ABSTRACT: Sepsis is a major cause of morbidity and mortality in children. While adverse outcomes can be reduced through prompt initiation of sepsis protocols including fluid resuscitation and antibiotics, provision of these therapies relies on clinician recognition of sepsis. Recognition is challenging in children because early signs of shock such as tachycardia and tachypnea have low specificity while hypotension often does not occur until late in the clinical course. This narrative review highlights the important context that has led to the rapid growth of pediatric sepsis screening in the United States. In this review, we (1) describe different screening tools used in US emergency department, inpatient, and intensive care unit settings; (2) highlight details of the design, implementation, and evaluation of specific tools; (3) review the available data on the process of integrating sepsis screening into an overall sepsis quality improvement program and on the effect of these screening tools on patient outcomes; (4) discuss potential harms of sepsis screening including alarm fatigue; and (5) highlight several future directions in sepsis screening, such as novel tools that incorporate artificial intelligence and machine learning methods to augment sepsis identification with the ultimate goal of precision-based approaches to sepsis recognition and treatment.

Pediatric Research (2022) 91:351–358; https://doi.org/10.1038/s41390-021-01708-y

IMPACT:
- This narrative review highlights the context that has led to the rapid growth of pediatric sepsis screening nationally.
- Screening tools used in US emergency department, inpatient, and intensive care unit settings are described in terms of their design, implementation, and clinical performance.
- Limitations and potential harms of these tools are highlighted, as well as future directions that may lead to a more precision-based approach to sepsis recognition and treatment.

INTRODUCTION
Sepsis, a life-threatening response to infection with organ dysfunction, is a major cause of morbidity and mortality in children. While adverse outcomes can be reduced through prompt initiation of sepsis protocols including fluid resuscitation and antibiotics, provision of these therapies relies on clinician recognition of sepsis. This recognition is particularly challenging in children due to the low specificity of abnormal vital signs such as fever, tachycardia, and tachypnea for identifying children in the early stages of septic shock.

Unlike existing algorithms that risk-stratify children upon likelihood of bacterial infection or general clinical deterioration, sepsis screening tools specifically focus on differentiating the small number of patients who have or will develop severe sepsis or septic shock from the many children with abnormal vital signs due to uncomplicated infection without associated organ dysfunction. Existing tools vary significantly in the framework they use for sepsis identification, how they interface with clinicians and the electronic health record (EHR), and how they are implemented into clinical workflows. An ideal sepsis screening tool should detect sepsis accurately, with sufficient sensitivity to prevent missed cases but a high enough positive predictive value (PPV) to minimize false positive alerts and the ensuing risk of alarm fatigue. It should also provide an alert early enough in the patient’s course to add value to the clinical team, rather than identifying a patient already suspected by the clinician to have sepsis. Finally, it should be easy to use, have minimal inter-rater variability, and incorporate seamlessly into clinical workflows.

This manuscript highlights the important context that has led to the rapid growth of pediatric sepsis screening nationally. In this narrative review, we (1) describe different screening tools used in US emergency department (ED), inpatient, and intensive care unit (ICU) settings; (2) highlight details of design, implementation, and evaluation of specific tools; (3) review the available data on the process of integrating sepsis screening into an overall sepsis quality improvement (QI) program and on the effect of these screening tools on patient outcomes; (4) discuss potential harms of sepsis screening including alarm fatigue; and (5) explore several future directions in sepsis screening. These include developing novel tools that incorporate artificial intelligence/machine learning methods to augment sepsis identification, with the ultimate goal of a precision-based approach to sepsis recognition and treatment.

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Published online: 20 August 2021
Received: 12 April 2021 Revised: 28 July 2021 Accepted: 4 August 2021

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GUIDELINES AND LEGISLATION
While efforts at systematic screening of children for sepsis date back more than a decade, much of the recent impetus for screening can be traced to the case of Rory Staunton, a 12-year-old New York boy who died of septic shock caused by Group A Streptococcus in 2012.15 Rory’s death received considerable publicity nationally and led his family to launch an advocacy campaign to increase awareness of sepsis and improve sepsis recognition and treatment in pediatric care. The culmination of this effort was the 2013 passage by the New York state legislature of Rory’s Regulations, which required all New York hospitals to implement evidence-based protocols to facilitate early recognition of sepsis through screening tools, identify individuals who qualify for sepsis care, and ensure they receive a care bundle consisting of fluid resuscitation, intravenous (IV) antibiotics, and a blood culture sample.16

Due in part to the success of Rory’s Regulations,6 other states enacted similar protocols. In 2016, Illinois passed Gabby’s law, named after 5-year-old Gabrielle Calbo who died of sepsis in 2012. The law requires Illinois hospitals to implement evidence-based guidelines to facilitate rapid recognition and treatment of adults and children with sepsis, train staff on sepsis treatment and identification, and report sepsis data.17 Several other states are considering similar legislation or have sponsored QI initiatives aimed at improving sepsis identification and treatment within their hospitals.18 Most recently, federal legislation based on Gabby’s law has been proposed that would mandate evidence-based sepsis identification and treatment protocols for all hospitals in the United States as a condition of Medicare enrollment.19

Along with legislative mandates, pediatric sepsis screening has been buoyed by the recommendations of professional organizations. In 2017, the American College of Critical Care Medicine recommended routine pediatric sepsis screening as part of its Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock.20 Specifically the national practice guideline recommends that each institution implement sepsis care bundles for children that include a “recognition bundle containing a trigger tool for rapid identification of patients with suspected septic shock at that institution.” This was followed in 2020 by the recommendation of the Surviving Sepsis Campaign that hospitals implement “systematic screening for timely recognition of septic shock and other sepsis-associated organ dysfunction” in acutely unwell children, though this recommendation was noted to be weak and based on a low quality of evidence.21

TYPES OF SCREENING
Given this pressure from regulators, legislatures, and professional societies, as well as increasing recognition of the value of sepsis QI programs,22,23 sepsis screening has proliferated in US pediatric acute care settings in the past decade. However, the tools employed vary significantly in terms of their parameters and form, with little consensus as to which tool best identifies children at high risk of septic shock while also minimizing false positive alerts. Additionally, reports of these tools in the medical literature have used different criterion standards for sepsis, making direct comparison of their performance difficult. Here we review the differences in sepsis screening tools that have been reported in the literature.

Framework for sepsis identification
While all sepsis screening tools rely on combinations of abnormal vital signs and physical exam findings in the presence of suspected infection, there are substantial differences between them depending on the framework they utilize for sepsis prediction and/or identification. Tools such as the Pediatric Septic Shock Collaborative’s (PSSC) sepsis trigger tool rely on abnormal vital signs and physical exam findings as well as the presence of medical conditions that confer increased risk of sepsis and in so doing aim to identify patients prior to the onset of septic shock or severe sepsis.24 Other screening tools utilize a framework for defining sepsis, such as the systemic inflammatory response syndrome (SIRS)/sepsis/severe sepsis definitions set out by the International Pediatric Sepsis Consensus Conference (Table 1).25 Some researchers created homegrown models of sepsis prediction, then used those models to create de novo screening tools.12,26 As a result, the various screening tools differ not just in which parameters they utilize but how they define the thresholds at which those parameters signify increased sepsis risk.

Form of tool
Even tools that share frameworks of sepsis identification can vary significantly in their form, how they are utilized clinically, and how they are incorporated into the EHR. In so doing, identical sets of criteria can actually have different clinical performance. The earliest screening tools, such as the PSSC trigger tool, were paper forms designed to be completed at the time of ED triage.24 After such tools are embedded in practice, the next step is usually incorporation into the EHR in electronic form.27 In addition to better integration into electronic documentation, EHR-embedded tools facilitate repeated screening, rather than only at the time of triage. Such repeat assessments can be triggered by clinician concern or by the patient meeting some other objective criteria, such as new onset of fever or a higher Pediatric Early Warning Score.11 Leveraging the learning health system, more recent automated tools continuously incorporate new data from the patient’s EHR and can therefore alert at any time in an encounter that pre-specified criteria are met.12,14

Population screened
A final difference in available screening tools is in the population screened. Some tools are utilized as part of a broad screening strategy for all patients. Other tools are designed for a more targeted approach—for instance, only those children with suspected infection or only those who have abnormal vital signs or other concerning clinical findings. The more targeted approaches have the advantage of fewer false positive alerts (since sicker patient groups will have a higher sepsis prevalence).

| SIRS       | Abnormal values for at least two of the following, one of which must be temperature or leukocyte count |
|------------|---------------------------------------------------------------------------------------------------|
| • Temperature                                |                                                                                           |
| • Leukocyte count                             |                                                                                           |
| • Heart rate                                  |                                                                                           |
| • Respiratory rate                            |                                                                                           |
| Sepsis     | SIRS in the presence of a suspected or proven infection                                         |
| Severe sepsis | Sepsis plus cardiovascular organ dysfunction and/or acute respiratory distress syndrome and/or two or more organ dysfunctions |
| Septic shock       | Sepsis and cardiovascular organ dysfunction                                                   |
but at the risk of missing sepsis cases in patients in whom the provider has not already identified a higher severity of illness.

**AVAILABLE SCREENING TOOLS**

**ED-based tools**

While sepsis screening tools are utilized in clinical practice settings as varied as ambulatory clinics and intensive care, the majority of reports of sepsis screening in the medical literature originate in the ED.

The first report of systemic screening of children in the ED for sepsis came from Texas Children’s Hospital in 2012 in the form of an electronic, triage-based ‘Best Practice Alert (BPA).’ The BPA was designed to calculate a heart rate corrected for pyrexia by adjusting the measured heart rate down 5 beats per minute for every 1 °C in temperature elevation and comparing that to age-appropriate normal values. When the heart rate was outside of the normal range, the BPA displayed a prompt alert for the triage nurse to ask about medical conditions that rendered a higher risk of sepsis. If positive, or if the child was ill-appearing, the patient would be transferred to a room for immediate evaluation and resuscitation as needed. While the tool was designed for use at triage, it could be repeated at any time during the ED stay. The tool proved to be sensitive in the prediction of sepsis (84.6%) and specific (91.1%), reflecting low sepsis prevalence due to having screened all ED patients, not just those with fever or suspected infection. To improve on the PPV of the screening algorithm, the authors created tiered alerts of increasing severity (termed SIRS, sepsis, and severe sepsis). As was done in Philadelphia, for patients with a SIRS or sepsis alert, the nurse caring for the patient was prompted to fill out a secondary screening form that queried for the presence of suspected infection, altered mental status, or altered pulses/perfusion (Fig. 3b). A patient was only considered to have a positive sepsis screen if this secondary screen was positive. However, all patients with a severe sepsis alert, triggered by the presence of either cardiac dysfunction or two dysfunctional organ systems, were considered to be at high risk of sepsis and required an urgent sepsis huddle.

A summary of the characteristics of these ED-based sepsis screening tools is shown in Table 2.

**Challenges in interpreting screening tool performance**

A number of limitations exist in all of the aforementioned reports of sepsis screening tool performance. First, it is important to note the reference standard against which a screening algorithm is applied when evaluating sepsis screening tools. Clinical definitions of sepsis used in the medical literature vary significantly, from those based on provider actions (‘intention to treat sepsis’ or use of a sepsis pathway) to use of diagnosis codes to comparison to published clinical criteria. As a result, it is difficult to directly compare the test characteristics of one reported tool to another unless the same reference standard was used and cases identified in a similar manner. Generally, reported test characteristics of tools that used a combination of existing hospital tracking systems and systematic medical record review to identify patients who may have been missed by the tool are likely more accurate than those that were derived solely from diagnostic codes for sepsis or tools that were not compared against a sepsis reference standard.

An additional challenge in evaluating pediatric screening tools is the difficulty of accurately identifying false positives. It is impossible to distinguish with current tools whether a child with a positive sepsis alert who received IV fluids and antibiotics and never developed organ dysfunction is a “false positive” who was unnecessarily treated or a “great catch” who would have gone on to develop severe sepsis or septic shock without those interventions. Additionally, alerts that identify a patient clinically deteriorating from an illness other than sepsis may count as “false positives” but actually have considerable value if they help to identify that deterioration and facilitate an intervention.
It is important to note that all of the above reports are single center. As such, it is unclear whether even the best-performing tools do as well at sepsis detection when used outside of the setting where they were developed.

Sepsis screening outside of the ED

Sepsis screening outside of the ED has been less frequently reported in the literature, though its use in these settings is increasing in clinical practice. Notably, these tools have generally employed different frameworks for sepsis detection than the ED-based tools, given different patient characteristics and sepsis prevalence in the inpatient and ICU settings. Inpatient tools have the benefit of longer observation times, which allows for utilization of changes or trends in vital signs or other clinical parameters to drive performance. Longitudinal evaluation, however, is a double-edged sword, as issues such as lock out time (i.e., the time after a given alert when additional alerts will no longer fire) following a positive alert must also be addressed. Additionally, while heterogeneous definitions of “time 0” in the ED can make benchmarking a challenge, it is even more difficult in the inpatient setting where specific time markers such as ED arrival or triage time cannot be used as a proxy for sepsis onset.

In response to Rory’s regulations, a team at New York University created a sepsis identification process for their inpatient pediatric unit consisting of a temperature-adjusted vital sign screen followed by physician examination. The tool identified 38/39 patients with possible sepsis/septic shock (sensitivity 97.4%) with PPV of 23.5% for possible sepsis, though only 3.7% for severe sepsis/septic shock.

Sepsis screening in the ICU entails a very different set of challenges, as sepsis itself is more common than in the ED or inpatient unit but so are a wide variety of other conditions that may mimic sepsis. A team at Cincinnati Children’s created a computerized sepsis alert that was triggered by the presence of abnormal temperature and an order for a blood culture in the unit consisting of a temperature-adjusted vital sign screen followed by physician examination. The tool identified 38/39 patients with possible sepsis/septic shock (sensitivity 97.4%) with PPV of 23.5% for possible sepsis, though only 3.7% for severe sepsis/septic shock.

**Effect on Patient Outcomes**

Many of the available screening tools have proven to be sensitive, specific, and well integrated into clinical practice. In order to lead to better clinical outcomes though, the tool must also show that it

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**Table 1. High risk conditions**

- Malignancy
- Asplenia (including SCD)
- Bone marrow transplant
- Central or indwelling line/catheter
- Solid organ transplant
- Severe MR/CP
- Immunodeficiency, immunocompromise or immunosuppression

**Table 2. Vital signs (PALS)**

| Age (y) | Heart rate (bpm) | Respiration rate (resp rate) | Systolic BP (mmHg) | Temp (°C) |
|---------|------------------|----------------------------|-------------------|-----------|
| 0 – 1 m | > 160 | 30 | < 90 | < 36 or >38.5 |
| 1 m – 3 y | > 140 | 30 | < 90 | < 36 or >38.5 |
| 3 y – 5 y | > 120 | 30 | < 90 | < 36 or >38.5 |
| 5 y – 10 y | > 100 | 30 | < 90 | < 36 or >38.5 |
| 10 y – 13 y | > 100 | > 16 | < 90 | < 36 or >38.5 |
| > 13 y | > 100 | > 16 | < 90 | < 36 or >38.5 |

**Table 3. Exam abnormalities**

| Pupils (central vs. peripheral) | Cold shock | Warm shock | Non-specific |
|---------------------------------|------------|------------|-------------|
| Decreased or weak | Bounding | | |
| Capillary refill (central vs. peripheral) | ≥ 3 s | Flash (< 1 s) | |
| Skin | Mottled, cool | Flushed, red, erythroderma (other than face) | Petechiae below the nipple, any purpura |
| Mental status | Decreased, irritability, confusion, inappropriate crying or drowsiness, poor interaction with parents, lethargy, diminished arousability, obtundation |
leads to improved sepsis recognition when compared to clinician gestalt. Only the tool in use in the CHOP ED showed a decrease in missed sepsis cases after implementation, from 17.3% of all patients with severe sepsis within 24 h of ED disposition to 3.8% after onset of sepsis screening.31

Even less clear are the effects of sepsis screening on clinical outcomes, such as organ dysfunction, ICU and hospital length of stay (LOS), ventilator or vasopressor days, and mortality. When screening tool deployment has been associated with improvement in these outcomes, it has always been as part of a systematic QI program, making it impossible to isolate the effect of the screening tool. At Texas Children’s Hospital, for example, Arikan and colleagues reported an impressive 46% reduction in acute kidney injury as well as shorter hospital and ICU LOS and improved mortality after introduction of a protocol-driven sepsis bundle that included a sepsis recognition tool.35 However, the bundle also included successful efforts to improve time to antibiotics and fluid administration and volume of fluid administered, interventions that have previously been strongly linked to improved sepsis outcomes.35 Conversely, when Eisenberg et al. looked specifically at whether sepsis outcomes improved after implementation of an automated screening tool in their ED, they found no differences in hospital or ICU LOS or mortality.37 The improved clinical outcomes reported with bundled sepsis care, but not with sepsis screening alone, suggest that there may be additional benefit from human factors that are elements of bundled care, such as a shared mental model among clinical team members.

### IMPLEMENTING SEPSIS SCREENING

While the effect of sepsis screening alone on patient outcomes may be uncertain, it is well established in the literature that comprehensive sepsis QI programs that include sepsis identification processes can save lives.13,35 This finding is intuitive—after all, sepsis identification is merely the first step in a process that must then lead to rapid and appropriate provision of fluids, antibiotics, vasoactive infusions, and other critical care interventions. At each step along the way, QI efforts can improve the care provided: a bedside huddle allows for rapid resuscitation when appropriate (and withholding of resuscitation when it is not); use of standardized order sets facilitates ordering recommended antibiotics, pressors, and fluids; skilled nursing and pharmacy care get those medications to the bedside and safely deliver them as quickly as possible; and critical care infrastructure allows for support for failing organ systems. A robust educational
curriculum supports each of these interventions by continually reinforcing best practices, and tracking of process, outcome, and balancing measures allows education and interventions to be targeted when and where they are most needed.

It is therefore natural that sepsis screening has been an important component of local, state, and national QI efforts. These QI efforts may be mandated by legislation, as in the case of New York and Illinois, or optional collaboratives such as those organized by the AAP and CHA. In New York, Rory’s regulations were associated with a 0.59 odds ratio of mortality compared to patients who did not receive the care bundle within an hour. While the results of the large, national Improving Pediatric Sepsis Outcomes collaborative run by CHA are not yet known, it has >50 hospitals enrolled with an aim of reducing sepsis-attributable mortalities. Partially, this is due to the lack of proven impact on patient outcomes. There are also concerns about the unintended effects of screening. There is concern that sepsis, but those without it. Potential adverse effects on the child with a false positive sepsis screen include unnecessary placement of venous catheters and inappropriate administration of IV antibiotics and IV fluid. The health care system itself may also be impacted by unnecessary hospital or ICU admission for children who would not otherwise have required such an admission without the concerns raised by a false positive sepsis screen. While the fear of these potential harms are legitimate, they have not been demonstrated in the medical literature. In fact, the only study that specifically examined this question showed that there was no change in administration of IV antibiotics or IV fluid, ED LOS, or hospital admission among patients with a false positive sepsis screen in a pediatric ED after implementation of automated sepsis screening.

A final concern that has been raised on systematic sepsis screening is that, once clinicians learn to rely on such screens, they may fail to identify patients who have sepsis but did not trigger an alert or positive screen. Such false negatives can, of course, be prevented by creating a screen that is sufficiently sensitive for detecting sepsis early in the ED or hospital stay, but no such screen will ever identify all sepsis cases. However, the available literature suggests that, if care for septic children is sometimes delayed by false negative sepsis screening, such cases are significantly outnumbered by the cases of sepsis identified by the screen that would have otherwise been missed. Whether this still holds true in general EDs, which have a lower sepsis prevalence than the pediatric EDs from which all of these published reports have originated, should be a priority in future research.

**FUTURE DIRECTIONS**

Machine learning and artificial intelligence offer the promise of creating better sepsis identification tools that leverage big data and can incorporate elements from the EHR that previously required manual input. Rather than utilize rule-based thresholds such as SIRS, the pediatric early warning score, or the sequential organ failure assessment, such algorithms are trained to run complex tasks on large amounts of data in order to predict adverse outcomes. This also allows integration of dynamic vital sign changes, which are likely to be more sensitive in detecting...
Table 2. Comparison of the published emergency department pediatric sepsis screens.

| Author (Year) | Framework | Form | Population screened | Sens (%) | PPV (%) |
|---------------|-----------|------|----------------------|----------|---------|
| Cruz et al. (2012) | Internally derived | Automated alert followed by manual screen | All ED patients | 87 | 50 |
| Sepanski et al. (2014) | Internal criteria derived from ACCM guidelines | Use of ED sepsis protocol or ICU admission meeting Goldstein severe sepsis criteria within 24 h | All ED patients | 99 | 20 |
| Lane et al. (2016) | Modified pSSC | Automated alert followed by manual screen | All ED patients | 86 | 25 |
| Balamuth et al. (2017) | PSSC | Use of ED sepsis protocol, Goldstein severe sepsis criteria within 24 h | All ED patients | NR | NR |
| Lloyd et al. (2018) | PSSC | Modified pSSC | All ED patients | 85 | 4 |

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AUTHOR CONTRIBUTIONS
M.A.E. and F.B. conceptualized the review, drafted the article, and gave final approval to the manuscript.

COMPETING INTERESTS
The authors declare no competing interests.

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