidence.(SOE: Insufficient)

##### 4.2.5.2.2.2 Emergency Department Setting

Two studies evaluated the impact of an alert in the ED on hospital or ICU length of stay.[26,34] The trial by Tarabichi, et al, found comparable median hospital and ICU lengths of stay in the intervention and comparison groups,

with hospital lengths of stay of 3.2 [interquartile range (IQR) 1.1-6.2] and 4.0 [IQR:1.4 to 7.0]), respectively.[34]

The observational study by Austrian and colleagues, which was also included in the SR by Hwang et al., demonstrated significantly shortened lengths of stay associated with the alert-based intervention: length of ICU stay after implementation of the alert system in the ED was reduced from 1.8 days (standard deviation [SD] 3.1) to 1.2 days (SD 3.1) ($p < 0.001$) and total hospital length of stay was reduced from 10.1 days (SD 10.1) to 8.6 days (SD 7.9) ($p < 0.001$).[25,26]

The studies conflicted and we are unable to draw conclusions about the impact of sepsis alerts in the ED on hospital or ICU length of stay (SOE: Insufficient).

#### 4.2.5.2.2.3 Ward or Hospitalwide Setting

Three studies conducted in the inpatient setting or hospitalwide assessed hospital or ICU length of stay.[28,30,31] The Downing, et al, trial evaluated a binary outcome of length of stay greater or less than 72 hours and found no difference between intervention arms.[30] The Horton, et al, interrupted times series analysis of the EWS alert reported a small decrease in median length of stay of 0.63 days (95% CI, -1.28 to 0.03, P=.059).[31] The Schootman, et al, observational study, which was also included in the SR by van der Vegt et al., also did not demonstrate a significant impact of the intervention on length of stay.[28]

Overall, there was no difference in the length of stay (SOE: Low).

### 4.2.5.2.3 Adherence to Clinical Guidelines or SEP-1 Measure

Two of the SRs reported the impact of a PSP on adherence to aspects of sepsis guidelines or the SEP-1 measure.[25,38] In one high quality study, included in the review by Hwang et al., there was no difference in antibiotics being given in the ED with the use of a sepsis alert system, but a different low quality study showed an improvement in the time to antibiotic therapy (29 minutes versus 61.5 minutes, $p < 0.001$).[25] The review graded the evidence as low quality.

All three studies included in the SR by Warrtig et al. included data regarding time to initiation of antibiotic therapy, but due to insufficient information being included in the studies, the data could not be pooled and the impact on antibiotic timing could not be evaluated.[38] The largest included study with 680 patients in the review by Warrtig, did show a decrease in median time to initiation of antibiotic therapy (5.6 hours versus 7.8 hours) although statistical significance could not be evaluated due to insufficient data.[38] This review assessed the quality of evidence for this outcome to be very low.

Hwang et al, included one high-quality study, which was the study by Austrian et al., that showed improvement in time to first lactate level being measured.[25,28] However, the same study showed no difference in lactate level

being collected more than 24 hours after ED arrival (90.7% versus 91.3%, p = 0.65) and another high-quality study showed no difference in lactate being collected at any time (OR, 1.7; 95% CI, 0.9 to 3.2]).[25] Another study showed increases in overall lactate testing (12.7% versus 5.2%, p < 0.001), but this was deemed to be a low-quality study.

The review by Hwang et al. also included two studies evaluating collection of blood cultures. In one high-quality study, which was the study by Austrian et al., there was no change in blood cultures being drawn prior to antibiotics, but there was an overall increase in blood cultures being collected in another high-quality study (OR, 2.9; 95% CI, 1.1 to 7.7]).[25,28]

The seven primary studies all reported on at least one SEP-1 measure. The most frequently reported outcome was antibiotic (or anti-infective) use.[28,30,32-34]

We report the findings from the primary studies by settings below.

#### 4.2.5.2.3.1 Prehospital Setting

In the study comparing the prehospital alert to the ED alert, the pre-hospital alert group had higher rates of antibiotic use within the first hour (59% versus 44%, p = 0.01) and a shorter time to administration of 48 minutes (IQR, 34 to 87) compared to 64 minutes (IQR, 47 to 99).[32] This study did not find a difference in fluid bolus use between groups (52% versus 43%, p = 0.5).[32] We were unable to draw a conclusion due to lack of evidence (SOE: Insufficient).

#### 4.2.5.2.3.2 Emergency Department

The three ED studies reported on a SEP-1 measure.[26,33,34] The RCT, by Tarabachi et al, evaluated any antibiotic utilization and found no important differences in use between the study arms by 28 days (70% and 68%, p = 0.55).[34] In this trial, the time to administration was shorter in the intervention group at 2.3 hours (95% CI, 1.4 to 4.7) compared to 3.0 hours (95% CI, 1.6 to 5.5) in the comparison group (p = 0.039).

In the observational study by Schertz, et al, the authors reported that the time to antibiotic delivery was shorter in the intervention group relative to the historical control group by 2.8 hours (-3.5 to -2.0 hours) in adjusted analyses; however, there was not a difference when comparing this intervention to a contemporaneous control using a SIRS alert system, with a difference of 0.01 hours (95% CI, -0.16 to 0.19 hours).[33] Those authors also reported results in subgroups based on sepsis severity, with similar findings.

In the observational study by Austrian and colleagues, which was also included in the review by Hwang et al., early blood culture collection was assessed.[25, 26] No difference was found in the culture-before-antibiotic rates when the intervention period was compared with the historical control period, with rates of 79% in both groups (IRR, 0.87; 95% CI, 0.56 to 1.4).[26] That study also assessed the measurement of lactate levels and did not find a significant difference in completion of lactate measurement (IRR, 1.7; 95%

CI, 0.86 to 3.25). However, the time to first lactate measurement was shorter after implementation of the alert system (0.19 days versus 0.16 days (IRR, 0.63; $p < 0.001$).

The RCT by Tarabichi and colleagues assessed the administration of intravenous fluids, and did not find differences in rates of use of fluid boluses, by 28 days, between the control and intervention groups with rates of 65% and 61%, respectively ($p = 0.34$).[34]

Overall, there was no difference in SEP-1 measures with the ED-based sepsis alerts (SOE: Low).

#### 4.2.5.2.3.3 Ward or Hospitalwide Setting

Two studies in ward or hospitalwide setting reported on the SEP-1 measures.[28,30,31] The RCT by Downing and colleagues did not find a significant difference in rates of use of antibiotics within 180 minutes in the usual care and active alert arms with rates around 36% in both arms (OR, 0.9; 95% CI, 0.72 to 1.2)[30] Schootman, et al,[28] evaluated antibiotic administration within 60 minutes of the alert, and this study was also included in the review by van der Vegt et al.[27] In the adjusted difference-in-difference analysis, relative to control hospitals, the change from baseline rates were non-significantly greater. Horton and colleagues' time series analysis of the EWS system found no difference in antibiotic use within 24 hours with implementation of the alert.[31]

The trial, by Downing et al, also assessed the timely administration of intravenous fluids, finding little difference between groups in fluid administration by 180 minutes (20% versus 24%, OR, 1.3; 95% CI, 0.94 to 1.7) or in large volume fluid administration within 180 minutes (1.5% in both arms, OR, 1.0; 95% CI, 0.37 to 2.7).[30]

In the Downing, et al, trial, there was not a difference in blood culture orders within 180 minutes across arms (5.1% versus 4.7%, OR= 0.9, p =1.0).[30] Similarly, there was no significant difference in lactate measurement within 180 minutes (OR, 1.4; 95% CI, 0.95 to 1.95).[30]

Overall, there was no difference in SEP-1 measures with implementation of the alert system hospitalwide (SOE: Low).

### 4.2.5.2.4 Secondary Outcomes

The outcomes that we considered to be secondary were those pertaining to the performance of the alert systems for detecting sepsis in patients suspected of impending sepsis. It is not meaningful to compare the positive predictive values (PPV) across studies as the populations that were exposed to the alert systems varied greatly. For example, the PPV of the alert system in the Downing et al trial was 61%—it was applied broadly on hospital wards and triggered with three or more SIRS criteria.[30] The PPV of the alert system in the Tarabichi et al trial was 27%—this study involved application of the EWS system to patients in the ED.[34] The PPV associated with measurement of CRP

in neonates was very low (less than 3%) regardless of the time of use (within 4 hours, 4-24 hours, or 24-72 hours (Table 4).[29]

**Table 4. Summary of sensitivity and specificity data reported in the primary studies by setting**

| Author, Year | N | Setting | Model | Sensitivity, % | Specificity, % | PPV, % |
|---|---|---|---|---|---|---|
| Dhudasia, 2023[29]<br><br>Neonate | 434 | ICU | CRP, ±4 hours from blood culture | 41.7 | 89.9 | 2.3 |
| | 1506 | ICU | CRP, 4-24 hours from blood culture | 80 | 76 | 1.6 |
| | 798 | ICU | CRP, 24-72 hours from blood culture | 89.5 | 55.7 | 2.1 |
| Austrian, 2018[26]<br><br>Adult | 97216 | ED | ED sepsis alert system | 80.4 | NR | 14.6 |
| Downing, 2019[30]<br><br>Adult | 1123 | Ward or Hospitalwide | EHR-based alert | NR | NR | 61 |
| Horton, 2020[31]<br><br>Adult | 12681 | Ward or Hospitalwide | mEWS ≥5 | 44 | 91 | NR |
| | 12681 | Ward or Hospitalwide | Systemic Inflammatory Response Syndrome | 94 | 44 | NR |
| Tarabichi, 2022[34]<br><br>Adult | 598 | ED | Early Detection of Sepsis Cognitive Computing Model | 90 | 68 | 27 |

CRP = C-reactive protein; ED = emergency department; EHR = electronic health record; ICU = intensive care unit; mEWS = modified Early Warning Score; N=sample size; NR = not reported; PPV = positive predictive value

### 4.2.6 Question 6. What Are Common Barriers and Facilitators to Implementing PSPs Targeting the Prediction or Recognition of Sepsis?

Only one systematic review reported both barriers and facilitators to implementation.[27] Five primary studies reported barriers to implementation of a sepsis PSP,[26,28,30-32] but none reported facilitators to implementation (Table 5).

A commonly described barrier to implementation was suboptimal performance of the predictive model, with poor PPV in particular being a major issue.[26,28,30] The poor PPV was found to lead to lower response rates to alerts among clinicians and likely contributed to alert fatigue, limiting the impact of the sepsis PSP on clinical outcomes.[26,28,30] Similarly, the review by van der Vegt et al. found that alert fatigue and dismissal of alerts due to no clinical signs of deterioration were among the most common barriers to implementation across included studies.[27] Austrian et al. noted that prior studies that demonstrated a significant change in process or clinical outcomes with the use of a sepsis PSP had much higher PPVs, which further supports this concern.[26]

Downing et al. also observed that in addition to false positives leading to non-response to alerts by clinicians, alerts may lag behind clinical judgment and clinicians often had already diagnosed sepsis and initiated appropriate treatment.[30] In the review by Vegt et al. it was noted that such delays in alerting may lead to clinicians believing they are better at diagnosing sepsis than the alert system.[27] The reasons for delayed alerts may vary, but Mixon et al. noted that the cumbersome interactions between clinicians and the EHR when manual input of data is required may be an important contributing factor.[32]

Furthermore, Downing et al. found that certain clinician beliefs and attitudes may limit the impact of a PSP. In their study, there were issues with fluid resuscitation of septic patients due to clinicians' prior beliefs regarding fluid resuscitation in patients with a diagnosis of heart failure. This highlighted the importance of change management and local culture shifts in addition to the implementation of a sepsis PSP to change behavior and improve outcomes.[30]

Similarly, beliefs and attitudes regarding machine learning or artificial intelligence may be barriers to successful implementation of sepsis PSPs that use such algorithms. A common barrier noted in the review by van der Vegt was lack of clinician trust in machine learning-based sepsis alert systems, possibly related to lack of machine learning foundational knowledge and experience, as well as performance issues.[27]

Limitations of the EHR were also found to be a barrier for sepsis alert systems that used EHR data. The review by van der Vegt noted that this may be due to inherent limitations of EHR data, such as missingness, inaccuracies, and changes in practice patterns over time.[27] Additionally, there may be data entry delays that lead to delayed predictions.

Another barrier to implementation that was noted by Horton et al. was the concurrent implementation of quality improvement initiatives during the time of the sepsis PSP implementation. This may have affected allocation of resources needed for successful implementation, and limited evaluation of the impact of the sepsis PSP on outcomes.[31] The review by van der Veght also noted that the substantial costs for infrastructure, implementation personnel time, and ongoing maintenance were barriers to implementation for machine learning based alert systems.[27]

The review by van Vegt et al. also identified implementation facilitators. A total of 26 facilitators were noted across studies in the review, although most were only noted in one or two studies. The most commonly reported facilitators were frequent communications to raise awareness of the sepsis PSP during and after clinical trials, conducting improvement cycles, clinician involvement at all stages of development and implementation, identification of clinical champions, and use of test versions of the PSP for training.[27] Other less commonly reported facilitators ranged from factors specific to development and design of the sepsis PSP, such as improved training methods and color-coded visual depiction of sepsis risk, to factors related to the implementation strategy, such as staggering deployment across sites and providing clinical end users with "fact sheets" about the PSP.[27]

**Table 5. Patient safety practice implementation facilitators and barriers**

| Author, Year | Implementation Barriers | Implementation Facilitators |
|---|---|---|
| van der Vegt, 2023[27]* | • Alert fatigue and dismissal of alerts due to no clinical signs of deterioration<br>• Delays in alerting, may lead to clinicians perceiving they are better at diagnosis sepsis than the alert system<br>• Lack of clinician trust in machine learning based sepsis alert systems<br>• Limitations of the electronic health record | • Frequent communication to raise awareness of the sepsis PSP during and after clinical trials<br>• Conducting improvement cycles<br>• Clinician involvement at all stages of development and implementation<br>• Identification of clinical champions<br>• Use of test versions of the PSP for training |
| Downing, 2019[30] | • Suboptimal performance of the predictive model due to poor positive predictive value<br>• Alerts lagged behind clinical impressions<br>• Changing behavior is difficult without change management and local culture shifts | NR |
| Schootman, 2022[28] | • Suboptimal performance of the predictive model due to poor positive predictive value | NR |
| Mixon, 2021[32] | • Delays in care due to cumbersome nature of initiating alerts in the ED (e.g., the need for EHR input and feedback, time needed to obtain point of care lactate testing) | NR |
| Horton, 2020[31] | • Concurrent quality improvement activities in the hospital | NR |
| Austrian, 2018[26] | • Suboptimal performance of the predictive model due to poor positive predictive value | NR |

* We summarize the list of barriers reported in this review. Please see the review for full list.
ED = emergency department; EHR = electronic health record; NR = not reported; PSP = patient safety practice

### 4.2.7 Question 7. What Resources (e.g., cost, staff, time) Are Required for Implementation?

None of the included primary studies or SRs reported specific information regarding resources that are required for implementation of sepsis PSPs. However, the review by van der Vegt et al. did note that that there may be substantial costs involved for infrastructure, implementation personnel time, and ongoing maintenance.[27] Similarly, Horton et al. described how competing resource allocation due to concurrent quality improvement initiatives may impact the effectiveness of a sepsis PSP.[31]

### 4.2.8 Question 8. What Toolkits Are Available To Support Implementation of the PSPs?

No primary studies described toolkits used or produced. However, the following toolkits related to sepsis are openly available.

- The *Surviving Sepsis Campaign*, led by the Society for Critical Care Medicine, is an ongoing effort to maintain international guidelines for sepsis recognition and treatment, and to disseminate tools to support adoption including protocols, apps, checklists, and an implementation guide.[43]
- *The CDC's Hospital Toolkit for Adult Sepsis Surveillance* provides resources for healthcare facility-level monitoring of the incidence and

outcomes of sepsis, and the related *Hospital Sepsis Program Core Elements* guide outlines key features of successful monitoring programs. These CDC toolkits do not focus on sepsis prediction or recognition for individual patient care, but for sepsis monitoring across an organization.[44,45]

# 5. Discussion

## 5.1 Summary and Interpretation of Findings

The Making Healthcare Safer (MHS) III report in 2020 concluded that there was moderate evidence of improvement in process measures in the hospital setting for both sepsis screening and patient monitoring system patient safety practices (PSPs), while there was only sparse evidence regarding process measure improvement in the prehospital setting and mixed findings for clinical outcome measures. All three included studies in the hospital setting for manual screening PSPs showed significant improvement in at least one process measure. PSPs focused on patient monitoring systems for sepsis were also found to improve process measures significantly across five of the six included studies, although only two of five studies found a significant effect on outcome measures.

In the current review, all PSPs in the included studies were multicomponent interventions. Studies occurred in either pediatric or adult populations and in pre-hospital, emergency department (ED), intensive care unit (ICU) and hospital ward settings.

In the neonatal population, we found some evidence of benefit for sepsis prediction and recognition PSPs on clinical outcomes, including reduced lab tests, empirical antibiotics, and ICU admissions for suspected (Early Onset Sepsis) EOS cases. These are not the types of clinical care measures typically considered in evaluating sepsis recognition and prediction PSPs (e.g., Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) components) but do represent improvements in quality of care or patient outcomes. The strength of evidence was insufficient for mortality and length of stay (LOS) due to inconsistency in study findings.

In the adult population, systematic reviews and primary studies reported that sepsis prediction and recognition PSPs did not demonstrate an effect on clinical process, LOS, or mortality outcomes. In primary studies of this population, strength of evidence was insufficient in the pre-hospital setting across the three outcome categories due to there being only one included study. Strength of evidence was low in ED and ward or hospitalwide settings for mortality and clinical process measures. For LOS, strength of evidence was low in ward or hospital settings and insufficient in the ED setting. Reasons for low and insufficient ratings included imprecision, inconsistency of findings, and moderate study limitations. However, the three studies in the ED setting reported a small decrease in mortality with use of sepsis PSPs, though none of the differences were significant.

Other outcomes that were assessed in the systematic reviews but not included in the above results were rates of septic shock and ICU transfer. One study in the review by Kausch et al., showed a decrease in the rates of septic shock after implementation of a machine learning algorithm to predict the onset of sepsis.[39] Another study in the review by Hwang et al., which was deemed to be of high-quality, showed a decrease in ICU transfers with the use of a sepsis alert system.[25]

The secondary outcome of the performance of alerting system (e.g., positive predictive value) could not meaningfully be compared across studies due to diversity in populations and interventions. However, as shown in Table 4, the performance of

these predictive systems varies widely. This has been demonstrated more comprehensively in reviews on manual scoring[46]and artificial intelligence systems[47,48] for predicting sepsis and is a common barrier to implementation.

Implementation barriers included poor performance of alerting systems, which included false positives as well as the timing of alerts lagging clinical judgement and flagging patients who already had a diagnosis of sepsis. Pre-existing attitudes and beliefs of clinicians about both clinical practices (e.g., fluid resuscitation for patients with heart failure) and machine learning or artificial intelligence were noted to impact use of sepsis PSPs. Poor electronic health record (EHR) data quality was cited as a contributing factor to poor system performance and implementation success. Finally, quality improvement interventions concurrent with sepsis PSP implementation may affect resource allocation and program evaluation. One review identified 26 implementation facilitators.[27] Many of them were common best practices for implementation (e.g., frequent communication, improvement cycles, clinician engagement throughout the process) and others were more specific to sepsis PSPs (e.g., model training methods, risk visualization). No articles included in this review reported specific information about resources required; however, one review noted that technical infrastructure and personnel costs involved in implementation and maintenance of these systems were substantial and potential barriers to implementation.[27]

These many challenges described as implementation barriers provide possible reasons why sepsis prediction and recognition PSPs are not more effective. Additionally, two aspects of the rationale for the effectiveness of the specific PSPs evaluated in the included studies have been challenged. First, the degree to which sepsis-associated mortality is preventable has been questioned in a recent retrospective cohort study which found that out of 300 sepsis-associated deaths, only 11 (3.7%) were definitely or moderately likely to have been preventable, and 25 (8.3%) were possibly preventable.[49] In this study, chronic comorbidities were the most common underlying cause of death. However, assessing preventability of harm is highly subjective. Second, a large retrospective study demonstrated that delays in time to antibiotics were significant for patients with septic shock (with each hour adding additional risk for mortality), but not for patients with sepsis without shock.[50] For the latter group, only delays greater than six hours were associated with higher mortality. Timeliness of care matters, but the impact depends on disease acuity. Finally, for sepsis prediction and recognition PSPs employing machine learning models or any statistical prediction model, the general phenomenon of model quality degradation over time may be a concern.[51] Simulation studies have demonstrated several forms of temporal phenomenon (i.e., changes in the distribution of predictors, changes in the relationship between predictors and targets, and the impact of major events) commonly referred to as model or data drift do impact the quality of sepsis prediction models.[52]

## 5.2 Limitations

We discuss both limitations of this rapid review and of the sepsis prediction and recognition PSP literature. Sepsis prevention has been an ongoing effort for over twenty years, with the international Surviving Sepsis Campaign having been launched

in 2002.[53-55] Additionally, more recent implementation of mandatory SEP-1 reporting in 2018 has further increased awareness of the clinical interventions and organizational efforts to improve sepsis management.[56] These concurrent trends may complicate detecting effects, and create confounders for observational and pre-post study designs, which are common in this literature.

A major limitation of the literature is heterogeneity of the PSPs. In MHS III, PSPs were reported in three broad categories. The literature reviewed here were all multi-component interventions, indicating that perhaps the field has matured in how sepsis prediction and recognition PSPs are developed and implemented. However, this creates challenges synthesizing evidence, which is further complicated by lack of detail in intervention descriptions in many studies. It is notable that the strongest evidence of benefit was found in systematic reviews of a single PSP (the EOS Calculator).

A second major limitation of the literature is study quality. Few RCTs were found, and studies often used pre-post study designs and small sample sizes.

Our review is also limited in that we restricted eligible publications to recent primary studies performed in the United States or reviews that included primary studies in the United States. Sepsis prevention, generally, and sepsis prediction and recognition PSPs are of interest globally and potential advances from outside the United States were not included in this review.

## 5.3 Implications for Clinical Practice and Future Research

Future research efforts should focus on higher quality studies of redesigned sepsis prediction and recognition PSPs, and address issues in disparities of care. The overall quality of research was low and dominated by observational studies. Many of the studies included here were probably underpowered; they were small and identified non-significant differences often favoring the sepsis prediction and recognition PSPs. Higher quality trials would increase the strength of evidence; however, given the findings of this review, the field may require redesign of PSPs before larger trials are conducted. It is increasingly clear that these PSPs are not generating the benefits identified in earlier MHS reports but it is unclear why. Many barriers have been identified in the literature, including those attributable to the interventions themselves (poor predictive performance), how they are implemented within the larger health IT ecosystem (poor data quality) and workflow (timing of alerts relative to clinician judgement). Future research should address the sizable disparities in sepsis-related mortality, with Black, Hispanic and Native American patients being at elevated risk compared to Whites.[53]

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# Disclaimers

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The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any

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# Afterword

Recognized for excellence in conducting comprehensive systematic reviews, the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) Program is developing a range of rapid evidence products to assist end-users in making specific decisions in a limited timeframe. AHRQ recognizes that people are struggling with urgent questions on how to make healthcare safer. AHRQ is using this rapid format for the fourth edition of its Making Healthcare Safer series of reports, produced by the EPC Program and the General Patient Safety Program. To shorten timelines, reviewers make strategic choices about which processes to abridge. However, the adaptations made for expediency may limit the certainty and generalizability of the findings from the review, particularly in areas with a large literature base. Transparent reporting of the methods used and the resulting limitations of the evidence synthesis are extremely important.

AHRQ expects that these rapid evidence products will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to AHRQ. If you have comments related to this report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to MHS@ahrq.hhs.gov.


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# Appendixes

## Appendix A. Methods

### Search Strategies for Published Literature

**Table A-1. PubMed search strategy**

| # | Concept | Search Terms |
|---|---|---|
| 1 | Sepsis | "sepsis prediction"[tiab:~2] OR "Sepsis onset"[tiab] OR "sepsis identification"[tiab:~1] OR "sepsis detection"[tiab:~1] OR "Sepsis development"[tiab:~1] OR "sepsis recognize"[tiab:~1] OR "sepsis diagnosis"[tiab:~1] OR "sepsis screening"[tiab:~1] OR "sepsis monitoring"[tiab:~1] OR "sepsis surveillance"[tiab:~1] OR "sepsis prognosis" [tiab:~1] OR "sepsis progress" [tiab:~1] OR "sepsis recognition" [tiab:~1] OR "sepsis treatment" [tiab:~0] OR “sepsis alert”[tiab:~0] OR “sepsis alerts”[tiab:~0] OR “severe sepsis” [ti:~0] |
| 2 | Sepsis #2 | sepsis[tiab] OR sepsis [mh] AND ("Triage Tool"[tiab] OR "Early Warning"[tiab] OR "clinical decision Support"[tiab] OR "prediction model*"[tiab] OR "prediction algorithm"[tiab] OR "predictive system"[tiab]) |
| 3 | | # 1 OR #2 |
| 4 | Patient safety and Harms | "patient safety"[mh] OR "patient safety" [tiab] OR "Patient Harm"[mh] OR "Patient Harm*"[tiab] OR "patient risk*"[tiab] OR "quality care" [tiab] OR "adverse event*"[tiab] OR "undesired event*"[tiab] OR "medical errors"[mh] OR "medical error*"[tiab] OR "Diagnostic Errors" [mh] OR "diagnostic error*"[tiab] OR "diagnostic mistake*"[tiab] OR "health care error*"[tiab] OR "healthcare error*"[tiab] OR "medical fault*"[tiab] OR "medical mistake*"[tiab] OR "erroneous diagnos*"[tiab] OR "failure to diagnose"[tiab] OR "false diagnos*"[tiab] OR "faulty diagnos*"[tiab] OR misdiagnos*[tiab] OR "mistaken diagnos*"[tiab] OR "wrong diagnos*"[tiab] OR "risk assessment"[Title/Abstract] OR "length of stay"[Title/Abstract] OR "Quality Improvement" [tiab] OR "Quality Improvement" [mh] OR mortality [tiab] OR mortality [mh:noexp] OR “hospital mortality”[mh:noexp] OR performance [tiab] OR compliance [tiab] OR bundle [tiab] OR “patient outcomes” [tiab:~1] OR “appropriate management”[tiab] OR adherence [tiab] OR “time to” [tiab:~0] OR “Costs and Cost Analysis”[Mesh] OR Cost*[Tiab] OR economic*[tiab] OR “economics”[Subheading] OR “health care costs” [tiab:~0] OR “hospital costs” [tiab] OR “healthcare costs” [tiab:~0] |
| 5 | Exclude | ("Animals"[Mesh] NOT "Humans"[Mesh]) OR address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR "periodical index"[pt] OR Comment[pt] OR Letter[pt] OR Editorial[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "study guide"[pt] OR “Study protocol” [ti] OR “trial protocol” [ti] OR “review protocol” [ti] OR editorial[pt] OR letter[pt] OR “case reports”[pt]OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep[tw] OR ovine [tw] OR murine[tw] OR "environmental scan"[ti] |
| 6 | | #5 NOT #6 |
| 7 | 8. PubMed filter [ publication date January 2018 – August 17th, 2023, | |
| 8 | 6. PubMed filter [English] | |

**Table A-2. Cochrane search strategy**

| # | Concept | Search Terms |
|---|---|---|
| 1 | Sepsis | ("sepsis prediction" OR "Sepsis onset" OR "sepsis identification" OR "sepsis detection" OR "Sepsis development" OR "sepsis recognize" OR "sepsis diagnosis" OR "sepsis screening" OR "sepsis monitoring" OR "sepsis surveillance" OR "sepsis prognosis" OR "sepsis progress" OR "sepsis recognition" OR "sepsis treatment" OR "sepsis alert" OR "sepsis alerts" OR "severe sepsis"):ti OR ("sepsis prediction" OR "Sepsis onset" OR "sepsis identification" OR "sepsis detection" OR "Sepsis development" OR "sepsis recognize" OR "sepsis diagnosis" OR "sepsis screening" OR "sepsis monitoring" OR "sepsis surveillance" OR "sepsis prognosis" OR "sepsis progress" OR "sepsis recognition" OR "sepsis treatment" OR "sepsis alert" OR "sepsis alerts"):ab |
| 2 | Sepsis #2 | (Sepsis:ti OR Sepsis:ab OR sepsis [mh]) AND (("Triage Tool" OR "Early Warning" OR "clinical decision Support" OR "prediction model*" OR "prediction algorithm" OR "predictive system"):ti OR ("Triage Tool" OR "Early Warning" OR "clinical decision Support" OR "prediction model*" OR "prediction algorithm" OR "predictive system"):ab) |
| 3 | | # 1 OR #2 |
| 4. | 4<br>Patient safety and Harms [additional terms added to the standard search string are highlighted] | ("patient safety" OR "patient harm" OR "patient risk" OR "quality care" OR "adverse event" OR "undesired event" OR "medical error" OR "diagnostic error" OR "diagnostic mistake" OR "health care error" OR "healthcare error" OR "medical fault" OR "medical mistake" OR "erroneous diagnose" OR "erroneous diagnoses" OR "failure to diagnose" OR "false diagnose" OR "false diagnoses" OR "faulty diagnose" OR "faulty diagnoses" OR "mistaken diagnose" OR "mistaken diagnoses" OR "wrong diagnose" OR "wrong diagnoses" OR "risk assessment" OR "length of stay" OR "quality improvement" OR "patient outcomes" OR "appropriate management" OR "time to" OR "health care costs" OR "hospital costs" OR "healthcare costs" OR misdiagnose OR misdiagnoses OR misdiagnosis OR mortality OR performance OR compliance OR bundle OR adherence OR cost OR economic):ti OR ("patient safety" OR "patient harm" OR "patient risk" OR "quality care" OR "adverse event" OR "undesired event" OR "medical error" OR "diagnostic error" OR "diagnostic mistake" OR "health care error" OR "healthcare error" OR "medical fault" OR "medical mistake" OR "erroneous diagnose" OR "erroneous diagnoses" OR "failure to diagnose" OR "false diagnose" OR "false diagnoses" OR "faulty diagnose" OR "faulty diagnoses" OR "mistaken diagnose" OR "mistaken diagnoses" OR "wrong diagnose" OR "wrong diagnoses" OR "risk assessment" OR "length of stay" OR "quality improvement" OR "patient outcomes" OR "appropriate management" OR "time to" OR "health care costs" OR "hospital costs" OR "healthcare costs" OR misdiagnose OR misdiagnoses OR misdiagnosis OR mortality OR performance OR compliance OR bundle OR adherence OR cost OR economic):ab OR "patient safety"[mh] OR "Patient Harm"[mh] OR "medical errors"[mh] OR "Diagnostic Errors" [mh] OR "Quality Improvement" [mh] OR mortality [mh:noexp] OR "hospital mortality"[mh:noexp] OR "Costs and Cost Analysis"[mh] OR "economics"[mh] |
| 5 | 5 | #3 AND #4 |
| 6 | 6 [ Exclude] | (address OR "autobiography" OR "bibliography" OR "biography" OR congress OR "dictionary" OR "directory" OR "festschrift" OR "historical article" OR lecture OR "legal case" OR "legislation" OR "periodical index" OR Comment OR Letter OR Editorial OR "news" OR "newspaper article" OR "patient education handout" OR "periodical index" OR "study guide" OR editorial OR letter OR "case reports"):pt OR ("Study protocol" OR "trial protocol" OR "review protocol" OR "environmental scan"):ti OR (rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine):kw |
| #7 | 7 | #5 NOT #6 |
| #8 | Cochrane filter [ publication date 2018 – August 17th, 2023 | |
| #9 | Cochrane filter [English] and HUMANS only | |

# Appendix B. List of Excluded Studies Upon Full-Text Review

1. Achten NB, Dorigo-Zetsma JW, van der Linden PD, et al. Sepsis calculator implementation reduces empiric antibiotics for suspected early-onset sepsis. Eur J Pediatr. 2018 May;177(5):741-6. doi: 10.1007/s00431-018-3113-2. PMID: 29455368. **- Non-USA based study or does not report data separately for USA**
2. Ackermann K, Baker J, Festa M, et al. Computerized Clinical Decision Support Systems for the Early Detection of Sepsis Among Pediatric, Neonatal, and Maternal Inpatients: Scoping Review. JMIR Med Inform. 2022 May 6;10(5):e35061. doi: 10.2196/35061. PMID: 35522467. **- Other: Scoping review**
3. Ackermann K, Baker J, Green M, et al. Computerized Clinical Decision Support Systems for the Early Detection of Sepsis Among Adult Inpatients: Scoping Review. J Med Internet Res. 2022 Feb 23;24(2):e31083. doi: 10.2196/31083. PMID: 35195528. **- Other: Scoping review**
4. Adams R, Henry KE, Sridharan A, et al. Prospective, multi-site study of patient outcomes after implementation of the TREWS machine learning-based early warning system for sepsis. Nat Med. 2022 Jul;28(7):1455-60. doi: 10.1038/s41591-022-01894-0. PMID: 35864252. **- Comparison group does not meet inclusion criteria**
5. Aguirre U, Urrechaga E. Diagnostic performance of machine learning models using cell population data for the detection of sepsis: a comparative study. Clin Chem Lab Med. 2023 Jan 27;61(2):356-65. doi: 10.1515/cclm-2022-0713. PMID: 36351434. **- Intervention does not include a prediction or recognition component**
6. Alessi LJ, Warmus HR, Schaffner EK, et al. A Computable Definition of Sepsis Facilitates Screening and Performance Improvement Tracking. Pediatr Qual Saf. 2018 Mar;3(2):e067. doi: 10.1097/pq9.0000000000000067. PMID: 29732457. **- Conference, meeting abstract, or poster**
7. Almutary A, Althunayyan S, Alenazi K, et al. National Early Warning Score (NEWS) as Prognostic Triage Tool for Septic Patients. Infect Drug Resist. 2020;13:3843-51. doi: 10.2147/idr.s275390. PMID: 33149629. **- Non-USA based study or does not report data separately for USA**
8. Alturki A, Al-Eyadhy A, Alfayez A, et al. Impact of an electronic alert system for pediatric sepsis screening a tertiary hospital experience. Sci Rep. 2022 Jul 20;12(1):12436. doi: 10.1038/s41598-022-16632-2. PMID: 35859000. **- Non-USA based study or does not report data separately for USA**
9. Ashana DC, Anesi GL, Liu VX, et al. Equitably Allocating Resources during Crises: Racial Differences in Mortality Prediction Models. Am J Respir Crit Care Med. 2021 Jul 15;204(2):178-86. doi: 10.1164/rccm.202012-4383OC. PMID: 33751910. **- No appropriate outcomes**
10. Bader MZ, Obaid AT, Al-Khateb HM, et al. Developing Adult Sepsis Protocol to Reduce the Time to Initial Antibiotic Dose and Improve Outcomes among Patients with Cancer in Emergency Department. Asia Pac J Oncol Nurs. 2020 Oct-Dec;7(4):355-60. doi: 10.4103/apjon.apjon_32_20. PMID: 33062830. **- Non-USA based study or does not report data separately for USA**
11. Ballester L, Martínez R, Méndez J, et al. Differences in Hypotensive vs. Non-Hypotensive Sepsis Management in the Emergency Department: Door-to-Antibiotic Time Impact on Sepsis Survival. Med Sci (Basel). 2018 Oct 10;6(4)doi: 10.3390/medsci6040091. PMID: 30309044. **- Non-USA based study or does not report data separately for USA**
12. Baniasadi A, Rezaeirad S, Zare H, et al. Two-Step Imputation and AdaBoost-Based Classification for Early Prediction of Sepsis on Imbalanced Clinical Data. Crit Care Med. 2021 Jan 1;49(1):e91-e7. doi: 10.1097/ccm.0000000000004705. PMID: 33156121. **- Intervention does not include a prediction or recognition component**
13. Bansal V, Festić E, Mangi MA, et al. Early Machine-Human Interface around Sepsis Severity Identification: From Diagnosis to Improved Management? Acta Med Acad.

2018 May;47(1):27-38. doi: 10.5644/ama2006-124.212. PMID: 29957969. **- No appropriate outcomes**

14. Barbara P, Graziano C, Caputo W, et al. The quick sequential organ failure assessment (qSOFA) identifies septic patients in the out-of-hospital setting. Am J Emerg Med. 2018 Jun;36(6):1022-6. doi: 10.1016/j.ajem.2018.01.073. PMID: 29426799. **- No appropriate outcomes**

15. Barbash IJ, Davis BS, Yabes JG, et al. Treatment Patterns and Clinical Outcomes After the Introduction of the Medicare Sepsis Performance Measure (SEP-1). Ann Intern Med. 2021 Jul;174(7):927-35. doi: 10.7326/m20-5043. PMID: 33872042. **- Intervention does not include a prediction or recognition component**

16. Barton C, Chettipally U, Zhou Y, et al. Evaluation of a machine learning algorithm for up to 48-hour advance prediction of sepsis using six vital signs. Comput Biol Med. 2019 Jun;109:79-84. doi: 10.1016/j.compbiomed.2019.04.027. PMID: 31035074. **- Intervention does not include a prediction or recognition component**

17. Barton C, Shimabakuru D, Feldman M, et al. Effect of a machine learning-based severe sepsis prediction algorithm on patient survival. Critical care medicine. 2018;46:699. doi: 10.1097/01.ccm.0000529432.50757.3c. PMID: CN-01452229. **- Conference, meeting abstract, or poster**

18. Beneyto-Ripoll C, Palazón-Bru A, Llópez-Espinós P, et al. A critical appraisal of the prognostic predictive models for patients with sepsis: Which model can be applied in clinical practice? Int J Clin Pract. 2021 Aug;75(8):e14044. doi: 10.1111/ijcp.14044. PMID: 33492724. **- No appropriate outcomes**

19. Bolte TB, Swanson MB, Kaldjian AM, et al. Hospitals That Report Severe Sepsis and Septic Shock Bundle Compliance Have More Structured Sepsis Performance Improvement. J Patient Saf. 2022 Dec 1;18(8):e1231-e6. doi: 10.1097/pts.0000000000001062. PMID: 35858483. **- Intervention does not include a prediction or recognition component**

20. Boskabadi H, Zakerihamidi M. Evaluate the diagnosis of neonatal sepsis by measuring interleukins: A systematic review. Pediatr Neonatol. 2018 Aug;59(4):329-38. doi: 10.1016/j.pedneo.2017.10.004. PMID: 29239828. **- Intervention does not include a prediction or recognition component**

21. Calderon K, Van Landingham E, Purcell S, et al. Identifying and treating sepsis in older people: a quality improvement project in hospitals and nursing homes in Texas. Nurs Older People. 2021 Jun 1;33(3):36-41. doi: 10.7748/nop.2021.e1308. PMID: 33565283. **- Intervention does not include a prediction or recognition component**

22. Carbó M, Fresco L, Osorio G, et al. Predictors of mortality in emergency department patients with sepsis scored 2 or 3 on the Quick Sequential Organ Failure Assessment scale. Emergencias. 2020 Jun;32(3):169-76. PMID: 32395924. **- Non-USA based study or does not report data separately for USA**

23. Champagne HA, Garabedian MJ. Routine Screening for Sepsis in an Obstetric Population: Evaluation of an Improvement Project. Perm J. 2020 Nov;24:1-10. doi: 10.7812/tpp/19.232. PMID: 33482959. **- No intervention**

24. Chen KF, Tsai MY, Wu CC, et al. Effectiveness of Treatments and Diagnostic Tools and Declining Mortality in Patients With Severe Sepsis: A 12-Year Population-Based Cohort Study. J Intensive Care Med. 2020 Dec;35(12):1418-25. doi: 10.1177/0885066619827270. PMID: 30700200. **- Non-USA based study or does not report data separately for USA**

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# Appendix C. Evidence Tables

**Evidence Table C-1. Included systematic review characteristics addressing effectiveness of sepsis prediction, recognition, and treatment**

Note: References are located in the reference list in the body of the report.

| Author, Year<br><br>Literature Search Date | Included Population | Setting | Comparisons |
|---|---|---|---|
| Deshmukh, 2021[36]<br><br>May 2019 | Neonates >34 weeks gestation; one included study only evaluated only neonates born to mothers with chorioamnionitis | Not specified but all studies included patients in the hospital setting | Comparator:<br>Standard of care<br><br>Intervention:<br>EOS calculator |
| Persad, 2021[37]<br><br>PubMed, CENTRAL, and EMBASE searched to August 17, 2020<br><br>Google Scholar searched to January 20, 2021 | Neonates; some studies only included VLBW infants or NICU patients | Not specified for many studies but all studies included patients in the hospital setting; some studies included only NICU | Comparator:<br>No monitoring (i.e., standard of care)<br><br>Intervention:<br>Clinical decision support algorithms including non-invasive vital sign measurements. 24 studies evaluated CDSAs using heart rate based parameters, 8 studies had CDSAs using one vital sign parameter alone, and all other studies evaluated a combination of parameters (e.g., vital signs and demographics). The two RCTs were machine learning algorithms.<br>RCTs both used HeRO algorithm which is based on HRC and demographics |
| Kausch, 2021[39]<br><br>October 1, 2018 | Adults | Nine models evaluated in ICU and two models evaluated on acute care floors<br><br>Studies with clinical outcomes were only in the ICU setting | Comparator:<br>Not specified<br><br>Intervention:<br>Machine learning models<br>RCT evaluating clinical outcomes used the Insight model<br>Pre-post study evaluating clinical outcomes had a monitor that displayed risk for clinical deterioration for each patient in the ICU. |

| Author, Year<br><br>Literature Search Date | Included Population | Setting | Comparisons |
|---|---|---|---|
| Hwang, 2020[25]<br><br>August 2, 2018 | Adults | Emergency department | Comparator:<br>Not specified. Standard of care for included pre-post studies.<br><br>Intervention:<br>Electronic systems that alert a healthcare provider of sepsis in real or near-real time.<br>Some were bundled (although not specified which ones) with other interventions such as response teams or order sets. |
| Warttig, 2019[38]<br><br>inception to 9/18/2017 | patients admitted to medical or surgical ICU | Medical or surgical ICU | Comparator:<br>Standard of care<br><br>Intervention:<br>Computerized automated monitoring systems to monitor and alert one or more of the care team when modified SIRS criteria were met |
| van der Vegt, 2023[27]<br><br>between January 1, 2012 and June 23,2022 | Patients admitted to care delivery setting | Hospitalwide | Comparator:<br>Standard of care<br><br>Intervention:<br>One of six groups of algorithms (EWS 2.0; Insight; Robot Laura; Sepsis watch; TREWScore; Sepsis sniffer; ESM) |
| Achten, 2019[35]<br><br>inception to 1/31/2019 | Neonates | Hospitalwide | Comparator:<br>Standard of care<br><br>Intervention:<br>EOS calculator |

CDSA=clinical decision support algorithms; ED=emergency department; EOS=early onset sepsis; ESM=Epic Sepsis Model; EWS=early warning system; HeRO=Heart Rate Observation Score; ICU=intensive care unit; NICU=neonatal intensive care unit; NR=not reported; RCT=randomized clinical trial; TREWScore=targeted real-time early warning score; VLBW=very low birthweight

**Evidence Table C-2. Included systematic review outcomes addressing effectiveness of sepsis prediction, recognition, and treatment**

| Author, Year | Primary Outcomes | Secondary Outcomes | Other Outcomes |
|---|---|---|---|
| Deshmukh, 2021[36] | Mortality:<br>Only one included study reported mortality; one death in each sepsis calculator and control group<br><br>Adherence to clinical guidelines:<br>Antibiotic use was significantly less in the sepsis calculator group compared to standard of care (1.4% vs 6%; OR 0.22 [0.14-0.36]) | NR | Laboratory Test for EOS: Five studies reported a significant reduction in lab testing for evaluation of EOS in calculator group (2.5% vs 15.5%; OR=0.14 [0.08-0.27]). NNT to prevent the use of lab testing for EOS in one neonate was 8.<br><br>Admission to NICU: Three of four studies reported significant reduction in admission to NICU (5.4% vs 19%; OR=0.24 [0.11-0.51])<br><br>Readmission to NICU: Three studies reported no difference in readmission to NICU (OR=0.87 [0.57-1.33])<br><br>Culture Positive EOS: Six studies reported no difference (OR 0.94 [0.51-1.74]) |
| Persad, 2021[37] | Mortality:<br>One study reported mortality in the HRC monitored group at 11.8% vs 19.6% in the unmonitored group (41/348 vs 68/352; absolute risk reduction 7.5%; NNT 13; p = 0.01)<br><br>One study reported mortality in the HRC monitored group at 10% compared to 16.1% in the unmonitored group (36/358 vs 61/379; absolute risk reduction 6.1%; NNT 17; p = 0.01) | Sensitivity:<br>Sensitivity ranging from 0.15 to 0.96 among all studies.<br>Not reported for the RCTs<br><br>Specificity:<br>Specificity ranging from 0.23 to 0.98 among all studies.<br>Not reported for the RCTs<br><br>PPV:<br>PPV ranging from 0.23 to 0.82 among all studies.<br>Not reported for the RCTs<br><br>NPV:<br>NPV ranging from 0.65 to 0.98 among all studies.<br>Not reported for the RCTs<br><br>AUC:<br>AUROC ranging from 0.63 to 0.88 among all | NR |

| Author, Year | Primary Outcomes | Secondary Outcomes | Other Outcomes |
|---|---|---|---|
| | | studies with average of 0.76.<br>Not reported for the RCTs | |
| Kausch, 2021[39] | Hospital length of stay:<br>Reduced LOS for patients in the treatment arm of the RCT.<br>No difference in LOS in the pre-post study.<br><br>ICU length of stay:<br>Reduced LOS for patients in the treatment arm of the RCT.<br>No difference in LOS in the pre-post study.<br><br>Mortality:<br>Reduced mortality for patients in the treatment arm of the RCT.<br>No difference in mortality in the pre-post study. | Sensitivity:<br>NR<br><br>Specificity:<br>NR<br><br>PPV:<br>NR<br><br>NPV:<br>NR<br><br>AUC:<br>AUROCs ranged from 0.61 to 0.96. For models evaluating AUROC for predicting sepsis or severe sepsis four hours prior to onset, AUROCs ranged from 0.74 to 0.96. | Rate of septic shock decreased in the pre-post study by more than half after the display of the monitor was implemented (rate ratio = 0.478, 95% CI: 0.25-0.88] |
| Hwang, 2020[25] | SEP-1 measure:<br>The high quality study by Austrian et al showed improved time to first lactate (0.19 days (0.94) vs. 0.16 days (0.58), p<0.001). The same study showed no difference in lactate being drawn >= 24 hours after ED arrival (90.7% vs. 91.3%, p=0.65) and Nelson et al showed no difference in lactate being collected at any time (OR 1.7 (0.9-3.2)). A low quality study by Berger et al did show increases in overall lactate testing (5.2% vs. 12.7% (95% CI, 6.0 to 9.0%) absolute increase p<0.001).<br><br>Austrian et al showed no change in blood cultures being drawn prior to antibiotics (Blood cultures drawn prior to antibiotics: 79.0% vs 79.2%, p=0.92). However, the other high quality study by Nelson et al showed improvement in blood cultures being collected (OR 2.9 [1.1-7.7]).<br><br>The high-quality study by Nelson et al showed no difference in antibiotics being given in the | Sensitivity:<br>Sensitivity ranged from 64-100%<br><br>Specificity:<br>Specificity ranged from 78-99%<br><br>PPV:<br>PPV ranged from 5.8%-54%<br><br>NPV:<br>NPV ranged from 99-100%<br><br>AUC:<br>NR | High quality study by Nelson et al showed increase in chest radiograph prior to admission (OR 3.2 (1.1-9.9)).<br><br>High quality study by Austrian et al showed decrease in ICU transfers (36.9% vs. 25.8%, p<0.001) |

| Author, Year | Primary Outcomes | Secondary Outcomes | Other Outcomes |
|---|---|---|---|
| | ED [OR 2.8 (0.9-8.6)] but a low quality study by Narayanan et al did show improvement in antibiotic being given within 60 mins (48.6% vs. 76.7%, p<.001) and a decrease in mean time to antibiotics (61.5 mins (33-171) vs. 29 mins (2-59), p<.001).<br><br>Hospital length of stay:<br>The high quality study by Austrian et al showed decrease in LOS ( 10.1 days (SD 10.1) vs. 8.6 days (SD 7.9), p<0.001).<br>A low quality study by Narayanan et al also showed improvement in LOS [OR 0.66 (0.53-0.82)].<br><br>ICU length of stay:<br>The high quality study by Austrian et al showed decrease in ICU LOS (1.8 days (SD 3.7) vs. 1.2 days (SD 3.1), p<0.001)<br><br>Mortality:<br>Two high quality studies were included (Austrian et al and Nelson et al) and neither showed improvement in mortality (8.5% vs 7%, p=0.22).<br><br>Two low quality studies evaluated mortality. One study showed no improvement in mortality (In-hospital survival rate with SSRT activation in full cohort: 0.69 (95% CI, 0.31 to 1.56) In-hospital survival rate with SSRT activation among severe sepsis/septic shock patients: 0.53 [95% CI, 0.26 to 1.11]). Other study showed improvement in mortality (Mortality: 36.3% vs. 26.1% Adjusted risk reduction for mortality: 36% [0.43-0.97]). | | |
| Warttig, 2019[38] | Adherence to clinical guidelines:<br>3 studies reported data in relation to time to initiation of ABX therapy but data could not be pooled. The largest study included 680 | NR | NR |

| Author, Year | Primary Outcomes | Secondary Outcomes | Other Outcomes |
|---|---|---|---|
| | participants and reported median time to initiation of first or new antibiotic was 5.6 hours (IQR 2.3 to 19.7) in the intervention group (n = not stated) and 7.8 hours (IQR 2.5 to 33.1) in the control group (n = not stated)<br><br>Hospital length of stay:<br>Median 3.0 (IQR 2 to 4) days for intervention and Median 3.0 (IQR 2 to 5) days for control in 1 study (n = 560), p = 0.22<br><br>Mortality:<br>1 study reported 14-day mortality and found no significant differences between groups (20% in the intervention, 21% in the control). 1 study reported mortality at 28 days or discharge and found no significant differences between groups (14% in the intervention, 10% in the control). Sample sizes were not reported adequately for these outcomes and so we could not estimate confidence intervals | | |
| van der Vegt, 2023[27] | Mortality:<br>9 studies evaluated mortality with all studies showing a decrease in mortality with use of a machine learning sepsis prediction algorithm, although this was statistically significant in only 5 studies. Only 1 study adjusted their findings for differences between cohorts in patient characteristics. | NR | NR |
| Achten, 2019[35] | Adherence to clinical guidelines:<br>All studies found a lower RR for antibiotic therapy, favoring use of the EOS calculator (range,3%-60%). Studies evaluating the EOS calculator in newborns born to mothers with the risk factor of chorioamnionitis reported stronger reductions (RR,3%-39%) compared with studies not limited to chorioamnionitis (RR,25%-60%). | NR | NR |

ABX=antibiotic; AUC=area under the curve; AUROC=area under the receiver operating characteristics curve; CI=confidence interval; ED=emergency department; EOS=early onset sepsis; HRC=heart rate characteristics; ICU=intensive care unit; IQR=interquartile range; LOS=length of stay; n=sample size; NICU=neonatal intensive care unit; NNT=number needed to treat; NPV=negative predictive value; NR=not reported; OR=odds ratio; PPV=positive predictive value; RCT=randomized clinical trial; RR=relevant risk; SD=standard deviation; SEP-1=The Severe Sepsis and Septic Shock Management Bundle; SSRT= sepsis and shock response team

**Evidence Table C-3. Included systematic review barriers and facilitators addressing effectiveness of sepsis prediction, recognition, and treatment**

| Author, Year | Barriers and Facilitators | Facilitators |
|---|---|---|
| van der Vegt, 2023[27] | • Lack of clinician trust<br>• MLA retraining concerns (feedback loops arise when alerts lead to timely treatment)<br>• Alerts dismissed for wrong reasons (e.g., pts with no sepsis symptoms or with higher acute complexity)<br>• Alert fatigue<br>• Differential nurse/doctor role, perceptions of role and value<br>• Inherent limitations of EHR data, which can be plagued by missingness, inaccuracies, and changes in practice patterns over time<br>• Data entry delays, leading to delayed predictions<br>• Inventors/company equity owners may have COI and inadvertently act in bias ways towards the evaluation of their system<br>• Surveillance bias<br>• Cost of infrastructure, personnel time and maintenance<br>• Lack of healthcare worker proficiency in use of hardware/software<br>• Clinicians believe they are better than MLA in diagnosis sepsis<br>• Lack of matching learning knowledge and experience<br>• Clinician concern over reliance on system | • Clinician involvement all all stages of development and integration into workflow<br>• Better AI model training methods<br>• Improvement initiatives (PDSA cycles) during implementation<br>• Frequent communication to increase awareness<br>• Appoint clinical champions<br>• Create test version for training<br>• Use table with training loaded plus feedback<br>• Implement alternative workflows during peak hours<br>• Use 'model facts' sheet to convey information<br>• Systems perceived as alleviating demands on attention and cognition<br>• Teach clinicians to interpret risk scores<br>• Iterative approach to design<br>• Visually depicting risks<br>• Perform post-implementation evaluation<br>• HCI was augmented by completion and fall out indicators to visually guide the clinician to timely and appropriate care<br>• Report cases AI detects that clinicians miss<br>• Track and monitor data and model drift<br>• Work with regulatory officials to classify as CDS and not diagnostic medical device<br>• Establish multi-disciplinary governance committee<br>• Full-time role to work with clinicians to implement<br>• Senior leadership support<br>• Establish a transdisciplinary team of data scientists, statisticians, hospitalists, intensivists, ED clinicians, RRT nurses, and information technology leaders and develop capabilities across domains<br>• Staggered deployment across sites<br>• Use patient cases with frontline to drive change<br>• Describe tool as supporting clinicians (not usurping authority)<br>• Trust in model increased with clinician experience with the system |

AI=artificial intelligence; CDS=cross domain solution; COI=conflict of interest; ED=emergency department; EHR=electronic health department; HCI=human–computer interface; MLA=machine learning algorithms; PDSA=Plan-Do-Study-Act; pts=patients; RRT=rapid response team

**Evidence Table C-4. Quality assessment as reported by the included systematic reviews addressing effectiveness of sepsis prediction, recognition, and treatment**

| Author, Year | Quality Assessment Tool | Strength of Evidence | Limitations | Conclusion |
|---|---|---|---|---|
| Deshmukh, 2021[36] | ROB: Newcastle-Ottawa<br>Quality of Evidence: GRADE | Quality of evidence was deemed as low for all outcomes considering the non-RCT design of included studies. Evidence was upgraded to moderate for outcomes of antibiotic usage, lab testing for EOS, and readmission to NICU in view of large sample size, and very large effect size. | 1. Data was from non-RCTs which are prone to biases and overestimate effect size.<br><br>2. All included studies were conducted in high-income countries.<br><br>3. Significant heterogeneity for outcome of lab testing for EOS despite sensitivity analysis excluding maternal chorioamnionitis. | Moderate-quality evidence indicates that implementation of sepsis calculator for management of EOS was associated with a significant reduction in usage of antibiotics, laboratory tests for evaluation, and admission to the NICU in neonates born >34 weeks' gestation. There was no increase in mortality and hospital readmission. |
| Persad, 2021[37] | ROB: Cochrane Risk of Bias Tool 2.0 and ROBINS-I tool<br>Quality of Evidence: GRADE | The two RCTs that contributed to the 30-day septicemia-related mortality involved an optimal number of participants and events, and the outcome was thus graded at an overall high certainty of evidence.<br><br>Certainty of evidence for AUROC, sensitivity, specificity, PPV, and NPV were graded as low. | 1. Searches designed for the review were limited in capturing mathematically oriented studies, requiring handsearching and reference list checking to capture all included studies.<br><br>2. Outcomes assessed within included studies were very diverse. Adapted protocol to reflect the outcomes reported in the majority of studies.<br><br>3. Only two RCTS on the same study population were included, limiting the quality of the evidence.<br><br>4. Due to diversity of study design and outcome reporting, performance of meta-analysis and presentation of quantitatively summarized results was not possible. | Currently, there is insufficient evidence to recommend a direct clinical implementation of the available CDSAs for prediction of neonatal sepsis outside of a research environment. Large RCTs in various settings worldwide are warranted to pinpoint the extent to which HR-based and other non-invasive parameters can be utilized in sepsis prediction to assess the safety and potential harms of applied CDSAs, ultimately improving neonatal care. |

| Author, Year | Quality Assessment Tool | Strength of Evidence | Limitations | Conclusion |
|---|---|---|---|---|
| Kausch, 2021[39] | CHARMS Checklist | NR | 1. Only reviewed articles in English, which may have caused relevant articles to be excluded.<br><br>2. Using machine learning models to predict clinical events is still a developing field and as such there has been a rapid proliferation of articles in this area with varying methodological rigor and approaches. | Machine learning models for sepsis prediction demonstrate promise towards the continued goal of reducing events of clinical deterioration and improving outcomes for patients at risk for sepsis. Twelve machine learning models of sepsis were developed that showed AUROCs ranging from 0.61 to 0.96 indicating moderate to strong predictive ability. However, direct comparison was imperfect as a result of the different sepsis definitions used, the varying sepsis onset times identified, the differences in how charts were evaluated for the presence or albescence of a sepsis event, and variations in how the AUROC was measured.<br><br>Two studies examined patient outcomes in the ICU and found evidence to support the idea that incidence of septic shock can be reduced when predictive analytic models are introduced in clinical practice. Further research is needed surrounding integration of these models in the clinical setting as well as the use of predictive models outside of the ICU setting. |

| Author, Year | Quality Assessment Tool | Strength of Evidence | Limitations | Conclusion |
|---|---|---|---|---|
| Hwang, 2020[25] | Quality of Diagnostic Accuracy: QUADAS-2<br><br>Quality of Evidence for Outcomes: GRADE | Quality of evidence was high for 5 out of 8 studies reporting diagnostic accuracy.<br><br>Quality of evidence was high for 2 out of 6 studies reporting outcomes (Austrian et al and Nelson et al).<br><br>"Overall, most of the study designs used to assess the impact of sepsis alerts were weak and the review authors had difficulty isolating the impact of the automated sepsis alert itself from broader interventions such as response teams or order set bundles. Thus, our review conclusions must be couched within the strength of the overall low-quality evidence." | 1. Risk of publication bias because we did not search gray literature or clinical trials for studies in progress. There are likely many hospital systems that have implemented sepsis alerts, collected data, and did not report it.<br><br>2. Consensus group was small in number, but the review followed a rigorous process using review rubrics guided by well-accepted grading criteria. | Automated sepsis alerts in the ED may be set to a high sensitivity. Process measures show moderate benefit; however, no single measure has consistently improved, and high-quality studies have yet to demonstrate a mortality benefit. Specific components of these systems, alarm fatigue, and sensitivity set points should be examined further. Sepsis alerts demonstrate utility and future research is indicated to build a more ideal alert system. |
| Warttig, 2019[38] | GRADE | studies reported insufficient information to enable us to assess adequately the quality of the evidence. | We made several review decisions after we had reviewed the study data, mainly because the studies reported insufficient data to enable us to progress with our planned approach. This may introduce a bias into the review process in that the outcomes reported in the studies may be subject to outcome reporting bias. | It is unclear what effect automated systems for monitoring sepsis have on any of the outcomes included in this review. Very low-quality evidence is only available on automated alerts, which is only one component of automated monitoring systems. It is uncertain whether such systems can replace regular, careful review of the patient's condition by experienced healthcare staff. |

| Author, Year | Quality Assessment Tool | Strength of Evidence | Limitations | Conclusion |
|---|---|---|---|---|
| van der Vegt, 2023[27] | ROBINS-I for nonrandomized studies and Cochrane RoB 2 for RCT | NR | Limitations relate to the small number of empirical studies of deployed sepsis-prediction algorithms, underreporting of post-implementation performance metrics, focus on adult hospital settings, and potential publication bias from under reporting of other sepsis MLA implementation studies. | Implementing MLAs within adult hospital care settings to predict sepsis has potential to reduce mortality, but no definitive causal link has been demonstrated. Implemented MLAs were few and only 2 provided some evidence of causation. The types of MLA models employed mattered less than their implementation accuracies and ability to alert clinicians to order antibiotics earlier. |
| Achten, 2019[35] | CHARMS GRADE | Moderate quality of evidence for reduction in use of empirical antibiotics; low quality of evidence for safety of use. | Meta-analysis was restricted to before-after implementation studies but included many newborns. The use of a 24-hour postpartum as the cut off to designate a missed case of EOS is arbitrary, but it reflects a common time frame for monitoring of at-risk newborns. Finally, owing to a limited scope, this review did not investigate potential secondary benefits of the EOS calculator, such as reductions in laboratory investigations, neonatal ward admissions, or related health care costs. | Use of the neonatal EOS calculator is associated with a substantial reduction in the use of empirical antibiotics for suspected EOS. Available evidence regarding safety of the use of the EOS calculator is limited but shows no indication of inferiority compared with conventional management strategies. |

AUROC=area under the receiver operating characteristics curve; CDSA=clinical decision support algorithms; CHARMS=Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies; ED=emergency department; EOS=early onset sepsis; GRADE=Grading of Recommendations, Assessment, Development, and Evaluations tool; HR=heart rate; ICU=intensive care unit; MLA=machine learning algorithms; NICU=neonatal intensive care unit; NPV=negative predictive value; NR=not reported; PPV=positive predictive value; QUADAS=Quality Assessment of Diagnostic Accuracy Studies tool; RCT=randomized clinical trial; ROB=risk of bias; ROBINS-I=Risk Of Bias In Nonrandomized Studies - of Interventions tool

**Evidence Table C-5. Study characteristics of included primary studies addressing effectiveness of sepsis prediction, recognition, and treatment**

| Author, Year | Study Period | Study Design | Setting | Location | Funding |
|---|---|---|---|---|---|
| Austrian, 2018[26] | January 2013 to April 2015 | Time series | ED | Urban | Agency for Healthcare Research and Quality |
| Dhudasia, 2023[29] | Period 1 (routine CRP use): January 2012 to December 2014<br>Period 2 (minimal CRP use): January 2018 to December 2020 | Observational study with a comparison group | ICU | Urban | Authors received individual funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Agency for Healthcare Research and Quality |
| Downing, 2019[30] | December 2014 to July 2016 | RCT | Ward or Hospitalwide | NR | No funding |
| Horton, 2020[31] | November 2014 to February 2017 | Time series | Ward or Hospitalwide | NR | University of Utah Health Sciences Center |
| Mixon, 2021[32] | January 2018 to June 2018 | Observational study with a comparison group | Pre-hospital | NR | No funding |
| Schertz, 2023[33] | June 2019 to December 2019 | Observational study with a comparison group | ED | NR | Wake Forest University School of Medicine Clinical and Translational Science Institute |
| Schootman, 2022[28] | January 2016 to June 2019 | Observational study with a comparison group | Ward or Hospitalwide | NR | No funding |
| Tarabichi, 2022[34] | August 2019 to December 2019 | RCT | ED | NR | Funding not reported |

CRP=C-reactive protein; ED=emergency department; ICU=intensive care unit; NR=not reported; RCT=randomized clinical trial

**Evidence Table C-6. Population characteristics of included primary studies addressing effectiveness of sepsis prediction, recognition, and treatment**

| Author, Year | Arm | N at Baseline | Population | Clinical Condition, n (%) | Gender, n (%) | Age, n (%) | Race or Ethnicity, n (%) |
|---|---|---|---|---|---|---|---|
| Austrian, 2018[26] | Arm 1<br>Prior to sepsis alert | 838 | Adult | Diabetes: NR (30.2)<br>COPD: NR (14.3)<br>Dementia: NR (14.6) | Female: NR (46.8)<br>Male: NR | Mean: 66 (SD 18.4) | Black or African American: NR (9.6) |
| Austrian, 2018[26] | Arm 2<br>After sepsis alert | 1306 | Adult | Diabetes: NR (30.7)<br>COPD: NR (16.8)<br>Dementia: NR (19.5) | Female: NR (47.5)<br>Male: NR | Mean: 67.8 (SD 19.3) | Black or African American: NR (8.4) |
| Dhudasia, 2023[29] | Arm 1<br>Routine CRP use | 4977 | Neonatal | Caesarean delivery: 2519 (50.6) | Female: NR<br>Male: 2712 (54.5) | Median: 37 (IQR 34 to 39) | Non-Hispanic-Black or African American: 2552 (51.3)<br>Non-Hispanic-White: 1555 (31.2)<br>Hispanic: 297 (6)<br>Other: 573 (11.5) |
| Dhudasia, 2023[29] | Arm 2<br>Minimal CRP use | 5135 | Neonatal | Caesarean delivery: 2340 (45.6) | Female: NR<br>Male: 2840 (55.3) | Median: 37 (IQR 34 to 39) | Non-Hispanic-Black or African American: 2388 (46.5)<br>Non-Hispanic-White: 1786 (34.8)<br>Hispanic: 400 (7.8)<br>Other: 561 (10.9) |
| Downing, 2019[30] | Arm 1<br>Control (silent alert) | 528 | Adult | NR | Female: 268 (51)<br>Male: NR | Mean: 63 (SD 19.1) | Black or African American: 36 (7)<br>White: 273 (52)<br>Asian: 78 (15)<br>American Indian/Alaska Native: 3 (1) |
| Downing, 2019[30] | Arm 2<br>Intervention (live alert) | 595 | Adult | NR | Female: 304 (51)<br>Male: NR | Mean: 63 (SD 18.6) | Black or African American: 36 (6)<br>White: 322 (54)<br>Asian: 86 (14)<br>American Indian/Alaska Native: 1 (0) |
| Horton, 2020[31] | Arm 1<br>Pre-intervention of mEWS | 10397 visits | Adult | NR | NR | NR | NR |

| Author, Year | Arm | N at Baseline | Population | Clinical Condition, n (%) | Gender, n (%) | Age, n (%) | Race or Ethnicity, n (%) |
|---|---|---|---|---|---|---|---|
| Horton, 2020[31] | Arm 2<br>Post-intervention of mEWS | 12681 visits | Adult | NR | NR | NR | NR |
| Mixon, 2021[32] | Arm 1<br>Field alert | 88 | Adult | NR | Female: NR<br>Male: 44 (50) | Median: 74.5 (IQR 64 to 83) | NR |
| Mixon, 2021[32] | Arm 2<br>ED alert | 419 | Adult | NR | Female: NR<br>Male: 194 (46.3) | Median: 67 (IQR 55 to 78) | NR |
| Schertz, 2023[33] | Arm 1<br>Historical data (site A) | 512 | Adult | NR | Female: 278 (54.3)<br>Male: 234 (45.7) | Median: 69.5 (IQR 56 to 79) | Black or African American: 111 (21.7)<br>White: 377 (73.6)<br>Latinx: 5 (1)<br>Other: 19 (3.7) |
| Schertz, 2023[33] | Arm 2<br>Contemporary SIRS alert | 3093 | Adult | NR | Female: 1467 (47.4)<br>Male: 1626 (52.6) | Median: 63 (IQR 50 to 74) | Black or African American: 589 (19.1)<br>White: 2330 (75.4)<br>Latinx: 121 (3.9)<br>Other: 49 (1.6) |
| Schertz, 2023[33] | Arm 3<br>Intervention SPM alert | 1673 | Adult | NR | Female: 862 (51.5)<br>Male: 811 (48.5) | Median: 66 (IQR 53 to 79) | Black or African American: 369 (22.1)<br>White: 1207 (72.1)<br>Latinx: 47 (2.8)<br>Other: 50 (2.9) |
| Schootman, 2022[28] | Arm 1<br>No implementation hospitals | Pre: 2064<br>Post: 317 | Adult | NR | Female: Pre-implementation: NR (47.7)<br>Implementation: NR (47.2)<br>Male: Pre-implementation: NR (52.3)<br>Implementation: NR (52.8) | Range: 18 to 80+ | Black or African American: Pre-implementation: NR (9.4)<br>Implementation: NR (9.5)<br>White: Pre-implementation: NR (87.6)<br>Implementation: NR (87.3) |

| Author, Year | Arm | N at Baseline | Population | Clinical Condition, n (%) | Gender, n (%) | Age, n (%) | Race or Ethnicity, n (%) |
|---|---|---|---|---|---|---|---|
| Schootman, 2022[28] | Arm 2<br>Intervention hospitals | Pre: 4862<br>Post: 671 | Adult | NR | Female: Pre-implementation: NR (51.4)<br>Implementation: NR (51.1)<br>Male: Pre-implementation: NR (48.6)<br>Implementation: NR (48.9) | Range: 18 to 80+ | Black or African American: Pre-implementation: NR (16.4)<br>Implementation: NR (21.3)<br>White: Pre-implementation: NR (80.2)<br>Implementation: NR (76.2) |
| Tarabichi, 2022[34] | Arm 1<br>Standard care | 313 | Adult | NR | Female: 144 (46)<br>Male: 146 (51.2) | Median: 62.2 (IQR 51.3 to 71.8) | Black or African American: 108 (34.5)<br>White: 183 (58.5)<br>Asian: 2 (0.6)<br>American Indian/Alaska Native: 2 (0.6) |
| Tarabichi, 2022[34] | Arm 2<br>Standard care + EWS | 285 | Adult | NR | Female: 139 (48.8)<br>Male: 169 (54) | Median: 61.5 (IQR 52.6 to 70.1) | Black or African American: 107 (37.5)<br>White: 150 (52.6)<br>Asian: 2 (0.7)<br>American Indian/Alaska Native: 1 (0.4) |

COPD=chronic obstructive pulmonary disease; CRP=C-reactive protein; IQR=interquartile range; mEWS=modified early warning system; N=sample size; NR=not reported; SD=standard deviation; SIRS=systemic inflammatory response syndrome

**Evidence Table C-7. intervention characteristics of included primary studies addressing effectiveness of sepsis prediction, recognition, and treatment**

| Author, Year<br><br>Source of Data | Comparator | Intervention | Predictors | Factors Triggering Intervention |
|---|---|---|---|---|
| Austrian, 2018[26]<br><br>EHR based | Prior to sepsis alert system | Duration: NR<br><br>Description: ED-based sepsis alert system. comprised 3 alerts that fired only while the patient was in the ED: the Systemic Inflammatory Response Syndrome (SIRS) advisory alert, which targeted ED nurses, and 2 versions of the sepsis advisory alert, 1 targeting nurses and the other targeting providers, including physicians, physician assistants, and nurse practitioners. | NR | SIRS advisory alert: required 2 of 4 triggers, Temperature>38C or <36C; heart rate > 90 beats/min (sinus rhythm); respiratory rate > 20 breaths/min or PaCO2 < 32mm Hg; white blood cell count < 4x10^9/L, >12x10^9/L or >10% bands. Sepsis advisory alert for nurses or provider: Systolic blood pressure <90mm Hg or lactate ≥4mg/dL. |
| Dhudasia, 2023[29] | Routine CRP use: Period 1, 2012-2014 time period, centers used categorical approach to early onset sepsis risk assessment and routine CRP measurement. | Duration: 5 years<br><br>Description: Minimal CRP use: Period 2, 2018-2020, Early onset sepsis risk assessment utilized the Neonatal Early Onset Sepsis Calculator, does not require CRP values for decision making. | NR | NR |
| Downing, 2019[30] | Control: silent alert visible retrospectively to study staff | Duration: 20 months<br><br>Description: Live alert transmitted to clinical staff. | NR | Co-occurrence of one or more criteria of suspected infection, one or more criteria of organ dysfunction and three or more criteria of systemic inflammatory response syndrome. |

| Author, Year<br><br>Source of Data | Comparator | Intervention | Predictors | Factors Triggering Intervention |
|---|---|---|---|---|
| Horton, 2020[31] | Pre-implementation of modified Early Warning Score | Duration: Post intervention period is 1 year<br><br>Description: Implemented modified Early Warning Score, displaying scores in the EHR patient list dashboard, and sending alerts when a patients modified Early Warning Score reached a threshold of 5. | NR | Patient's vital signs suggested sepsis clinical decompensation based on mEWS. |
| Mixon, 2021[32] | Field sepsis alert | Duration: NR<br><br>Description: ED sepsis alert. | NR | Field sepsis alert: Two or more systemic inflammatory response syndrome criteria are met a best practice alert notifies the nurse to order a lactate<br>EMS sepsis alert: Similar to Field sepsis alert, but includes a nurse driven, computer based screening tool. Two or more systemic inflammatory response syndrome (SIRS) criteria are met a best practice alert (BPA) notifies the nurse to order a lactate. |
| Schertz, 2023[33] | Historic data from when SIRS alert was in place; contemporaneous data that used a PPS score but no navigator bundle | Duration: NR<br><br>Description: PSS score and EHR based navigator bundle (with order sets). | Demographic, comorbidity, vital sign, laboratory, medication, and procedural variables | Predicting Sepsis Score threshold score of 10 for activating the sepsis alert. |

| Author, Year<br><br>Source of Data | Comparator | Intervention | Predictors | Factors Triggering Intervention |
|---|---|---|---|---|
| Schootman, 2022[28] | Hospitals that did not implement predictive model; difference in difference design | Duration: NR<br><br>Description: Model implemented in select hospitals, training conducted, new order sets launched. | Predictive model uses a number of weighted variables most of which are derived from laboratory evaluation done at the time of the health provider's clinical evaluation during a face-to-face encounter. | Set at 6% in the emergency department prior to the implementation of the predictive tool. |
| Tarabichi, 2022[34] | Standard care: clinician not aware of flag | Duration: NR<br><br>Description: Standard care plus visible sepsis Early Warning System Alert: Alert triggered two events: 1) a flag was displayed as an icon change in a column on a widely used ED patient tracking tool (“track board”) and 2) a message was sent to an EHR-based messaging pool monitored by the ED pharmacists. | NR | NR |

C=Celsius; CRP=C-reactive protein; ED=emergency department; EHR=electronic health record; Hg=mercury; L=liter; mEWS=modified early warning system; mg/dL=milligram per deciliter; NR=not reported; PaCO2= partial pressure of carbon dioxide in arterial blood; PSS=Predicting Sepsis Score; SIRS=systemic inflammatory response syndrome

**Evidence Table C-8. Mortality outcomes (categorical data) of included primary studies addressing effectiveness of sepsis prediction, recognition, and treatment in a neonatal population**

| Author, Year | Arm | Arm Name | Outcome Definition | Timepoint at Analysis | N at Analysis | Patients With Events, n (%) | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|
| Dhudasia, 2023[29] | Arm 1 | Routine CRP use | Mortality in ≤7 days | 7 days | 4977 | 24 (0.5) | Ref | No |
| Dhudasia, 2023[29] | Arm 2 | Minimal CRP use | Mortality in ≤7 days | 7 days | 5135 | 33 (0.6) | Comparison: Routine CRP use<br>p-value only: p=0.28 | No |
| Dhudasia, 2023[29] | Arm 1 | Routine CRP use | Mortality before discharge | NR | 4977 | 38 (0.8) | Ref | No |
| Dhudasia, 2023[29] | Arm 2 | Minimal CRP use | Mortality before discharge | NR | 5135 | 44 (0.9) | Comparison: Routine CRP use<br>p-value only: p=0.6 | No |

CRP=C-reactive protein; N=sample size; Ref=reference arm

**Evidence Table C-9. Hospital or ICU length of stay outcomes (continuous data) of included primary studies addressing effectiveness of sepsis prediction, recognition, and treatment in a neonatal population**

| Author, Year | Arm | Arm Name | Outcome Definition | Followup Timepoint | N at Analysis | Results | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|
| Dhudasia, 2023[29] | Arm 1 | Routine CRP use | Length of stay, days | NR | 4977 | Median 4 (IQR 3 to 15) | Ref | No |
| Dhudasia, 2023[29] | Arm 2 | Minimal CRP use | Length of stay, days | NR | 5135 | Median 4 (IQR 3 to 15) | Comparison: Routine CRP use<br>p-value only: p=0.84 | No |
| Dhudasia, 2023[29] | Arm 1 | Routine CRP use | Length of stay, days (Subgroup: <37 weeks gestational age) | NR | NR | Median 15 (IQR 6 to 36) | Ref | No |
| Dhudasia, 2023[29] | Arm 2 | Minimal CRP use | Length of stay, days (Subgroup: <37 weeks gestational age) | NR | NR | Median 15 (IQR 6 to 32) | Comparison: Routine CRP use<br>p-value only: p=0.37 | No |
| Dhudasia, 2023[29] | Arm 1 | Routine CRP use | Length of stay, days (Subgroup: ≥37 weeks gestational age) | NR | NR | Median 3 (IQR 2 to 4) | Ref | No |
| Dhudasia, 2023[29] | Arm 2 | Minimal CRP use | Length of stay, days (Subgroup: ≥37 weeks gestational age) | NR | NR | Median 3 (IQR 2 to 4) | Comparison: Routine CRP use<br>p-value only: p=0.64 | No |

CRP=C-reactive protein; IQR=interquartile range; N=sample size; Ref=reference arm

**Evidence Table C-10. SEP-1 measure outcomes (categorical data) of included primary studies addressing effectiveness of sepsis prediction, recognition, and treatment in a neonatal population**

| Author, Year | Arm | Arm Name | Outcome Definition | Timepoint at Analysis | N at Analysis | Patients With Events, n (%) | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|
| Dhudasia, 2023[29] | Arm 1 | Routine CRP use | Antibiotic initiated, days 0-3 | Days 0-3 | 4977 | 3233 (65) | Ref | No |
| Dhudasia, 2023[29] | Arm 2 | Minimal CRP use | Antibiotic initiated, days 0-3 | Days 0-3 | 5135 | 2607 (50.7) | Comparison: Routine CRP use p-value only: p<0.001 | No |
| Dhudasia, 2023[29] | Arm 1 | Routine CRP use | New antibiotic initiated, days 4-7 | Days 4-7 | 4977 | 88 (1.8) | Ref | No |
| Dhudasia, 2023[29] | Arm 2 | Minimal CRP use | New antibiotic initiated, days 4-7 | Days 4-7 | 5135 | 54 (1.1) | Comparison: Routine CRP use p-value only: p=0.002 | No |
| Dhudasia, 2023[29] | Arm 1 | Routine CRP use | Blood culture obtained, days 0-3 | Days 0-3 | 4977 | 3709 (74.5) | Ref | No |
| Dhudasia, 2023[29] | Arm 2 | Minimal CRP use | Blood culture obtained, days 0-3 | Days 0-3 | 5135 | 2592 (50.5) | Comparison: Routine CRP use p-value only: p<0.001 | No |
| Dhudasia, 2023[29] | Arm 1 | Routine CRP use | Blood culture obtained, days 4-7 | Days 4-7 | 4977 | 146 (2.9) | Ref | No |
| Dhudasia, 2023[29] | Arm 2 | Minimal CRP use | Blood culture obtained, days 4-7 | Days 4-7 | 5135 | 109 (2.1) | Comparison: Routine CRP use p-value only: p=0.009 | No |
| Dhudasia, 2023[29] | Arm 1 | Routine CRP use | CSF culture obtained, days 0-3 | Days 0-3 | 4977 | 431 (8.7) | Ref | No |
| Dhudasia, 2023[29] | Arm 2 | Minimal CRP use | CSF culture obtained, days 0-3 | Days 0-3 | 5135 | 63 (1.2) | Comparison: Routine CRP use p-value only: p=<0.001 | No |
| Dhudasia, 2023[29] | Arm 1 | Routine CRP use | CSF culture obtained, days 4-7 | Days 4-7 | 4977 | 77 (1.6) | Ref | No |
| Dhudasia, 2023[29] | Arm 2 | Minimal CRP use | CSF culture obtained, days 4-7 | Days 4-7 | 5135 | 17 (0.3) | Comparison: Routine CRP use p-value only: p=<0.001 | No |

CRP=C-reactive protein; CSF=cerebrospinal fluid; N=sample size; Ref=reference arm; SEP-1=The Severe Sepsis and Septic Shock Management Bundle

**Evidence Table C-11. Mortality outcomes (categorical data) of included primary studies addressing effectiveness of sepsis prediction, recognition, and treatment in an adult population**

| Author, Year | Arm | Arm Name | Outcome Definition | Timepoint at Analysis | N at Analysis | Patients With Events, n(%) | Within-Arm Comparison | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|---|
| Austrian, 2018[26] | Arm 1 | Prior to sepsis alert | Mortality | NR | 838 | NR (8.5) | Odds relative to prior month: 1.04 (95% CI: 0.97 to 1.12) | Ref | Demographics, vital signs, clinical conditions, and whether the patient had an ICU stay |
| Austrian, 2018[26] | Arm 2 | After sepsis alert | Mortality | NR | 1306 | NR (7) | Odds relative to prior month: 0.96 (95% CI: 0.87 to 1.06) | Comparison: Prior to sepsis alert<br>Incidence rate ratio: 0.58 (95% CI: 0.29 to 1.19), p=0.22 | Same as Arm 1 |
| Downing, 2019[30] | Arm 1 | Control (silent alert) | Death within 30 days | 30 days | 528 | NR (6.8) | NR | Ref | No |
| Downing, 2019[30] | Arm 2 | Intervention (live alert) | Death within 30 days | 30 days | 595 | NR (6.2) | NR | Comparison: Control (silent alert)<br>Odds ratio: 0.9 (95% CI: 0.56 to 1.46), p=1 | No |
| Mixon, 2021[32] | Arm 1 | Field alert | In-hospital mortality at 60 days | 60 days | 88 | NR (16.28) | NR | Ref | No |
| Mixon, 2021[32] | Arm 2 | ED alert | In-hospital mortality at 60 days | 60 days | 419 | NR (9.64) | NR | Comparison: Field alert<br>p-value only: p=0.07 | No |
| Schertz, 2023[33] | Arm 1 | Historical data (site A) | Mortality at 30 day | 30 days | 512 | 44 (8.6) | NR | NR | No |
| Schertz, 2023[33] | Arm 2 | Contemporary SIRS alert | Mortality at 30 day | 30 days | 3093 | 287 (9.3) | NR | NR | No |
| Schertz, 2023[33] | Arm 3 | Intervention SPM alert | Mortality at 30 day | 30 days | 1673 | 163 (9.7) | NR | NR | No |

| Author, Year | Arm | Arm Name | Outcome Definition | Timepoint at Analysis | N at Analysis | Patients With Events, n(%) | Within-Arm Comparison | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|---|
| Schootman, 2022[28] | Arm 1 | No implementation hospitals | Mortality rate | Nov 2018-April 2019 | 316 | Pre-implementation: 10.3 Implementation: 9.5 | % change from baseline: -1 (95% CI: -3.1 to 1) | Ref | ICU stay; severe sepsis or septic shock present on the date of diagnosis; primary source of payment; number of comorbidities based on Elixhauser comorbidity score; day of the week of admission; age group; sex; race; type of admission; sepsis type; length of stay in days; and number of acute organ failures |
| Schootman, 2022[28] | Arm 2 | Intervention hospitals | Mortality rate | June 2018-Oct 2019 | 671 | Pre-implementation: 10.3 Implementation: 9.5 | % change from baseline: -2 (95% CI: -5.1 to 1.2) | Comparison: Control hospitals Difference in difference: -1, p=0.174 | Same as Arm 1 |
| Tarabichi, 2022[34] | Arm 1 | Standard care | Hospital mortality | NR | 313 | 25 (8) | NR | Ref | No |
| Tarabichi, 2022[34] | Arm 2 | Standard care + EWS | Hospital mortality | NR | 285 | 13 (4.6) | NR | Comparison: Standard care p-value only: p=0.086 | No |
| Tarabichi, 2022[34] | Arm 1 | Standard care | Mortality at 28 days | 28 days | 313 | 31 (9.9) | NR | Ref | No |
| Tarabichi, 2022[34] | Arm 2 | Standard care + EWS | Mortality at 28 days | 28 days | 285 | 17 (6) | NR | Comparison: Standard care p-value only: p=0.077 | No |

CI=confidence interval; ED=emergency department; EWS=early warning system; ICU=intensive care unit; N=sample size; NR=not reported; Ref=reference arm; SIRS=systemic inflammatory response syndrome; SPM=Sepsis Prediction Model

**Evidence Table C-12. Mortality outcomes (continuous data) of included primary studies addressing effectiveness of sepsis prediction, recognition, and treatment in an adult population**

| Author, Year | Arm | Arm Name | Outcome Definition | Followup Timepoint | N at Analysis | Results | Within-Arm Comparison | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|---|
| Horton, 2020[31] | Arm 1 | Pre-intervention of mEWS | Monthly percent | NR | 1546 | NR | NR | Ref | Seasonality |
| Horton, 2020[31] | Arm 2 | Post-intervention of mEWS | Monthly percent | NR | 2118 | NR | NR | Comparison: Postintervention Level change: -3.14 (SE 2.69)(95% CI: -8.76 to 2.48), p=NR | Same as Arm 1 |

CI=confidence interval; mEWS=modified early warning system; N=sample size; NR=not reported; Ref-reference arm; SE=standard error

**Evidence Table C-13. Hospital or ICU length of stay outcomes (categorical data) of included primary studies addressing effectiveness of sepsis prediction, recognition, and treatment in an adult population**

| Author, Year | Arm | Arm Name | Outcome Definition | Timepoint at Analysis | N at Analysis | Patients With Events, n (%) | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|
| Downing, 2019[30] | Arm 1 | Control (silent alert) | Length of stay greater than 72 hours | 72 hours | 528 | NR (3.2) | Ref | No |
| Downing, 2019[30] | Arm 2 | Intervention (live alert) | Length of stay greater than 72 hours | 72 hours | 595 | NR (3.2) | Comparison: Control (silent alert)<br>Odds ratio: 1 (95% CI: 0.5 to 1.95), p=1 | No |

CI=confidence interval; N=sample size; NR=not reported; Ref-reference arm

**Evidence Table C-14. Hospital or ICU length of stay outcomes (continuous data) of included primary studies addressing effectiveness of sepsis prediction, recognition, and treatment in an adult population**

| Author, Year | Arm | Arm Name | Outcome Definition | Followup Timepoint | N at Analysis | Results | Within-Arm Comparison | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|---|
| Austrian, 2018[26] | Arm 1 | Prior to sepsis alert | Length of stay, days | NR | 838 | Mean 10.1 (SD NR) | NR | Ref | Demographics, vital signs, clinical conditions, and whether the patient had an ICU stay |
| Austrian, 2018[26] | Arm 2 | After sepsis alert | Length of stay, days | NR | 1306 | Mean 8.6 (SD NR) | NR | Comparison: Prior to sepsis alert incidence rate ratio: 0.84, p<0.001 | Same as Arm 1 |
| Austrian, 2018[26] | Arm 1 | Prior to sepsis alert | Length of ICU stay, days | NR | 838 | Mean 1.8 (SD NR) | NR | Ref | Demographics, vital signs, clinical conditions, and whether the patient had an ICU stay |
| Austrian, 2018[26] | Arm 2 | After sepsis alert | Length of ICU stay, days | NR | 1306 | Mean 1.2 (SD NR) | NR | Comparison: Prior to sepsis alert incidence rate ratio: 0.98, p<0.001 | Same as Arm 1 |
| Horton, 2020[31] | Arm 1 | Pre-intervention of mEWS | Length of stay, days | NR | 1546 | NR | NR | Ref | Seasonality |
| Horton, 2020[31] | Arm 2 | Post-intervention of mEWS | Length of stay, days | NR | 2118 | NR | NR | Comparison: Postintervention Level change: -0.63 (SE 0.31)(95% CI: -1.28 to 0.03), p=NR | Same as Arm 1 |
| Mixon, 2021[32] | Arm 1 | Field alert | Hospital length of stay, days | NR | 88 | Median 3.77 (IQR 2.1 to 7.0) | NR | Ref | No |

| Author, Year | Arm | Arm Name | Outcome Definition | Followup Timepoint | N at Analysis | Results | Within-Arm Comparison | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|---|
| Mixon, 2021[32] | Arm 2 | ED alert | Hospital length of stay, days | NR | 419 | Median 3.94 (IQR 2.4 to 6.0) | NR | Comparison: Field alert<br>p-value only: p=0.72 | NR |
| Mixon, 2021[32] | Arm 1 | Field alert | ICU length of stay, days | NR | 88 | Median 2 (IQR 1.0 to 4.0) | NR | Ref | NR |
| Mixon, 2021[32] | Arm 2 | ED alert | ICU length of stay, days | NR | 419 | Median 2 (IQR 1.0 to 3.0) | NR | Comparison: Field alert<br>p-value only: p=0.62 | NR |
| Schootman, 2022[28] | Arm 1 | No implementation hospitals | Inpatient stay | NR | 316 | Baseline: Mean 6.8 (SD NR)<br>Followup: Mean 5.8 (SD NR) | % change from baseline: 1.04 (95% CI: 1.01 to 1.06) | Ref | Adjusted for multiple testing using Benjamini-Hochberg false discovery rate |
| Schootman, 2022[28] | Arm 2 | Intervention hospitals | Inpatient stay | NR | 671 | Baseline: Mean 7.5 (SD NR)<br>Followup: Mean 7 (SD NR) | % change from baseline: 1.07 (95% CI: 1.01 to 1.14) | Comparison: Control hospitals<br>Difference in difference: 1.03, p=0.652 | Same as Arm 1 |
| Schootman, 2022[28] | Arm 1 | No implementation hospitals | ICU stay | NR | 316 | Baseline: Mean 20.8 (SD NR)<br>Followup: Mean 21.2 (SD NR) | % change from baseline: 1.6 (95% CI: -2.6 to 5.8) | Ref | Adjusted for multiple testing using Benjamini-Hochberg false discovery rate |
| Schootman, 2022[28] | Arm 2 | Intervention hospitals | ICU stay | NR | 671 | Baseline: Mean 27.6 (SD NR)<br>Followup: Mean 24.1 (SD NR) | % change from baseline: -2.6 (95% CI: -5.7 to 0.5) | Comparison: Control hospitals<br>Difference in difference: -4.2, p=0.174 | Same as Arm 1 |
| Tarabichi, 2022[34] | Arm 1 | Standard care | Length of stay | NR | 313 | Median 4 (IQR 1.4 to 7.0) | NR | Ref | NR |

| Author, Year | Arm | Arm Name | Outcome Definition | Followup Timepoint | N at Analysis | Results | Within-Arm Comparison | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|---|
| Tarabichi, 2022[34] | Arm 2 | Standard care + EWS | Length of stay | NR | 285 | Median 3.2 (IQR 1.1 to 6.2) | NR | Comparison: Standard care p-value only: p=0.124 | NR |
| Tarabichi, 2022[34] | Arm 1 | Standard care | ICU length of stay | NR | 313 | Median 3.4 (IQR 2.0 to 6.0) | NR | Ref | NR |
| Tarabichi, 2022[34] | Arm 2 | Standard care + EWS | ICU length of stay | NR | 285 | Median 3.6 (IQR 2.0 to 5.4) | NR | Comparison: Standard care p-value only: p=0.937 | NR |

CI=confidence interval; EWS=early warning system; ICU=intensive care unit; IQR=interquartile range; mEWS=modified early warning system; N=sample size; NR=not reported; Ref=reference arm; SD=standard deviation

**Evidence Table C-15. SEP-1 measure outcomes (categorical data) of included primary studies addressing effectiveness of sepsis prediction, recognition, and treatment in an adult population**

| Author, Year | Arm | Arm Name | Outcome Definition | Timepoint at Analysis | N at Analysis | Patients With Events, n (%) | Within-Arm Comparison | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|---|
| Austrian, 2018[26] | Arm 1 | Prior to sepsis alert | Blood cultures prior to antibiotics | NR | 838 | NR (79) | Odds relative to prior month: 1.04 (95% CI: 0.99 to 1.09) | Ref | Demographics, vital signs, clinical conditions, and whether the patient had an ICU stay |
| Austrian, 2018[26] | Arm 2 | After sepsis alert | Blood cultures prior to antibiotics | NR | 1306 | NR (79.2) | Odds relative to prior month: 0.95 (95% CI: 0.89 to 1.00) | Comparison: Prior to sepsis alert Incidence rate ratio: 0.87 (95% CI: 0.56 to 1.37), p=0.92 | Same as Arm 1 |
| Austrian, 2018[26] | Arm 1 | Prior to sepsis alert | Lactate | NR | 838 | NR (90.7) | Odds relative to prior month: 0.99 (95% CI: 0.93 to 1.07) | Ref | Demographics, vital signs, clinical conditions, and whether the patient had an ICU stay |
| Austrian, 2018[26] | Arm 2 | After sepsis alert | Lactate | NR | 1306 | NR (91.3) | Odds relative to prior month: 0.96 (95% CI: 0.88 to 1.04) | Comparison: Prior to sepsis alert Incidence rate ratio: 1.67 (95% CI: 0.86 to 3.25), p=0.65 | Same as Arm 1 |
| Downing, 2019[30] | Arm 1 | Control (silent alert) | Blood cultured ordered at 180 minutes | 180 minutes | 528 | NR (5.1) | NR | Ref | No |
| Downing, 2019[30] | Arm 2 | Intervention (live alert) | Blood cultured ordered at 180 minutes | 180 minutes | 595 | NR (4.7) | NR | Comparison: Control (silent alert) Odds ratio: 0.9 (95% CI: 0.53 to 1.59), p=1 | No |
| Downing, 2019[30] | Arm 1 | Control (silent alert) | Fluids (any) at 180 minutes | 180 minutes | 528 | NR (19.9) | NR | Ref | No |
| Downing, 2019[30] | Arm 2 | Intervention (live alert) | Fluids (any) at 180 minutes | 180 minutes | 595 | NR (23.7) | NR | Comparison: Control (silent alert) Odds ratio: 1.3 (95% CI: 0.94 to 1.68), p=0.74 | No |

| Author, Year | Arm | Arm Name | Outcome Definition | Timepoint at Analysis | N at Analysis | Patients With Events, n (%) | Within-Arm Comparison | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|---|
| Downing, 2019[30] | Arm 1 | Control (silent alert) | Fluids (at least 2L) at 180 minutes | 180 minutes | 528 | NR (1.5) | NR | Ref | No |
| Downing, 2019[30] | Arm 2 | Intervention (live alert) | Fluids (at least 2L) at 180 minutes | 180 minutes | 595 | NR (1.5) | NR | Comparison: Control (silent alert)<br>Odds ratio: 1 (95% CI: 0.37 to '2.71), p=1 | No |
| Downing, 2019[30] | Arm 1 | Control (silent alert) | Lactate ordered at 180 minutes | 180 minutes | 528 | NR (10.8) | NR | Ref | No |
| Downing, 2019[30] | Arm 2 | Intervention (live alert) | Lactate ordered at 180 minutes | 180 minutes | 595 | NR (14.1) | NR | Comparison: Control (silent alert)<br>Odds ratio: 1.4 (95% CI: 0.95 to 1.95), p=0.65 | No |
| Downing, 2019[30] | Arm 1 | Control (silent alert) | Anti-infectives given at 180 minutes | 180 minutes | 528 | NR (36.7) | NR | Ref | No |
| Downing, 2019[30] | Arm 2 | Intervention (live alert) | Anti-infectives given at 180 minutes | 180 minutes | 595 | NR (35) | NR | Comparison: Control (silent alert)<br>Odds ratio: 0.9 (95% CI: 0.72 to 1.18), p=NR | No |
| Mixon, 2021[32] | Arm 1 | Field alert | Patients receiving antibiotics within 60 min | NR | 88 | NR (59.1) | NR | Ref | No |
| Mixon, 2021[32] | Arm 2 | ED alert | Patients receiving antibiotics within 60 min | NR | 419 | NR (44) | NR | Comparison: Field alert<br>p-value only: p=0.01 | No |
| Mixon, 2021[32] | Arm 1 | Field alert | Appropriate 30 mL/kg fluid bolus utilization | NR | 88 | NR (51.61) | NR | Ref | No |

| Author, Year | Arm | Arm Name | Outcome Definition | Timepoint at Analysis | N at Analysis | Patients With Events, n (%) | Within-Arm Comparison | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|---|
| Mixon, 2021[32] | Arm 2 | ED alert | Appropriate 30 mL/kg fluid bolus utilization | NR | 419 | NR (43.3) | NR | Comparison: Field alert<br>p-value only: p=0.5 | No |
| Schootman, 2022[28] | Arm 1 | No implementation hospitals | Antibiotic administration ≤1 h of time zero | Nov 2018-April 2019 | 316 | Pre-implementation: 54.8<br>Implementation: 62.3 | % change from baseline: 7.6 (95% CI: 1.8 to 13.4) | Ref | ICU stay; severe sepsis or septic shock present on the date of diagnosis; primary source of payment; number of comorbidities based on Elixhauser comorbidity score; day of the week of admission; age group; sex; race; type of admission; sepsis type; length of stay in days; and number of acute organ failures |
| Schootman, 2022[28] | Arm 2 | Intervention hospitals | Antibiotic administration ≤1 h of time zero | June 2018-Oct 2019 | 671 | Pre-implementation: 49.2<br>Implementation: 60.2 | % change from baseline: 11.7 (95% CI: 7.9 to 15.4) | Comparison: Control hospitals<br>Difference in difference: 41, p=0.084 | Same as Arm 1 |

| Author, Year | Arm | Arm Name | Outcome Definition | Timepoint at Analysis | N at Analysis | Patients With Events, n (%) | Within-Arm Comparison | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|---|
| Schootman, 2022[28] | Arm 1 | No implementation hospitals | Antibiotic administration ≤3 h of time zero | Nov 2018-April 2019 | 316 | Pre-implementation: 87.7<br>Implementation: 90.8 | % change from baseline: 2.7 (95% CI: -1 to 6.4) | Ref | ICU stay; severe sepsis or septic shock present on the date of diagnosis; primary source of payment; number of comorbidities based on Elixhauser comorbidity score; day of the week of admission; age group; sex; race; type of admission; sepsis type; length of stay in days; and number of acute organ failures |
| Schootman, 2022[28] | Arm 2 | Intervention hospitals | Antibiotic administration ≤3 h of time zero | June 2018-Oct 2019 | 671 | Pre-implementation: 82.3<br>Implementation: 90 | % change from baseline: 8.6 (95% CI: 5.8 to 11.4) | Comparison: Control hospitals<br>Difference in difference: 6.7, p=0.174 | Same as Arm 1 |

| Author, Year | Arm | Arm Name | Outcome Definition | Timepoint at Analysis | N at Analysis | Patients With Events, n (%) | Within-Arm Comparison | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|---|
| Schootman, 2022[28] | Arm 1 | No implementation hospitals | Sepsis bundle completion | Nov 2018-April 2019 | 316 | Pre-implementation: 49.7 Implementation: 56.3 | % change from baseline: 6.6 (95% CI: 0.7 to 12.5) | Ref | ICU stay; severe sepsis or septic shock present on the date of diagnosis; primary source of payment; number of comorbidities based on Elixhauser comorbidity score; day of the week of admission; age group; sex; race; type of admission; sepsis type; length of stay in days; and number of acute organ failures |
| Schootman, 2022[28] | Arm 2 | Intervention hospitals | Sepsis bundle completion | June 2018-Oct 2019 | 671 | Pre-implementation: 43.2 Implementation: 55.6 | % change from baseline: 13.3 (95% CI: 9.7 to 17) | Comparison: Control hospitals Difference in difference: 6.7, p=0.105 | Same as Arm 1 |
| Tarabichi, 2022[34] | Arm 1 | Standard care | Antibiotic utilization | 28 days | 313 | 219 (70) | NR | Ref | No |
| Tarabichi, 2022[34] | Arm 2 | Standard care + EWS | Antibiotic utilization | 28 days | 285 | 193 (67.7) | NR | Comparison: Standard care p-value only: p=0.553 | No |
| Tarabichi, 2022[34] | Arm 1 | Standard care | Fluid bolus administration | 28 days | 313 | 203 (64.9) | NR | Ref | No |
| Tarabichi, 2022[34] | Arm 2 | Standard care + EWS | Fluid bolus administration | 28 days | 285 | 174 (61.1) | NR | Comparison: Standard care p-value only: p=0.336 | No |

CI=confidence interval; ED=emergency department; EWS=early warning system; h=hour; ICU=intensive care unit; min=minute; ml/kg=milliliter per kilogram; N=sample size; NR=not reported; Ref=reference arm; SEP-1=The Severe Sepsis and Septic Shock Management Bundle

**Evidence Table C-16. SEP-1 measure outcomes (continuous data) of included primary studies addressing effectiveness of sepsis prediction, recognition, and treatment in an adult population**

| Author, Year | Arm | Arm Name | Outcome Definition | Followup Timepoint | N at Analysis | Results | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|
| Austrian, 2018[26] | Arm 1 | Prior to sepsis alert | Time to first lactate, days | NR | 838 | Mean 0.19 (SD NR) | Ref | Demographics, vital signs, clinical conditions, and whether the patient had an ICU stay |
| Austrian, 2018[26] | Arm 2 | After sepsis alert | Time to first lactate, days | NR | 1306 | Mean 0.16 (SD NR) | Comparison: Prior to sepsis alert incidence rate ratio: 0.63, p<0.001 | Same as Arm 1 |
| Horton, 2020[31] | Overall | All participants | Anti-infective agents within 24 hours after SIRS, % | NR | NR | Baseline: Beta 90.03 (SE 1.24) | Level change: 1.76 (SE 2.69)(95% CI: -3.88 to 7.4) | No |
| Mixon, 2021[32] | Arm 1 | Field alert | Time to antibiotics (min) | NR | 88 | Median 48.5 (IQR 34 to 87) | Ref | No |
| Mixon, 2021[32] | Arm 2 | ED alert | Time to antibiotics (min) | NR | 419 | Median 64.5 (IQR 47 to 99) | Comparison: Field alert p-value only: p<0.001 | No |
| Mixon, 2021[32] | Arm 1 | Field alert | Arrival to antibiotic order (min) | NR | 88 | Median 33.5 (IQR 14.5 to 61) | Ref | No |
| Mixon, 2021[32] | Arm 2 | ED alert | Arrival to antibiotic order (min) | NR | 419 | Median 45 (IQR 26 to 73) | Comparison: Field alert p-value only: p=<0.01 | No |
| Mixon, 2021[32] | Arm 1 | Field alert | Antibiotic order to administration (min) | NR | 88 | Median 18 (IQR 10 to 26.5) | Ref | No |
| Mixon, 2021[32] | Arm 2 | ED alert | Antibiotic order to administration (min) | NR | 419 | Median 18 (IQR 12 to 28) | Comparison: Field alert p-value only: p=0.45 | No |
| Schertz, 2023[33] | Arm 1 | Historical data (site A) | Time to antimicrobial delivery, hours | NR | 512 | Median 6.2 (IQR 3.49 to 11.61) | Ref | Propensity score weighted |
| Schertz, 2023[33] | Arm 3 | Intervention SPM (navigator)alert | Time to antimicrobial delivery, hours | NR | 1673 | Median 3.33 (IQR 2.10 to 5.37) | Comparison: Historical data<br>Adjusted difference: -2.78 (95% CI: -3.52 to -2.03), p<0.001 | Same as Arm 1 |
| Schertz, 2023[33] | Arm 2 | Contemporary SIRS alert | Time to antimicrobial delivery, hours | NR | 3093 | Median 3.22 (IQR 1.97 to 5.60) | Ref | Propensity score weighted |

| Author, Year | Arm | Arm Name | Outcome Definition | Followup Timepoint | N at Analysis | Results | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|
| Schertz, 2023[33] | Arm 3 | Intervention SPM (navigator)alert | Time to antimicrobial delivery, hours | NR | 1673 | Median 3.33 (IQR 2.10 to 5.37) | Comparison: Contemporary SIRS alert<br>Adjusted difference: 0.01 (95% CI: -0.16 to 0.19), p=NS | Same as Arm 2 |
| Schertz, 2023[33] | Arm 1 | Historical data (site A) | Time to antimicrobial delivery, hours (Subgroup: PSS ≥ 10) | NR | NR | NA | NR | Propensity score weighted |
| Schertz, 2023[33] | Arm 2 | Contemporary SIRS alert | Time to antimicrobial delivery, hours (Subgroup: PSS ≥ 10) | NR | NR | Median 2.85 (IQR 1.75 to 4.90) | Ref | Same as Arm 1 |
| Schertz, 2023[33] | Arm 3 | Intervention SPM (navigator)alert | Time to antimicrobial delivery, hours (Subgroup: PSS ≥ 10) | NR | NR | Median 2.76 (IQR 1.78 to 4.42) | Comparison: Contemporary SIRS alert<br>Adjusted difference: -0.21 (95% CI: –0.47 to 0.04), p=NR | Same as Arm 1 |
| Schertz, 2023[33] | Arm 1 | Historical data (site A) | Time to antimicrobial delivery, hours (Subgroup: PSS ≥ 10 and antimicrobials given after threshold) | NR | NR | NA | NR | Propensity score weighted |
| Schertz, 2023[33] | Arm 2 | Contemporary SIRS alert | Time to antimicrobial delivery, hours (Subgroup: PSS ≥ 10 and antimicrobials given after threshold) | NR | NR | Median 3.07 (IQR 2.07 to 5.30) | Ref | Same as Arm 1 |

| Author, Year | Arm | Arm Name | Outcome Definition | Followup Timepoint | N at Analysis | Results | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|
| Schertz, 2023[33] | Arm 3 | Intervention SPM (navigator)alert | Time to antimicrobial delivery, hours (Subgroup: PSS ≥ 10 and antimicrobials given after threshold) | NR | NR | Median 2.68 (IQR 1.80 to 4.62) | Comparison: Contemporary SIRS alert<br>From emergency department arrival: -0.57 (95% CI: -0.89 to -0.24), p<0.05<br>From threshold score: -0.15 (95% CI: -0.40 to 0.10), p=NS | Same as Arm 1 |
| Schertz, 2023[33] | Arm 1 | Historical data (site A) | Time to antimicrobial order, hours | NR | 512 | Median 5.5 (IQR 3.17 to 10.92) | NR | NR |
| Schertz, 2023[33] | Arm 2 | Contemporary SIRS alert | Time to antimicrobial order, hours | NR | 3093 | Median 2.95 (IQR 1.78 to 5.20) | NR | NR |
| Schertz, 2023[33] | Arm 3 | Intervention SPM (navigator)alert | Time to antimicrobial order, hours | NR | 1673 | Median 3.03 (IQR 1.97 to 4.78) | NR | NR |
| Tarabichi, 2022[34] | Arm 1 | Standard care | Time to antibiotic administration, hours | NR | 313 | Median 3 (IQR 1.6 to 5.5) | Ref | NR |
| Tarabichi, 2022[34] | Arm 2 | Standard care + EWS | Time to antibiotic administration, hours | NR | 285 | Median 2.3 (IQR 1.4 to 4.7) | Comparison: Standard care<br>p-value only: p=0.039 | NR |

CI=confidence interval; ED=emergency department; ICU=intensive care unit; IQR=interquartile range; N=sample size; NR=not reported; NS=not significant; PSS=Predicting Sepsis Score; Ref=reference arm; SE=standard error; SEP-1=The Severe Sepsis and Septic Shock Management Bundle; SIRS=systemic inflammatory response syndrome; SPM=Sepsis Prediction Model

**Evidence Table C-17. Financial measures of included primary studies addressing effectiveness of sepsis prediction, recognition, and treatment in an adult population**

| Author, Year | Arm | Arm Name | Outcome Definition | Followup Timepoint | N at Analysis | Results | Between-Arm Comparison | Adjusted |
|---|---|---|---|---|---|---|---|---|
| Horton, 2020[31] | Arm 1 | Pre-intervention of mEWS | Total visit direct cost (normalized median) | NR | 1546 | NR | Ref | Seasonality |
| Horton, 2020[31] | Arm 2 | Post-intervention of mEWS | Total visit direct cost (normalized median) | NR | 2118 | NR | Comparison: Postintervention Level change: -23.363 (SE 10.97)(95% CI: -46.32 to -0.393), p=NR | Same as Arm 1 |

CI=confidence interval; mEWS=modified early warning system; N=sample size; NR=not reported; Ref-reference arm; SE=standard error

**Evidence Table C-18. Pre-post studies addressing effectiveness of sepsis prediction, recognition, and treatment in an adult population**

| Author, Year | Intervention Type | Setting | Outcomes Reported |
|---|---|---|---|
| Roney, 2020[57] | Simple prediction recognition tool | Ward or Hospitalwide | Mortality |
| Davis 2022[58] | Bundle | Ward or Hospitalwide | Hospital length of stay<br>Mortality<br>SEP-1 measure |
| Simon, 2022[59] | Bundle | ED | Hospital length of stay<br>Mortality<br>SEP-1 measure |
| MacMillan, 2019[60] | Bundle | ICU | SEP-1 measure |
| Gibbs, 2021[61] | Bundle | Ward or Hospitalwide | Mortality<br>SEP-1 measure |
| Eisenberg, 2021[62] | Bundle | ED | Mortality<br>SEP-1 measure<br>Validity |
| Vidrine, 2020[63] | Bundle | ICU | Mortality<br>SEP-1 measure |
| Borrelli, 2019[64] | Bundle | Pre-hospital | Hospital length of stay<br>Mortality<br>SEP-1 measure |
| Huff, 219[65] | Bundle | Ward or Hospitalwide | Mortality |
| Lipatov, 2022[66] | Simple prediction recognition tool | ED, ICU | SEP-1 measure<br>Validity |
| Baker, 2021[67] | Simple prediction recognition tool | ED | ED length of stay<br>SEP-1 measure |
| Miller, 2023[68] | Bundle | Ward or Hospitalwide | Hospital length of stay<br>SEP-1 measure |
| Mittal, 2019[69] | Bundle | ED | Hospital length of stay<br>Mortality |
| Oddiri, 2023[70] | Bundle | Wards | SEP-1 measure |
| Threatt, 2020[71] | Bundle | ED | ED length of stay<br>Mortality<br>SEP-1 measure |
| Toews, 2022[72] | Bundle | ED | Cost<br>Hospital length of stay<br>ICU length of stay |

| Author, Year | Intervention Type | Setting | Outcomes Reported |
|---|---|---|---|
| Majid, 2019[73] | Bundle | Ward or Hospitalwide | Cost<br>Hospital length of stay<br>Mortality<br>SEP-1 measure |
| Jung, 2018[74] | Simple prediction recognition tool | ICU | Hospital length of stay<br>ICU length of stay<br>SEP-1 measure |
| Moore, 2019[75] | Bundle | ED | Cost<br>ED length of stay<br>Hospital length of stay |
| Dewan, 2020[76] | Simple prediction recognition tool | ICU | SEP-1 measure<br>Validity |
| Alnababteh, 2020[77] | Bundle | Ward or Hospitalwide | Bundle compliance<br>Hospital length of stay<br>ICU length of stay<br>Mortality<br>Validity |
| Burdick, 2020[78] | Simple prediction recognition tool | Ward or Hospitalwide | Hospital length of stay<br>Mortality |
| Delaveris, 2020[79] | Bundle | Ward or Hospitalwide | Bundle compliance<br>Mortality |
| Perlin, 2020[80] | Bundle | Ward or Hospitalwide | Mortality |
| Mitzkewich, 2019[81] | Simple prediction recognition tool | ED | SEP-1 measure |
| Shah, 2018[82] | Bundle | ED | Bundle compliance<br>ED length of stay<br>Hospital length of stay<br>ICU length of stay<br>Mortality<br>SEP-1 measure |
| Ahmed, 2023[83] | Bundle | Pre-hospital | Mortality<br>SEP-1 measure<br>Validity |
| Colorafi, 2019[84] | Simple prediction recognition tool | Ward or Hospitalwide | Bundle compliance<br>ICU length of stay<br>Mortality<br>Validity |
| Iannello, 2021[85] | Bundle | Ward or Hospitalwide | Mortality |

| Author, Year | Intervention Type | Setting | Outcomes Reported |
|---|---|---|---|
| Gaieski, 2022[86] | Bundle | ED, ICU | Bundle compliance<br>Mortality<br>SEP-1 measure |
| Cull, 2023[87] | Simple prediction recognition tool | Ward or Hospitalwide | Hospital length of stay<br>ICU length of stay<br>Mortality<br>Validity |
| Stellpflug, 2021[88] | Bundle | Ward or Hospitalwide | Cost<br>ICU length of stay |
| Polito, 2022[89] | Simple prediction recognition tool | Pre-hospital | Bundle compliance<br>Hospital length of stay<br>ICU length of stay<br>Mortality<br>SEP-1 measure |
| Giannini, 2019[90] | Bundle | Ward or Hospitalwide | ICU length of stay<br>Mortality<br>SEP-1 measure<br>Validity |
| Forget, 2023[91] | Bundle | ICU | SEP-1 measure |
| Gaieski, 2023[92] | Bundle | ED | SEP-1 measure<br>Validity |

ED=emergency department; ICU=intensive care unit; SEP-1=The Severe Sepsis and Septic Shock Management Bundle

**Evidence Table C-19. Strength of evidence for included primary studies**

| Outcome | Population | Setting | Number of Studies, Design | Study Limitations | Directness | Consistency | Precision | Reporting Bias | Strength of Evidence |
|---|---|---|---|---|---|---|---|---|---|
| Mortality | Pediatric | ICU | 1 observational study[29] | High | Direct | NA | Precise | Undetected | Insufficient |
| | Adult | Pre-hospital | 1 observational study[32] | High | Direct | NA | Imprecise | Undetected | Insufficient |
| | Adult | ED | 1 RCT[34]<br>2 observational studies[26, 33] | Moderate | Direct | Consistent | Imprecise | Undetected | Low |
| | Adult | Ward or Hospitalwide | 1 RCT[30]<br>2 observational study[28, 31] | Moderate | Direct | Consistent | Imprecise | Undetected | Low |
| Hospital or ICU length of stay | Pediatric | ICU | 1 observational study[29] | High | Direct | NA | Precise | Undetected | Insufficient |
| | Adult | Pre-hospital | 1 observational study[32] | High | Direct | NA | Imprecise | Undetected | Insufficient |
| | Adult | ED | 1 RCT[34]<br>1 observational studies[26] | Moderate | Direct | Inconsistent | Precise | Undetected | Insufficient |
| | Adult | Ward or Hospitalwide | 1 RCT[30]<br>2 observational study[28, 31] | Moderate | Direct | Consistent | Precise | Undetected | Low |
| Adherence to clinical guideline or SEP -1 measure | Pediatric | ICU | 1 observational study[29] | High | Direct | NA | Precise | Undetected | Insufficient |
| | Adult | Pre-hospital | 1 observational study[32] | High | Direct | NA | Imprecise | Undetected | Insufficient |
| | Adult | ED | 1 RCT[34]<br>2 observational studies[26, 33] | Moderate | Direct | Inconsistent | Precise | Undetected | Low |
| | Adult | Ward or Hospitalwide | 1 RCT[30]<br>2 observational studies[28, 31] | Moderate | Direct | Consistent | Imprecise | Undetected | Low |

ED=emergency department; ICU=intensive care unit; NA=not available