

This is the author-created version of the following work:

Alberto, L., Marshall, A.P., Walker, R., and Aitken, L.M. (2017) *Screening for sepsis in general hospitalized patients: a systematic review*. *Journal of Hospital Infection*, 96 (4) pp. 305-315.

Access to this file is available from:

<https://researchonline.jcu.edu.au/84254/>

© 2017 The Healthcare Infection Society. Published by Elsevier Ltd. All rights reserved. AAM may be made open access under a CC BY-NC-CD license after a 12 month embargo.

Please refer to the original source for the final version of this work:

<https://doi.org/10.1016/j.jhin.2017.05.005>

Screening for sepsis in general hospitalized patients: a systematic review

Author links open overlay panelL. Alberto ^a, A.P. Marshall ^{b c}, R. Walker ^{b d}, L.M. Aitken ^{b e}

<https://doi.org/10.1016/j.jhin.2017.05.005>Get rights and content

Background

Sepsis is a condition widely observed outside critical care areas.

Aim

To examine the application of sepsis screening tools for early recognition of sepsis in general hospitalized patients to: (i) identify the accuracy of these tools; (ii) determine the outcomes associated with their implementation; and (iii) describe the implementation process.

Methods

A systematic review method was used. PubMed, CINAHL, Cochrane, Scopus, Web of Science, and Embase databases were systematically searched for primary articles, published from January 1990 to June 2016, that investigated screening tools or alert mechanisms for early identification of sepsis in adult general hospitalized patients. The review protocol was registered with PROSPERO (CRD42016042261).

Findings

More than 8000 citations were screened for eligibility after duplicates had been removed. Six articles met the inclusion criteria testing two types of sepsis screening tools. Electronic tools can capture, 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 appears to be enhanced; however, demonstrating improved outcomes is more challenging. Implementation details are rarely reported. Heterogeneity of studies prevented meta-analysis.

Conclusion

Clinicians, researchers and health decision-makers should consider these findings and limitations when implementing screening tools, research or policy on sepsis recognition in general hospitalized patients.

- Previous article in issue
- Next article in issue

Keywords

Sepsis

Sepsis screening

Hospital wards

General hospitalized patients

Introduction

Sepsis is a physical response to a source of infection that triggers mechanisms that compromise organ function, leading to death if not treated early. Over the past 25 years there has been an increasing interest in providing recommendations to diagnose and manage this condition [1], [2]. In spite of these efforts sepsis mortality remains unacceptably high. Global mortality rates based on data collected in 37 countries averaged 39%, but ranged from 22% in Australia to 56% in Brazil [3]. Other recent studies have reported rates of 38% across the Americas and Europe, 32% in Uganda, and 24% in Australia and New Zealand [4], [5], [6]. In view of these high mortality rates, timely recognition of sepsis is crucial to enable early and adequate intervention.

Septic patients were previously predominantly cared for in intensive care units (ICUs), but this is now changing with more septic patients being cared for in hospital wards [7], [8]. In various countries across North America and Europe it is reported that 14–80% of patients in medical–surgical wards develop sepsis [9], [10], [11]. Furthermore, within acute medical and surgical ward settings, sepsis is frequently the cause of organ failure and clinical deterioration, leading to rapid response activation or death [9], [10], [12], [13]. This growing evidence suggests that identification of septic patients in hospital wards is paramount.

The earlier that sepsis is identified the sooner the patient can be rescued from clinical deterioration [14], [15]. Timely recognition of this condition is a perennial concern stressed by clinicians and researchers [1], [16], [17]. To address the issue, hospital-wide quality improvement initiatives on sepsis recognition have been implemented, with some resulting in improved patient outcomes [18], [19]. Sepsis alerts mediated by technology embedded in electronic medical records have also been proposed as an effective screening mechanism [20], [21]. The most effective method of screening patients in acute care is not clear, therefore the purpose of this review was to examine the application of sepsis screening tools or alert mechanisms for early recognition of sepsis in general hospitalized patients to: (i) identify the accuracy of these screening tools; (ii) determine the outcomes associated with their implementation; and (iii) to describe the implementation process.

Methods

A systematic review method was used to search, identify, and appraise the available literature. The review was previously registered with the international prospective register of systematic reviews (PROSPERO registration number: CRD42016042261).

Inclusion and exclusion criteria

The aim was to identify primary research that tested a screening tool or alert mechanism for early identification of sepsis in hospitalized general medical, surgical, and trauma (including intermediate care) patients aged ≥ 16 years. Outcomes of interest included accurate diagnosis, early implementation of the 6 h bundle, shorter ICU and hospital length of stay, and lower rates of mortality [2]. Studies conducted in the emergency department and ICU were excluded, as were studies in patients aged ≤ 15 years, pregnant, obstetrics, haemodialysis, oncology and immunocompromised (HIV, bone marrow transplant, neutropenia) patients, as these patients may have an altered response to sepsis and therefore not be representative of general hospitalized populations. Languages of publications were limited to English and Spanish. The search was limited to publications from January 1990 to June 2016. This timeframe was considered adequate as it preceded the publication of first sepsis consensus conference results [1].

Search strategy

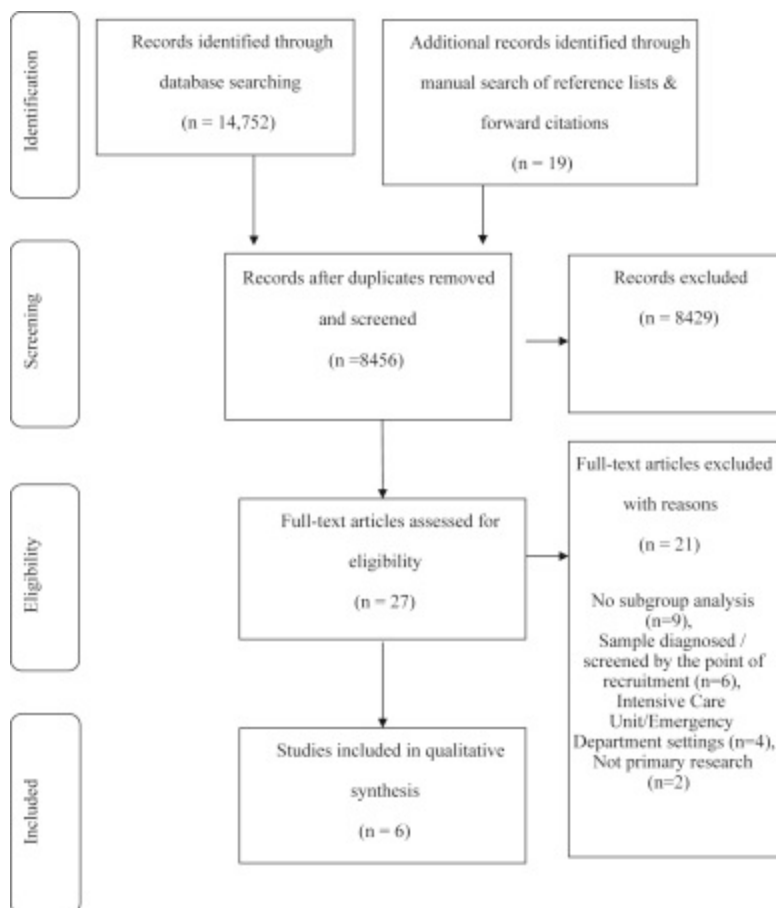
United States National Library of Medicine National Institutes of Health (PubMed), Cumulative Index to Nursing and Allied Health (CINAHL), Cochrane, Scopus, Web of Science, and Embase databases were systematically searched (Supplementary Appendix 1). Medical subject headings and keywords used were: screen, screening, early warning system, early identification, early diagnosis, mass screening, early detection, early recognition, sepsis, septic shock, severe sepsis, hospital, inpatient, hospital ward, hospitalized patient. The article search-and-retrieval process was undertaken by one author (L.A.) assisted by a librarian. Others articles were identified through manual searching, reviewing the reference list section of relevant publications, and using the 'cited by' function of Google Scholar with details of those publications. Identified citations were screened for eligibility by two independent reviewers (L.A. and either R.W., A.M. or L.M.A.). Disagreements were discussed and resolved within the entire team.

Appraisal and data extraction

An appraisal and data extraction tool was developed (Supplementary Appendix 2) based on the BMJ Diagnostic test studies and critical appraisal, the Critical Appraisal Skills Programme (CASP) Diagnostic Test Study Checklist, the STARD checklist for reporting of studies of diagnostic accuracy, and the template for intervention description and replication (TIDieR) checklist and guide [22], [23], [24], [25]. The tool was used to assess the study validity, adequacy of population, blinding, testing and accuracy, methods for the screening test, implementation of the test, its results and process if reported. Accuracy tests of the screening tools were reconstructed using the reported number of patients who did and did not activate the alerts, and the number of patients who were actually diagnosed as septic in both groups. If more than one cohort or group were studied, accuracy tests were combined when the sample characteristics and results of the groups were similar. If relevant information was not available in the publication, the author was contacted.

Results

The search resulted in 14,771 citations retrieved from six search engines and manual searching. After eliminating duplicates, 8456 citations including titles and abstracts were screened for eligibility (Figure 1) [26]. Six articles met the inclusion criteria, including two prospective observational pilot studies, one prospective observational study, two pre–post studies and one retrospective cohort study (Table I) [27], [28], [29], [30], [31], [32]. Heterogeneity of studies in terms of instruments used to screen patients and outcomes measured (Table I, Table II, Table III) prevented meta-analysis and minimal detail was reported on the implementation of the screening tools.



1. Download: Download high-res image (290KB)
2. Download: Download full-size image

Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram.

Table I. Study characteristics

Author (year) country	Aim	Design	Setting, sample	Definition of sepsis	Accuracy tests	Outcomes not significant
Gyang et al., 2015 [27], USA	To examine the performance of a nurse-driven sepsis screening tool	Prospective pilot study	26-bed medical/surgical intermediate care unit, 613-bed university tertiary referral hospital, N = 245	ICD-9 codes for sepsis, severe sepsis, or septic shock	Medical patients: Se = 1 Sp = 0.96 PPV = 0.70 NPV = 1 Surgical patients: Se = 0.93 Sp = 0.90 PPV = 0.48 NPV = 0.99	Fluids ICU transfer

Author (year) country	Aim	Design	Setting, sample	Definition of sepsis	Accuracy tests	Outcomes not significant
MacQueen et al., 2015 [29], USA	To evaluate the usage of a vital sign-based screening protocol for identifying sepsis	Observational, prospective screen	Non-monitored, general surgical units, hospital network, <i>N</i> = 478 (abdominopelvic surgery only)	Systemic inflammatory response syndrome plus presence of perioperative infection	Se ^a = 1 Sp ^a = 0.94 PPV ^a = 0.56 NPV ^a = 1	NR
Manaktala et al., 2016 [31], USA	To develop and implement a clinical decision support system, and to evaluate its test characteristics and the resultant sepsis-related outcomes	Quasi-experimental, with pre- and post-test analysis	Two hospital floors, respiratory and general medicine, 941-bed tertiary care hospital, <i>N</i> = 778 (pre and post)	ICD 9 codes for sepsis	Se = 0.95 Sp = 0.82 PPV = 0.50 NPV = 0.98	ICD-9 sepsis diagnosis Readmission rate Length of stay in the study units
Sawyer et al., 2011 [28], USA	To evaluate whether the implementation of an automated sepsis screening and alert system facilitated early appropriate interventions	Prospective pilot study with an intervention	Six medical wards, 1250-bed academic centre, <i>N</i> = 270 (non-intervention plus intervention)	Surviving Sepsis Campaign definition	NA	Microbiological cultures and radiographic images ICU transfer ICU transfer <12 h after alert Mortality Hospital length of stay
Thiel et al., 2010 [32], USA	To identify early predictors of septic shock	Retrospective cohort analysis	Medical, non-ICU units, 1200-bed academic centre, <i>N</i> = 27 674 (derivation plus validation)	ICD-9 codes for acute infection matched to codes for acute organ dysfunction and the need for vasopressors	Se ^b = 0.17 Sp ^b = 0.97 PPV ^b = 0.20 NPV ^b = 0.96	NA

Author (year) country	Aim	Design	Setting, sample	Definition of sepsis	Accuracy tests	Outcomes not significant
Umscheid et al., 2015 [30], USA	To describe the development, implementation and impact of an early warning and response system for sepsis	Pre and post study	Non-ICU acute inpatient units, three urban academic hospitals of >1500 beds, <i>N</i> = 31,069 (pre and post implementation)	Sepsis discharge diagnosis	Pre: Se ^c = 0.22 Sp ^c = 0.97 PPV ^c = 0.39 NPV ^c = 0.94 Post: Se ^c = 0.23 Sp ^c = 0.98 PPV ^c = 0.45 NPV ^c = 0.94	Hospital and ICU length of stay Vasopressors Mortality ICU transfer <6 h after alert

ICU, intensive care unit; NA, not applicable; NR, not reported; ATB, antibiotics; ICD, International Classification of Diseases; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

a

Test reproduced using the negative alert patients (*N* = 419) who did not develop sepsis (confirmed by author e-mail communication).

b

Test reproduced combining 2006 and 2007 cohorts without arterial blood gas values for prediction.

c

Test reproduced considering the sepsis discharge diagnosis instead of the composite variables reported by authors.

Table II. Screening tool variables

Study	General variables	Inflammatory	Haemodynamic	Organ dysfunction	Tissue perfusion	Other
Gyang et al., 2015 [27]	Temperature >38 °C, <36 °C HR > 90 beats/min RR > 20 breaths/min Change mental status	WBC >12 000 or <4000 or >10% bands	SBP <90 mmHg >40 mmHg decrease in SBP from patient's baseline MAP <65 mmHg	UO < 0.5 mL/kg/h for 2 h (or <30 mL/h for 2 h) Increase O ₂ to maintain SpO ₂ >90% Absence bowel sounds (except recent post-surgery) Platelet count <10 ⁵ /μL Serum creatinine increased by 0.3 g/dL in past 48 h INR >1.5 or PTT >60 s Total bilirubin >4 mg/d	Capillary refill >3 s Lactate >2.0 mmol/L	PCO ₂ <32 mmHg Question of possible sepsis
MacQueen et al., 2015 [29]	Temperature >38 °C or <36 °C HR > 90 beats/min RR > 20 breaths/min	–	SBP <90 mmHg, or MAP <65 mmHg	–	–	–
Manaktala et al., 2016 [31]	Vital signs ^a	–	–	–	–	Demographics Medications Laboratory values ^a Documented elements Medical problems Symptoms infection
Sawyer et al., 2011 [28]	–	WBC ≥15.7 × 10 ³ /μL	MAP <68 mmHg	INR ≥1.5 INR ≥1.6 Bilirubin <0.4 mg/dL Bilirubin ≥2.5 mg/dL	–	Albumin ≥3.2 g/dL Albumin <2.6 mg/dL Haemoglobin <10.9 g/dL Haemoglobin

Study	General variables	Inflammatory	Haemodynamic	Organ dysfunction	Tissue perfusion	Other
						≥11.7 g/dL Sodium ≥146 mmol/L Neutrophil ≥15.9 × 10 ³ /μL Shock index
Thiel et al., 2010 [32]	–	WBC ≥15.6 × 10 ³ /μL	MAP <68 mmHg	INR ≥1.5 INR ≥1.6 Bilirubin <0.4 mg/dL Bilirubin ≥2.5 mg/dL	–	Albumin ≥3.2 g/dL Albumin <2.5 mg/dL Haemoglobin g/dL Haemoglobin g/dl Sodium ≥146 mmol/L Shock index Neutrophil ≥16 × 10 ³ μ
Umscheid et al., 2015 [30]	Temperature <36 °C or >38 °C HR > 90 beats/min RR > 20 breaths/min	WBC <4000 or >12 000 or >10% bands	SBP <100 mmHg	–	Lactate >2.2 mmol/L	PaCO ₂ <32

HR, heart rate; RR, respiratory rate; WBC, white blood cells; SBP, systolic blood pressure; MAP, main arterial pressure; INR, international normalized ratio; UO, urinary output; O₂, oxygen; SpO₂, pulse oximeter oxygen saturation; PTT, partial thromboplastin time; PaCO₂, partial pressure of carbon dioxide.

a

No cut-off values of variables were supplied.

Table III. Screening process and response

Study	Screening tool name	Review periods for variables to screen	Frequency of screening	Screening mechanism	Alert mechanism	Response
Gyang et al., 2015 [27]	Severe Sepsis	Within the previous 8 h	At the beginning of	Nurse-driven,	Nurse to call primary team	Nurse to initiate guideline. Primary team to order

Study	Screening tool name	Review periods for variables to screen	Frequency of screening	Screening mechanism	Alert mechanism	Response
	Screening Tool	of the time of assessment	every nursing shift	paper-based		diagnostic tests, administration of broad spectrum ATB and fluids, ICU consultation/transfer.
MacQueen et al., 2015 [29]	Sepsis Until Proven Otherwise	NR	NR	Nurse-based	Nurse to call a provider	Provider to prescribe antibiotics and intravenous fluid boluses as recommended by the protocol
Manaktala et al., 2016 [31]	Electronic sepsis surveillance and alerting system	NR	Real-time surveillance	Electronic	Alert sent to nurses on mobile and desktop computer. Four types of alerts could be activated: informational, diagnosis, advice and reminders.	Nurses accepted or overrode the alert; they were directed to contact physicians about all diagnosis alert
Sawyer et al., 2011 [28]	Prediction tool	Immediately after registered in electronic medical record	Continuously	Electronic	Automatic alert sent to the nurse	Nurse assess the patient, and referred the patient to a physician. Physician to prescribe antibiotic, escalation, administration of fluids and oxygen, diagnostic tests.
Thiel et al., 2010 [32]	Prediction tool	24 to 2 h previous ICU admission (cases) 48 h controls	NA	NA	NA	NA

Study	Screening tool name	Review periods for variables to screen	Frequency of screening	Screening mechanism	Alert mechanism	Response
Umscheid et al., 2015 [30]	Early warning and response system	Vital signs 24 h Laboratory values 48 h	Continuously	Electronic	Alert sent to bedside nurse, RRC and covering provider	Bedside nurse, RRC and covering provider to evaluate the patient within 30 min and enact changes in management

NR, not reported; NA, not applicable; ICU, intensive care unit; RRC, rapid response co-ordinator; ATB, antibiotics.

Variables of screening tools and alert mechanism

The reviewed sepsis screening tools and alert mechanisms varied. Four out of six tools were mediated by technology, with the alert criteria and mechanism embedded in electronic medical records [28], [30], [31], [32]. In one study it was not clear whether the tool was paper or electronic [29]. The remaining study introduced a paper-based screening tool [27]. The variables of all the alert/screening tools identified are summarized in Table II.

The electronic tools collected, in real time, a set of laboratory values and vital signs. One prediction tool was based on an algorithm with five levels of decision-criteria, with some variables used twice in different levels [32]. The same prediction tool was later applied in the same setting [28]. The alerts were sent to a nurse who reviewed the patient and activated further referral to physicians in order to inform alert and patient condition [28]. Similarly, an electronic algorithm-based sepsis surveillance provided additional prompts of isolated clinical changes, diagnostic variables, and treatment reminder alerts [31]. Nurses received the alerts and referred the patient to a physician [31]. Another electronic sepsis alert using additional vital signs was investigated. The Early Warning and Response System (EWRS) for sepsis, comprising a set of six-point risk criteria, activated an alert when four out of six criteria were met [30]. Similar clinical variables were applied in a three tier nurse-led paper-based screening tool [27]. Nurses assessed patients against the tool, evaluating vital signs and inflammatory indicators (first tier), clues of infection (second tier), and tissue perfusion and organ dysfunction variables (third tier). If the screening process was positive, the nurse initiated a protocol and called the treating physician. Finally, based on vital signs the sepsis until proven otherwise (SUPO) protocol was examined [29]. If a positive screen was identified, nurses referred the patient to a medical provider and collected blood cultures and lactate samples unless advised otherwise. Screening processes are summarized in Table III.

Accuracy of screening tools

The accuracy of screening tools tested in these studies differed. Reference standards varied across the studies and included ICD-9 codes for sepsis, ICD-9 codes for acute infection matched to codes for acute organ dysfunction, and the need for vasopressors within 24 h of ICU transfer, systemic inflammatory response syndrome plus presence of infection, and Surviving Sepsis Campaign definition [27], [29], [31], [32]. One study reported accuracy tests calculated against (i) any ICU transfer, (ii) rapid response call, (iii) death, or a composite of (i, ii, and iii) variables [30]. One study

was excluded from this analysis because only positively screened patients were included and no data regarding patients who screened negative were available [28].

The sensitivity, specificity, and predictive values of each of the screening tools are summarized in Table I. In one case, the reproduced specificity (0.94) and positive predictive value (0.56) resulted in higher values than those reported by authors (specificity: 0.88; positive predictive value: 0.10) [29]. 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 [27], [29], [31]. However, two studies had small sample sizes with accuracy tests calculated on random numbers of negatively screened participants [27], [29]. The remaining study reported control data collected retrospectively outside of the study period [31]. Lower sensitivity and positive predictive values were reproduced and reported in the larger studies where arguably more robust designs were used [30], [32]. 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 [30], [32].

Response to sepsis alerts

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 [27], [28], [29], [30], [31]. Nurses were also responsible for initiating a sepsis protocol or escalating the care (Table III) [27], [28], [29], [31]. Sepsis management, mainly related to the 6 h bundle, including antibiotics prescription or escalation, fluid resuscitation, and diagnostic tests were frequently specified and further consultation or transfer to ICU were outlined in one protocol [27], [28], [29], [31].

Frequency of screening and review periods for variables to screen

The screening tools were used to identify clinical indicators of sepsis in two ways: continuously and at intervals (Table III). Tools that were applied continuously were electronically mediated and integrated into electronic medical records [28], [30], [31]. By contrast, a paper-based screening tool was used by nurses at the beginning of their shift [27]. SUPO was universally used across the study hospital but the format of the tool and frequency of screening were unclear [29]. In terms of the review periods for variables to be searched for when screening, different times were incorporated and ranged from 2 to 72 h, with the most usual being 24–48 h.

Patient outcomes

Important improvements in sepsis management were identified in the reviewed studies and these are summarized in Table I. 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 [31]. Other studies showed positive trends in hospital mortality, hospital and ICU length of stay, and ICU transfer [27], [28], [30].

Implementation of screening tools

The process used to implement the screening tools into routine practice was rarely reported. Gyang et al. described support provided to nurses before and during the intervention [27]. Clinical nurse specialists, assistant nurse managers and educators provided more than 8 h of education on infection- and sepsis-related topics six months before the implementation. In addition a sepsis education module was available with completion being optional. An extra hour of self-study time was provided a month before data collection was initiated where clinicians could learn about severe

sepsis. In addition, designated champions conducted in-service training on completion of the screening tools the month prior to implementation. Manaktala et al. reported that the governance process was led by nursing and physician steering committees and a ward nurses team [31]. They were responsible for defining, training and following-up implementation processes, including conducting changes in the nursing documentation procedures that contained variables to be captured by the surveillance system [31]. A 'standardized education strategy' delivered during physicians' and nurses' meetings prior to the alert system going live was identified in another study [28]. Data about process compliance after sepsis alerts were reported in only one study and included the name of the provider, notifications sent to the provider, nurse review alert, nursing tasks, team presence at bedside within 30 min, team awareness of sepsis before alert and changes in management [30]. Compliance results ranged from a low of 32% (any change in management) to 99% (nursing task verified: vital signs assessment) [30].

Strengths and limitations of studies

The studies identified have some strengths and limitations to consider. Strengths included large sample sizes, common laboratory variables and vital signs used for developing the tools, inter-rater agreement for sepsis diagnosis evaluated, details about implementation process, and details about process evaluation [27], [28], [29], [30], [31], [32]. Limitations comprised small sample size, particular populations studied such as intermediate care and patient's having abdominopelvic surgery, a random sample of true negative patients studied, control group data collected out of the study period, and incomplete or lack of implementation details [27], [28], [29], [30], [31].

Discussion

The evidence related to sepsis screening in acute care is examined in this review. Six studies were identified that investigated predominantly electronic tools, with only one paper-based tool reported. Whereas process-of-care measures appear to be improved, demonstrating improved outcomes is more challenging. Electronic tools assisted by computing systems were able to capture, recognize abnormal variables and activate an alert immediately, or even facilitate prediction of organ dysfunction [28], [30], [31], [32]. However, these tools performed poorly in identifying septic patients [30], [32]. When tools did perform better, comparisons were based on control data collected out of the study period [31]. Paper-based, nurse-led tools and alert mechanisms appeared to be more sensitive in the identification of septic patients but were only studied in small samples and particular populations [27], [29]. Further investigation is needed to determine the effectiveness of the types of alerts, whether they are electronic or health practitioner-mediated [33].

Screening tools consisted of a combination of laboratory indicators of organ dysfunction, haemodynamic, inflammatory, tissue perfusion, vital signs, and other variables. When considering the performance of a given combination of variables in screening instruments, evidence is not consistent regarding accuracy. For example, a tool based on vital signs appears to perform better (sensitivity: 1; specificity: 0.94) than a more complex prediction tool based on laboratory values (sensitivity: 0.17; specificity: 0.97) or a combination of laboratory and vital signs variables (sensitivity: 0.23; specificity: 0.98) [29], [32]. It has been argued that sepsis has no reference standard for identification and diagnosis, with early signs and symptoms being non-specific [34], [35]. Thus the underlying spectrum of clinical variables may be difficult to capture by the tools, resulting in limitations in accuracy [36]. Thus, the most accurate set of variables for sepsis screening is yet to be elucidated.

Nurses were the primary responders to sepsis alerts, even though on occasion rapid response system and medical providers also responded. Nurses' involvement in timely identification and response to sepsis alerts hospital-wide has been previously reported as decreasing overall mortality by 43% ($P < 0.01$) in a multicentre quality improvement programme in the USA [37]. The initiative was based on (i) sepsis screening, (ii) diagnostic testing, and (iii) timely treatment. Nurses apply complex clinical reasoning about patient condition, respond according to protocols, and serve as a safety mechanism [27]. Evidence favours nurses in responding to sepsis alerts, but to what extent their response influences patient outcomes in other settings merits further investigation.

Evidence identified was limited to hospital ward settings, intermediate care or a particular type of surgery (abdominopelvic) patients in the context of a developed economy, specifically the USA [27], [28], [29], [30], [31], [32]. The technology and the staff available, such as the nurse:patient ratio and the supporting steering committees, played a pivotal role in developing a strategy for sepsis screening in these studies [27], [28], [30], [31], [32]. Whereas quality improvement initiatives are frequently being implemented in developed health systems and technology is changing the way clinicians identify sepsis in well-resourced hospital ward settings, little is known about sepsis screening practices in less developed settings [4], [28], [30], [31], [32]. For example, in Brazil, a hospital-wide, paper-based sepsis screening strategy led by nurses resulted in a reduction in patient mortality from 61.7% to 36.5% ($P < 0.001$) [19]. Importantly, when technology is not available for assisting real-time surveillance in hospital wards, nurses, physicians and other healthcare practitioners are the only safety mechanism patients have. However, health system decision-makers play a key role in allocating resources for sepsis care. Whereas a nationwide 'sepsis six' initiative has been implemented in the UK, low- and middle-income countries' decision-makers are challenged by different priorities [38], [39], [40]. Research to help understand the role of healthcare providers in sepsis care in diverse settings is urgently needed.

Details about implementation of screening tools and alert mechanisms were infrequently reported. Education on sepsis screening and care prior to, and throughout, the implementation period, as well as compliance with the process were the main components reported [27], [30], [31]. Sepsis screening and response are complex processes of care that involve various disciplines necessitating roles of each of the professionals be made explicit. Details about implementation (such as activities for staff engagement and follow-up) provide evidence about intervention fidelity, help to gain understanding of the setting, and promote future reproducibility [41].

This systematic review addressed early sepsis identification in acute care settings. It has a number of strengths and limitations. The review is limited to studies that tested a screening tool, were published in English and Spanish, and included quantitative analysis of accuracy and outcome measures. No publication that met the inclusion criteria was identified in Spanish. There may be strategies published in different languages that were not identified. The search was undertaken in six search engines only, but the keywords and medical subject headings were purposively broad to capture as many studies as possible. Finally, studies identified were heterogeneous in terms of the settings, resources, patients, and outcomes defined, which prevented meta-analysis [36].

Implication for practice and research

The evidence examined uncovered important implications for practice and research. 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 were 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. The roles of health professional within the multi-disciplinary team, especially nurse/physician:patient ratios and supporting staff, should be made explicit to promote optimal sepsis screening processes. Strategies to implement a new instrument should be carefully considered and explicitly described. Robust prospective designs should be encouraged, as should hybrid trials. Larger sample sizes, across health settings, with differing levels of resource allocation should be studied, as should be the implementation process in these contexts.

In conclusion, six studies were identified that examined predominantly electronic tools, with only one paper-based tool reported. Variables used were a combination of vital signs, laboratory indicators of organ dysfunction, inflammatory, tissue perfusion, and other variables. After alert activation, nurses were the first responders and responsible for initiating a sepsis protocol to escalating the care. Electronic tools assisted by computing systems captured, recognized abnormal variables and activated alerts in real time and facilitated prediction of organ dysfunction. However, these tools performed poorly in identifying septic patients. Only one tool performed better, but findings were based on control data collected prior to the study period. Paper-based, nurse-led tools and alert mechanisms appeared to be more sensitive in the identification of septic patients but were only studied in small samples and in certain patient populations. The evidence regarding sepsis screening in hospitalized patients is limited. Clinicians, researchers and health decision-makers should consider these findings and limitations when implementing screening tools, future research or policy on sepsis recognition in general hospitalized patients.

Acknowledgement

We acknowledge Ms K. Henderson, Health Librarian from Library and Learning Services, Griffith University, for assisting article search-and-retrieval process.

Conflict of interest statement

Download all supplementary files included with this article

What's this?

None declared.

Funding sources

This systematic review is part of L.A.'s PhD candidature, which is funded by Griffith University International Postgraduate Research Scholarship and Griffith University Postgraduate Research Scholarship.

Appendix A. Supplementary data

The following are the supplementary data related to this article:Download: Download Word document (79KB)Download: Download Word document (106KB)

References

1. [1]

R.C. Bone, R.A. Balk, F.B. Cerra, R.P. Dellinger, A.M. Fein, W.A. Knaus, *et al.*

Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine

Chest, 101 (1992), pp. 1644-1655

2. [2]

R.P. Dellinger, M.M. Levy, A. Rhodes, D. Annane, H. Gerlach, S.M. Opal, *et al.*

Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012

Crit Care Med, 41 (2013), pp. 580-637

3. [3]

R. Beale, K. Reinhart, F.M. Brunkhorst, G. Dobb, M. Levy, G. Martin, *et al.*

Promoting Global Research Excellence in Severe Sepsis (PROGRESS): lessons from an international sepsis registry

Infection, 37 (2009), pp. 222-232

4. [4]

M.M. Levy, A. Rhodes, G.S. Phillips, S.R. Townsend, C.A. Schorr, R. Beale, *et al.*

Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study

Intensive Care Med, 40 (2014), pp. 1623-1633

5. [5]

A. Amir, K.J. Saulters, S. Olum, K. Pitts, A. Parsons, C. Churchill, *et al.*

Outcomes of patients with severe sepsis after the first 6 hours of resuscitation at a regional referral hospital in Uganda

J Crit Care, 33 (2016), pp. 78-83

6. [6]

K. Kaukonen, M. Bailey, S. Suzuki, D. Pilcher, R. Bellomo

Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012

JAMA, 311 (2014), pp. 1308-1316

7. [7]

M. Rangel-Frausto, D. Pittet, M. Costigan, T. Hwang, C.S. Davis, R.P. Wenzel

The natural history of the systemic inflammatory response syndrome (sirs): a prospective study

JAMA, 273 (1995), pp. 117-123

8. [8]

D.C. Angus, W.T. Linde-Zwirble, J. Lidicker, G. Clermont, J. Carcillo, M.R. Pinsky

Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care

Crit Care Med, 29 (2001), pp. 1303-1310

9. [9]

J.M. Rohde, A.J. Odden, C. Bonham, L. Kuhn, P.N. Malani, L.M. Chen, *et al.*

The epidemiology of acute organ system dysfunction from severe sepsis outside of the intensive care unit

J Hosp Med, 8 (2013), pp. 243-247

10. [10]

A. Esteban, F. Frutos-Vivar, N.D. Ferguson, O. Penuelas, J.A. Lorente, F. Gordo, *et al.*

Sepsis incidence and outcome: contrasting the intensive care unit with the hospital ward

Crit Care Med, 35 (2007), pp. 1284-1289

11. [11]

T. Stiermaier, H. Herkner, S. Tobudic, K. Burgmann, T. Staudinger, P. Schellongowski, *et al.*

Incidence and long-term outcome of sepsis on general wards and in an ICU at the General Hospital of Vienna: an observational cohort study

Wien Klin Wochenschr, 125 (2013), pp. 302-308

12. [12]

M. Le Guen, A. Tobin

Epidemiology of in-hospital mortality in acute patients admitted to a tertiary-level hospital

Intern Med J, 46 (2016), pp. 457-464

13. [13]

G. Cross, I. Bilgrami, G. Eastwood, P. Johnson, B.P. Howden, R. Bellomo, *et al.*

The epidemiology of sepsis during rapid response team reviews in a teaching hospital

Anaesth Intensive Care, 43 (2015), pp. 193-198

14. [14]

F. Mearelli, D. Orso, N. Fiotti, N. Altamura, A. Breglia, M. De Nardo, *et al.*

Sepsis outside intensive care unit: the other side of the coin

Infection, 43 (2015), pp. 1-11

15. [15]

J.K. Roney, B.E. Whitley, J.C. Maples, L.S. Futrell, K.A. Stunkard, J.D. Long

Modified early warning scoring (MEWS): evaluating the evidence for tool inclusion of sepsis screening criteria and impact on mortality and failure to rescue

J Clin Nurs, 24 (2015), pp. 3343-3354

16. [16]

L.M. Aitken, G. Williams, M. Harvey, S. Blot, R. Kleinpell, S. Labeau, *et al.*

Nursing considerations to complement the Surviving Sepsis Campaign guidelines

Crit Care Med, 39 (2011), pp. 1800-1818

17. [17]

M. Singer, C.S. Deutschman, C.W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, *et al.*

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

JAMA, 315 (2016), pp. 801-810

18. [18]

S.L. Jones, C.M. Ashton, L. Kiehne, E. Gigliotti, C. Bell-Gordon, M. Disbot, *et al.*

Reductions in sepsis mortality and costs after design and implementation of a nurse-based early recognition and response program

Jt Comm J Qual Patient Saf, 41 (2015), pp. 483-491

19. [19]

G.A. Westphal, A. Koenig, M. Caldeira Filho, J. Feijo, L.T. de Oliveira, F. Nunes, *et al.*

Reduced mortality after the implementation of a protocol for the early detection of severe sepsis

J Crit Care, 26 (2011), pp. 76-81

20. [20]

R.C. Amland, K.E. Hahn-Cover

Clinical decision support for early recognition of sepsis

Am J Med Qual, 31 (2016), pp. 103-110

21. [21]

R.C. Amland, J.J. Lyons, T.L. Greene, J.M. Haley

A two-stage clinical decision support system for early recognition and stratification of patients with sepsis: an observational cohort study

JRSM Open, 6 (2015)

2054270415609004

22. [22]

BMJ Clinical Evidence

Diagnostic test studies: assessment and critical appraisal

(2014)

Available at:

<http://clinicalevidence.bmj.com/x/set/static/ebm/toolbox/665061.html>

[last accessed October 2015]

23. [23]

Critical Appraisal Skills Programme (CASP)

12 questions to help you make sense of a diagnostic test study

(2013)

Available at:

http://media.wix.com/ugd/dded87_3815f02af1b34c21b8c3b2b5020024c3.pdf

[last accessed October 2015]

Google Scholar

24. [24]

EQUATOR Network

STARD checklist for reporting of studies of diagnostic accuracy

(2003)

Available at:

<http://www.equator-network.org/>

[last accessed October 2015]

25. [25]

T.C. Hoffmann, P.P. Glasziou, I. Boutron, R. Milne, R. Perera, D. Moher, *et al.*

Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide

BMJ, 348 (2014)

g1687

26. [26]

D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman

Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement

PLoS Med, 6 (2009)

e1000097

27. [27]

E. Gyang, L. Shieh, L. Forsey, P. Maggio

A nurse-driven screening tool for the early identification of sepsis in an intermediate care unit setting

J Hosp Med, 10 (2015), pp. 97-103

28. [28]

A.M. Sawyer, E.N. Deal, A.J. Labelle, C. Witt, S.W. Thiel, K. Heard, *et al.*

Implementation of a real-time computerized sepsis alert in nonintensive care unit patients

Crit Care Med, 39 (2011), pp. 469-473

29. [29]

I.T. MacQueen, A.J. Dawes, T. Hadnott, K. Strength, G.J. Moran, C. Holschneider, *et al.*

Use of a hospital-wide screening program for early detection of sepsis in general surgery patients

Am Surg, 81 (2015), pp. 1074-1079

30. [30]

C.A. Umscheid, J. Betesh, C. VanZandbergen, A. Hanish, G. Tait, M.E. Mikkelsen, *et al.*

Development, implementation, and impact of an automated early warning and response system for sepsis

J Hosp Med, 10 (2015), pp. 26-31

31. [31]

S. Manaktala, S.R. Claypool

Evaluating the impact of a computerized surveillance algorithm and decision support system on sepsis mortality

J Am Med Inform Assoc, 24 (2017), pp. 88-95

32. [32]

S.W. Thiel, J.M. Rosini, W. Shannon, J.A. Doherty, S.T. Micek, M.H. Kollef

Early prediction of septic shock in hospitalized patients

J Hosp Med, 5 (2010), pp. 19-25

33. [33]

A.N. Makam, O.K. Nguyen, A.D. Auerbach

Diagnostic accuracy and effectiveness of automated electronic sepsis alert systems: a systematic review

J Hosp Med, 10 (2015), pp. 396-402

34. [34]

C.W. Seymour, V.X. Liu, T.J. Iwashyna, F.M. Brunkhorst, T.D. Rea, A. Scherag, *et al.*

Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

JAMA, 315 (2016), pp. 762-774

35. [35]

P.M.C. Klein Klouwenberg, D.S.Y. Ong, M.J.M. Bonten, O.L. Cremer

Classification of sepsis, severe sepsis and septic shock: the impact of minor variations in data capture and definition of SIRS criteria

Intensive Care Med, 38 (2012), pp. 811-819

36. [36]

M.M. Leeflang, K.G. Moons, J.B. Reitsma, A.H. Zwinderman

Bias in sensitivity and specificity caused by data-driven selection of optimal cutoff values: mechanisms, magnitude, and solutions

Clin Chem, 54 (2008), pp. 729-737

37. [37]

J. Kligler, S.J. Singer, F.H. Hoffman

Using the integrated nurse leadership program to reduce sepsis mortality

Jt Comm J Qual Patient Saf, 41 (2015), pp. 264-272

38. [38]

L. McMenemy, N. Murch, R. Daniels

Severe sepsis, social media and the #Sepsis 6: 'Tweeting' national innovations

Acute Med, 12 (2013), pp. 83-88

39. [39]

D.H.S.A. Anne Mills

Health care systems in low- and middle-income countries

N Engl J Med, 370 (2014), pp. 552-557

Google Scholar

40. [40]

V. Wiseman, C. Mitton, M.M. Doyle-Waters, T. Drake, L. Conteh, A.T. Newall, *et al.*

Using economic evidence to set healthcare priorities in low-income and lower-middle-income countries: a systematic review of methodological frameworks

Health Econ, 25 (2016), pp. 140-161

41. [41]

G.M. Curran, M. Bauer, B. Mittman, J.M. Pyne, C. Stetler

Effectiveness–implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact

Med Care, 50 (2012), pp. 217-226