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Automated monitoring compared to standard care for the early detection of sepsis in critically ill patients (Review)

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TABLE OF CONTENTS

[Intervention Review]

Automated monitoring compared to standard care for the early detection of sepsis in critically ill patients

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ABSTRACT

Background

Sepsis is a life-threatening condition that is usually diagnosed when a patient has a suspected or documented infection, and meets two or more criteria for systemic inflammatory response syndrome (SIRS). The incidence of sepsis is higher among people admitted to critical care settings such as the intensive care unit (ICU) than among people in other settings. If left untreated sepsis can quickly worsen; severe sepsis has a mortality rate of 40% or higher, depending on definition. Recognition of sepsis can be challenging as it usually requires patient data to be combined from multiple unconnected sources, and interpreted correctly, which can be complex and time consuming to do. Electronic systems that are designed to connect information sources together, and automatically collate, analyse, and continuously monitor the information, as well as alerting healthcare staff when pre-determined diagnostic thresholds are met, may offer benefits by facilitating earlier recognition of sepsis and faster initiation of treatment, such as antimicrobial therapy, fluid resuscitation, inotropes, and vasopressors if appropriate. However, there is the possibility that electronic, automated systems do not offer benefits, or even cause harm. This might happen if the systems are unable to correctly detect sepsis (meaning that treatment is not started when it should be, or it is started when it shouldn't be), or healthcare staff may not respond to alerts quickly enough, or get 'alarm fatigue' especially if the alarms go off frequently or give too many false alarms.

Objectives

To evaluate whether automated systems for the early detection of sepsis can reduce the time to appropriate treatment (such as initiation of antibiotics, fluids, inotropes, and vasopressors) and improve clinical outcomes in critically ill patients in the ICU.

Search methods

We searched CENTRAL; MEDLINE; Embase; CINAHL; ISI Web of science; and LILACS, clinicaltrials.gov, and the World Health Organization trials portal. We searched all databases from their date of inception to 18 September 2017, with no restriction on country or language of publication.

Selection criteria

We included randomized controlled trials (RCTs) that compared automated sepsis-monitoring systems to standard care (such as paper-based systems) in participants of any age admitted to intensive or critical care units for critical illness. We defined an automated system as any process capable of screening patient records or data (one or more systems) automatically at intervals for markers or characteristics that are indicative of sepsis. We defined critical illness as including, but not limited to postsurgery, trauma, stroke, myocardial infarction,

arrhythmia, burns, and hypovolaemic or haemorrhagic shock. We excluded non-randomized studies, quasi-randomized studies, and cross-over studies . We also excluded studies including people already diagnosed with sepsis.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane. Our primary outcomes were: time to initiation of antimicrobial therapy; time to initiation of fluid resuscitation; and 30-day mortality. Secondary outcomes included: length of stay in ICU; failed detection of sepsis; and quality of life. We used GRADE to assess the quality of evidence for each outcome.

Main results

We included three RCTs in this review. It was unclear if the RCTs were three separate studies involving 1199 participants in total, or if they were reports from the same study involving fewer participants. We decided to treat the studies separately, as we were unable to make contact with the study authors to clarify.

All three RCTs are of very low study quality because of issues with unclear randomization methods, allocation concealment and uncertainty of effect size. Some of the studies were reported as abstracts only and contained limited data, which prevented meaningful analysis and assessment of potential biases.

The studies included participants who all received automated electronic monitoring during their hospital stay. Participants were randomized to an intervention group (automated alerts sent from the system) or to usual care (no automated alerts sent from the system).

Evidence from all three studies reported 'Time to initiation of antimicrobial therapy'. We were unable to pool the data, but the largest study involving 680 participants reported median time to initiation of antimicrobial therapy in the intervention group of 5.6 hours (interquartile range (IQR) 2.3 to 19.7) in the intervention group (n = not stated) and 7.8 hours (IQR 2.5 to 33.1) in the control group (n = not stated).

No studies reported 'Time to initiation of fluid resuscitation' or the adverse event 'Mortality at 30 days'. However very low-quality evidence was available where mortality was reported at other time points. One study involving 77 participants reported 14-day mortality of 20% in the intervention group and 21% in the control group (numerator and denominator not stated). One study involving 442 participants reported mortality at 28 days, or discharge was 14% in the intervention group and 10% in the control group (numerator and denominator not reported). Sample sizes were not reported adequately for these outcomes and so we could not estimate confidence intervals.

Very low-quality evidence from one study involving 442 participants reported 'Length of stay in ICU'. Median length of stay was 3.0 days in the intervention group (IQR = 2.0 to 5.0), and 3.0 days (IQR 2.0 to 4.0 in the control).

Very low-quality evidence from one study involving at least 442 participants reported the adverse effect 'Failed detection of sepsis'. Data were only reported for failed detection of sepsis in two participants and it wasn't clear which group(s) this outcome occurred in.

No studies reported 'Quality of life'.

Authors' conclusions

It is unclear what effect automated systems for monitoring sepsis have on any of the outcomes included in this review. Very low-quality evidence is only available on automated alerts, which is only one component of automated monitoring systems. It is uncertain whether such systems can replace regular, careful review of the patient's condition by experienced healthcare staff.

PLAIN LANGUAGE SUMMARY

Automated monitoring for the early detection of sepsis in patients receiving care in intensive care units

Review question

Can automated systems for the early detection of sepsis reduce the time to treatment and improve outcomes in patients in the intensive care unit (ICU), in comparison to standard care?

Background

Sepsis happens when a person develops an infection and their immune system overreacts to it. If sepsis is not managed it can quickly develop into septic shock, which causes organs such as the liver and heart to stop working properly. People can be affected by sepsis at any time but people in intensive care settings are more likely to be affected by it. Septic shock is fatal for 20% to 70% of people admitted to intensive care in Europe. There is no single diagnostic test that can tell if someone has sepsis or not. Instead, the results of several tests (such as blood tests) have to be reviewed along with other information about the patient (such as their medical history), and clinical observations (such as heart rate, temperature, and blood pressure). This process can be time consuming and complicated to do. People already admitted to intensive care are likely to be very unwell and it can be difficult to tell if abnormal results are because of the problem that caused them to be admitted to intensive care, or because of sepsis.

Automated monitoring systems are electronic systems that can collect and analyse information from different sources, and can be used to alert staff when the signs and symptoms of sepsis have been identified. This may mean that sepsis is diagnosed at the earliest possible time, enabling treatment to begin before organ damage happens. However, there is the possibility that automated monitoring systems don't help, or even cause harm. This might happen if the systems are unable to correctly detect sepsis (meaning that treatment is not started when it should be, or it is started when it shouldn't be), or health care staff may not respond to alerts quickly enough, especially if the systems give too many false alarms.

Study characteristics

We conducted a search to identify evidence published before September 2017. Studies were eligible for inclusion if they compared automated sepsis monitoring to standard care (such as paper-based systems) in people admitted to intensive or critical care units for critical illness. We did not include non-randomized studies (studies where participants were not allocated to treatment groups by chance), quasi-randomized studies (studies where participants were allocated to treatment groups by a method that is not truly down to chance, such as date of birth or medical number), and cross-over studies (where participants first receive one treatment and then cross over to receive the other treatment). Studies including people already diagnosed with sepsis were also excluded.

Key results

We included three randomized controlled trials (studies where participants were allocated to treatment groups by chance), involving 1199 participants 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 in mortality at 14 days, 28 days or discharge (very low-quality evidence) when automated monitoring systems were compared to standard care. Very low-quality evidence was available on failed detection of sepsis but data reporting was too unclear to enable us to analyse this in a meaningful way. Other outcomes that we wished to assess like 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 were not reported in any of the studies.

Quality of the evidence

Results of this review show limited, very low-quality evidence, which has prevented us from drawing meaningful conclusions. It is unclear what effect automated systems for monitoring sepsis have on any outcomes included in this review, and therefore we are uncertain if automated sepsis monitoring is beneficial or not. Additional, high-quality evidence is needed to help address our review question.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Automated monitoring systems compared to standard care for detecting sepsis

Automated monitoring systems compared to standard care for detecting sepsis

Patient or population: participants of any age admitted to the intensive care or critical care unit for any reason (including, but not limited to postsurgery, trauma, stroke, myocardial infarction, arrhythmia, burns, and hypovolaemic or haemorrhagic shock)

Settings: hospitals in USA

Intervention: automated monitoring systems (any process capable of screening patient records or data (one or more systems) automatically at intervals for markers or characteristics that are indicative of sepsis)

Comparison: standard care such as paper-based systems

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard care	Automated monitoring				
Time to initiation of antimicrobial therapy (Time to initiation starts at the time of admission)	3 studies reported data in relation to this outcome but data could not be pooled. The largest study included 680 participants and reported median time to initiation of first or new antibiotic was 5.6 hours (IQR 2.3 to 19.7) in the intervention group (n = not stated) and 7.8 hours (IQR 2.5 to 33.1) in the control group (n = not stated)			Unclear for this outcome (3 studies containing approximately 1200 participants overall)	Very low[1,2]	
Time to initiation of fluid resuscitation (Time to initiation starts at the time of admission)	Not reported	Not reported	Not reported	-	-	None of the included studies reported this outcome
30-day mortality*	*No studies reported 30-day mortality. 1 study reported 14-day mortality and found no significant differences between groups (20% in the intervention, 21% in the control). 1 study reported mortality at 28 days or discharge and found no significant differences between groups (14% in the intervention, 10% in the control).			-	Very low[1,2]	

	Sample sizes were not reported adequately for these outcomes and so we could not estimate confidence intervals					
Length of stay in ICU (in days)	Median 3.0 (IQR 2 to 4) days	Median 3.0 (IQR 2 to 5) days	-	442 (1 study)	Very low[1,3]	P = 0.22
Failed detection of sepsis (as reported by studies)	1 study reported failed detection of sepsis in 2 participants but did not state which group(s) they occurred in.			560 (1 study)	Very low[1,2]	
Quality of life measured at the latest available time point post-discharge from ICU (preferred measure SF-36 then EQ-5D)	Not reported	Not reported	Not reported	-		None of the included studies reported this outcome.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IQR**: interquartile range

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded two levels for risk of bias due to unclear randomization methods, allocation concealment and blinding.
[2]Downgraded two levels for precision because of missing effect estimates and wide uncertainty.
[3]Downgraded one level for precision due to missing study data.

BACKGROUND

Description of the condition

Sepsis is a life-threatening clinical syndrome. The criteria for the diagnosis of sepsis have evolved over time and are generally defined by international consensus groups (ACCP/SCCM 1992; Levy 2003; Singer 2016). It is usually diagnosed when a patient has a suspected or documented infection, alongside systemic inflammatory response syndrome (SIRS). The criteria for diagnosing SIRS typically include the presence of two or more of the following abnormalities in the absence of other known causes, such as chemotherapy.

1. Temperature greater than 38.3°C (hyperthermia) or less than 36.0°C (hypothermia)
2. Heart rate greater than 90 beats per minute (tachycardia)
3. Breathing greater than 20 breaths per minute (tachypnoea) or arterial carbon dioxide concentration ($PaCO^2$) less than 32 mmHg (hyperventilation)
4. Blood glucose greater than 7.7 mmol/L (hyperglycaemia) in the absence of diabetes mellitus
5. New altered behaviour or mental state
6. White blood cell count greater than 12,000 per microlitre (leukocytosis) or less than 4000 per microlitre (leukopenia) or normal white blood cell count with greater than 10% immature forms.

If left untreated, sepsis can develop into severe sepsis (sepsis with organ dysfunction) or septic shock (severe sepsis with hypotension despite adequate fluid resuscitation). Mortality for this group of patients can be 40% or even higher depending on definitions used (Szakmany 2018). Patients with sepsis often require admission to the intensive care unit (ICU). The incidence of sepsis in people admitted to ICU for other critical illnesses is also high (20% to 70% of people admitted to ICU in Europe, with considerable variance by country, Vincent 2006). Diagnosing sepsis is challenging and time consuming. It often requires the combination of information from several sources to be reviewed (e.g. patient history, laboratory data, and physiological data) at regular intervals (Cohen 2015). Further, although many options are available to guide therapy (Andriolo 2017), and many interventions have been tested (Annane 2015; Borthwick 2017), early detection offers the prospect of a better therapeutic response. In addition, the complexity of diagnosis combined with the degree of illness results in a significant cost for treating sepsis in the ICU. For example, the cost of treating each patient with sepsis in the ICU was recently estimated as approximately EUR 29,000 in the Netherlands (Koster-Brouwer 2014), or GBP 20,000 in the UK (UK Sepsis Trust 2013).

Description of the intervention

Automated monitoring systems provide a means of monitoring patient data continuously, and can facilitate the assembly of data from unconnected information systems (Hooper 2012). These tools are variously referred to as alert systems, detection systems and monitoring systems (Makam 2015). In essence, the systems process clinical data - that are routinely collected - to identify sepsis according to predetermined diagnostic thresholds, and include an electronic means of alerting staff. Although the algorithms (i.e. criteria) used to identify sepsis vary between the different automated systems (Buck 2014; Nachimuthu 2012), their key feature is an ability to monitor one or more electronic systems (e.g. patient electronic health records) for potential indicators of sepsis. For example, a system may 'listen' for modified SIRS criteria (Hooper 2012), although SIRS criteria have recently been deemed to have inadequate specificity and sensitivity for the detection of sepsis (Singer 2016). Following detection of potential sepsis, the system should provide an automated notification (e.g. via email, phone message or pager) to the relevant physician or nurse, flagging the requirement for clinical evaluation and potential initiation of therapy (Hooper 2012; Koenig 2011). The use of electronic early-recognition tools has previously been validated in the critical care setting for detection of acute respiratory distress syndrome (ARDS) (Koenig 2011). Potential adverse effects of automated systems might include the failure to detect sepsis and alarm fatigue (i.e. where frequent false alarms cause staff to ignore notification of potential sepsis).

How the intervention might work

Automated detection systems monitor patient data continuously to facilitate the early detection of sepsis in the ICU. The diagnosis of sepsis or septic shock is particularly time-sensitive, as the length of time until initiation of appropriate antimicrobial therapy or fluid resuscitation is a critical determinant of survival in these patients (Dellinger 2013; Kumar 2006; Rivers 2001; Yealy 2014). Therefore, guidelines recommend early fluid resuscitation of the septic patient within six hours of recognition of sepsis, and administration of broad-spectrum antibiotics within one hour of the recognition of septic shock or severe sepsis without septic shock (Dellinger 2013). Automated detection systems offer the possibility of monitoring patients in 'real time' (Meurer 2009), and can alert the relevant physicians or nurses (e.g. by email or pager) to the need for timely clinical evaluation and potential initiation of treatment.

Why it is important to do this review

Although the rate of mortality from sepsis has improved (Kaukonen 2014; McPherson 2013), national audits indicate that clinical standards relevant to the management of patients with sepsis are not being met, despite ongoing education programmes (CEM 2012). The UK Parliamentary Ombudsman recently published a detailed report that identified common themes in 10 case studies of patients that died following sepsis (Parliamentary Ombudsman 2013). Failings were identified throughout the care pathway, from carrying out a timely initial assessment and identifying the source of infection, to adequate monitoring and timely initiation of treatment (Parliamentary Ombudsman 2013). Automated monitoring systems for the detection of sepsis may facilitate earlier detection and treatment of sepsis in the ICU, potentially increasing adherence to clinical standards and improving patient outcomes.

Additionally, sepsis is the most expensive condition treated in hospitals, accounting for approximately 5% of total hospitalization costs and an overall annual cost of USD 20.3 billion in the USA (Torio 2011), and more than GBP 2.5 billion in the UK (UK Sepsis Trust 2013). Early detection of sepsis via automated systems and subsequent timely intervention may reduce treatment costs and overall resource use. The UK Sepsis Trust estimates that there are more than 100,000 hospitalizations per year for sepsis, and that achieving 80% delivery of basic standards of care could result in a potential cost saving of GBP 170 million per year, even after allowing for increased survival-related costs (UK Sepsis Trust 2013).

Finally, it is now recognized that sepsis is associated with significant mortality, long-term morbidity and a reduction in health-related quality of life (Winters 2010), thus reinforcing the importance of early effective treatment from both a patient and resource utilization perspective. In summary, there is clear rationale to synthesize the evidence relating to the use of automated systems for the detection of sepsis.

OBJECTIVES

To evaluate whether automated systems for the early detection of sepsis can reduce the time to appropriate treatment (such as initiation of antibiotics, fluids, inotropes, and vasopressors) and improve clinical outcomes in critically ill patients in the ICU.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) reported as full text, or published as abstract only, and unpublished data. We did not exclude unblinded studies. We excluded cross-over studies as it would not be feasible to evaluate automated monitoring followed by standard care (or vice-versa) in the same participant as the detection of sepsis requires treatment. We also excluded quasi-RCTs (studies using inadequate methods for randomization, such as date of birth of participant or date of ICU admission).

Types of participants

We included participants of any age who were admitted to intensive or critical care units for critical illness (including, but not limited to postsurgery, trauma, stroke, myocardial infarction, arrhythmia, burns, and hypovolaemic or haemorrhagic shock). We excluded participants admitted with confirmed sepsis.

Types of interventions

We included studies that randomized participants to receive monitoring for sepsis using an automated system versus standard care (i.e. systems where paper-based or other formats of observation charts are reviewed by staff directly). We defined an automated system as any process capable of screening patient records or data (one or more systems) automatically at intervals for markers or characteristics that are indicative of sepsis. The parameters/algorithm used by the system (for example, the thresholds of blood pressure indicative of hypotension or the nature of the biomarkers employed) may vary. However, if the system identifies a potential case of sepsis, it should flag the patient's record and alert the relevant healthcare professional (via email, pager or phone message).

Types of outcome measures

Primary outcomes

1. Time to initiation of antimicrobial therapy* (in minutes)
2. Time to initiation of fluid resuscitation* (in minutes)
3. 30-day mortality

*Time to initiation starts at the time of admission.

Note: studies were not required to distinguish between sepsis that is detected via standard care pathways and sepsis detected via the automated system in the intervention group; if studies employ adequate control groups and sample sizes, and if automated monitoring confers a benefit, a difference between groups should be detectable.

Secondary outcomes

1. Length of stay in ICU (in days)
2. Failed detection of sepsis (during ICU stay), as reported by studies
3. Quality of life measured at the latest available time point post-discharge from ICU (preferred measure SF-36 then EQ-5D)

Search methods for identification of studies

Electronic searches

We identified RCTs through literature searching with systematic and sensitive search strategies as outlined in Chapter 6.4 of the *Cochrane Handbook of Systematic reviews of Interventions* (Lefebvre 2011). We did not apply restrictions to language or publication status.

We searched the following databases for relevant trials.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 8) in the Cochrane Library
2. MEDLINE (Ovid SP, 1966 to 18 September 2017)
3. Embase (Ovid SP, 1988 to 18 September 2017)
4. CINAHL (Cumulative Index to Nursing and Allied Health Literature, EBSCO, 1937 to 18 September 2017)
5. Web of science (1900 to 18 September 2017)
6. LILACS (Bireme, 1982 to 18 September 2017)

We developed a subject-specific search strategy in MEDLINE and used that as the basis for the search strategies in the other databases listed. Where appropriate, the search strategy was expanded with search terms for identifying RCTS. All search strategies can be found in Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, and Appendix 6.

We scanned the following trials registries for ongoing and unpublished trials:

1. The World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en/)
2. ClinicalTrials.gov (clinicaltrials.gov)

We developed the search strategy in consultation with Cochrane Dementia's Information Specialist.

Searching other resources

We scanned the reference lists and citations of included studies and any relevant systematic reviews identified for further references to additional studies. When necessary we contacted study authors by email for additional information.

Data collection and analysis

Our methods for data collection and analysis differed from those stated in the published protocol (Evans 2016). The differences and reasons for them are detailed in the section 'Differences between protocol and review'.

Selection of studies

Two review authors (SW, PA) independently screened titles and abstracts arising from the searches, for possible inclusion in the review; we retrieved and assessed the full-text articles of the potentially relevant studies and two review authors (SW, PA) independently identified: a) studies for inclusion in the review; and b) ineligible studies; recording the reasons for exclusion in the 'Characteristics of excluded studies' table. We planned to resolve disagreements by discussion or, if required, through consultation with a third review author (IK). We identified and excluded duplicate records. We also planned to collate multiple reports of the same study so that the study is the unit of interest. The results of this selection process is summarized in a PRISMA flow diagram (Moher 2009).

Data extraction and management

Two authors (SW, IK) extracted the following information for each study:

1. methods: study design; total duration of study; number of study centres and location; study setting; date of study;
2. participants: number of participants that were:
   a. randomly assigned,
   b. discontinued the study, and
   c. excluded from the analyses after randomization; condition and severity of condition; inclusion and exclusion criteria;
3. intervention: intervention, comparator, algorithm/criteria used by the automated system;
4. outcomes: primary and secondary outcomes including details of time points;
5. other information: trial funding and potential conflicts of interest of authors

Another review author (PA) checked data extraction accuracy.

Assessment of risk of bias in included studies

Two review authors (SW, PA) independently assessed study risk of bias according to criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the risk of bias for the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

For each domain, we graded the risk of bias as high, low or unclear, and provided justification for our judgement in the 'Risk of bias' table.

Measures of treatment effect

We planned to analyse dichotomous data using risk ratios with 95% confidence intervals, and continuous data with mean differences and 95% confidence intervals.

Unit of analysis issues

All studies were randomized by individual, and outcome data were reported for participants.

Dealing with missing data

We contacted study investigators to obtain missing outcome data and to verify important study characteristics, but did not receive any responses.

Assessment of heterogeneity

Insufficient data were available to permit assessment of heterogeneity.

Assessment of reporting biases

We planned to explore small study and publication biases by creating and examining a funnel plot if we were able to pool data from more than 10 trials.

To assess within-study reporting bias of outcomes, we planned to search for trial protocols matching included studies published after 1 July 2005 in the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (www.who.int/ictrp/en/), and Clinicaltrials.gov (clinicaltrials.gov/), for the trial protocols.

Data synthesis

Insufficient data were available to permit meta-analysis or a meaningful summary of the evidence.

'Summary of findings' table and GRADE

We used the principles of the GRADE system (Guyatt 2008), to assess the quality of the body of published and unpublished evidence associated with the following outcomes in our review: time to initiation of antimicrobial therapy, time to initiation of fluid resuscitation, 30-day mortality, length of stay in ICU, failed detection of sepsis, and quality of life (postdischarge).

Two authors (SW, PA) independently assessed the quality of the evidence. We used the five GRADE considerations (study limitations, inconsistency, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it relates to the studies that contribute data to the prespecified outcomes. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence takes into consideration within-study risk of bias (methodologic quality) (Guyatt 2011a), the directness of the evidence (Guyatt 2011b), heterogeneity of the data (Guyatt 2011c), precision of effect estimates (Guyatt 2011d), and risk of publication bias (Guyatt 2011e). We used methods and recommendations described in Chapter 8 (section 8.5 and 8.7; Higgins 2011), Chapter 11 (Schünemann 2011) and Chapter 13 (section 13.5; Reeves 2011) of the *Cochrane Handbook for Systematic Reviews of Interventions*, using GRADEpro software (GRADEpro GDT 2015). We justified all decisions to downgrade the quality of studies using footnotes.

Subgroup analysis and investigation of heterogeneity

Insufficient data were available to permit subgroup analysis.

Sensitivity analysis

Insufficient data were available to permit sensitivity analysis.

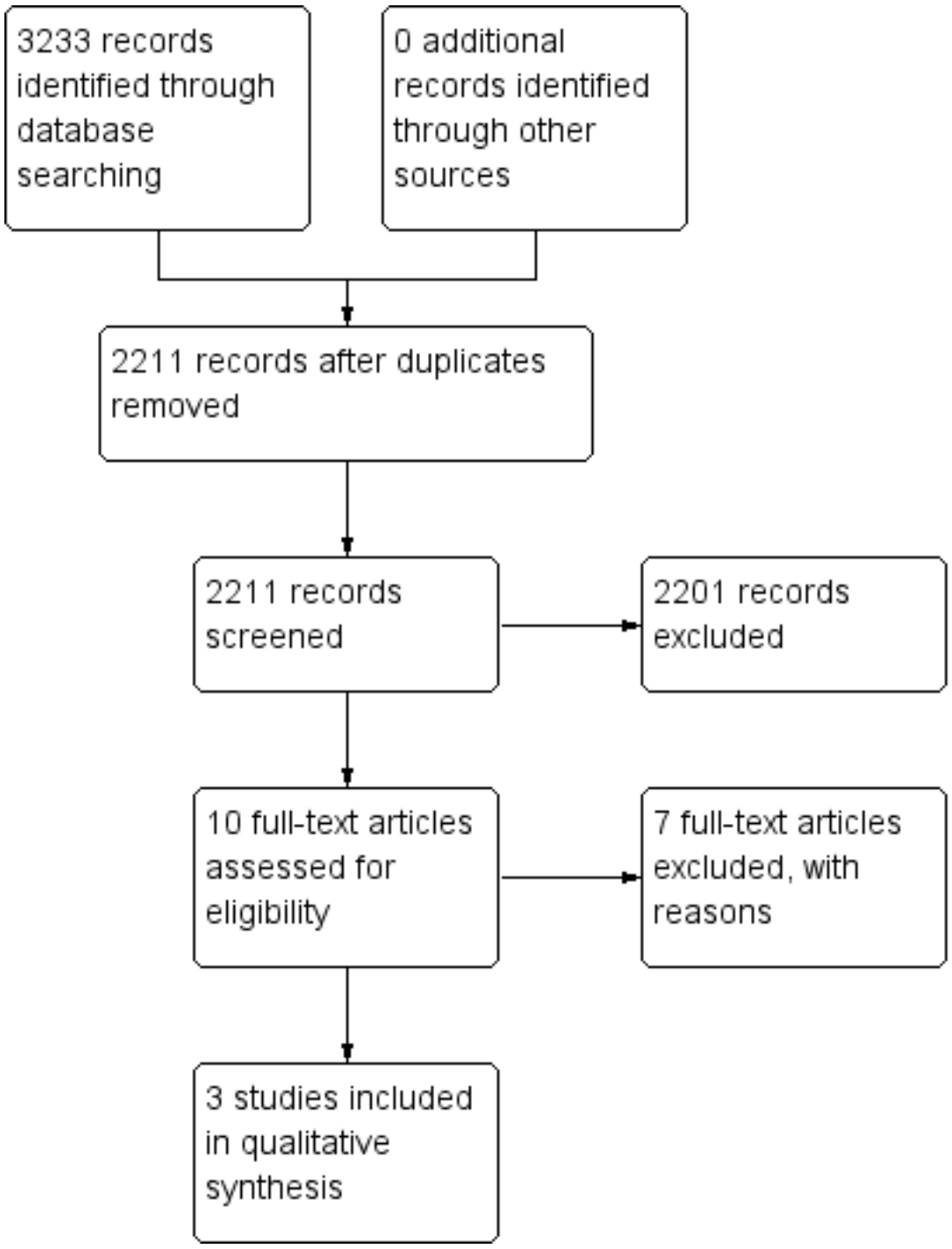
RESULTS

Description of studies

Results of the search

The search retrieved 3233 results, we selected 10 studies for full text consideration, and included three in this review. We have summarized the selection process in Figure 1.

Figure 1. Study flow diagram



Included studies

We included three studies in this review (total of 1199 participants) (Hooper 2010; Hooper 2011; Hooper 2012). However, two of the studies were abstracts from conferences and contained limited data (Hooper 2010; Hooper 2011). We tried to contact the lead author of the studies to obtain additional information, and to check if the studies were different reports relating to a single study but we were unable to make contact. The three publications quote one grant number in common, which appears to be a programme grant, and have the same first author. However they contain different data and we have treated them as three separate studies for this review.

Study populations

The studies included participants admitted to the medical or surgical ICU but no details on the participants' underlying conditions were provided. Some of the participants were receiving mechanical ventilation.

Settings

The studies were described as being conducted in medical intensive care units (MICU) or in a tertiary care centre. One study stated that it was conducted in the USA but two studies did not provide this information although it can be reasonably assumed that they were conducted in the USA too.

Interventions

The interventions included in this review included computerized automated monitoring systems to monitor and alert one or more of the care team when modified SIRS criteria were met. One study described this as a 'listening application' but none of the studies described how the system worked or what information it monitored or listened to.

All of the included studies assessed the automated alert component of the monitoring system. All participants received automated electronic monitoring during their hospital stay, and were randomized to an intervention group (automated alerts sent from the system to the care team) or to usual care (no automated alerts sent from the system). Only one study explained the process for alerting the care team once modified SIRS criteria were met, where a text message notification was sent to the pagers of the care and admissions teams. It also flagged the patient's name on the primary team physician's electronic patient list, and flagged the patient's medical record so that any physicians taking care of the patient could see the information. Physicians were asked to acknowledge receipt of the notification and indicate if the participant had sepsis. If a physician failed to respond, a reminder was resent after one hour. The system did not give any management recommendations and providers were not instructed to treat alerted participants in a different manner than any other patient. If physicians determined a participant to be septic, further notifications by the system were suspended for seven days. If they determined a participant not to be not septic, further notifications were suspended for two days unless a previously normal white blood cell count or temperature became abnormal.

None of the included studies assessed other components of the monitoring systems, such as the underlying sepsis-detection algorithm.

Comparators

The comparator included in this review was standard care. Two of the studies stated that the comparator was 'usual care' but did not state what this entailed. One study described participants in the usual-care group as receiving computerized monitoring, which generated a time stamp when modified SIRS criteria were met but notifications were not relayed to any of the care team.

Funding sources

All studies stated that they received funding, but only provided initials of the funders. It can be reasonably assumed that all three studies were funded by the National Institutes of Health (NIH), and one study also received funding from National Centre for Research Resources/National Intitutes of Health (NCRR/NIH), and National Science Foundation (NSF).

Excluded studies

We excluded seven studies from the review.

Three of the seven studies were excluded because they did not report the results from RCTs (Croft 2014; Karch 2016; Slotman 2000). A further three studies were excluded because the participants were diagnosed with sepsis at enrolment (Semler 2013; Semler 2015; Zhang 2013). One study was excluded because it was not based in the ICU (Sawyer 2011).

Studies awaiting classification

There are no studies awaiting classification.

Ongoing studies

We identified no ongoing studies.

Risk of bias in included studies

See Figure 2; Figure 3

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

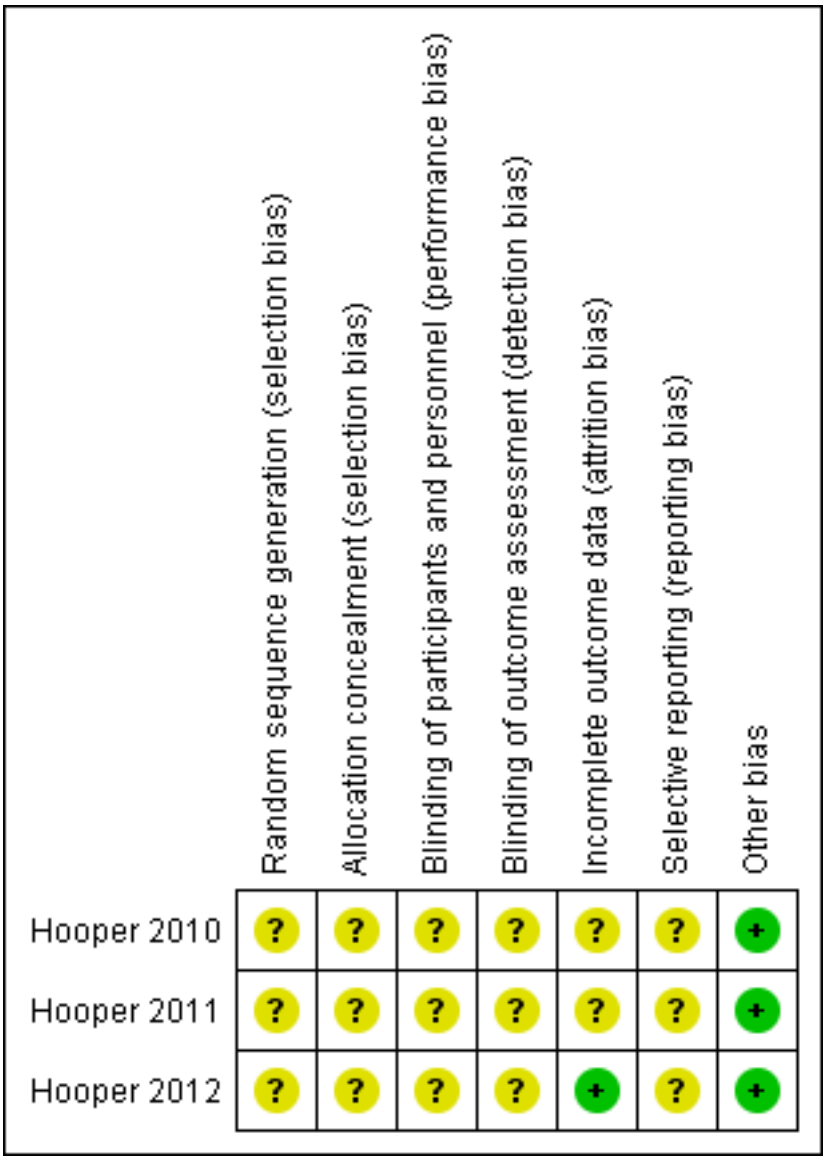
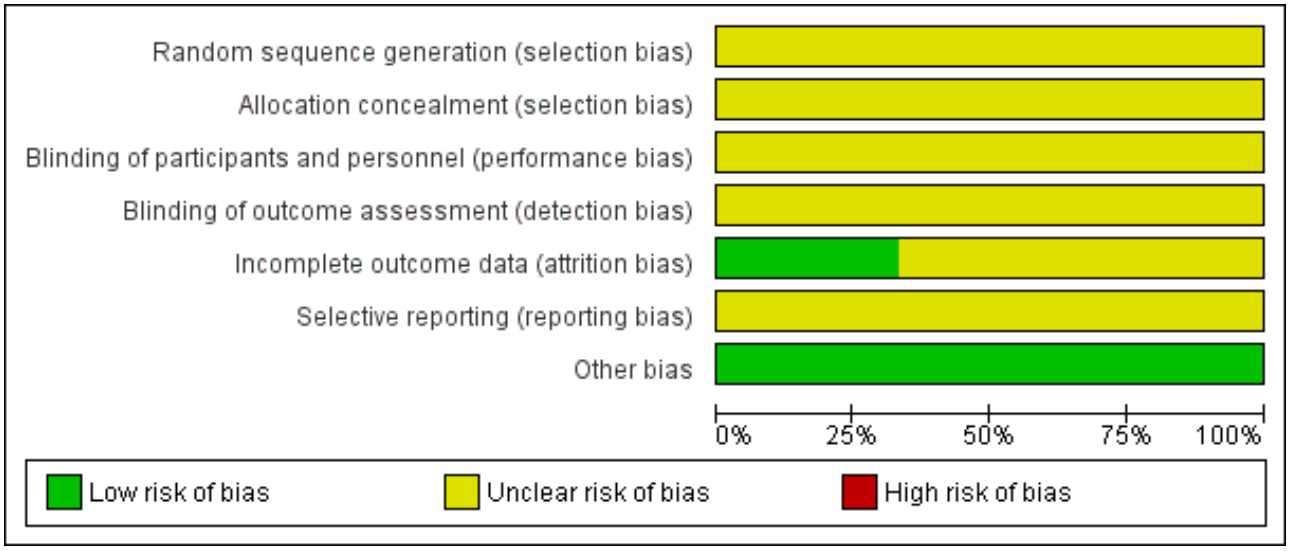


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

All three included studies were described as RCTs and we therefore considered them to be at low risk of selection bias. However, none of the three studies provided details of the randomization procedure and so it is unclear if the methods used influenced results.

Blinding

None of the three studies stated if participants or personnel involved in the study were blinded to study group allocation. Patients receiving care in the ICU would usually be unconscious or very unwell and so study participants are likely to be unaware of allocation. In addition it is unlikely that study participants could influence any of the outcomes considered in this review. Therefore participant blinding, or lack of, is unlikely to have any effect on study outcomes. A lack of study investigator or staff blinding could influence behaviour, such that participants in the standard care group are monitored more closely if staff have a heightened awareness of sepsis, or that participants in the intervention group are monitored less closely if staff feel they can rely on the intervention to alert them to deteriorating patient condition. This may mean that potential differences between groups are reduced such that there is no detectable differences between them.

Incomplete outcome data

Insufficent information was provided to assess this in two studies (Hooper 2010; Hooper 2011). One participant in Hooper 2012 was excluded after randomization as they died before an alert could be generated. Otherwise in this study, all participants appear to have been followed up to death or discharge from hospital.

Selective reporting

We were unable to locate the trial protocols by searching on trials registers as listed in the methods, and so we identified no reporting biases.

Other potential sources of bias

We did not identify any other sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Automated monitoring systems compared to standard care for detecting sepsis

Primary outcomes

1. Time to initiation of antimicrobial therapy

Three studies (n = 1199) reported median time to initiation of first or new antimicrobial therapy.

Hooper 2012 reported a median time of 6.0 hours (interquartile range (IQR) 2.4 to 18.8) for the intervention group (n = 220) and 6.1 hours (IQR 2.5 to 21.0) for the control group (n = 222). No clear difference between the groups was seen (P = 0.95). Hooper 2011 also reported this outcome. This study included 680 participants but did not state the number of participants allocated to each group. In this study, median time to initiation of first or new antibiotic was 5.6 hours (IQR 2.3 to 19.7) in the intervention group (n = not stated) and 7.8 hours (IQR 2.5 to 33.1) in the control group (n = not stated).

Hooper 2012 also reported subgroup analyses for this outcome. Among only those participants diagnosed with sepsis (n = 61), median time to initiation of antimicrobial therapy was 3.4 hours (IQR 1.7 to 12.3) in the intervention subgroup (n = 28), and 3.5 hours (IQR 1.2 to 13.8) in the control subgroup (n = 33). No clear difference between the groups was seen (P = 0.93). Among only those participants not on antibiotics at the time of enrolment (n = 231), 131 were subsequently administered antibiotics at a median time of 5.2 hours (IQR 2.1 to 13.0) in the intervention group (n = 66), and 5.1 hours (IQR 1.5 to 17.0) in the control group (n = 65). No clear difference was seen.

Although Hooper 2010 did not report this outcome for the study group (n = 77), it did report it for a subgroup of participants who were diagnosed with sepsis and received antibiotics at enrolment

(n = 9), reporting that there were no differences between groups. Median time to first or new antibiotic initiation was 12.2 hours (0.96 to 29.0, (IQR as this is not stated in the results)) in the intervention group (n = 4), and 6.2 hours (2.4 to 23.5) in the control group (n = 5). Lack of meaningful differences for this result is likely to be because of a small sample size, but the findings are counter-intuitive and in the opposite direction to results from the other studies, since the median time to initiation is almost double the time in the intervention group, which received alerts, than in the control group. It is unclear why.

Overall we assessed the evidence for this outcome to be very low (see Summary of findings for the main comparison).

2. Time to initiation of fluid resuscitation

None of the included studies reported this outcome.

3. 30-day mortality

None of the included studies specifically reported this outcome (30-day mortality), but two studies reported mortality over different time frames and involved a total of 519 participants.

Hooper 2010 (n = 77) reported 14-day mortality, which was 20% in the intervention group (numerator and denominator not stated) and 21% in the control group (numerator and denominator not stated, P = 0.94).

Hooper 2012 (n = 442) also reported mortality, with the methods stating follow-up to 28 days or hospital discharge, whichever occurred first. Overall there was 14% mortality in the intervention group, and 10% mortality in the control group (numerators not reported, P = 0.29).

Overall, we assessed the evidence for this outcome to be very low (see Summary of findings for the main comparison).

Secondary outcomes

1. Length of stay in ICU

One study, Hooper 2012 involving 442 participants, reported this outcome. Median length of stay in the ICU was 3.0 days (IQR 2.0 to 5.0) in the intervention group (n = 220) and 3.0 days (IQR 2.0 to 4.0) in the control group (n = 222). No clear difference between groups was seen (P = 0.22).

Overall, we assessed the quality of the evidence for this outcome to be low (see Summary of findings for the main comparison).

2. Failed detection of sepsis during ICU stay

One study, Hooper 2012, reported this outcome. Although this study states that it involved a total of 442 participants who met modified SIRS criteria and were randomized, it reports that 60 out of 560 participants admitted to the medical ICU did not meet modified SIRS criteria at any point, but determined two participants to be septic during their ICU stay. It is unclear if the 560 participants involved in this outcome were different from the 442 randomized to the study, or why all 560 were not included in the study. Therefore it is also unclear if any of the participants with failed detection of sepsis belonged to one of the study groups.

Overall, we assessed the evidence for this outcome to be very low (see Summary of findings for the main comparison).

3. Quality of life measured at the latest available time point post-discharge from ICU

None of the included studies reported this outcome.

DISCUSSION

Summary of main results

We included evidence from three studies involving 1199 participants in this review, although it is unclear if the study populations in the three studies were independent of each other. We did not undertake any meta analysis of the data, and we are confident that our conclusions would not change even if the populations were not independent of each other.

All three studies assessed the alert component of the monitoring system. All three studies reported time to initiation of first or new antimicrobial therapy (n = 1999). There were no meaningful differences between those receiving automated monitoring alerts and those receiving standard care (automated monitoring and no alerts) in any of the three studies (Hooper 2010; Hooper 2011; Hooper 2012). This was also the case in subgroup analyses of 61 people diagnosed with sepsis, and 131 people not on antibiotics at time of enrolment to the study who were subsequently administered antibiotics (Hooper 2012). It was not possible to pool the results due to insufficient data reported in the studies, and lack of similar subgroup analysis between studies.

None of the included studies reported our prespecified outcome '30-day mortality'. Instead, one study (Hooper 2010) reported 14-day mortality, and another study (Hooper 2012), reported mortality up to 28 days or discharge from hospital, whichever came soonest. Neither of these studies included information on the number of participants included in each study group, and none of the studies found meaningful differences between those receiving automated monitoring and those receiving standard care.

One study reported length of stay in ICU (Hooper 2012), but did not report the number of participants in each study group. No meaningful differences were reported between people receiving automated monitoring and those receiving standard care.

None of the included studies reported time to fluid resuscitation in minutes, or quality of life after the participant was discharged from the ICU. One study did report failed detection of sepsis (Hooper 2012), but did not report whether the cases occurred in participants receiving automated monitoring, standard care, or were from outside the study population.

Overall completeness and applicability of evidence

All of the included studies assessed the automated alert component of the monitoring system, but none of the studies assessed the whole system or its other components, such as the underlying algorithm

All of the automated monitoring technologies used the same criteria for detecting when a patient met the criteria for alerting staff, and all included patient populations that are likely to be representative of those in the intensive or critical care unit. All of the evidence appears to be generated in the USA, therefore the evidence is likely to be applicable to similar care settings in the USA. However, it is unclear if the evidence would be applicable

to similar settings in other countries, where care standards and processes may be different to the USA (such as staffing ratios and standard monitoring practices for example). The evidence can be considered to be incomplete, as included studies often reported relevant outcomes without providing sufficient information to enable analysis, or reporting dissimilar subgroup analyses. Some primary and secondary outcomes that we wanted to include in this review were not reported at all. Therefore we are unable to draw meaningful conclusions about automated sepsis monitoring.

Quality of the evidence

In general, studies reported insufficient information to enable us to assess adequately the quality of the evidence. All of the included studies were considered to be RCTs and so biases due to selection processes are likely to be low. The included studies did not state if participants or investigators were blinded to treatment allocation and so we were uncertain if allocation biases were present. We felt that lack of participant blinding was unlikely to influence study results, but if staff delivering care to patients were not adequately blinded, this could mean that potential differences between groups were reduced such that there were no detectable differences between them. Data relating to attrition were not well reported in the studies so it is unclear if all participants have been followed up to death or discharge from hospital. Attrition in short-term studies in hospital such as those included in this review should be low, but we were unable to be sure.

Reporting of the measured outcomes was poor. Two studies appeared only as conference abstracts and therefore lacked detailed information about outcomes. This made it hard to assess either the results themselves or their consistency and precision. Overall this reduced our confidence in the body of evidence, particularly as results from some whole studies seemed to be missing.

Potential biases in the review process

We made several review decisions after we had reviewed the study data, mainly because the studies reported insufficient data to enable us to progress with our planned approach (see Differences between protocol and review). This may introduce a bias into the review process in that the outcomes reported in the studies may be subject to outcome reporting bias.

Agreements and disagreements with other studies or reviews

We are not aware of other systematic reviews addressing this question.

AUTHORS' CONCLUSIONS

Implications for practice

Results of this review reveal limited very low-quality evidence, which has prevented us from drawing meaningful conclusions. It is unclear what effect automated systems for monitoring sepsis have on any outcomes included in this review, and therefore the implications for practice are unclear. While it might be logical to use systems to integrate clinical information, there is a lack of evidence about the use of such systems for triggering clinical review and intervention. It is uncertain whether such systems can replace regular, careful review of the patient's condition by experienced healthcare staff.

Implications for research

There remains an important question about whether automated monitoring and alerting can help in the early recognition of sepsis and early intervention. As patients in intensive care are routinely monitored using integrated information systems, the infrastructure required for such studies is readily available. High-quality randomized controlled trials are needed, which should use appropriate randomization methods and adequate blinding of clinicians and outcome assessors. The relevant outcomes are short term and therefore data collection should be feasible.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Hooper 2010

Methods	Conference abstract of a parallel-group, RCT. Unclear if single- or multicentre
Participants	77 participants admitted to the MICU, who met modified SIRS criteria (defined at 2 out of 4 SIRS criteria, but mandates that white blood cell count or temperature be abnormal) were enrolled into the trial. **Age**: not stated **Gender**: not stated Unclear where the trial took place, but presume USA

Hooper 2010 *(Continued)*

Interventions	**Listening application: (n = not stated)** programmed to monitor participants for modified SIRS criteria, that when met sends an automated notification to their ICU team **Usual care (n = not stated):** further information on what this group received is not stated.
Outcomes	1. Time to antibiotic treatment 2. Time to drawing of blood cultures 3. Intubation rates 4. Rate of shock development 5. 14-day mortality 6. Presence of sepsis
Notes	We contacted study author by email to check relationship between this study and Hooper 2011 and Hooper 2012. Email bounced back and we could not find up-to-date contact information. States that the abstract was funded by: a model-integrated, guideline driven process management system for sepsis (RC1 LM10310) **Declarations of interest**: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States that participants were randomized, but methods for randomization not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	No other sources of bias identified
Other bias	Low risk	Not identified

Hooper 2011

Methods	Conference abstract of a single-centre, parallel-group RCT
Participants	10,727 participants admitted to a tertiary care centre were monitored by an electronic application to detect modified SIRS criteria (defined as 2 out of 4 SIRS criteria but mandates that white blood cell count or temperature be abnormal).

Hooper 2011 *(Continued)*

	680 patients met modified SIRS criteria at some point during their hospitalisation and underwent analysis. **Age:** 57 years (median) **Gender**: not stated Unclear where the trial took place, but presume USA
Interventions	**Physician alerts (n = not stated):** no further details reported **Control group receiving usual care (n = not stated):** no further details reported
Outcomes	1. Time from ICU admission to modified SIRS criteria 2. Receipt of new antibiotics after reaching modified SIRS criteria
Notes	We contacted study author by email to check relationship between this study and Hooper 2010, and Hooper 2012. Email bounced back and we could not find up-to-date contact information. States that the abstract is funded by: NIH 1RC1LM010310-01 **Declaration of interest**: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States that participants were randomized, but methods for randomization not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	No other sources of bias identified
Other bias	Low risk	Not identified

Hooper 2012

Methods	Study reported in full: single-centre, parallel-group RCT taking place between May and August 2009
Participants	442 participants under the care of the MICU were enrolled in the study

Hooper 2012 *(Continued)*

	Patients were eligible to be included if they met modified SIRS criteria, defined as ≥ 2 of the 4 SIRS criteria within a rolling 24-h window, with at least 1 being an abnormal temperature or white blood cell count. **SIRS criteria** 1. Temperature > 38 °C or < 36 °C 2. Heart rate > 90 beats per minute 3. Respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mmHg 4. White blood cell count > 12000 cells mm^3 or < 4000 cells mm^3, or > 10% immature (band) forms Patients were excluded from the study if they had been previously enrolled during the same hospital admission, or if they were being cared for in the MICU by a team other than one of the MICU teams. Enrollment time was considered to be the first time a participant met modified SIRS criteria while under the care of the MICU. Participants were followed up for 28 days After discharge from hospital participants were eligible for re-enrolment if they were subsequently readmitted. **Age in years**: intervention = 55 (mean), 18 (SD); control = 54 (mean), 18 (SD) **Gender (male/female)**: intervention = 125:95; control = 118:104 Study took place in Vanderbilt University, USA
Interventions	**Computerized monitoring + notifications (n = 220)**: notifications that modified SIRS criteria had been met were sent via text message to the pagers of the primary team physician contact. A flag appeared against the participant's name on the physician's electronic patient list. Pages were sent to those who were listed as the current primary contact for the admitting team, but notifications in the medical record were available to all physicians taking care of the participant. Physicians were asked to acknowledge receipt of the notification and indicate if the participant had sepsis. if a physician failed to respond, a reminder was resent after 1 hour. System gave no management recommendations and providers were not instructed to treat alerted participants in a different manner than any other patient. If physicians determined participants to be septic, further system notifications suspended for 7 days. If physicians determined participant not to be septic, further notifications suspended for 2 days unless a previously normal white blood cell count or temperature became abnormal **Computerized monitoring + no notification control group (n = 222)**: participants received computerized monitoring that generated a time stamp when modified SIRS criteria were met. However notifications were not relayed to any physicians.
Outcomes	1. Follow-up to 28 days or hospital discharge, whichever occurred first 2. Time to administration of first or changed antibiotic 3. 6-h fluid intake/output 4. Daily fluid intake/output 5. Lactate measurement 6. Daily vasopressor administration 7. Hypotensive at enrolment 8. ICU length of stay 9. Hospital length of stay 10.Mortality 11.Sepsis diagnosed
Notes	We contacted study author by email to check relationship between this study and Hooper 2010, and Hooper 2011. Email bounced back and we could not find up-to-date contact information.

Hooper 2012 *(Continued)*

States that this study was grant supported by 1RC1LM010310-01 from NIH, 1UL1 RR024975 from NCRR/NIH, and CCF0424422 from NSF

Declaration of interest: states that the study authors have not disclosed any potential conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States that participants were randomized, but methods for randomization not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 post-randomization exclusion due to early death. No other apparent loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No other sources of bias identified
Other bias	Low risk	Not identified

ICU: intensive care unit
MICU: medical intensive care unit
RCT: randomized controlled trial
SIRS: systemic inflammatory response syndrome

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Croft 2014	The study describes the implementation of a computerized system in a before and after study
Karch 2016	Study describes the derivation of a data-based diagnostic model
Sawyer 2011	Ward-based study comparing implementation of a sepsis alert system in intervention and control wards
Semler 2013	Patients already had sepsis to enter the study
Semler 2015	Patients already had sepsis to enter the study
Slotman 2000	Study describes the derivation of a data-based predictive model

Study	Reason for exclusion
Zhang 2013	Protocol for a trial where patients already have sepsis or ARDS or both

ARDS: acute respiratory distress syndrome

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Decision Support Systems, Clinical] explode all trees
#2 ((automat* or electronic) near/5 (monitoring or detect* or evaluat* or diagnos* or tool* or decision*)) or (early near/3 (monitoring or detect* or treat* or recogn* or initiat* or therap* or diagnos*)) or ((predefined or pre defined) near/3 criteria) or (system* near/5 (paper or computer or monitoring or recogn* or detection or automated)) or alert* or surveillance
#3 #1 or #2
#4 MeSH descriptor: [Sepsis] explode all trees
#5 MeSH descriptor: [Shock, Septic] explode all trees
#6 septic* or sepsis or septic*emia or systemic inflammatory response syndrome or py*emia
#7 #4 or #5 or #6
#8 #3 and #7
#9 #8 in Trials

Appendix 2. MEDLINE (Ovid SP) search strategy

1 exp Decision Support Systems, Clinical/ or ((automat* or electronic) adj5 (monitoring or detect* or evaluat* or diagnos* or tool* or decision*)).mp. or (early adj3 (monitoring or detect* or treat* or recogn* or initiat* or therap* or diagnos*)).mp. or ((predefined or pre defined) adj3 criteria).mp. or (system* adj5 (paper or computer or monitoring or recogn* or detect* or automated)).mp. or alert*.mp. or surveillance.mp.
2 exp sepsis/ or Shock, Septic/ or (septic* or sepsis or septic?emia or systemic inflammatory response syndrome or py?emia).mp.
3 ((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)
4 1 and 2 and 3

Appendix 3. Embase (Ovid SP) search strategy

1 exp clinical decision support system/ or ((automat* or electronic) adj5 (monitoring or detect* or evaluat* or diagnos* or tool* or decision*)).mp. or (early adj3 (monitoring or detect* or treat* or recogn* or initiat* or therap* or diagnos*)).mp. or ((predefined or pre defined) adj3 criteria).mp. or (system* adj5 (paper or computer or monitoring or recogn* or detect* or automated)).mp. or alert*.mp. or surveillance.mp.
2 exp sepsis/ or septic shock/ or (septic* or sepsis or septic?emia or systemic inflammatory response syndrome or py?emia).mp.
3 ((crossover procedure or double blind procedure or single blind procedure).sh. or (crossover* or cross over*).ti,ab. or placebo*.ti,ab,sh. or (doubl* adj blind*).ti,ab. or (controlled adj3 (study or design or trial)).ti,ab. or allocat*.ti,ab. or trial*.ti,ab. or randomized controlled trial.sh. or random*.ti,ab.) not ((exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.))
4 1 and 2 and 3

Appendix 4. Cinahl Plus search strategy

S1 ((MH "Sepsis+") OR (MH "Shock, Septic+") OR TX sepsis OR TX septic* OR TX septic*emia OR TX systemic inflammatory response syndrome OR TX py*emia)

S2 ((MM “Decision Support Systems, Clinical”) OR (((TX automated OR electronic) N3 (TX monitoring OR detect* OR evaluat* OR diagnos* OR tool* OR decision*)) OR (TX early N3 (TX monitoring OR detect* OR treat* OR recogn* OR initiat* OR therap* OR diagnos*)) OR (TX pre*defined N3 criteria) OR (TX system* N5 (TX paper OR computer OR monitoring OR recogn* OR detection OR automated))) OR (TX alert* OR TX surveillance))

S3 ((MM "Randomized Controlled Trials") OR (MM "Random Assignment") OR (MM "Prospective Studies+") OR (MM "Clinical Trial Registry") OR (MM "Double-Blind Studies") OR (MM "Single-Blind Studies") OR (MM "Triple-Blind Studies") OR (MM "Multicenter Studies") OR (MM "Placebos")) OR (random* or placebo* or trial*)

S4 S1 AND S2 AND S3

Appendix 5. Web of science search strategy

TS=(sepsis OR "septic shock")

AND TS=((((automated OR electronic) NEAR/3 (monitoring OR detect*)) OR (early NEAR/3 (monitoring OR detect* OR treat* OR recogn* OR initiat*)) OR (pre*defined NEAR/3 criteria) OR (system* NEAR/3 (paper OR computer OR monitoring OR detection OR automated))))

AND TS=((random* or (trial* NEAR/3 (control* or clinical*)) or placebo* or multicenter* or prospective* or ((blind* or mask*) NEAR/3 (single or double or triple or treble))))

Appendix 6. LILACS (Bireme) search strategy

((MH:sepsis OR “septic shock”) OR (AB:sepsis OR septic OR septic?emia OR systemic inflammatory response syndrome OR py?emia)) AND ((AB: automated AND (monitor OR detect OR treat OR recognize OR therapy OR diagnose OR tool OR decision)) OR (automated AND (monitoring OR detection)) OR (electronic AND (monitor OR detect OR treat OR recognize OR therapy OR diagnose or tool OR decision)) OR (electronic AND (monitoring OR detection)) OR (“early monitoring” AND (detect OR treat OR recognize OR initiate)) OR (“predefined criteria”) OR (system AND (paper OR computer OR monitoring OR detection OR automated)))

WHAT'S NEW

Date	Event	Description
3 January 2019	Amended	Editorial team changed to Cochrane Emergency and Critical Care

HISTORY

Protocol first published: Issue 10, 2016
Review first published: Issue 6, 2018

Date	Event	Description
4 October 2018	Amended	Acknowledgement section amended to include Co-ordinating Editor

CONTRIBUTIONS OF AUTHORS

Sheryl Warttig (SW), Phil Alderson (PA), David JW Evans (DE), Sharon R Lewis (SL), Irene Kourbeti (IK) and Andrew F Smith (AS)

Conceiving the review: DE

Co-ordinating the review: SW

Undertaking manual searches: SL

Screening search results: SW, PA, SL,

Organizing retrieval of papers: SL

Screening retrieved papers against inclusion criteria: SW, PA, IK

Appraising quality of papers: SW, PA, IK

Abstracting data from papers: SW, PA, IK

Writing to authors of papers for additional information: SW

Providing additional data about papers: not applicable

Obtaining and screening data on unpublished studies: not applicable

Data management for the review: SW, PA

Entering data into Review Manager 5 (RevMan 2014): SW, PA

RevMan statistical data: not applicable

Other statistical analysis not using Review Manager 5: not applicable

Interpretation of data: SW/PA

Statistical inferences: not applicable

Writing the review: SW, PA

Securing funding for the review: AS, PA, SL

Performing previous work that was the foundation of the present study: not applicable

Guarantor for the review (one author): AS

Person responsible for reading and checking review before submission: SW

DECLARATIONS OF INTEREST

Sheryl Warttig: none known

David JW Evans: provides freelance writing services to medical communication agencies.

Sharon R Lewis: none known

Andrew F Smith: none known

Phil Alderson: none known

Irene Kourbeti: none known

See Sources of support

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, via Cochrane Programme Grant, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol (Evans 2016).

1. We changed the title to include the comparator.
2. In the Background section text under the heading 'Description of the condition' we added a definition of sepsis and made sentences clearer.
3. We added text in the Objectives section to make it clearer what we consider to be appropriate treatment.
4. We included additional search terms in the search strategy.
5. We did not use Covidence 2015 to manage the review process.
6. We did not analyse data using risk ratios or mean differences with confidence intervals because none of the included studies directly reported this information and, in some cases, reported insufficient data to enable us to calculate these estimates.
7. We did not assess heterogeneity as planned because too few studies were included in this review.
8. We did not assess reporting biases with a funnel plot, as too few studies were included in this review.

9. We could not synthesize data using meta analysis because insufficient data were available for this to be meaningful.
10. We could not perform sensitivity analyses because too few studies were included in this review.
11. We planned to use '30-day mortality' as an outcome for this review. None of the included studies included this outcome, but did report mortality measured at other time points. We made a post-hoc decision to include the other time points in this review as we felt that it would be helpful for the reader to know that it was reported and what the results were.

INDEX TERMS

Medical Subject Headings (MeSH)

*Critical Illness; Anti-Bacterial Agents [therapeutic use]; Early Diagnosis; Intensive Care Units; Length of Stay; Randomized Controlled Trials as Topic; Sepsis [*diagnosis] [drug therapy]; Time-to-Treatment

MeSH check words

Adult; Humans