3. Sepsis Recognition

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Introduction

Sepsis has been a leading cause of hospitalization and death in U.S. healthcare settings for many years, and accounts for more hospital admissions and spending than any other condition.[1] As a result, preventing, diagnosing, and treating sepsis effectively has been a focus of patient safety and public health in recent years. In this chapter, we discuss two patient safety practices that aim to identify signs of sepsis and septic shock as quickly as possible so that treatment can be started: manual screening tools and electronic patient monitoring systems (PMSs).

Screening tools are manually administered paper or electronic forms that guide clinicians through a set of criteria as they are assessing a patient. The screening process is administered either at a care transition (e.g., presentation at the emergency department [ED] or to emergency medical services [EMS]) or at regular intervals (e.g., the start of every nursing shift). Current evidence indicates that performance (sensitivity/specificity) of the tools varies, especially in the prehospital setting. Evidence for process measure improvement (i.e., time to initiation of treatment) was of moderate strength in both the hospital and prehospital setting. Evidence for outcome measure improvement (mortality, hospital length of stay [LOS], intensive care unit [ICU] transfer, and ICU LOS) was sparse but showed a trend toward improvement. More high-quality studies are needed in diverse settings to test the effects of sepsis screening tools.

Automated systems continuously monitor patient status, such as vital signs, and alert a clinician if criteria for possible sepsis are met. These systems are becoming more widespread, especially in hospitals, which have sophisticated technology infrastructures. While the studies were inconsistent, there appears to be evidence of moderate strength in the current literature for improvement in both process and outcome measures for PMSs. More high-quality studies are needed to confirm these findings, and to identify implementation best practices and lessons learned.

Importance of Harm Area

Sepsis is a syndrome of life-threatening organ dysfunction due to a person's systemic dysregulated response to infection.[2] Sepsis can be caused by many types of infection (bacterial, fungal, and viral) and can affect any age group, from neonatal to geriatric. It is a common reason for hospital admission and readmission, with an estimated incidence of 6 percent of all hospital admissions, or more than 1 million admissions in the United States every year.[3,4] Sepsis also has one of the highest mortality rates of any hospital condition, estimated at 15–30 percent.[4,5] Tracking incidence and mortality over time is challenging due to shifting definitions and an increasing awareness of sepsis. Some studies show an increase in incidence and a decrease in mortality in recent years, but some show no significant change in either.[4,6] Among subgroups, older adults and nursing home residents are much more likely to develop and die from sepsis compared with younger adults and non-nursing home residents.[7] In 2013, $24 billion was spent treating sepsis, more than any other condition treated in U.S. hospitals.[1]

The symptoms of sepsis (e.g., high temperature, high blood pressure) are shared by many other conditions, making sepsis difficult to diagnose, especially in the early stages.[8] In addition, sepsis can start suddenly and quickly lead to organ dysfunction and death.[8] In response to this, international

organizations such as the Society for Critical Care Medicine have focused on addressing the two problems that sepsis presents: delay in recognition and diagnosis of sepsis, and delay in start of treatment, which combined contribute to the high mortality rate for sepsis.[9]

The need for early recognition and rapid treatment have led to guidelines about how to treat septic patients, with aggressive interventions and timeframes. The most commonly adopted of these is the Surviving Sepsis Campaign (SSC) bundle, which has gone through many iterations, and includes starting broad-spectrum antibiotics and intravenous (IV) fluids, and obtaining blood culture and lactate measurements within a 1- to 6-hour timeframe.[10] Many government agencies across the world have proposed measuring and evaluating hospital compliance with the bundle elements to strongly encourage its use. Most notably, since October 2015, the Centers for Medicare & Medicaid Services requires U.S. hospitals to report their performance on a composite process-of-care measure for severe sepsis and septic shock, and ties reimbursement to the measure results. There is occasionally tension between the goals of antibiotic stewardship and sepsis guidelines, with the former focused on reducing inappropriate use of broad-spectrum antibiotics, and the latter requiring rapid and barrier-free initiation of broad-spectrum antibiotics.[11] Clinicians sometimes perceive antibiotic stewardship goals as being purely restrictive, thereby creating tension in decisions about antibiotics; however, good antibiotic stewardship encompasses appropriate administration of antibiotics, including when there is clinical suspicion for severe sepsis or septic shock. In addition, many clinicians have apprehension about the IV fluid level due to the risk of fluid overload.[12]

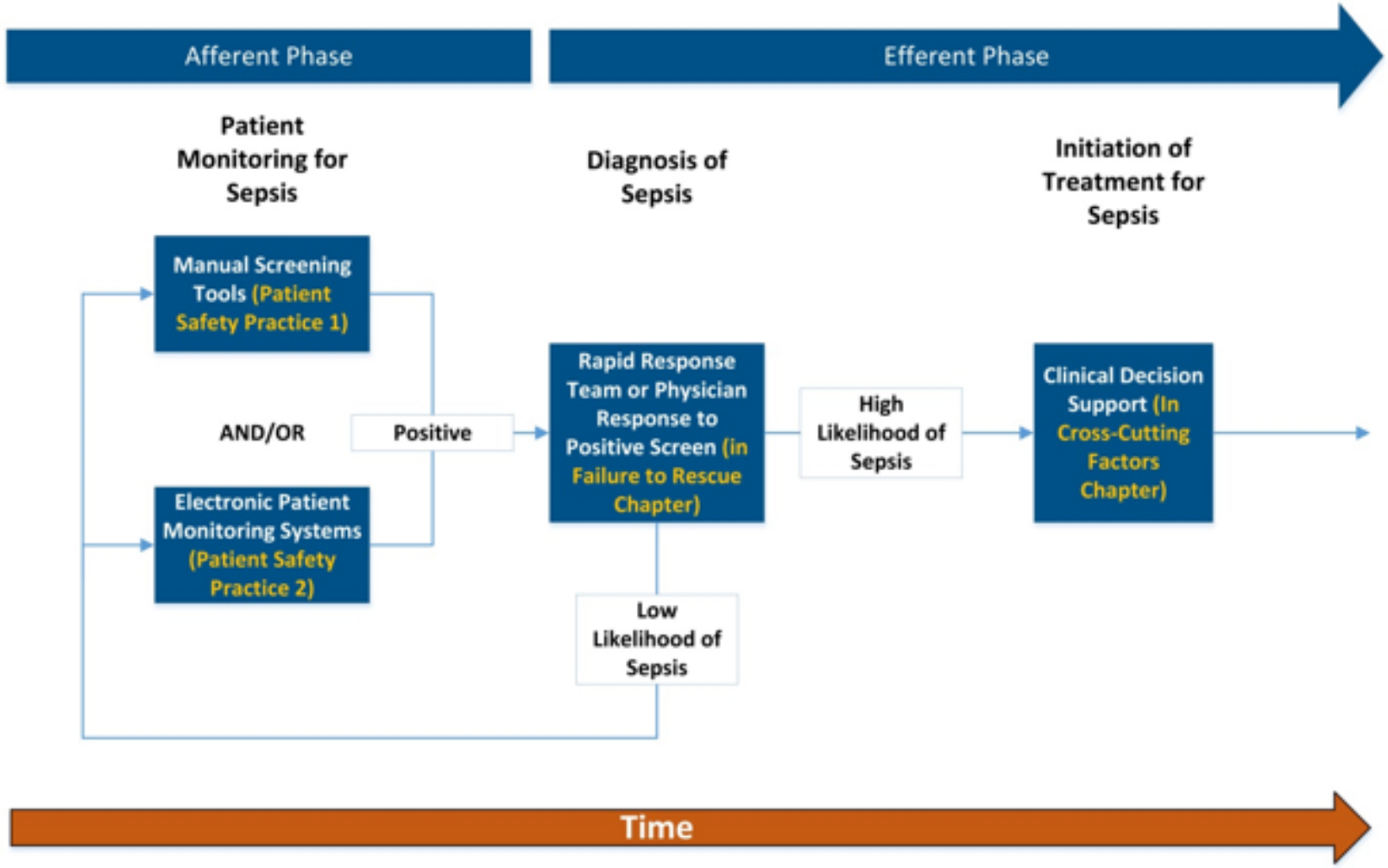
The need to diagnose sepsis unambiguously and quickly has led to development of various diagnostic criteria. The signs and thresholds used in these criteria vary but always include at least one vital sign with abnormal thresholds (heart rate [HR], respiratory rate [RR], blood pressure [BP], temperature, etc.), and sometimes include clinical assessments (mental status, suspicion of infection) and laboratory results (lactate, creatinine). The most commonly used criteria are the qSOFA (quick Sequential Organ Failure Assessment), the NEWS (National Early Warning Score), and the increasingly abandoned SIRS (systemic inflammatory response syndrome) criteria.[13]

Patient Safety Practice (PSP) Selection

A literature search was conducted on six sepsis PSPs in three databases (CINAHL®, MEDLINE®, and Cochrane), and resulting abstracts were reviewed for relevance. Some identified sepsis PSPs (e.g., clinical decision support) spanned multiple harm areas and appear in cross-cutting chapters. One sepsis PSP about readily available antibiotics did not have enough information to warrant a review. The two remaining PSPs (screening tools and patient monitoring systems) are specific to sepsis and have enough evidence to support a review.

Borrowing from the “failure to rescue” literature, diagnostic and treatment processes for sepsis can be grouped into two phases, afferent and efferent, each containing its own related practices.[14] Figure 1 below is a conceptual model related to sepsis. The focus of the PSPs contained in this chapter is the afferent phase: how clinicians and hospitals use diagnostic criteria to recognize sepsis quickly, using either manual screening or continuous electronic monitoring. Because of the changing criteria for sepsis, the PSPs do not compare the accuracy of the various diagnostic criteria but rather the effect of these strategies in clinical practice settings. The efferent phase, including treatment for sepsis, occurs after screening/surveillance and is outside the scope of this chapter.

Figure 1: Conceptual Model for Sepsis



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3.1 Patient Safety Practice 1: Sepsis Screening Tools

3.1.1 Practice Description

Identifying signs of sepsis as early as possible is critical to averting organ failure and risk of death.[1] However, sepsis does not have a simple diagnostic test or specific symptoms that unambiguously indicate onset. International organizations have developed diagnostic criteria and have recommended screening patients at risk of sepsis using these criteria.[2] Manual paper or electronic tools guide clinicians through the criteria as they assess a patient. The screening process generally takes place either during a care transition (e.g., presentation at the ED or to EMS) or at regular intervals (e.g., the start of every nursing shift). A tool's embedded logic determines if the patient is suspected of having sepsis. If so, the clinician must start treatment as quickly as possible, which has been shown to increase survival.[3,4]

3.1.2 Methods

To answer the question, "Do sepsis screening tools improve patient outcomes?" three databases (CINAHL®, MEDLINE®, and Cochrane) were searched for "sepsis" and related synonyms, as well as "screening," "algorithm," "triage tool," "Early Warning Score," "early alert," and other similar terms from 2008 to 2018. The initial search yielded 998 results; after duplicates were removed, 923 were screened for inclusion and 53 full-text articles were retrieved. Of those, 26 were selected for inclusion in this review. Articles were excluded if the outcomes were not relevant, the article was out of scope (including no quantitative results), or the study design was insufficiently described. Studies in which screening tool implementation was accompanied by other significant sepsis interventions (e.g., changes in antibiotic delivery) are considered in Section 3.3.

General methods for this report are described in the Methods section of the full report.

Key Findings:

- Performance of screening tools varied widely, especially in the prehospital setting. More research is needed to determine the optimal variables and thresholds for a sepsis screening tool.
- There was moderate evidence of process measure improvement in the hospital setting with screening, including time to antibiotics. Prehospital evidence was sparse but showed improvement as well.
- Evidence for outcome measures (e.g., mortality, ICU LOS, ICU transfer) was sparse but showed a trend toward improvement, although the improvement was not always significant.
- Higher quality studies in diverse settings are needed to test the effects of sepsis screening tools.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report appendixes A through C.

3.1.3 Evidence Summary

A summary of key findings related to sepsis screening tools is located in the Key Findings box. The following section reviews the applicable studies in more depth, by measure type and setting.

Fifteen of the 26 studies examining the use of sepsis screening tools took place in a hospital setting, 10 took place in a prehospital setting, and 1 took place in a nursing home. Over 20 different screening tools that incorporate somewhat different diagnostic criteria were used in the 26 studies. The indicators and thresholds used to determine if a patient screens positive for sepsis also differed across tools. Vital signs (HR, RR, BP, temperature, etc.) were present in all tools; clinical assessments (mental status, suspicion of infection) were also common, while laboratory results (lactate, creatinine) were used in only a few tools

due to the time it takes to run lab tests and receive results back. Many studies used diagnostic criteria developed by consensus-based professional organizations, such as the qSOFA, MEWS (Modified Early Warning Score), and the SIRS criteria, but some studies tested other indicators and thresholds.

3.1.3.1 Sensitivities/Specificities of Screening Tools

Diagnostic performance of various screening tools for sepsis was reported in 20 of the 26 studies. None reported process measures or outcomes other than diagnostic performance. Twelve studies were retrospective cohort analyses that assessed whether the screening tool would have identified or ruled out sepsis correctly. Such studies support validity testing of the tools but have a lower strength of evidence than prospective studies because they were not implemented in a clinical setting. Despite these limitations, it is important to have a high-performing tool that reliably identifies and rules out sepsis before testing its effect on processes or outcomes of care. The hospital was the setting in 11 studies, while 8 were focused on the prehospital setting, and 1 focused on the nursing home setting.

The studies each report some or all of the following performance metrics for screening tools: sensitivity, specificity, positive predictive value, negative predictive value, and area under the receiver operating curve. The most widely reported were sensitivity and specificity. When deciding on an acceptable level of sensitivity and specificity for a tool, it is important to consider where the tool is implemented and the processes surrounding its use. For example, in a prehospital setting (EMS) or nursing home, high sensitivity is usually valued over specificity because patients will be reevaluated at the hospital before treatment is started. In a hospital setting, high specificity is also important to reduce alert fatigue and unnecessary treatment.[5]

3.1.3.1.1 Prehospital and Nursing Home

The sensitivity and specificity of the prehospital and nursing home screening tools varied widely. Seven of the eight prehospital studies were retrospective and they were addressed in a 2016 systematic review by Smyth and colleagues that found low to very-low quality evidence for the accuracy of prehospital sepsis screening tools. The authors attributed this to lack of EMS personnel training about sepsis and the inaccuracy of using SIRS criteria alone.[a] They conclude that more validation studies are needed to determine the efficacy of prehospital sepsis screening tools.[6] Hunter et al. (2016) was the only prospective study, and it produced the highest sensitivity of any prehospital screening tool (0.90). That tool was implemented with EMS personnel and was based on SIRS criteria and end tidal carbon dioxide ($ETCO_2$) measurement. Specificity of the tool was 0.54.[7] The only study in a nursing home setting was a retrospective analysis of five different sepsis screening tools, which had sensitivity ranging from 0.27 to 0.79 and specificity ranging from 0.69 to 0.93.[5] The performance of the prehospital tools is summarized in Table 1.

[a]SIRS criteria include: temperature higher than 100.4°F or lower than 96.8°F, HR higher than 90 beats/min, RR higher than 20 breaths/min or arterial carbon dioxide tension lower than 32 mm Hg, and white blood cell count higher than 12,000/µL or lower than 4000/µL or with 10 percent immature (band) forms.

Table 1: Sensitivities and Specificities of Prehospital Studies

Author, Year	Variables	Sensitivity	Specificity
Bayer et al., 2015[20] (PRESEP)	Temperature (temp), oxygen saturation (SaO2), respiratory rate (RR,) and Glasgow Coma Sclae (GCS)	0.85	0.86
Hunter et al. 2016[7]	Systemic inflammatory response syndrome (SIRS) (temp, heart rate [HR], RR) and end tidal carbon dioxide (ETCO2)	0.90	0.58
Hunter et al., 2018[13]	ETCO2 Quick sequential organ failure assessment (qSOFA) (GCS, blood pressure [BP], RR)	ETCO2: 0.80 qSOFA: 0.68	ETCO2: 0.42 qSOFA: 0.40
McClelland et al., 2015[24] (SST)	SIRS: HR, temp, white blood cells (WBC), RR, arterial carbon dioxide pressure (PaCO2)	0.43	0.14
Polito et al., 2015[25] (PRESS)	HR, RR, BP	0.86	0.47
Seymour et al., 2017[3]	BP, HR, RR, GCS,pulse oximetry (POx)	0.22	0.98
Shiuh et al., 2012[26]	SIRS: HR, RR, temp, plus suspicious of infection and lactate measurement	NR	NR
Sloane et al., 2018[5] (Nursing Home)	Temp, qSOFA (GCS, BP, RR), SIRS (temp, HR, RR), 100-100-100 (temp, HR, BP)	Temp>100.2F: 0.40 qSOFA: 0.27 SIRS: 0.36 100-100-100: 0.79 Temp >99.0F: 0.51	Temp >100.2F: 0.93 qSOFA: 0.88 SIRS: 0.86 100-100-100: 0.69 Temp >99.0F: 0.85
Wallgren et al., 2014[7]	Robson: temp, HR, RR, alert, verbal, pain, unresponsive (AVPU) (glucose, infection possible BAS 90-30-30 Sacle: BP, RR, SaO2	Robson: 0.75 BAS 90-30-90: 0.43	NR

3.1.3.1.2 Hospital

Performance of screening tools in the hospital setting was tested in 11 studies: 7 in the ED, 3 in medical and/or surgical wards, and 1 in a surgical ICU. In the ED setting, Goerlich and colleagues' triage screening tool had the most balanced performance, with sensitivity of 0.85 and specificity of 0.78. The tool was prospectively implemented in the ED of a tertiary hospital and used standard vital signs and muscle oxygen saturation (StO2) to generate a cumulative screening score.[8] The other prospective screening tool, used in the ED setting by Singer and colleagues, achieved a high specificity (0.82) but a low sensitivity (0.34). This tool was implemented in a suburban academic medical center ED and used SIRS criteria and lactate measurement.[9] In medical and/or surgical wards, Gyang et al. reported on a highly sensitive (0.95) and specific (0.92) tool that was prospectively implemented in a 26-bed medical/surgical intermediate care unit based on SIRS criteria and suspicion of infection.[10] MacQueen et al. also reported on a highly sensitive (1.00) and specific tool (0.88) implemented in a general surgical unit that used routinely collected vital signs.[11] In the one surgical ICU study, Wawrose and colleagues found that a screening tool based on vital signs outperformed a more complex tool on sensitivity (0.75 vs. 0.45) while maintaining a high specificity (0.85).[12] The performance of the hospital tools is summarized in Table 2.

Table 2: Sensitivities and Specificities of Hospital Studies

Author	Variables	Sensitivity	Specificity	Unit
Berger et al., 2013[28]	Hear rate (HR), blood pressure (BP)	0.71	0.41	Emergency Department (ED)
Filbin et al., 2018[22]	Quick sequential organ failure assessment (qSOFA): respiratory rate (RR), Glasgow Coma Sclae (GCS), SBP Sepsis Prediction and Optimization Therapy (SPoT): HR, BP	qSOFA: 0.28 SPoT: 0.56	qSOFA: 0.97 SPoT: 0.95	ED
Goerlich et al., 2014[8]	oxygen saturationStO2, HR, RR, temp	0.86	0.78	ED
Gyang et al., 2015[10]	Systemic Inflammatory Response Syndrome (SIRS): HR, temperature , white blood cells (WBC), RR, arterial carbon dioxide pressure (PaCO2)	0.95	0.92	Medical/Surgery
MacQueen et al., 2015[11]	Temp, HR, RR, spontaneous bacterial peritonitis (SBP), mean arterial pressure (MAP)	1.00	0.88	Surgical
Scott et al., 2014[29]	Cytokine release syndrome (CRS): mental status, capillary refill, peripheral pulse quality, cold/mottled extremities	0.08-0.54	0.84-0.98	Children's ED
Shapiro et al., 2008[30]	Temp, BP, HR, RR, blood culture results	0.97-0.98	0.29	ED
Shetty et al., 2016[35]	SIRS (temp, HR, RR), Muscle oxygen saturation/ Fraction of inspired oxygen (SpO2/FiO2), creatine, bilirubin, platelet count	0.20-0.82	0.57-0.95	ED
Singer et al., 2014[9]	SIRS (temp, HR, RR) and lactate measurement	0.34	0.82	ED
Tirotta et al., 2017[31]	Modified Early Warning Score (MEWS) [temp, HR, RR, BP, and alert, verbal, pain, unresponsive (AVPU)	0.35	0.83	Medical wards
Wawrose et al., 2016[12]	Sepsis Severity Score (SSS): temp, RR, WBC, mental status St. John's Sepsis Agent (SJSA): temp, HR, RR, glucose level, urinalysis results, and blood culture results	SJSA: 0.45 SSS: 0.75	SJSA: 0.85 SSS: 0.86	Surgical Intensive Care Unit

3.1.3.2 Effect on Process Measures

Process measures for a sepsis screening tool were reported in five studies, two in a prehospital setting and three in a hospital setting. The tools used in the studies were not independently validated, but the studies target important process goals, including timely administration of antibiotics and fluids, that have been shown to improve outcomes in patients with sepsis.[3,4] Time to antibiotic administration was reported in all five studies, while time to lactate measurement was reported in four, time to fluid administration in three, and blood culture draw was reported in one study.

3.1.3.2.1 Prehospital

Both prehospital studies showed that use of a sepsis screening tool affected process timeliness measures, although only one effect reached significance; these studies had sample sizes of less than 300 and a moderate risk of bias. Hunter et al. (2019) showed that EMS personnel using a sepsis screening tool decreased time to IV fluid administration, blood culture draw, lactate level draw, and administration of antibiotics compared with septic patients who were not screened. They attribute this

effect to hospitals preparing staff and supplies for a septic patient arrival, and EMS staff gaining IV access and/or starting IV fluids before hospital arrival.[13] Guerra and colleagues found a non-significant decrease in time to antibiotics (p=0.07) for septic patients who were identified by EMS personnel using a screening tool, compared with those not identified by EMS and did not find a significant effect on any other process measures of timeliness.[14]

3.1.3.2.2 Hospital

Among the hospital screening tools that were evaluated for their effect on care processes, one was implemented in the ED and two in the ICU. While the study designs varied, all three studies showed a significant decrease in time to antibiotic administration or an increase in compliance with the SSC time guideline for antibiotic administration. For example, Patocka and colleagues showed that mean time to antibiotics decreased by 21 percent (p= 0.0074) after the implementation of an ED triage screening tool in a 637-bed urban tertiary hospital.[15] Rincon et al. used a tele-health approach for ICU sepsis screening across 10 hospitals and found that it increased compliance with the SSC antibiotic administration guideline from 55 percent to 74 percent (p= 0.001), as well as increasing compliance with the guideline for IV fluids from 23 percent to 70 percent (p = 0.001).[16] A significant improvement in time to lactate measurement was also found in all three studies, in both the ED and the ICU. [15-17]

3.1.3.3 Effect on Outcome Measures

The ultimate goal of a patient safety practice is to improve the patient outcomes. Three sepsis screening tools were studied prospectively and measured patient outcomes: one in the prehospital setting and two in the hospital setting. All three studies were observational in design and had low to moderately sized samples. The outcomes studied were mortality, ICU admissions rate, and ICU LOS. Attributing improvement in these outcomes to sepsis screening tools is difficult, however, because patients with sepsis are generally older, have multiple comorbidities, and may have advance directives for end-of-life care. In addition, reasons for ICU transfer and ICU LOS are multifactorial and not necessarily correlated with sepsis or the use of a screening tool.[13]

3.1.3.3.1 Prehospital

Hunter et al. (2018 was the only prehospital study that measured patient outcomes. This study involved an EMS screening tool with a subsequent alert to the hospital; it found a significant reduction in ICU admissions rate (33% with screening vs. 52% without screening, p=0.003), and a non-significant reduction in mortality (11% with screening, 14% without screening, p=0.565).[13]

3.1.3.3.2 Hospital

In the hospital setting, one study focused on the ICU and one on the ED. Tedesco and colleagues found that a nurse-administered screening tool in the ED of a 320-bed community hospital led to a significant reduction in mortality (18.4% vs. 13.2% days; P = 0.015).[18] Larosa and colleagues implemented an ICU sepsis screening tool in a 673-bed urban teaching hospital and found a significant reduction in mortality after controlling for factors such as mortality in emergency department sepsis (MEDS) score, leucopenia, and age (p=0.01). However, the sample size for this study was quite small (n=58).[17]

3.1.4 Implementation

Despite the lack of conclusive evidence of effectiveness, use of tools to screen patients for signs of sepsis is widespread due to the urgency for identifying sepsis, and based on guidelines and hospital

quality performance measures. However, implementing these tools can prove challenging in terms of resource use and workflow change for staff.

3.1.4.1 Facilitators

Two common facilitators mentioned across studies were education of the clinical staff who will be responsible for administering the screening, and a tool that is easy to learn and use. First, educating nurses and EMS staff about sepsis pathophysiology helps them to better understand and interpret screening parameters, just as these staff are trained to recognize signs of stroke or cardiac arrest. [19] This education may have the additional effect of increasing sepsis care quality, independent of the screening tool itself. Authors stressed that screening tools cannot substitute for the clinical acumen of staff.[10] Second, a tool should be as easy as possible to fit into a clinician's workflow, such as a checklist using a selected number of readily available or routinely collected variables.[20] As a result, lab test results were generally excluded from screening tools. However, it is important to balance the simplicity of a tool and its ease of use with strong sensitivity and specificity. Other facilitators mentioned in these studies included consistent and complete documentation of vital signs on which screening algorithms are based, and standardized use of the tool across hospital units to reduce confusion and communication breakdowns when patients or staff move between units.[5,21]

3.1.4.2 Barriers

Screening every patient for signs of sepsis on a regular basis is labor and time intensive, regardless of the setting. The yield in terms of identifying emerging sepsis may also be low, depending on the prevalence of sepsis in the setting in question. Additionally, the frequency of screening (for example, once per hospital shift) can delay diagnosis of sepsis, defeating the purpose of the screening tool. As a result, transitions of care such as EMS ambulance transport and ED admission are often targeted as optimal times for screening.[22,23] Other potential barriers include alert fatigue if the tool used is not specific enough, and a possible increase in drug resistance from more and longer use of antibiotics. However, there is no reported evidence about these effects. Finally, without proper training and an easy-to-use tool, adherence by clinical staff may be suboptimal, as reported by O'Shaughnessy et al., diminishing potential benefits.[19]

3.1.5 Resources

- The SSC website offers numerous paper screening tools for different settings: http://www.survivingsepsis.org/Resources/Pages/Protocols-and-Checklists.aspx.
- The Minnesota Hospital Association published their sepsis toolkit for the ED and long-term care settings, including the screening tool, posters, and sepsis order set: https://www.mnhospitals.org/quality-patient-safety/quality-patient-safety-initiatives/sepsis-and-septic-shock#/videos/list
- The New Jersey Hospital Association published a sepsis toolkit for post-acute care settings that includes a screening tool, educational materials and quizzes, and a communication tool: http://www.njha.com/media/328416/NJSepsisLACToolkitPost-AcuteCareSettings.pdf
- The Hospital Improvement Innovation Network (HIIN) held a webinar on sepsis screening in 2017 that includes some examples of tools and lessons learned: http://www.hret-hiin.org/Resources/sepsis/17/Sepsis%20020917_508.pdf
- Finally, the U.S. Centers for Disease Control and Prevention (CDC) published a toolkit on sepsis surveillance in 2018 that includes processes for tracking sepsis incidence in a hospital: https://www.cdc.gov/sepsis/pdfs/Sepsis-Surveillance-Toolkit-Aug-2018_508.pdf

3.1.6 Gaps and Future Directions

It is clear from the available literature that higher quality studies (e.g., robust prospective, randomized, quasi-experimental) with larger sample sizes and diverse settings would quantify the effects of sepsis screening tools on process and outcome measures. In addition, the optimal set of variables and thresholds for rapidly identifying a septic patient is not completely settled.

With the emergence of automated electronic screening (see Section 3.2), the use of paper screening tools may be less common in the hospital setting, and more appropriate for prehospital settings such as EMS, nursing home, and home health. Robust studies on the effects of screening tools in these settings would be beneficial.

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3.2 Patient Safety Practice 2: Sepsis Patient Monitoring Systems

3.2.1 Practice Description

Identifying signs of sepsis in a patient as early as possible is critical to averting organ failure and risk of death.[1] However, sepsis does not have a simple diagnostic test or specific symptoms that unambiguously indicates onset. International organizations have developed diagnostic criteria and recommend screening patients at risk of sepsis using these criteria.[2] Automated electronic patient monitoring (i.e., surveillance) for signs of emerging sepsis is becoming more widespread, especially in hospitals, which have sophisticated technology infrastructures. Such systems automatically and continuously monitor data from telemetry devices and/or electronic health record (EHR) entries, and alert a clinician if set criteria for sepsis are met. If, after evaluation, a clinician determines that the patient has sepsis, the clinician must start treatment immediately to reduce mortality and improve patient outcomes.[2] The goal is to decrease the time to treatment initiation for sepsis, which has been shown to increase survival.[3,4]

3.2.2 Methods

To answer the question, "Does continuous patient monitoring for sepsis improve patient outcomes?" three databases (CINAHL®, MEDLINE®, and Cochrane) were searched for "sepsis" and related synonyms, as well "monitoring," "surveillance," and other similar terms, from 2008 to 2018. Additional relevant articles from other sources were added as they were found. The initial search yielded 345 results; after duplicates were removed and additional articles added, 350 were screened for inclusion and 55 full-text articles were retrieved. Of those, 15 were selected for inclusion in this review. Articles were excluded if the outcomes were not relevant, the article was out of scope (including not quantitative), or study design was insufficiently described. Studies about PMS implementation that also included significant sepsis interventions (e.g., changes in antibiotic delivery) are considered in Section 3.3.

Key Findings:

- There was moderate evidence of process measure improvement across multiple types of hospital units, and evidence was most consistent outside of the ICU.
- Evidence for outcome measures (e.g., mortality, ICU LOS, ICU transfer) was mixed, but over half of the studies showed a significant improvement, and several showed an absolute improvement that did not reach statistical significance.
- Higher quality studies are needed to test the effects of sepsis monitoring systems on process and outcome measures.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report appendixes A through C.

3.2.3 Evidence Summary

A summary of key findings related to sepsis PMS is located in the Key Findings box. This section reviews applicable studies in more depth, by measure type (process and outcome) and setting. Please note that sensitivities and specificities of PMSs are not examined because the algorithms within PMSs that scan for sepsis can be constantly adjusted to fit the needs of the setting and optimize performance, as opposed to a static manual screening tool. Upon designing and implementing a sepsis PMS, the

clinicians/administrators typically test the system performance and adjust variable thresholds to best balance speed, sensitivity, and specificity for their setting.

All included studies took place in the hospital setting: five in the ICU, five in the ED, three in general units, one in a telemetry unit, and one in multiple hospital units (ICU, pediatric ICU, and medical/surgical units).

3.2.3.1 Effect on Process Measures

While assessing PMSs for effects on outcome measures (e.g., mortality) is the ultimate goal of this PSP, it is also important to evaluate whether a PMS improves sepsis care processes. Process measures are typically based on evidence-based clinical recommendations, and an improvement in process measures would indicate that patients are receiving care that has been shown to lead to better outcomes. Processes that are commonly targeted for improvement are the timely administration of antibiotics, lactate measurement, blood culture draw, and fluid administration. One or more process measures for sepsis PMSs were reported in nine studies: four in the ED, three in the ICU, and two in noncritical care units. Studies had various designs, including two randomized controlled trials (RCTs), one quasi-experimental study, and six observational pre/post studies. In addition, four systematic reviews covered this topic to some degree. The most commonly reported process measure was time to antibiotic administration (n=8), followed by time to lactate measurement and blood culture draw (n=5 each), and time to fluid administration (n=3).

A systematic review by Warttig and colleagues, which included RCTs conducted in the ICU through September 2017, determined that there is very low-quality evidence for any improvement in time to antibiotic administration after implementation of a PMS, and none of the studies they reviewed showed a significant improvement.[5] None of these studies reported on any other process measures. Three other systematic reviews (Despins, Makam et al., and Alberto et al.) included both non-RCT and non-ICU studies, and found mixed results on improvement in sepsis process measures. Despins searched for automated sepsis detection in the hospital setting from 2005 to 2015;[6] Makam and colleagues searched for electronic sepsis systems through June 2014;[7] and Alberto and colleagues searched for both continuous monitoring and intermittent monitoring through June 2016.[1] Several studies these authors reviewed (all observational and all outside of the ICU) reported that PMSs significantly improved time to administration of antibiotics, lactate draw, blood culture draw, and/or fluid administration. For example, Narayanan and colleagues, after implementing a PMS monitoring vital signs in the ED of an academic medical center, found that average time to antibiotic administration decreased from 61.5 minutes to 29.0 minutes ($p=<0.001$).[8] The authors of one systematic review hypothesized that PMSs in the ICU may not be as effective as those outside of the ICU because clinicians in the ICU are already vigilant for signs of patient deterioration, so a sepsis alert may be redundant, among other reasons. [7]

Of the six studies we reviewed that were published after the systematic reviews were conducted, five found a significant effect of a PMS on at least one process measure. Of these five, one was an RCT and the others were observational studies. An RCT in two ICU units with a total of 32 beds at an urban medical center (Shimabukuro et al.) found that patients with automated sepsis monitoring received antibiotics an average of 2.76 hours earlier than patients in the control group and had blood cultures drawn an average of 2.79 hours earlier than patients in the control group.[9] Austrian et al. was the only new study that found no effect of a PMS on time to first lactate measurement or antibiotic administration prior to blood cultures. This study was conducted in the ED and urgent care units of an

urban academic medical center;[10] it was a pre/post observational study with control of possible cofounders, and the authors suggested that alert fatigue from a tool with low positive predictive value contributed to the lack of impact on process measures.

3.2.3.2 Effect on Outcome Measures

The patient outcomes in the studies of automated PMSs included mortality, ICU transfer rate, hospital LOS, and ICU LOS. Outcome measures for sepsis PMSs were reported in 12 studies: 3 in the ED, 5 in the ICU, 2 in general units, 1 in a telemetry unit, and 1 in multiple hospital units (ICU, PCU, and medical/surgical units). It is difficult to attribute effects on any of these measures, or lack thereof, to a PMS intervention, because many patients who develop sepsis are older, have multiple comorbidities, and may have advance directives for end-of-life care, all of which also affect the outcomes of interest. In addition, reasons for ICU transfer and ICU LOS are multifactorial and not necessarily correlated with sepsis or the PMS.[11]

Eight of the 12 studies found a significant effect of a sepsis PMS in improving at least one outcome measure, and others showed absolute, but not statistically significant, improvements. The studies that showed a significant improvement included two RCTs, one quasi-experimental study, and five observational studies. Six of the 12 studies that reported mortality showed a statistically significant decrease after implementing a PMS. For example, Manaktala and Claypool found a 41–53 percent drop in sepsis mortality ($p = 0.03$-0.06) after implementing a PMS in the three general units of a 941-bed tertiary teaching hospital.[12] A study in nine neonatal ICUs across the United States showed a significant reduction in mortality (8.1% vs. 10.2%, $p = 0.04$) after implementing a neonatal sepsis PMS.[13] Several studies showed an absolute reduction in mortality that was not statistically significant. For example, Hooper and colleagues conducted an RCT of a "listening application" that monitored patient vital signs in the 35-bed medical ICU of a large academic tertiary medical center, and found 14 percent mortality in the control group and 10 percent in the intervention group ($p = 0.29$).[14]

Nine studies reported on hospital LOS, and four found a significant effect of the sepsis PMS. For example, McCoy and Das found a 9.55-percent decrease in hospital LOS after the implementation of a machine learning-based PMS in multiple hospital units (ICU, PCU, and medical/surgical units) in a 242-bed regional community hospital.[15] In contrast, Manaktala and Claypool, described above, showed a significant decrease in mortality but did not find a significant decrease in hospital LOS.[12]

Only one of the four studies (Jung et al.) that reported on ICU LOS found a significant effect from a PMS. This was an observational study of a PMS implemented in a 34-bed surgical ICU in a large academic medical center.[16] The studies that found no effect on ICU LOS varied in setting, with one implemented in the ED, one in a medical ICU, and one in all noncritical care units.[b] One study attributed lack of impact on ICU LOS to a PMS with poor predictive value,[10] and one credited the already vigilant ICU staff;[14] the third was underpowered to detect modest changes in ICU LOS. Two studies reported on ICU transfer rate, and neither found a significant effect on this or any other outcome measure.[10,17] Several studies that showed significant effects on process measures showed no significant effects on outcome measures; for example Umschied and colleagues.[17]

[b]Studies conducted outside of the ICU measured subsequent ICU LOS in patients who were transferred to the ICU from their unit.

3.2.4 Implementation

An automated surveillance system is less time consuming for staff than manual screening for sepsis and alerts clinicians in near real time to a patient's deteriorating condition, more quickly than most manual screening strategies. However, implementing an automated PMS for sepsis can be difficult technologically, financially, and in terms of workflow changes for staff. The studies we reviewed identified supporting factors that facilitate PMS implementation, as well as barriers to successful PMS implementation.

3.2.4.1 Facilitators

As with manual screening tools, implementing a PMS will be effective only if the system has a high level of sensitivity and specificity, to engender clinician trust and reduce false-positive alerts. To achieve this, some prospective studies iteratively revised thresholds for key values, with input from the clinicians, to optimize tool performance.[15,18] Some more recent studies used machine learning to optimize system performance. [9,18] To improve system usability, input from clinicians was solicited in some studies, followed by adaptations. These included allowing a nurse to "snooze" an alert for 6 hours if the patient is already under assessment for sepsis, or implementing a "traffic light" system on a dashboard to visually show clinicians which patients are in a warning zone (yellow) or need urgent attention (red).[15,19] Other facilitators mentioned in the studies included: consistent and complete input of vital signs on which the PMS relies, having a specific staff member assigned to receive all alerts and determine if a physician needs to be called, and designing the PMS to work reliably even if data are incomplete.[15,20,21] Building an automated PMS from scratch is costly, but several PMS systems are now available as an add-on EHR or telemedicine module, which is more efficient for a hospital than designing and testing a de novo system.

3.2.4.2 Barriers

The nonspecific nature of sepsis makes achieving a highly predictive system difficult, whether on paper or in an automated PMS. This is particularly difficult in pediatric settings because the "normal" ranges for vital signs are age dependent and more difficult to fine tune.[22] In addition, if the electronic monitoring and alerting system is poorly designed or difficult to use, it can lead to clinician confusion, frustration, and possibly to worse patient care. [23] For example, if the alert physicians receive contains too little information (or too much), or if the action required is not clear, physicians may find the system too difficult or burdensome to use. [23,24] Lack of adequate staff training on using the system is also a potential barrier, even if a system has high sensitivity and specificity. Additionally, the cost of designing and implementing a PMS can be prohibitive for smaller hospitals, and while an EHR add-on can reduce cost, it may result in less customizable functionality. Finally, after a system is implemented, refining the algorithm and updating it based on changing sepsis criteria require close work with the facility's IT department, which can be resource and time intensive.

3.2.5 Resources

The nonprofit Patient Safety Movement Foundation offers a toolkit on early sepsis detection that includes a technology plan for an automated PMS: http://patientsafetymovement.org/wp-content/uploads/2016/02/10-Sepsis-April-2016.pdf.

3.2.6 Gaps and Future Directions

Due to the mixed results, more high-quality studies could help to understand the effects of sepsis PMSs on important process and outcome measures in different hospital units.

The emergence of machine learning technology has the potential to improve the accuracy, consistency, and customizability of PMSs. Rather than rules-based patient monitoring with predetermined thresholds, machine learning can continually learn from sepsis and nonsepsis cases, and be able to better and more quickly predict when a patient is at risk of sepsis.[15] More studies testing the effect of these systems on processes and outcomes are needed. In addition, the design and usability of systems could benefit from additional studies to determine the optimal display of alerts, dashboards, and other clinical decision support.

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3.3 Multicomponent Sepsis Interventions

3.3.1 Overview

Identifying sepsis as quickly as possible is of critical importance to improving outcomes, but there are other areas of sepsis care and management that can improve outcomes, such as test ordering and results delivery, and initiation of treatment following a sepsis diagnosis. In response to this complexity, some institutions have implemented multicomponent quality improvement (QI) programs aimed at improving the full spectrum of sepsis recognition and care. Several studies found in the search results for the PSPs Patient Monitoring Systems and Screening Tools concern such multifaceted QI initiatives. We did not include these studies in the PSPs above, because it is impossible to know which elements of an initiative are responsible for any process or outcome effects. However, five such studies are briefly discussed here.

All five studies were in the hospital setting, three of them in the ED.[1-5] All five included a manual screening tool or a PMS accompanied by an education program for clinicians and other components that varied by study. Four of the five included a sepsis-specific EHR order set so that clinicians could efficiently order the initial workup and goal-directed therapy (i.e., broad-spectrum antibiotics, IV fluid) specified in the SSC bundle. Several programs aimed to improve time from antibiotic ordering to initiation of treatment and used strategies such as ensuring that antibiotics are well stocked on the unit. One study increased the number of nurses in the ED and provided more space for triage. All studies were observational in design and therefore more prone to bias than randomized or quasi-experimental studies.

3.3.2 Evidence Summary

All five multicomponent studies reported an improvement in at least one process measure, including time to antibiotic administration or compliance with the SSC bundle. For example, Judd and colleagues found that time to antibiotic administration fell from 154 minutes to 57 minutes (p=<0.001) after implementing a screening and fast antibiotics program in all units of a 433-bed tertiary care medical center.[3] Gatewood and colleagues implemented a manual screening tool, EHR alerts, and an order set in the ED of a 450-bed academic hospital, and found that SSC bundle compliance increased from 28 percent to 71 percent (p=<0.001).[2]

Despite these process improvements, only two of the five studies found a significant effect on outcome measures. Judd et al., described above, reported a significant reduction in ICU LOS (5.85 vs. 4.21 days, p=0.003).[3] MacRedmond and colleagues reported a decrease in hospital mortality rate (51.4% vs. 27.0%, p=0.02) after implementation of a screening and order set QI program in the ED of a 500-bed tertiary care teaching hospital.[4] Three studies reported absolute improvements in mortality or hospital LOS that did not reach statistical significance. One study reported an improvement in a sepsis-related mortality index, but did not report a p score or confidence interval to assess significance.[1]

3.3.3 Implementation

Many of the barriers and facilitators to the implementation of a multicomponent intervention are similar to those for implementing a screening tool or PMS, including the importance of clinician education to identify signs of sepsis onset and consistent protocols across hospital units. Additional facilitators mentioned in these five studies included strong teamwork among providers, pharmacy staff, and nursing personnel, and empowering the pharmacy staff to take a more active role in prescribing and

ensuring initiation of antibiotics. One study found that additional nursing staff and space for triage were needed to overcome delays in diagnosis and treatment of sepsis.[5]

3.3.4 Gaps and Future Directions

While implementing complex QI for sepsis care is difficult to study in an evidence-based systematic review, the complexity of sepsis detection and treatment may require a multicomponent approach to reduce mortality and improve other process and outcome measures. More studies with consistent sepsis QI components and rigorous designs (randomized, quasi-experimental, etc.) would be needed to be able to review the consistent effects across studies.

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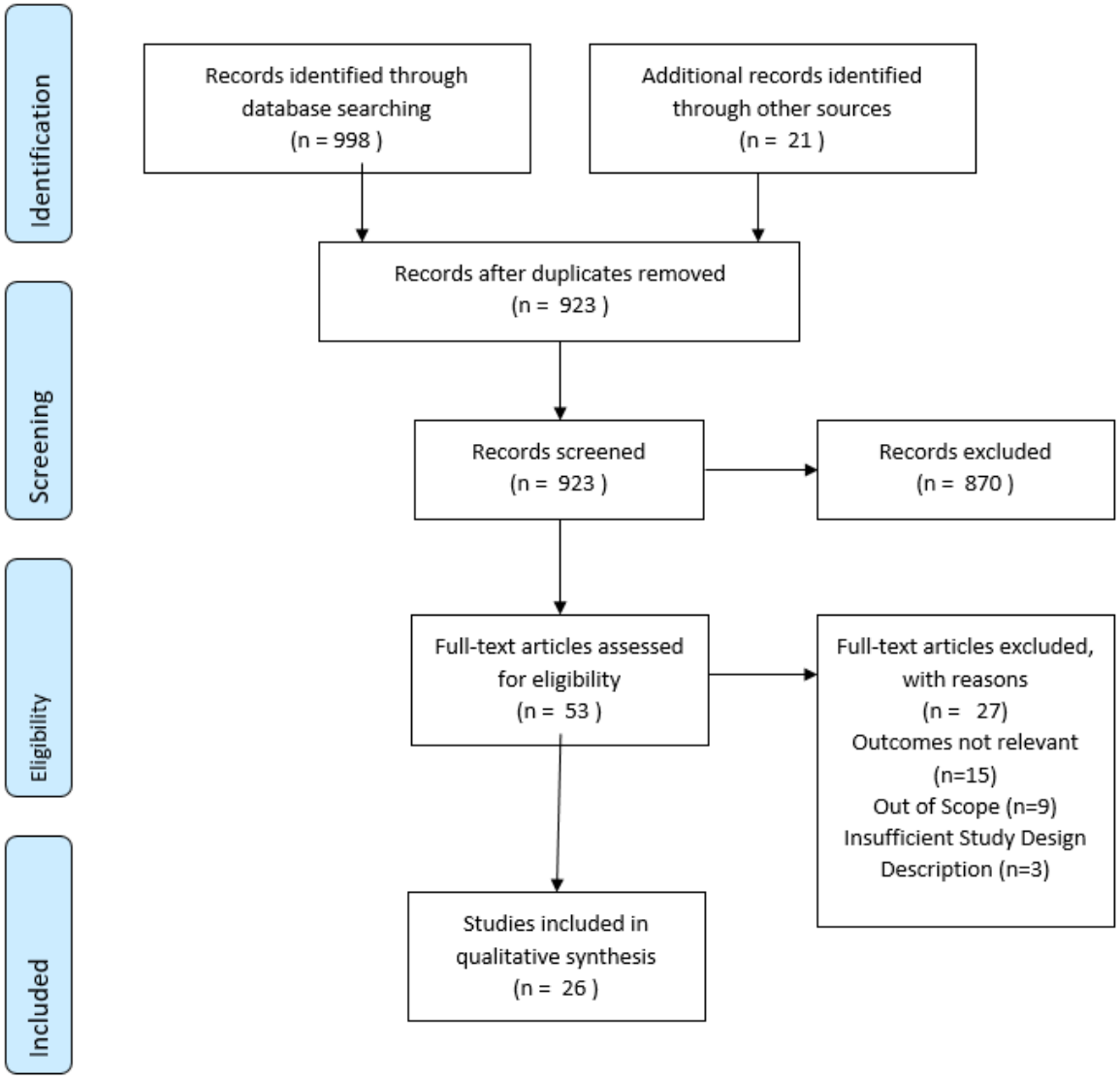
Conclusion and Comment

The two PSPs reviewed in this chapter aim to reduce the time to recognition of sepsis so that treatment can be initiated quickly, with improvement in important patient outcomes. The review of evidence shows that manual screening tools can improve time to treatment, but the effect on mortality and other outcome measures is uncertain. Such tools may be most useful in non-hospital settings such as EMS and nursing homes, but many more studies are needed to test their effects in these settings. Evidence for PMSs in the hospital setting showed some improvement in both process and outcome measures, especially in non-ICU units. However, many studies were observational in design, limiting their strength and increasing the risk of bias. More rigorous studies are needed to test the effects of these systems.

Implementing a screening tool or PMS for sepsis requires dedicated resources and effective staff training, and it can be costly. Either type of tool can be effective if it demonstrates acceptable and sustained sensitivity and specificity, which requires pre-validation and regular monitoring. A manual screening tool is more time intensive for clinicians, but an electronic PMS may be more costly to implement and more difficult for staff to use. The customizability of a PMS's features (e.g., "snooze" button) can add flexibility to the complexities of sepsis care, but this comes with a higher cost to implement than a manual screening tool. The decision to implement a sepsis recognition PSP, and whether it should be manual or automated, should be based on the needs and constraints of the particular setting rather than a "one-size-fits-all" approach.

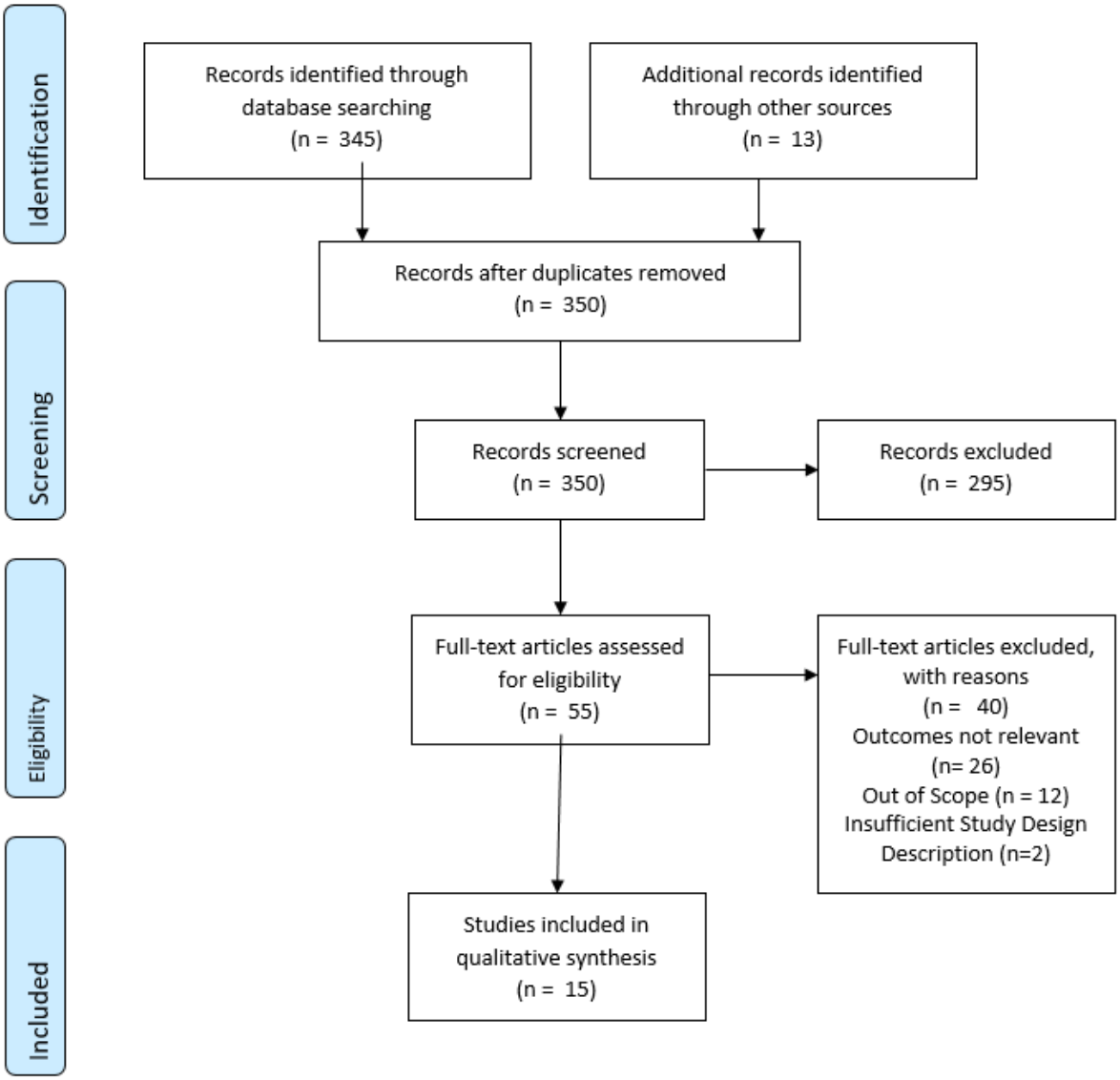
Appendix A. Sepsis PRISMA Diagrams

Figure A.1: Sepsis Recognition, Sepsis Screening Tools—Study Selection for Review



PRISMA criteria described in Moher D, Liberati A, Tetzlaff J, et al.. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Figure A.2: Sepsis Recognition, Sepsis Patient Monitoring Systems—Study Selection for Review



PRISMA criteria described in Moher D, Liberati A, Tetzlaff J, et al.. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Appendix B. Sepsis Evidence Tables

Table B.1: Sepsis Recognition, Sepsis Screening Tools—Single Studies

Note: Full references are available in the Section 3.1 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Bayer et al., 2015[20]	Early sepsis detection score (PRESEP)	A retrospective analysis of consecutive patients who were admitted by emergency medical services (EMS) to the emergency department (ED); 375 patients.	EMS admission into ED	The area under the receiver operating characteristic curve (AUC) of the PRESEP score was 0.93 and was larger than the AUC of the MEWS. The PRESEP score surpassed MEWS and BAS 90-60-90 for sensitivity (0.74 and 0.62, respectively), specificity (0.75 and 0.83), positive predictive value (PPV) (0.45 and 0.51), and negative predictive value (NPV) (0.91 and 0.89). The Robson screening tool had a higher sensitivity and NPV (0.95 and 0.97), but its specificity and PPV were lower (0.43 and 0.32).	The PRESEP tool is simple and fast to calculate in the prehospital setting because all parameters are readily available and routinely assessed. One prospective observational study of patients with severe sepsis showed a significantly shortened time to initiation of antibiotic treatment (70 minutes vs. 122 minutes) and early goal-directed therapy (69 minutes vs. 131 minutes) if sepsis was already diagnosed by the EMS provider.	Low (based on Smyth, 2016)
Berger et al., 2013[28]	Shock index (SI) for the early recognition of sepsis	Retrospective cohort analysis. Adult patients presenting to the ED with a suspected infection; 2,524 patients.	ED at an academic community trauma center with 95,000 annual visits	Subjects with an abnormal SI of 0.7 or greater (15.8%) were three times more likely to present with hyperlactatemia than those with a normal SI (4.9%). The NPV of an SI ≥ 0.7 was 95%, identical to the NPV of SIRS. SI ≥ 1.0 was the most specific predictor of both outcomes.	Not provided	Low/ moderate

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Filbin et al., 2018[22]	ED sepsis screening at triage	Retrospective, outcome-blinded chart review of a 1-year cohort; 19,670 ED patients.	ED in a large, urban tertiary care hospital	The triage concern-for-infection (tCFI) criterion improved specificity without substantial reduction of sensitivity. At triage, sepsis screens (positive quick sequential organ failure [qSOFA] vital signs and tCFI, or positive Shock Precautions on Triage [SPoT] vital-signs and tCFI) were 28% and 56% sensitive, respectively, and specificities were 97% and 95%.	Taken altogether, the findings of this analysis affirm the feasibility of sepsis screening at triage. Most septic shock patients could be identified upon triage, or shortly thereafter, using only vital signs and the patient's risk factors and symptoms. Such patients can and should be prioritized for rapid evaluation and diagnostic testing to confirm infection and initiate treatment expeditiously.	Low/ moderate
Goerlich et al., 2014[8]	Screening tool for the early identification of sepsis	Prospective, observational study of all patients who were seen at triage. Of 500 patients screened, 42 screened positive.	Academic tertiary referral hospital	The screening tool yielded a sensitivity of 85.7%, a specificity of 78.4%, a PPV of 26.7%, and an NPV of 98.4%.	Future modifications of the tool should elucidate the possibility of a source of infection. Thus, a modification of the screening tool that incorporates simple screening questions (analogous to a mini "review of systems" for tuberculosis screening) may aid in determining a potential source of infection and help limit false positives and false negatives.	Low/ moderate
Guerra et al., 2013[14]	A screening tool using point-of-care venous lactate meters	Prospective pilot cohort study. Patients with severe sepsis transported by EMS	Three tertiary care hospitals collectively care for > 80,000 ED patients annually	Trained EMS providers transported 67 severe sepsis patients. They identified 32 of the 67 severe sepsis patients correctly (47.8%). Sepsis alert protocol patients were intubated less frequently than nonalert patients (8% vs. 35%; p=0.003). Antibiotic administration was more prompt in the Alert protocol sample than non-Alerts, but the result did not reach statistical significance. There was no significant difference between alert patients and nonalert patients receiving central lines.	Unlike hospital-based Early Goal-Directed Therapy, no complex procedures, such as central-line placement, are required of EMS to initiate sepsis treatment. All procedures initiated are used frequently by EMS providers to treat hypoperfusion and shock. These prehospital measures, nearly universally available in the United States, can easily be applied by most EMS agencies. An EMS provider's sepsis knowledge base did not correlate with years of training or experience as an EMS provider.	Moderate/ high

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Gyang et al., 2015[10]	Three-tiered, paper-based, nurse-driven sepsis assessment tool administered every 8 hours	Retrospective testing of a prospectively implemented tool on consecutive patients admitted to the unit. Of 245 patients screened, 39 screened positive.	Twenty-six-bed medical/ surgical intermediate care unit at a 613-bed academic medical center	Screening tool sensitivity and specificity were 95% and 92%, respectively. NPV was 99% and PPV was 54%. Overall test accuracy was 92%. There was no statistically significant difference in tool performance between medical and surgical patients. The authors did not find a significant difference in the proportion of patients receiving a sepsis-related clinical action before a screening result (positive or negative), which suggests that a positive screening test may have led to increased clinical action.	The researchers relied heavily on the nursing staff to assess for the presence or absence of infection and believe that the educational component prior to initiating the screening protocol was vital. EMR-based screening tools that rely purely on physiologic data have been considered for the early detection and management of sepsis, although they lack the specificity gained through the incorporation of clinical judgment.	Low/ moderate
Hunter et al., 2016[7]	Prehospital sepsis screening protocol	Retrospective analysis of a prospectively implemented tool. All patients admitted to the ED with a "sepsis alert"; 330 patients.	Eight advanced life support EMS agencies	Sepsis alerts that followed the protocol had a sensitivity of 90% (95% confidence interval [CI], 81-95%), a specificity of 58% (95% CI, 52-65%), and an NPV of 93% (95% CI, 87-97%) for severe sepsis.	While early identification and resuscitative efforts may improve outcomes in severe sepsis, obtaining lactate levels in the field can be difficult and expensive. However, prior studies have shown that prehospital providers can accurately obtain ETCO2 levels simultaneously with traditional vital signs. This suggests that using ETCO2 as an objective marker for hypoperfusion may help discriminate between potentially septic and severely septic patients.	Low/ moderate
Hunter et al., 2018[13]	Comparison of ETCO2 with qSOFA	Retrospective cohort study among patients transported by EMS; 287 patients.	A single EMS system for several regional hospitals	Sensitivity and specificity for ETCO2 as a mortality predictor were higher than for qSOFA score—80% (95% CI, 59-92) vs. 68% (95% CI, 46-84) for sensitivity and 42% (95% CI, 36-48) vs. 40% (95% CI, 34-46) for specificity.	Not provided	Low/ moderate

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Hunter et al., 2019[32]	Prehospital identification of sepsis	Retrospective cohort study among septic patients who were identified as "sepsis alerts" in the ED. Of the 272 total patients, 162 had pre-arrival notification (prehospital sepsis alerts) and 110 did not.	Eight Advanced Life Support EMS agencies	Patients with prehospital sepsis alerts had a higher admission rate (100% vs. 95%, p=0.006) and a lower intensive care unit (ICU) admission rate (33% vs. 52%, p=0.003). There was no difference in mortality (11% vs. 14%, p=0.565) between groups.	Prehospital sepsis alerts were associated with a higher overall hospital admission rate but a lower ICU admission rate, which may reflect successful early resuscitative efforts. Both groups had similar mortality and lactate levels, suggesting that a differing disease severity was not the cause for these findings. Mortality is a difficult primary outcome to interpret in early sepsis intervention considering that many septic patients are older, have multiple comorbidities, and may have advanced directives for end-of-life care.	Low/ moderate
Larosa et al., 2012[17]	Written screening tool and an early alert system (Code SMART)	Prospective observational study; 447 screened, 58 patients were enrolled: 34 Code SMART and 24 non-Code SMART. All adult patients.	An ICU in a tertiary care, urban teaching hospital of 673 beds	The Code SMART group achieved greater compliance with timely antibiotic administration (p<0.001), lactate draw (p<0.001), and steroid use (p=0.02). Raw survival (p<0.05) and survival adjusted for age, leucopenia, and severity of illness scores (p=0.01) were greater in the Code SMART group	Not provided	Moderate

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
MacQueen et al., 2015[11]	Vital sign-based screening protocol	Retrospective cohort analysis. All general surgery inpatients undergoing abdominopelvic surgery. Of 478 total patients screened, 59 had positive screening tests.	Single public Safety Net hospital	The screening protocol had sensitivity 100% and specificity 88% for severe sepsis.	Not provided	Moderate
McClelland et al., 2015[24]	Prehospital sepsis recognition, including the use of a sepsis screening tool	Retrospective cohort analysis. Adult (>16 years) patients with sepsis documented by the hospital; 49 patients.	Regional ambulance service	EMS correctly identified 18/42 patients with sepsis (43% sensitivity, 14% specificity). EMS correctly identified 8/27 patients with severe sepsis (30% sensitivity, 77% specificity).	Not provided	Moderate
Patocka et al., 2014[15]	Triage screening tool	Retrospective chart review; 185 patients with severe sepsis or septic shock in the pre-triage tool group and 170 patients in the post-triage tool group.	Urban tertiary teaching hospital; 637 beds	Mean time to antibiotics decreased by 21%. Compared with the pre-triage tool cohort, patients in the post-triage tool cohort were more likely to have a serum lactate measured in the ED (20% in the pre-triage cohort versus 89.9% in the post-triage tool cohort; p<.0001) and less frequently admitted to hospital (88% vs. 79%).	The number of patients receiving antibiotics within an hour of triage was not different. Rather, the gains in time were seen between 1 and 4 hours after arrival in the ED. This suggests that very sick patients were identified regardless of the triage tool, whereas those with more occult sepsis might preferentially benefit from this tool.	Low/ moderate

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Polito et al., 2015[25]	EMS screening tool for severe sepsis (PRESS)	Retrospective cohort study. Sequential adult, nontrauma, nonarrest, at-risk, EMS-transported patients; 555 patients.	A single EMS system	The PRESS score demonstrates a sensitivity of 86% and a specificity of 47%.	One of the advantages of the PRESS score is that it comprises various types of routinely and practically collected EMS data.	Low (based on Smyth, 2016)
Rincon et al., 2011[16]	Tele-ICU sepsis screening	Prospective observational study. Every ICU patient admitted. Of 89,921 screened, 5,437 patients met criteria for sepsis.	One hundred sixty-one ICUs at 10 hospitals across a geographical range of 500 miles.	Statistically significant increases in compliance with SSC's bundled care recommendations were realized during this study period with four initial elements: antibiotic administration increased from 55% in 2006 to 74% in 2008 (p=0.001), serum lactate measurement increased from 50% to 66% (p=0.001), the initial fluid bolus of ≥20 mL/kg increased from 23% to 70% (p=0.001), and central line placement increased from 33% to 50% (p=0.001).	Tele-screening is a viable solution to mitigate disparities of care across a large health system.	Low/ moderate
Scott et al., 2014[29]	Recording of clinical recognition signs by clinicians on a form	Prospective cohort study, Patients <19 years with fever and tachycardia and undergoing phlebotomy; 239 patients.	ED of a free-standing children's hospital	The sensitivity of exam findings ranged from 8% to 54%; specificity from 84% to 98%.	Not provided	Low/ moderate

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Seymour et al., 2017[3]	Score for out-of-hospital prediction of development of critical illness during hospitalization	Retrospective cohort analysis of patients transported by EMS; 144,913 patients.	EMS system that transports to 16 receiving facilities	Using a score threshold of 4 or higher, sensitivity was 0.22 (95% CI, 0.20-0.23), specificity was 0.98 (95% CI, 0.98-0.98), positive likelihood ratio was 9.8 (95% CI, 8.9-10.6), and negative likelihood ratio was 0.80 (95% CI, 0.79-0.82). A threshold of 1 or greater for critical illness improved sensitivity (0.98; 95% CI, 0.97-0.98) but reduced specificity (0.17; 95% CI, 0.17-0.17).	Not provided	Low (based on Smyth, 2016)
Shapiro et al., 2008[30]	Clinical decision rule for obtaining blood cultures	Prospective, observational cohort study. ED patients with suspected infection: 3,730 (96%) were enrolled, with 305 (8.2%) episodes of true bacteremia.	ED in a 490-bed urban academic tertiary care center	The rule is highly sensitive in identifying patients who will have a positive blood culture. The sensitivity was 98.0% (95% CI, 96–100%) in the derivation set and 97.0% (95% CI, 94–100%) in the validation set. The specificity was 29.0% (95% CI, 27–31%) and 28.8% (95% CI, 26.2–31.4%) for each respective set.	If used in this population, the rule could appropriately reduce the use of blood cultures by approximately 27%, resulting in approximately 1,053 fewer cultures per year. At an estimated cost of $15.91 and a charge of $118 per culture set, this represents a potential savings of $16,758 in costs and $124,286 in charges (institutional data).	Low/ moderate
Shetty et al., 2016[35]	Severe sepsis screening algorithm	Retrospective analysis, Patients presenting to the ED with suspected sepsis; 747 patients.	ED in a tertiary hospital	Sensitivity and specificity of algorithms to flag severe sepsis ranged from 20.2% to 82.3% and 57.8% to 94.8%, respectively.	Not provided	Low/ moderate

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Shiuh et al., 2012[26]	EMS Sepsis Protocol with Point-of-Care Lactate	Prospective cohort of consecutive out-of-hospital patients treated under an EMS sepsis protocol; 219 patients.	EMS patients transported to a large urban/ suburban 2-hospital health system	There was a final hospital diagnosis of severe infection or sepsis for 76.7% of sepsis alert patients (n=66) and 74.2% of sepsis advisory patients (n=72). In these patients, median time from arrival to broad-spectrum antibiotics was 59 min (IQR 42–91) in sepsis alert patients and 81 min (IQR 49.5–127.3) in sepsis advisory patients. ICU admission occurred in 50% and 23% of sepsis alert and advisory, respectively.	Not provided	Moderate
Singer et al., 2014[9]	Sepsis screening tool with subsequent lactate measurement if criteria met.	Prospective, observational study, A convenience sample of adult ED patients with suspected infection; 258 patients.	A suburban academic ED with an annual census of 90,000	Sensitivity was 34%, specificity 82%, PPV 89% (95% CI, 80%–94%), and NPV 23%.	Not provided	Low/ moderate
Sloane et al., 2018[5]	Comparison of five sepsis screening tools	Retrospective chart audit of all residents who had been hospitalized and returned to participating nursing homes (NH) during the study period; 236 NH residents.	Thirty-one community NHs in North Carolina, The mean NH bed size was 11.	Documentation of 1 or more vital signs was absent in 26%–34% of cases. Among people with complete vital sign documentation during the 12 hours prior to hospitalization, the most sensitive screening tools were the 100-100-100 Criteria (79%) and an oral temperature >99.0F (51%); and the most specific tools were a temperature >100.2F (93%), the qSOFA (88%), the Systemic Inflammatory Response Syndrome criteria (86%), and a temperature >99.0F (85%). Many SOFA data points were missing from the record; despite this, 65% of cases met criteria for sepsis.	Over a quarter of NH residents lacked documentation of vital signs in the 72 hours prior to hospital transfer. Better surveillance of people who undergo changes in status is, therefore, an important element of improved detection of early sepsis. During the 12 hours prior to transfer, only 19% of the sepsis admissions and 16% of the nonsepsis admissions had a medical note or other indication of a provider examination. A possible solution is telemedicine if the resources were put in place to make on-call physicians able to have a robust virtual visit to patients with changes in medical status, and if reimbursement were provided at an appropriate level for such services.	Low/ moderate

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Tedesco et al., 2017[18]	Sepsis Management Algorithm	Prospective pre-post observational study. Patients in the ED; 247 patients	A community hospital ED with 320 beds that had approximately 40,000 ED visits each year	Mortality from sepsis was significantly reduced ($\chi 2$ [1, n=5.889, p=0.015]) from 18.4% in 2015 compared with 13.2% for the same timeframe in 2016, which represented a 28% reduction in mortality.	Not provided	Moderate
Tirotta et al., 2017[31]	MEWS	Retrospective analysis of a multicentric prospective study. Consecutive septic patients with positive blood culture; 526 patients.	Thirty-one medical hospital wards in Italy	When dichotomized as low risk vs. high risk (MEWS <4 vs. >4), the MEWS had a sensitivity of 35% and a specificity of 83%.	Not provided	Low
Wallgren et al., 2014[27]	Comparison of two prehospital sepsis screening tools with clinical judgment by EMS personnel	Retrospective cross-sectional study of adult patients transported by the EMS, with a hospital discharge International Classification of Diseases code consistent with sepsis; 353 patients.	EMS services in Sweden	For sepsis, Robson tool: sensitivity was 75% (p<0.001), BAS 90-30-90: sensitivity was 43% (p<0.001), EMS clinical judgement: 12% accuracy (95% CI not reported).	A possible contributing factor toward the low detection of sepsis by clinical judgment in the current study is the lack of guidelines on documentation of the primary impression in EMS records in Sweden.	Moderate/ high (from Smyth, 2016)

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)
Wawrose et al., 2016[12]	Comparison of a sepsis screening tool, the Sepsis Screening Score (SSS), with a commercially available sepsis screening tool, the St. John's Sepsis Agent (SJSA)	Prospective observational study of each patient in the surgical intermediate care unit (SIMU). SSS was twice daily, SJSA was EHR monitoring. Of 348 patients included in the study, 47 (13.5%) developed sepsis.	SIMU at Memorial Hermann Hospital, a tertiary referral hospital in Houston, Texas	The SJSA was determined to have a sensitivity of 44.7%, a specificity of 84.7%, a PPV of 31.3%, and an NPV of 90.7%, while the SSS was determined to have a sensitivity of 74.5%, a specificity of 86.4%, a PPV of 46.1%, and an NPV of 95.6%. The differences in sensitivity ($p < 0.001$), PPV ($p < 0.001$), and NPV ($p = 0.011$) were found to be statistically significant.	Unlike the SJSA, the SSS is based on parameters that are easily measurable from the bedside, which allows for rapid sepsis diagnosis and subsequent treatment.	Low/ moderate

Table B.2: Sepsis Recognition, Sepsis Screening Tools—Systematic Reviews

Note: Full references are available in the Section 3.1 reference list.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings
Nannan Panday et al., 2017[33]	Early warning scores (EWS)	Emergency Department (ED) and acute medical unit (AMU)	Forty-two studies were included: 36 studies reported on mortality as an endpoint, 13 reported Intensive Care Unit (ICU) admission, and 9 reported the composite outcome of mortality and ICU admission. For mortality prediction, National Early Warning Score (NEWS) was the most accurate score in the general ED population and in those with respiratory distress; Mortality in Emergency Department Sepsis score (MEDS) had the best accuracy in patients with an infection or sepsis. ICU admission was best predicted with NEWS; however, in patients with an infection or sepsis, Modified Early Warning Score (MEWS) yielded better results for this outcome.	Uniformity in the EWS used across all departments of the healthcare chain might be beneficial for the improvement of patient care. The ideal prognostic score should be easy to calculate, preferably without the need of laboratory results, and should show good predictive value. Simple bedside systems such as RTS, CRB-65, or quick Sepsis Related Organ Failure Assessment (qSOFA) are appealing due to their simplicity and ease of use; however, it is difficult to combine both simplicity and accuracy, as this review shows that simple prognostic scores were outperformed by more elaborate scoring systems such as the NEWS and MEDS.
Roney et al., 2015[34]	Modified early warning scoring system tools utilization	Adult medical-surgical/ telemetry units	There were limited high-level data, and no clinical trials linking use of modified early warning scoring system tool to robust outcomes were found. The literature review found no MEWS assessment tool combining nursing assessment findings adjusted for SIRS vital sign criteria and laboratory values to aid in identification of both at-risk and septic patients. Literature review research findings suggest MEWS tools' scoring of physiologic findings, including vital signs, have a positive relationship with earlier detection of clinical deterioration.	Critical assessment of patients prior to deterioration requires critically thinking nurses, not mere gathering and recording of vital signs. The clinical picture may be quantified with a scoring tool to assist bedside nurses' clinical decision making, thus leading to improved outcomes and decreased incidence of failure to rescue.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings
Smyth et al., 2016[6]	Prehospital sepsis screening tools	Prehospital EMS	Recognition of sepsis by ambulance clinicians is poor. The use of screening tools based on the Surviving Sepsis Campaign (SSC) diagnostic criteria improves prehospital sepsis recognition. Screening tools derived from EMS data have been developed, but they have not yet been validated in clinical practice. There is a need to undertake validation studies to determine whether prehospital sepsis screening tools confer any clinical benefit. The studies identified provide low-quality or very low-quality evidence to suggest that accuracy of prehospital sepsis recognition by ambulance clinicians varies considerably.	In many areas, paramedic education programs have not focused sufficient attention on sepsis as a clinical syndrome, and paramedic knowledge of sepsis is often poor.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings
Alberto et al., 2017[1]	Sepsis screening tools	General hospitalized patients	Electronic tools can recognize abnormal variables and activate an alert in real time. However, accuracy of these tools was inconsistent across studies, with only one demonstrating high specificity and sensitivity. Paper-based, nurse-led screening tools appear to be more sensitive in the identification of septic patients but were only studied in small samples and particular populations. The process of care measures appear to be enhanced with the use of screening tools; however, demonstrating improved outcomes is more challenging. High levels of accuracy were reported in the studies and reproduced for the purpose of this review with the screening tools used in three studies. However, two studies had small sample sizes, with accuracy tests calculated on random numbers of negatively screened participants. The remaining study reported control data collected retrospectively outside of the study period. Lower sensitivity and PPVs were reproduced and reported in the larger studies, where arguably more robust designs were used. The more complex screening tools appear to be more effective in ruling out patients with sepsis, but they performed poorly in correctly identifying septic patients. Nurses were always the first responders to sepsis alerts, although sometimes the rapid response coordinator and the covering medical provider were also alerted at this time. Overall, the frequency and time to use of diagnostic measures (lactate orders, blood cultures) improved significantly, whereas results pertaining to treatment (fluids and vasopressors) were inconsistent across studies, with some but not all demonstrating improvement. One study reported significant decrease in mortality and risk of death. Other studies showed positive trends in hospital mortality, hospital and ICU LOS, and ICU transfer.	The technology and the staff available, such as the nurse to patient ratio and the supporting steering committees, played a pivotal role in developing a strategy for sepsis screening in these studies. Reviewed screening tools have different levels of sensitivity and specificity, which need to be considered prior to identifying an instrument for implementation; this applies not only to the variables incorporated in the instrument but also the medium that is used, specifically either electronic or paper-based. If technology is available, electronic tools may be preferred over paper-based tools. However, due to the resource-limited settings worldwide, implementation of paper-based, nurse-driven tools could make a difference in sepsis care. Frequency of screening practice and review periods of variables to screen may depend on patient characteristics, staffing, and available technology.

Table B.3: Sepsis Recognition, Sepsis Monitoring Systems—Single Studies

Note: Full references are located in the Section 3.2 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Austrian et al., 2018[10]	Electronic health record-based sepsis alert system	Interrupted time series retrospective cohort study. Patients 18+ years of age who were seen in the urgent care center or emergency department (ED); 2,144 total hospitalizations with a final diagnosis of severe sepsis or septic shock.	ED and urgent care units in an urban academic medical center; 726 beds	The alerts had no effect on any intermediate outcome measures, including intensive care unit (ICU) admissions and length of stay (LOS), nor on the process of care measures for sepsis, including time to first lactate measurement or antibiotics prior to blood cultures. There was a 16% decrease in LOS with introduction of the sepsis alert system. However, this decrease did not quite reach statistical significance when accounting for multiple testing (p=.007). The authors found no evidence for differences in mortality in the pre- and post-alert period after adjustment. The alerts had no effect on any intermediate outcome measures, including ICU admissions and LOS.	Not provided	Because of the poor positive predictive value (PPV) of the alert system, repeated firings likely contributed to the well-documented phenomenon of alert fatigue. The isolated alert system trigger may have been insufficient to effect robust changes in ED workflow and clinical outcomes. High PPV is critical for successful deployment of clinical decision support interventions.	Low/ moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Berger et al., 2010[25]	Computer alert that automatically recognizes systemic inflammatory response syndrome (SIRS) criteria and recommends lactate testing	Quasi-experimental pre-post interventional design. All visits by ED patients 19+ were screened for SIRS; 5,796 subjects met SIRS criteria and had suspected infection during the study period.	Urban ED, a tertiary care level 1 trauma center with an established emergency medicine residency program and an annual adult volume of 70,000	Increase in lactate collection in the ED (5.2% before vs. 12.7% after alert implemented, absolute increase of 7.5%, 95% confidence interval [CI], 6.0% to 9.0%). Increase in lactate collection among hospitalized patients (15.3% vs. 34.2%, absolute increase of 18.9%, 95% CI, 15.0% to 22.8%); decrease in the proportion of abnormal lactate values (21.9% vs. 14.8%, absolute decrease of 7.6%, 95% CI, -15.8% to -0.6%). No significant difference in mortality (5.7% vs. 5.2%, absolute decrease of 0.5%, 95% CI, -1.6% to 2.6%, p=.6).	Not provided	The absolute number of patients with elevated lactate levels was higher in the alert phase of the study. However, the proportion of patients tested who had high lactate levels was lower in the alert phase. This reflects the trade-off between the ability to uncover occult severe sepsis through use of an alert to increase lactate testing as a screening tool versus the expense of testing a greater number of lactate levels among ED patients with sepsis. The mortality benefit of early goal-directed therapy in the treatment of patients with severe sepsis may make it worthwhile to cast a wide net and screen patients liberally to identify those who qualify for enrollment in the study.	Moderate	In Makam et al., 2015

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Croft et al., 2014[29]	System to provide surveillance, diagnosis, and protocolized management of surgical intensive care unit (SICU) sepsis	Prospective pre-post analysis. A paper system was used to manage 77 consecutive sepsis encounters in 65 patients. Then a computerized system was used to manage 132 consecutive sepsis encounters in 119 patients.	SICUs at UFHealth	Recognition of early sepsis tended to occur more using the computerized system (paper, 23%; computer, 35%). Hospital mortality rate for surgical ICU sepsis (paper, 20%; computer, 14%) was less with the computerized system.	Not provided	Not provided	Moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Hooper et al., 2012[14]	Listening application with automated identification, with physician notification of the systemic inflammatory response syndrome	A prospective, randomized, controlled, single-center study; 442 consecutive patients.	Medical ICU of an academic, tertiary care medical center	The median time from detection of modified SIRS by the listening application (LA) to an assessment by a physician was 0.9 (interquartile range .18 to 3.47) hours. The median time to new antibiotics was similar between the intervention and usual care groups, whether comparing among all patients (6.0h vs. 6.1h, p=0.95), patients with sepsis (5.3h vs. 5.1h, p=0.90), patients on antibiotics at enrollment (5.2h vs. 7.0h, p=0.27), or patients not on antibiotics at enrollment (5.2h vs. 5.1h, p=0.85). The amount of fluid administered following detection of symptoms matching modified SIRS criteria was similar between groups whether comparing all patients or only patients hypotensive at enrollment. Other clinical outcomes, including ICU length of stay, hospital length of stay, and mortality, were not shown to be different between patients in the intervention and control groups.	Not provided	Both ICU nurses and physicians are experienced in the early recognition and management of septic patients. The high rate of antibiotic administration prior to enrollment in our study suggests that infection had already been suspected, with treatment initiated, in many patients. Thus, as was the case with an electronic monitoring study in the emergency department, the biggest shortcoming of the LA may have been the failure to identify patients with modified SIRS before the treating physician did.	Low	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Jung et al., 2018[16]	Bedside clinical surveillance visualization system with a visual sepsis screen score (SSS)	Prospective observational. All SICU patients; 232 total patients, 37 with positive score.	Thirty-four-bed SICU in a single large academic medical center	SICU LOS was significantly shorter in the post-SSS group (19.1 +- 3.3 d vs. 7.6 +- 2.5 d, p<0.01) as was the total hospital LOS (29.6 +- 4.3 d vs. 10.8 +- 3.1 d, p<0.01). There was no significant difference in mortality between the two patient cohorts.	Not provided	Sequential organ failure assessment (SOFA) and quick SOFA use subjective data that require manual input into the electronic medical record. This manual input can be a source of delay in alert notification and identification of sepsis. Thus, the authors decided to incorporate the SSS, which is calculated based on automatically populated objective data, into the surveillance system. Nevertheless, physical examination and patient evaluation remain of utmost importance, and the authors stress that this alert system is a screening tool, and does not replace bedside evaluation and sound clinical judgment.	Moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Manaktala et al., 2017[12]	Real-time surveillance of electronic medical record (EMR) data and delivered alerts to nursing staff's mobile devices at the point of care	Single-center, quasi-experimental study, with pre- and post-test analysis; 778 patients.	Two hospital floors, containing two respiratory units and one general medicine unit, comprising a total 58 inpatient beds.	Authors observed a 43-53% decrease in sepsis mortality on hospital units where the sepsis initiative had been implemented. A 30.8% change was noted in the study screening units, with an observed readmission rate of 19.08% during the control period and 13.21% during the study period (p=0.057). Difference in LOS was not significant.	Not provided	The sepsis screening algorithms used in the study were based on standard IHI guidelines. However, these algorithms also contained additional specifications to adjust for comorbid medical conditions and medications. The authors believe that the complexity of the system's algorithms is responsible for its high sensitivity and high specificity, and is a key contributor to the impressive outcomes reported.	Low/ moderate	In Alberto et al., 2017

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
McCoy et al., 2017[15]	Machine learning-based sepsis prediction algorithm with alerts to physicians	Prospective pre-post quality improvement study. All patients over 18 in the included units; pre-implementation period consisting of 407 cases and two post-implementation periods consisting of 336 cases and 381 cases, as well as 204 cases in the post-implementation steady-state period.	One regional community hospital; 242 beds; ED, ICU, progressive care unit, and medical/ surgical patients	Relative to in the pre-implementation period, the post-implementation period sepsis-related in-hospital mortality rate decreased by 60.24%, the sepsis-related hospital length of stay decreased by 9.55%, and the sepsis-related 30-day readmission rate decreased by 50.14%. There were approximately $3.6 million of cost savings per year due to shorter stays. The average annual 2016 SEP-1 (sepsis CMS core measure) bundle compliance rate at the CAPE Regional Medical Center was 49%; however, this rate increased to 72.7% following the use of the MLA.	Not provided	Clinicians indicated that more patients required bedside assessment due to the use of the algorithm than the clinical staff could accommodate. The quality improvement team responded by adjusting the alert threshold to reduce the number of flagged patients, increasing specificity of the alert. Furthermore, per request from end users, the quality improvement team incorporated a 6-hour “snooze” feature to prevent reassessment by the algorithm of any given patient in a 6-hour period. Due to the distance between the ED and other hospital units, it was quicker to direct all ED alerts to a charge nurse or clinical coordinator rather than to a hospitalist. Accordingly, calls were streamed based on patient location.	Moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
McRee et al., 2014[26]	EMR sepsis surveillance	Retrospective review of pre- and post-implementation; patients admitted to an adult medical telemetry unit; 171 total sample. Seventy-five records were pre-EMR sepsis surveillance implementation and 96 were post implementation of the alert.	An adult medical telemetry unit in one hospital	Implementing EMR sepsis surveillance significantly improved home discharge (49.0% vs. 25.3%, p<.05) and reduced hospital mortality (1.0% vs. 9.3%, p<.05). Although there was no difference in the length of hospital stay for the whole group, patients in the surveillance group who triggered an alert on the EMR surveillance had a decreased length of hospital stay compared with those without an alert (7.2 +- 4.2 vs. 11.6 +- 9.4 days, p<.05).	Not provided	Not provided	Moderate	In Makam et al., 2015
Moorman et al., 2011[13]	Use of heart rate characteristics (HRC) monitoring to detect sepsis in infants in the neonatal ICU	Two-group, parallel, individually randomized controlled clinical trial of 3.003 very-low-birthweight infants.	Nine NICUs in the United States	There was a statistically significant and clinically important 22% relative reduction in mortality in infants whose HRC index was displayed (8.1 vs. 10.2%; p=0.04).	The tradeoff for lower mortality was 10% more blood cultures obtained, and 5% more days on antibiotics in the group with HRC monitor display.	Not provided	Low	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Narayanan et al., 2016[8]	Severe Sepsis Best Practice Alert (SS-BPA), automated, real-time, algorithm-based detection of severe sepsis or septic shock via the electronic medical record system	Single-center, before-and-after observational study. Adult patients in the ED; 214 patients.	Single academic medical center	Time to antibiotics was significantly reduced in the SS-BPA cohort (29 vs. 61.5 minutes, pb .001). In addition, a higher proportion of patients received antibiotics within 60 minutes (76.7 vs. 48.6%; pb .001). On multivariable analysis, in-hospital mortality was not significantly reduced in the intervention group (odds ratio, 0.64; 95% CI, 0.26 to 1.57). Multivariable analysis of LOS indicated a significant reduction among patients in the SS-BPA cohort.	Not provided	Not provided	Low/ moderate	None
Nelson et al., 2011[27]	An automated, real-time electronic medical record query and caregiver notification system	Before-and-after, prospective study with consecutive enrollment; 398 patients activated sepsis notification system.	Academic ED with 68,000 annual visits	Only blood culture testing was performed significantly faster in the presence of decision support (median time to culture before intervention 86 minutes, IQR 31, 296 minutes; median time to culture after intervention 81 minutes, IQR 37, 245 minutes; p.032 by Cox proportional hazards modeling). The predominant shortcoming of the strategy was failing to detect severely septic cases before caregivers. The other two endpoints improved, but not in a statistically significant way (blood lactate OR 1.7, 95% CI, 0.9 to 3.2; administering antibiotics OR 2.8, 95% CI, 0.9 to 8.6).	Not provided	That patients require time to fully manifest their illness in the ED is not surprising, although the magnitude of this interval—with 50% requiring more than 2½ hours to meet severe sepsis criteria—was unexpected. Given that routine clinical practice in the department detected the condition more quickly in about half of cases, future algorithms should focus on identifying the subtler cues that prompt experienced caregivers before much of the formal sepsis-defining data are available.	Moderate	In Makam et al., 2015

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Sawyer et al., 2011[28]	Real-time computerized sepsis alert	Prospective, observational, pilot study. Patients identified by the sepsis screen while admitted to a medicine ward were included in the study. A total of 300 consecutive patients were identified, comprising the nonintervention group (n=200) and the intervention group (n=100).	Six medicine wards in Barnes-Jewish Hospital, a 1,250-bed academic medical center	Within 12 hours of the sepsis alert, interventions by the treating physicians were assessed, including new or escalated antibiotics, intravenous fluid administration, oxygen therapy, vasopressors, and diagnostic tests. Within 12 hours of the sepsis alert, 70.8% of patients in the intervention group had received ≥1 intervention vs. 55.8% in the nonintervention group (p=.018). Antibiotic escalation, intravenous fluid administration, oxygen therapy, and diagnostic tests were all increased in the intervention group.	Not provided	Not provided	Low	In Alberto et al., 2017
Shimabukuro et al., 2017[9]	Machine learning-based severe sepsis prediction system with alerts	Randomized controlled clinical trial. Adult patients (18+) admitted to participating units were eligible for this factorial, open-label study; it had 75 patients in the control and 67 patients in the experimental group.	Two medical-surgical intensive care units; 32 total unit beds	No adverse events were reported during this trial. Patients in the experimental group received antibiotics an average of 2.76 hours earlier than patients in the control group and had blood cultures drawn an average of 2.79 hours earlier than patients in the control group. Average length of stay decreased from 13.0 days in the control group to 10.3 days in the experimental group (p=0.042). In-hospital mortality decreased by 12.4 percentage points when using the MLA (p=0.018), a relative reduction of 58.0%.	Not provided	With extra time for intervention in the experimental group, patients might not have ultimately progressed to septic shock; this may have produced different prevalences in the experimental (1.5%) and control (5.3%) groups.	Low	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Umscheid et al., 2015[17]	Early warning and response system for sepsis	A prospective pre/post study with multivariable adjustment–measured impact. Adult non-ICU patients admitted to acute inpatient units. All inpatients on non-critical care services; 595/15,567 triggered alert in pre period; 545/15,526 in the post period.	Noncritical care units in an urban academic healthcare system; 1,500 beds	In unadjusted and adjusted analyses, ordering of antibiotics, intravenous fluid boluses, lactate, and blood cultures within 3 hours of the trigger increased significantly, as did ordering of blood products, chest radiographs, and cardiac monitoring within 6 hours of the trigger. Hospital and ICU LOS were similar in the pre and post periods. There was no difference in the proportion of patients transferred to the ICU following the alert. All mortality measures were lower in the post period, but no differences reached statistical significance.	Not provided	Not provided	Low/ moderate	In Alberto et al., 2017

Table B.4: Sepsis Recognition, Sepsis Patient Monitoring Systems—Systematic Reviews

Note: Full references are available in the Section 3.2 reference list.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings
Alberto et al., 2017[1]	Sepsis screening tools (electronic and paper)	General hospitalized patients	Electronic tools can capture and recognize abnormal variables and activate an alert in real time. However, accuracy of these tools was inconsistent across studies, with only one demonstrating high specificity and sensitivity. Paper-based, nurse-led screening tools appear to be more sensitive in the identification of septic patients than electronic tools but were studied only in small samples and particular populations. The process of care measures appears to be enhanced with both types of screening tools; however, demonstrating improved outcomes is more challenging. High levels of accuracy were reported in the studies and reproduced for the purpose of this review, with the screening tools used in three studies. However, two studies had small sample sizes, with accuracy tests calculated on random numbers of negatively screened participants. The remaining study reported control data collected retrospectively outside of the study period. Lower sensitivity and positive predictive values were reproduced and reported in the larger studies, where arguably more robust designs were used. The more complex screening tools appear to be more effective in ruling out patients with sepsis, but they performed poorly in correctly identifying septic patients. Nurses were always the first responders to sepsis alerts, although sometimes the rapid response coordinator and the covering medical provider were also alerted at this time. Overall, the frequency and time to use of diagnostic measures (lactate orders, blood cultures) improved significantly with screening tool use, whereas results pertaining to treatment (fluids and vasopressors) were inconsistent across studies, with some but not all demonstrating improvement. One study reported a significant decrease in mortality and risk of death. Other studies showed positive trends in hospital mortality, hospital	The technology and the staff available (e.g., nurse to patient ratio and the supporting steering committees) played a pivotal role in developing a strategy for sepsis screening in these studies. Reviewed screening tools have different levels of sensitivity and specificity that need to be considered prior to identifying an instrument for implementation; this applies not only to the variables incorporated in the instrument but also to the medium that is used, specifically either electronic or paper-based. If technology were available, electronic tools might be preferred over paper-based tools. However, due to the resource-limited settings worldwide, implementation of paper-based, nurse-driven tools could make a difference in sepsis care. Frequency of screening practice and review periods of variables to screen may depend on patient characteristics, staffing, and available technology.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings
			and intensive care unit (ICU) length of stay, and ICU transfer.	
Despins, 2017[6]	Automated detection of sepsis using electronic medical record data	Emergency department (ED) and hospitalized neonatal, pediatric, or adult patients. All the studies except one took place at academic medical centers.	Care team alerts did not consistently lead to earlier interventions. Earlier interventions did not consistently translate to improved patient outcomes. Performance measures were inconsistent. Three studies noted decreased time to sepsis-related interventions (Nelson et al., 2011; Sawyer et al., 2011; Umscheid et al., 2015). Conversely, Hooper et al. (2012) found no difference in time to initiation of sepsis-related therapies. One study noted improved patient outcomes. McRee et al. (2014) observed a shorter hospital length of stay, more patients discharged to home, and fewer deaths. However, other researchers reported no significant effect of sepsis alerts on patient outcomes (Sawyer et al., 2011; Umscheid et al., 2015). Sepsis alerts prompting increased initiation of interventions did not significantly impact patient outcomes, such as ICU transfer rates, ICU and hospital length of stay, and mortality rates.	While automated approaches enable earlier recognition and therapy initiation, the risk of alert fatigue increases if these approaches have low to moderate positive predictive values and thus high false discovery rates. Microbiology culture studies provide results 24–72 hours after obtaining the sample, making them impractical in screening for early sepsis. More research is needed to determine the optimal variables to include in a detection algorithm, and the optimal performance indexes that minimize the risk of recognition delay and alert fatigue. It is possible that research should also focus on developing reliable automated early detection of general clinical deterioration that triggers secondary detection queries, which would provide the care team with a list of possible syndromes, including sepsis. Those developing sepsis detection algorithms should consider not only sensitivity and prediction indexes to minimize alert fatigue but also the timing of data availability to select algorithm components that optimize early sepsis detection. Likewise, sepsis alert development needs to incorporate knowledge of the workflow and care delivery process for each point-of-care discipline (e.g., physician, nurse). Knowledge pertaining to current alert notification processes and clinicians' EMR interaction is important to identify both the best discipline to receive the sepsis alert and the best means of delivering it.
Makam et al., 2015[7]	Automated electronic sepsis alert systems	ED or hospital	Diagnostic accuracy varied greatly, with positive predictive value (PPV) ranging from 20.5 to 53.8%; negative predictive value (NPV) 76.5 to 99.7%; positive likelihood ratio (LR+) 1.2 to 145.8; and negative likelihood ratio (LR-) 0.06 to 0.86. The alert system (Nelson et al.) that was triggered by a combination of SIRS criteria and hypotension (PPV=53.8%; LR+ =145.8; NPV =99.7%; LR- =0.37) outperformed the alert system (Meurer et al.) that was triggered by SIRS criteria alone. There was modest evidence for improvement in process measures (i.e., antibiotic escalation), but only among patients in non-	The fact that sepsis alert systems improve intermediate process measures among ward and ED patients but not ICU patients likely reflects differences in both the patients and the clinical settings. First, patients in the ICU may already be prescribed broad-spectrum antibiotics, be aggressively fluid-resuscitated, and have had other diagnostic testing performed before the activation of a sepsis alert, so one would be less likely to see an improvement in the rates of process measures assessing initiation or escalation of therapy compared with among patients treated on the wards or in the ED. The apparent lack of benefit of these systems in the ICU may merely

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings
			critical care settings (medical ward and ED vs. medical ICU). Neither of the two high-quality studies that included a contemporaneous control found evidence for improving inpatient mortality or hospital and ICU length of stay. Minimal data were reported on potential harms due to false-positive alerts. Berger et al. showed an overall increase in the number of lactate tests performed but a decrease in the proportion of abnormal lactate values (21.9% vs. 14.8%, absolute decrease of 7.6%, 95% confidence interval [CI], -15.8% to -0.6%), suggesting potential over-testing in patients at low risk for septic shock. Automated sepsis alerts derived from electronic health data may improve care processes but tend to have poor positive predictive value and do not improve mortality or length of stay.	represent a "ceiling" effect. Second, nurses and physicians are already vigilantly monitoring patients in the ICU for signs of clinical deterioration, so additional alert systems may be redundant. Third, patients in the ICU are connected to standard bedside monitors that continuously monitor for the presence of abnormal vital signs. An additional sepsis alert system triggered by SIRS criteria alone may be superfluous to the existing infrastructure. Fourth, most patients in the ICU will trigger the sepsis alert system, so there likely is a high noise-to-signal ratio with resultant alert fatigue. Little data exist to suggest the optimal design of sepsis alerts, or the frequency with which they are appropriately acted upon or dismissed. In addition, the authors found little data to support whether effectiveness of alert systems differed based on whether clinical decision support was included with the alert itself (e.g., direct prompting with specific clinical management recommendations), or the configuration of the alert (e.g., interruptive alert or informational). Most of the studies reviewed employed alerts primarily targeting physicians; little evidence was found for systems that also alerted other providers (e.g., nurses or rapid response teams).
Warttig et al., 2018[5]	Automated systems for the early detection of sepsis (randomized trials only)	Med/surg ICU; 1,199 participants in total	Three studies were included in this review .Overall there were no significant differences in time to start of antimicrobial therapy (such as antimicrobial and antifungal treatments, very-low-quality evidence); length of stay in the intensive care setting (very-low-quality evidence); or mortality at 14 days, 28 days, or discharge (very-low-quality evidence), when automated monitoring systems were compared with standard care. Very-low-quality evidence was available on failed detection of sepsis, and data reporting was too unclear to enable analysis of this in a meaningful way. Other outcomes that the authors wanted to assess were not reported in any of the studies, such as time to initiation of fluid resuscitation (the process of increasing the amount of fluids in the body), mortality at 30 days, and quality of life.	Not provided

Table B.5: Sepsis Recognition, Multicomponent Sepsis Interventions—Systematic Reviews

Note: Full references are located in the Section 3.3 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Beardsley et al., 2016[1]	(1) Nurse-conducted screening for sepsis using a standard assessment instrument; (2) pager alerts notifying rapid-response, pharmacy, and other personnel of cases of suspected sepsis; (3) activation of an electronic order set including guideline-based antibiotic therapy recommendations based on local pathogen patterns; and (4) a protocol allowing pharmacists to select an antibiotic regimen if providers are busy with other patient care duties.	Prospective pre–post study. Sample size unknown.	Tertiary academic medical center with 885 beds and over 180 adult intensive care unit (ICU) beds	After the Code Sepsis initiative was implemented, the mean time from rapid response nurse arrival on the unit to antibiotic administration decreased from 396 minutes to 51 minutes for patients in noncritical care units. The time from a positive sepsis screen to antibiotic administration also decreased in the ICUs as the Code Sepsis rollout was extended to the various critical care units. The institution's sepsis-related mortality index dropped from a mean value of 1.65 for the five quarters prior to Code Sepsis implementation to 0.8 for the period April 2013–March 2014.	The Code Sepsis program enhanced cooperation among prescribers, pharmacy staff, and nursing personnel. Pharmacy personnel worked with representatives of the medical and nursing staffs to analyze all aspects of the medication-use process relating to antibiotics for sepsis. Processes were then improved, and antibiotic turn-around time decreased to a point that exceeded the expectations of most program participants. An important aspect of the Code Sepsis initiative was the implementation of a protocol that allows pharmacists to choose sepsis antibiotics. Allowing pharmacists to take on this responsibility freed up physicians to focus on other critical aspects of the patient's care without delaying the administration of antimicrobial therapy. It appears that this type of protocol is unique, as the authors were unaware of the existence of similar protocols at other institutions.	Moderate/ high	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Gatewood et al., 2015[2]	The three-tiered intervention consisted of (1) a nurse-driven screening tool and management protocol to identify and initiate early treatment of patients with sepsis; (2) a computer-assisted screening algorithm that generated a "Sepsis Alert" pop-up screen in the electronic medical record for treating clinical healthcare providers; and (3) automated suggested sepsis-specific order sets for initial workup and resuscitation, antibiotic selection, and goal-directed therapy	A before and after retrospective cohort study. All patients admitted to the emergency department (ED); 624 patients.	ED in a 450-bed academic hospital managing more than 18 000 inpatient admissions each year. A quaternary care facility.	Overall bundle compliance increased by 154%, from 28% at baseline to 71% in the last quarter of the study (p<0.001). Institution of nurse triage screening tool, nurse-initiated sepsis order set, and provider order sets increased total Surviving Sepsis Campaign (SSC) bundle compliance to 50%. Introduction of the automated sepsis icon and EMR alerts resulted in further performance improvement to 70% compliance. Bundle antibiotic and intravenous fluid compliance all increased significantly after launch of the sepsis initiative: bundle and intravenous fluid compliance increased by 74% and 54%, respectively (p<0.001). The mortality rate for patients in the ED admitted with sepsis was 13.3% before implementation and fell to 11.1% after implementation (p=0.230); mortality in the last two quarters of the study was 9.3% (p=0.107).	Not provided	Low/ moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Judd et al., 2014[3]	An electronic sepsis screening tool administered once per shift and a fast antibiotics program.	A retrospective observational study of consecutive adults with sepsis.Baseline data were collected for 181 patients; the intervention group included 216 patients.	Tertiary medical center with 433 beds.	After implementing the First-Dose STAT policy, average time from antibiotic order entry to administration was reduced from 154 ± 134 minutes to 84 ± 55 minutes by the end of the phase 1 intervention period (p<0.001). Average time from order entry to administration decreased to 57 ± 37 minutes by week 15 (p<0.001). The percentage of patients who received a first-dose intravenous (IV) antibiotic within 60 minutes increased from 25.6% to 54.3%. Similarly, the percentage of patients who received a first-dose IV antibiotic within 90 minutes increased from 36.6% to 80% by the end of week 15. Nonsignificant decreases in overall length of stay (LOS) (7.43 ± 5.68 days vs. 6.77 ± 5.0 days; p=0.138) and in-hospital mortality (13.8% vs. 8.8%; p=0.113) were observed in patients with sepsis Diagnosis-related groups (DRGs). Early recognition and treatment contributed to significant reductions in ICU LOS (5.85 ± 4.38 days vs 4.21 ± 3.64 days; p=0.003) and total cost per case ($14,378 vs. $12,311; p=0.033).	The average time from order entry to medication delivery remained low throughout the 3-month intervention period despite a significant improvement in the overall time to administration. These data suggest that efforts to improve antibiotic administration times should focus on the time from delivery to nurse administration. During the phase 1 intervention period, scheduled completion of an electronic sepsis screening tool aided in converting the sepsis population to a lower severity of illness based on the change in sepsis-related DRG coding assignments.	Low/ moderate	Bundle with fast antibiotics program.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
MacRedmond et al., 2010[4]	Manual management algorithm including early goal-directed therapy, a computerized physician order entry set for suspected sepsis, introduction of invasive hemodynamic monitoring and antibiotics stocked in the ED, and an extensive education campaign involving ED nurses and physicians.	Prospective pre–post study. Patients in the ED who had sepsis; 74 patients total, 37 pre and 37 post.	ED in a tertiary care teaching hospital of 500 beds, a "closed" medical-surgical ICU of 15 beds staffed by dedicated intensivists, and an ED that serves >60 000 patients per year.	Significant improvements were observed in mean time to initiation of early goal-directed therapy (3.2 vs. 10.4 h, p=0.001) and to achievement of resuscitation goals (10.4 vs. 30.1 h, p=0.007). There was a trend toward more rapid administration of antibiotics (1.4 vs. 2.7 h, p=0.06). This was associated with a decrease in crude hospital mortality rate from 51.4% to 27.0% (absolute risk reduction=24%, 95% CI, 3% to 47%). Improvements were sustained in the followup audit at 16 months.	After the education sessions, the researchers found significant improvement in the early identification of patients who had potential sepsis; they believe that increased awareness of the time-critical nature of sepsis treatment among ED nurses and physicians was key to the successful implementation of the protocol. The researchers did not measure compliance with specific elements.	Moderate	None
Mittal et al., 2018[5]	Increased the number of nurses, provided space for triage, and created a triage tool for recognizing patients with severe sepsis, which took less than a minute to complete.	Prospective pre–post observational. Children age 2 months to 17 years of age with severe sepsis were eligible for enrollment; 41 pediatric patients.	ED in a tertiary care hospital.	The median interquartile range time to administration of antibiotics from the time of admission decreased significantly, from 50 minutes (18, 65) to 20 minutes (15, 20) (p=0.02). Duration of hospital stay was longer in phase 1 than in phase 2 (12 days vs. 6 days). However, the difference was not statistically significant (p=0.1).	The major hurdles causing delay in antibiotic administration in phase 1 of the study were overcrowding, high patient load, difficult IV access, and atypical presentation leading to delayed recognition of severe sepsis The shortage of nurses in phase 1 was a hurdle in early initiation of antibiotics in the ED.	Moderate	None

Appendix C. Sepsis Recognition Search Terms

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review	Screening Tools	(((MH Sepsis/DI/PC) OR (AB "Blood Poisoning" OR "Poisoning, Blood" OR "Pyaemia" OR "Pyemia" OR "Pyohemia" OR "Septicemia" OR "Severe Sepsis" OR "Septic Shock" OR ("Systemic Inflammatory Response Syndrome" AND Infection)) AND ((MH "Mass Screening") OR (AB "Mass Screening" OR "Decision Support Techniques" OR "Screening" OR "Screening tool" OR "Screening algorithm" OR "Algorithm" OR "Triage Tool" OR "Early Warning Score" OR "Early Detection" OR "Early Alert" OR "Pre-Hospital Screening" OR "Risk Assessment")))	(((MH Sepsis/DI/PC OR "Shock, Septic" OR "Systemic Inflammatory Response Syndrome") OR (AB "Blood Poisoning" OR "Poisoning, Blood" OR "Pyaemia" OR "Pyemia" OR "Pyohemia" OR "Septicemia" OR "Severe Sepsis" OR "Septic Shock" OR ("Systemic Inflammatory Response Syndrome" AND Infection)) AND ((MH "Mass Screening" OR "Decision Support Techniques") OR (AB "Mass Screening" OR "Decision Support Techniques" OR "Screening" OR "Screening tool" OR "Screening algorithm" OR "Algorithm" OR "Triage Tool" OR "Early Warning Score" OR "Early Detection" OR "Early Alert" OR "Pre-Hospital Screening" OR "Risk Assessment")))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review • Systematic Review			
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III	Surveillance	(((MH (Sepsis/DI/PC) OR (AB "Blood Poisoning" OR "Poisoning, Blood" OR "Pyaemia" OR "Pyemia" OR "Pyohemia" OR "Septicemia" OR "Severe Sepsis" OR "Septic Shock" OR ("Systemic Inflammatory Response Syndrome" AND Infection))) AND (AB "Surveillance" OR "Monitoring and Surveillance" OR	(((MH (Sepsis/DI/PC) OR (AB "Blood Poisoning" OR "Poisoning, Blood" OR "Pyaemia" OR "Pyemia" OR "Pyohemia" OR "Septicemia" OR "Severe Sepsis" OR "Septic Shock" OR ("Systemic Inflammatory Response Syndrome" AND Infection))) AND (AB "Surveillance" OR "Monitoring and Surveillance" OR

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis		"Epidemiologic Surveillance" OR "Infectious Diseases Surveillance" OR "Ongoing Surveillance" OR Monitoring" OR "Routine Screening" OR "Regular Screening"))	"Epidemiologic Surveillance" OR "Infectious Diseases Surveillance" OR "Ongoing Surveillance" OR Monitoring" OR "Routine Screening" OR "Regular Screening"))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Practice Guidelines • Randomized Controlled Trial • Research Review • Systematic Review			
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study	Performance Review	(((MH Sepsis/DI/PC) OR (AB "Blood Poisoning" OR "Poisoning, Blood" OR "Pyaemia" OR "Pyemia" OR "Pyohemia" OR "Septicemia" OR "Severe Sepsis" OR "Septic Shock" OR ("Systemic Inflammatory Response Syndrome" AND Infection))) AND (AB "Performance Review" OR "Performance Feedback" OR "Root Cause Analysis" OR "Peer Review" OR "Audit" OR "Audit and Feedback"))	(((MH Sepsis/DI/PC) OR (AB "Blood Poisoning" OR "Poisoning, Blood" OR "Pyaemia" OR "Pyemia" OR "Pyohemia" OR "Septicemia" OR "Severe Sepsis" OR "Septic Shock" OR ("Systemic Inflammatory Response Syndrome" AND Infection))) AND (AB "Performance Review" OR "Performance Feedback" OR "Root Cause Analysis" OR "Peer Review" OR "Audit" OR "Audit and Feedback"))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review • Systematic Review			
Search 2008-Present, English Only	Antibiotics	(((MH Sepsis/DI/PC) OR (AB "Blood Poisoning" OR "Poisoning, Blood" OR "Pyaemia" OR "Pyemia"	(((MH Sepsis/DI/PC) OR (AB "Blood Poisoning" OR "Poisoning, Blood" OR "Pyaemia" OR "Pyemia" OR "Pyohemia" OR

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies		OR "Pyohemia" OR "Septicemia" OR "Severe Sepsis" OR "Septic Shock" OR ("Systemic Inflammatory Response Syndrome" AND Infection))) AND (AB "Readily Available Antibiotics" OR "Accessible Antibiotic" OR "Antibiotic Access" OR "Available Antibiotic" OR "Antibiotic Availability"))	"Septicemia" OR "Severe Sepsis" OR "Septic Shock" OR ("Systemic Inflammatory Response Syndrome" AND Infection))) AND AB ("Readily Available Antibiotics" OR "Accessible Antibiotic" OR "Antibiotic Access" OR "Available Antibiotic" OR "Antibiotic Availability"))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review • Systematic Review			
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial	Performance Improvement	(((MH Sepsis/DI/PC) OR (AB "Blood Poisoning" OR "Poisoning, Blood" OR "Pyaemia" OR "Pyemia" OR "Pyohemia" OR "Septicemia" OR "Severe Sepsis" OR "Septic Shock" OR ("Systemic Inflammatory Response Syndrome" AND Infection))) AND (AB "Performance Improvement Programs" OR "Performance Improvement" OR "Performance Enhancement" OR	(((MH Sepsis/DI/PC) OR (AB "Blood Poisoning" OR "Poisoning, Blood" OR "Pyaemia" OR "Pyemia" OR "Pyohemia" OR "Septicemia" OR "Severe Sepsis" OR "Septic Shock" OR ("Systemic Inflammatory Response Syndrome" AND Infection))) AND (AB "Performance Improvement Programs" OR "Performance Improvement" OR "Performance Enhancement" OR "Quality Improvement" OR

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review		"Quality Improvement" OR "Compliance" OR "Compliance Improvement" OR "Guideline Compliance"))	"Compliance" OR "Compliance Improvement" OR "Guideline Compliance"))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Systematic Review			
Search Limiters: 2008-Present Language: English Only Limit to Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies	Clinical Decision	(((MH Sepsis/DI/PC) OR (AB "Blood Poisoning" OR "Poisoning, Blood" OR "Pyaemia" OR "Pyemia" OR "Pyohemia" OR "Septicemia" OR "Severe Sepsis" OR "Septic Shock" OR ("Systemic Inflammatory Response Syndrome" AND Infection))) AND ((MH "Decision Support Systems, Clinical" OR "Clinical Decision Making") OR (AB "Clinical Decision Support" OR "Medical Decision Making" OR "Decision Support Techniques" OR "Medical Order Entry Systems" OR "Computerized Physician Order Entry" OR "Alert Systems, Medication" OR "CPOE" OR "Computerized Physician Order Entry" OR "Computerized Physician Order Entry System" OR "Computerized Provider Order Entry" OR "Computerized Provider Order Entry System" OR "Medication Alert	(((MH Sepsis/DI/PC) OR (AB "Blood Poisoning" OR "Poisoning, Blood" OR "Pyaemia" OR "Pyemia" OR "Pyohemia" OR "Septicemia" OR "Severe Sepsis" OR "Septic Shock" OR ("Systemic Inflammatory Response Syndrome" AND Infection))) AND ((MH "Decision Support Systems, Clinical" OR "Clinical Decision Making") OR (AB "Clinical Decision Support" OR "Medical Decision Making" OR "Decision Support Techniques" OR "Medical Order Entry Systems" OR "Computerized Physician Order Entry" OR "Alert Systems, Medication" OR "CPOE" OR "Computerized Physician Order Entry" OR "Computerized Physician Order Entry System" OR "Computerized Provider Order Entry" OR "Computerized Provider Order Entry System" OR "Medication Alert

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
		Systems" OR "Order Entry Systems, Medical")))	Systems" OR "Order Entry Systems, Medical")))