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Diagnosis, Investigation and Management of Sepsis: Literature Review

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Preface

The Australian Commission on Safety and Quality in Health Care (the Commission) engaged KP Health to conduct this literature review to inform the development of the *Sepsis Clinical Care Standard*. The development of the *Sepsis Clinical Care Standard* is one of eight components of the National Sepsis Program being implemented by the Commission.

The review aimed to identify relevant evidence-based guidelines and to compare their definitions for sepsis and their intervention recommendations. Programs addressing sepsis care delivery were examined, including variation in outcomes and indicators used in data collection.

The definition of sepsis has evolved over time and the most recent international definition is not universally accepted. Six international guidelines and two Australian guidelines were identified, with varying levels of supportive evidence. Recommendations across guidelines were inconsistent. Both the NICE guidelines and the International Consensus Guidelines were noted as relevant to the Australian health system.

The variation in the definition of sepsis leads to challenges in outcome measurement, in the studies and reviews identified, the predominant outcome measure was mortality. Program and intervention evaluation was evidenced in 24 systematic reviews across a range of programs, however only two were of high quality evidence.

Indicators to support the measurement of sepsis care were only identified in one of the six guidelines.

Results from this review highlight the challenges of sepsis management, from variation in definitions, best practice evidence through to process and outcome indicators. A clinical care standard for sepsis will support best practice and consistency of care in the Australian setting.

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List of abbreviations

Abbreviation	
ACCM	American College of Critical Care Medicine
ACSHQC	Australian Commission on Safety and Quality in Health Care
AGREE II	Appraisal of Guidelines for Research and Evaluation II
AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews
APACHE II	Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
AUROC	Area Under the Receiver Operating Characteristics
AVPU	Alert, Voice, Pain, Unresponsive scale
BP	Blood pressure
CI	Confidence interval Cardiac Index
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMS	Center for Medicare and Medicaid Services
CO	Cardiac output
CRP	C-reactive protein
CRRT	Continuous renal replacement therapy
CVP	Central venous pressure
DIC	Disseminated Intravascular Coagulation
ECG	Electrocardiogram
ECMO	Extra-corporeal membrane oxygenation
ED	Emergency Department
EMBASE	A biomedical and pharmacological bibliographic database
EOS	Early Onset Sepsis
ESICM	European Society for Intensive Care Medicine
EWS	Early Warning Score
FFP	Fresh Frozen Plasma
GCS	Glasgow Coma Score
GI	Gastro-Intestinal
GP	General Practitioner
h	hours
HFOV	High Frequency Oscillatory Ventilation
H-HES	A Hydroxy-Ethyl Starch formulation

Abbreviation	
HR	Heart Rate
ICU	Intensive Care Unit
IL-6	Interleukin-6
iNO	inhaled Nitric Oxide
INR	International Normalized Ratio
IV	Intravenous
IVCCI	inferior Vena Cava Collapsibility Index
IVIG	Intravenous Immunoglobulin
LMWH	Low Molecular Weight Heparin
LOS	Late Onset Sepsis
MAP	Mean Arterial Pressure
MD	Mean Difference
MeSH	Medical Subject Headings
MEWS	Modified Early Warning Score
mmHg	Millimetres Mercury
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
OR	Odds Ratio
PAOP	Pulmonary Artery Occlusion Pressure
PARDS	Paediatric Acute Respiratory Distress Syndrome
pCO2	Partial Pressure of Carbon Dioxide
PDA	Patent Ductus Arteriosus
PDEI	Phosphodiesterase Inhibitor
PEDro	Physiotherapy Evidence Database
PEEP	Positive End-Expiratory Pressure
PICU	Paediatric intensive care unit
PIV	Peripheral Intravenous
PMX-HP	polymyxin B-Immobilised Haemoperfusion
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses
RBC	Red Blood Cells
RCT	Randomized Controlled Trial
RR	Relative Risk Risk Ratio
SCCM	Society for Critical Care Medicine
SIGN	Scottish Intercollegiate Guidelines Network
SMD	Standardised Mean Difference
SIRS	Systemic Inflammatory Response Syndrome

Abbreviation	
SOFA	Sequential Organ Failure Assessment - qSOFA quick SOFA - omSOFA Obstetrically Modified SOFA - omqSOFA Obstetrically Modified quick SOFA
SOMANZ	Society of Obstetric Medicine Australia and New Zealand
SpO2	Oxygen Saturation
SSC	Surviving Sepsis Campaign
SvCO2	Central Venous Oxygen Saturation
SVR	Systemic Vascular Resistance
TAMOF	Thrombocytopaenia-Associated Multiple Organ Failure
UAC	Umbilical Artery Catheter
UFH	Unfractionated Heparin
VA	Veno-Arterial
VLBW	Very Low Birth Weight
VTE	Venous Thromboembolism
VV	Veno-Venous

Background

This literature review has been prepared for the Australian Commission on Safety and Quality in Health Care (the Commission). The review describes recent guidelines and published evidence regarding the diagnosis, investigation and management of sepsis and identifies issues and gaps in knowledge. This review will inform the development of a national clinical care standard.

A review protocol was developed and approved by the Commission to agree the review methodology.

Research questions

The literature review addresses the following research questions:

1. What relevant evidence-based clinical guidelines and systematic reviews are available that can be used as an evidence-base for the Sepsis Clinical Care Standard? What is the quality of these guidelines and systematic reviews?
2. What do current guidelines and systematic reviews recommend regarding the diagnosis, investigation and management of sepsis and what is the evidence level for these? What if any, are the differences between key current guidelines?
3. How is variation in sepsis outcomes measured? What evidence is available to indicate that health care delivery for sepsis in Australia is not in line with best available evidence?
4. What programs or interventions have been used to improve health care delivery and outcomes for sepsis and what were their outcomes?
5. What audits, indicators and data collection mechanisms have been developed or are in use to support the measurement of care improvement for sepsis?

Specific questions that are addressed are as follows:

- How is sepsis defined and what are the diagnostic criteria?
- What are the risk factors for sepsis and for a recurrent septic episode?
- Are there any clinical conditions, patient characteristics or procedures that are associated with a higher incidence of sepsis?
- What is the evidence regarding timing of initiating antimicrobials in sepsis?
- What is the evidence regarding fluid resuscitation in sepsis?
- What factors contribute to poor outcomes in sepsis management?
- What factors contribute to better outcomes in sepsis management?
- What is the evidence for timely review of antimicrobials (after the first dose) in sepsis management?

Review methods

We searched for publications published in English in the five years to 2020. The date of last search was 7 June 2020.

We searched the peer-reviewed and 'grey' literature using Medical Subject Heading (MeSH) terms and keywords of broad relevance. We interrogated the following databases and literature sources:

- Medline (via OVID)
- EMBASE
- CINAHL
- Cochrane Library
- PEDro
- Australian Clinical Practice Guidelines Portal
- National Institute for Health and Clinical Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- Canadian Medical Association InfoBase
- US National Guideline Clearinghouse
- New Zealand Ministry of Health Guides and Standards
- proprietary search engines (Google, Google Scholar, Edge)
- Commonwealth, State and Territory health department websites.

The search terms that were used to identify relevant studies in bibliographic databases (specific to Medline via Ovid) are described at Table 1). Terms for each database were tailored to the requirements of each database.

We downloaded all titles and abstracts retrieved by electronic searching to the reference management database EndNote. We removed duplicates and examined all references for their relevance. Full text articles were sourced for all potentially eligible guidelines, systematic reviews and meta-analyses and these were assessed against the eligibility criteria. We tabulated reasons for exclusion for all full text guidelines, reviews and meta-analyses that did not meet the criteria. These are provided at Appendix 1.

At the same time, we coded abstracts for relevant randomised controlled trials and observational studies that were identified in the above searches. We retained these abstracts in a separate file for full text review later if clinical experts identify gaps in the evidence identified from guidelines, systematic reviews and meta-analyses.

Table 1: MEDLINE via Ovid

#1	exp Sepsis [MeSH] OR sepsis[tiab]
#2	Clinical pathway[mh] OR Clinical protocol[mh] OR Consensus[mh] OR Consensus development conferences as topic[mh] OR Critical pathways[mh] OR Guidelines as topic [Mesh:NoExp] OR Practice guidelines as topic[mh] OR Health planning guidelines[mh] OR guideline[pt] OR practice guideline[pt] OR consensus development conference[pt] OR consensus development conference, NIH[pt] OR position statement*[tiab] OR policy statement*[tiab] OR practice parameter*[tiab] OR best practice*[tiab] OR standards[ti] OR guideline[ti] OR guidelines[ti] OR ((practice[tiab] OR treatment*[tiab]) AND guideline*[tiab]) OR CPG[tiab] OR CPGs[tiab] OR consensus*[tiab] OR ((critical[tiab] OR clinical[tiab] OR practice[tiab]) AND (path[tiab] OR paths[tiab] OR pathway[tiab] OR pathways[tiab] OR protocol*[tiab])) OR recommendat*[ti] OR (care[tiab] AND (standard[tiab] OR path[tiab] OR paths[tiab] OR pathway[tiab] OR pathways[tiab] OR map[tiab] OR maps[tiab] OR plan[tiab] OR plans[tiab])) OR (algorithm*[tiab] AND (screening[tiab] OR examination[tiab] OR test[tiab] OR tested[tiab] OR testing[tiab] OR assessment*[tiab] OR diagnosis[tiab] OR diagnoses[tiab] OR diagnosed[tiab] OR diagnosing[tiab])) OR (algorithm*[tiab] AND (pharmacotherap*[tiab] OR chemotherap*[tiab] OR chemotreatment*[tiab] OR therap*[tiab] OR treatment*[tiab] OR intervention*[tiab]))
#3	meta-analysis.pt. or meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw. or ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw. or ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw. or (data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw. or (handsearch* or hand search*).ti,ab,kf,kw. or (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw. or (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw. or (meta regression* or metaregression*).ti,ab,kf,kw. or (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. or (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. or (cochrane or (health adj2 technology assessment) or evidence report).jw. or (meta-analysis or systematic review).mp. or (comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw. or (outcomes research or relative effectiveness).ti,ab,kf,kw. or ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw.
#4	#1 AND #2 AND #3
#5	#4 NOT (Comment OR Congress OR Editorial OR Letter OR News).pt.
#6	limit to yr="2015 -Current"

Guidelines

Assessing the eligibility of identified guidelines

We considered all guidelines relevant to sepsis that were of broad relevance to the review. Included guidelines described a methodology for guideline development and a review of evidence to support the development of the guideline.

We downloaded all titles and abstracts retrieved by electronic searching to the reference management database EndNote. We removed duplicates and examined all references for their relevance.

Data extraction and quality appraisal

From the identified guidelines we extracted relevant recommendations and level of evidence (including GRADE where available) into evidence tables. We also extracted any evidence relevant to the questions this literature review addresses.

The quality of recommendations in identified guidelines was appraised using AGREE-II. Extracted data, together with quality appraisal results for each guideline, is provided at Appendix 2.

Systematic reviews and meta-analyses

Eligibility criteria

Types of studies

We considered all systematic reviews and meta-analyses regardless of study design of included studies, quantitative or qualitative. Where there were two or more reviews that addressed the same question we included all reviews that met inclusion criteria, but reporting focusses on the highest level of evidence and most recent search date. Only studies published from 2015 were considered for inclusion.

Types of Participants

We considered all systematic reviews and meta-analyses regardless of age or gender of participant.

Types of Interventions

We considered all systematic reviews and meta-analyses of interventions for the diagnosis, investigation or management of sepsis.

Types of Comparators

We considered all systematic reviews and meta-analyses of studies with and without comparators.

Types of Outcome measures

We considered all systematic reviews and meta-analyses regardless of outcomes measures used. Studies that did not report outcomes relevant to the review were not included.

Evidence in languages other than English

Studies in languages other than English were only included where a full-text translation into English was available.

Assessing the eligibility of identified articles

We downloaded all titles and abstracts retrieved by electronic searching to the reference management database EndNote. We removed duplicates and examined all references for their relevance. Full text articles were sourced for all potentially eligible reviews/meta-analyses, and these were assessed against the eligibility criteria. We tabulated reasons for exclusion for all articles that do not meet the criteria (Appendix 1).

Data extraction and quality appraisal

We extracted relevant data from included studies using a pre-defined template included in our review protocol. Data extracted from included studies and quality appraisal of each study is described at Appendix 3 (adult studies) and Appendix 4 (neonatal and paediatric studies).

We assessed the methodological quality of systematic reviews that met inclusion criteria using the AMSTAR 2 measurement tool. We applied AMSTAR assessment criteria to rate overall confidence in the results of each systematic review using methods outlined by Shea et al. (2017)[1]. There are 16 questions in the AMSTAR 2 assessment tool. Of these, there are seven critical domains that describe critical methodological flaws that influence the quality of the review:

- Protocol registered before commencement of the review (item 2)
- Adequacy of the literature search (item 4)
- Justification for excluding individual studies (item 7)
- Risk of bias from individual studies being included in the review (item 9)
- Appropriateness of meta-analytical methods (item 11)
- Consideration of risk of bias when interpreting the results of the review (item 13)
- Assessment of presence and likely impact of publication bias (item 15).

Each included systematic review has been rated in accordance with the assessment of each of the 16 items and these seven critical domains:

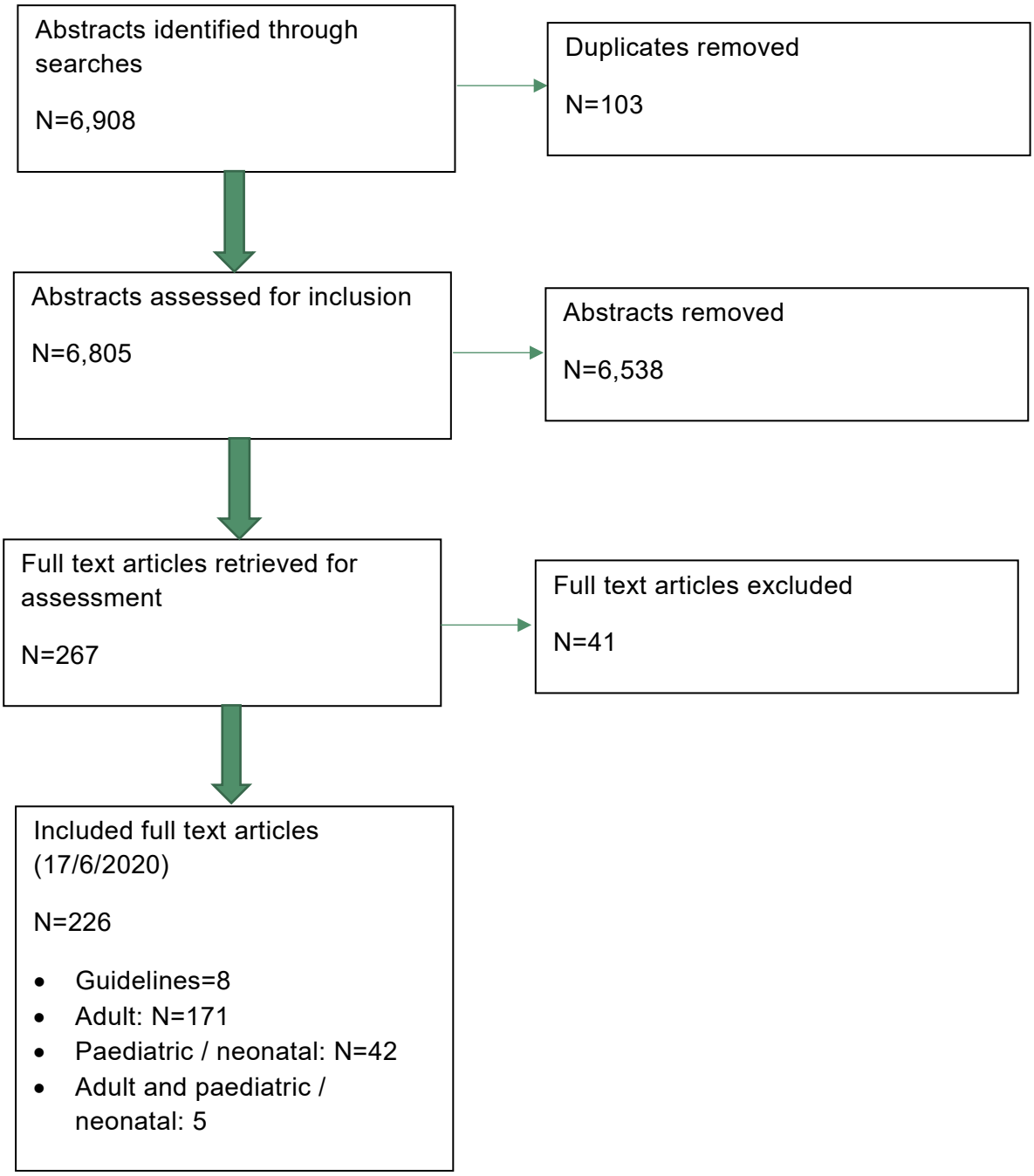
- High – no or one non-critical weakness
- Moderate – more than one non-critical weakness
- Low – one critical flaw with or without non-critical weaknesses
- Critically low – more than one critical flaw with or without non-critical weaknesses.

[1] Shea B, Reeves B, Wells G et al. AMSTAR: a critical appraisal tool for systematic reviews that include randomized or non-randomised studies of healthcare interventions or both. BMJ 2017; 358: j4008.

Results

The results of our searches identified the following peer-reviewed materials of broad relevance to the review (Figure 1).

Figure 1: PRISMA Statement (preliminary coding results of peer-reviewed publications)



The following additional materials of importance in the Australian context were identified through grey literature searches. These materials did not meet criteria for inclusion as guidelines or systematic reviews / meta-analysis for the purposes of this review:

- Australia: Antibiotic Expert Group. Therapeutic guidelines: antibiotic. Version 16. Melbourne: Therapeutic Guidelines Limited; 2019.
- Australian Sepsis Network. Resources.
- NSW Clinical Excellence Commission Sepsis Kills program tools and resources.
- NSW Emergency Care Institute and Agency for Clinical Innovation. Clinical tools.
- Queensland Paediatric Guideline: Sepsis – Recognition and emergency management in children.
- Queensland Ambulance Services: Clinical practice guideline – sepsis.
- Clinical Excellence Queensland. Sepsis Resources.
- Better Safer Care Victoria. Sepsis Kills resources.
- Better Care Victoria. Think Sepsis Act Fast Scaling Collaborative resources and evaluation.
- Royal Children's Hospital Melbourne: SEPSIS – assessment and management.
- SA Health. Sepsis for health professionals.
- Perth Children's hospital. Sepsis Management.
- RACGP Aged Care Clinical Guide. Infection and Sepsis.

Question 1

This section addresses the following review questions:

- What relevant evidence-based clinical guidelines and systematic reviews are available that can be used as an evidence-base for the Sepsis Clinical Care Standard?
- What is the quality of these guidelines and systematic reviews?

We identified 226 materials of broad relevance to the research questions defined in the protocol for this review. Of these, eight were clinical guidelines and 218 were systematic reviews and / or meta-analyses of the literature.

There were six international and two Australian guidelines included in this review.

International guidelines

1. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock (Davis 2017).
2. National Institute for Health and Care Excellence (NICE). Sepsis: recognition, diagnosis and early management (NICE 2017) AND Sepsis: Quality Standard (NICE 2020).
3. Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock (Nishida 2018)
4. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock (Rhodes 2017).
5. Third international consensus definitions for sepsis and septic shock (sepsis-3) (Shankar 2016).
6. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children (Weiss 2020).

National guidelines

1. SOMANZ guidelines for the investigation and management of sepsis in pregnancy (Bowyer 2017).
2. Spleen Australia guidelines for the prevention of sepsis in patients with asplenia and hyposplenism in Australia and New Zealand (Kanhutu 2017).

The methodological quality of international guidelines was rated according to AGREE II criteria as 7/7 for one guideline (NICE 2016 guidelines and related NICE 2020 clinical care standard), 6/7 for two guidelines (Rhodes 2017 and Weiss 2020) and 5/7 for the remaining three international guidelines.

There was one Australian guideline rated as 4/7 for methodological quality (Bowyer, 2017) and the other rated as 3/7 (Kanhutu, 2017).

There were 171 systematic reviews / meta-analysis performed in adults, 42 in paediatric or neonatal population groups and five that included both adult and paediatric / neonatal populations.

The quality of the included systematic reviews was appraised using the AMSTAR II assessment tool. There were 30 high quality reviews (no or one non-critical weakness),

27 moderate quality reviews (more than one non-critical weakness), 59 low quality reviews (one critical flaw) and 102 critically low quality reviews (more than one critical flaw).

Levels of evidence and quality scoring in included international guidelines

Levels of evidence supporting each recommendation in included guidelines were not clearly described in any guidelines. The highest quality guidelines (NICE 2016) provide evidence tables for most recommendations. Levels of evidence can be derived for many (but not all) recommendations from these tables.

The other guidelines included in this review did not clearly describe what level of evidence supported each guideline recommendation.

Instead, guidelines provided a statement for each recommendation describing the quality of evidence identified to support the recommendation (quality rating). Methods used to derive quality ratings, and definitions of quality, varied between the main international guidelines included in this review.

NICE guidelines applied the GRADE methodology in assigning a quality rating to each recommendation. The quality rating was assigned based on the study design (for intervention studies RCTs started as high, observational studies as low and uncontrolled case series as low or very low; for diagnostic studies the quality rating started at high for prospective and retrospective cross sectional studies).The rating was then downgraded after assessment of bias, inconsistency, indirectness, imprecision and publication bias. This was then summed into an overall quality rating.

International Consensus Guidelines (Rhodes et al. 2017 and Weiss et al. 2020) based their quality rating on an initial determination of the underlying study method which was then downgraded based on GRADE quality categories or upgraded (for observational studies) based on magnitude of effect or dose response gradient (high=RCTs; moderate=downgraded RCTs or upgraded observational studies; low=well-done observational studies with RCTs and very low=downgraded controlled studies or expert opinion or other evidence). Best Practice Statements were drafted where evidence was hard to assess or summarise but the Working Group felt benefit or harm were unequivocal.

For the ACCM guidelines (Davis et al.) subcommittees were formed to review the literature and make recommendations using GRADE categories. A strong recommendation received the “number” grade 1 and a weak recommendation received the number grade 2. The strength of the literature used to support these number recommendations was given “letter” grades with A equals to multiple randomized controlled trials and at least one meta-analysis, B equals to one randomized controlled trial, C equals to cohort, case control studies, and D equals to expert opinion and case reports.

Question 2

This section addresses the following review questions:

- What do current guidelines and systematic reviews recommend regarding the diagnosis, investigation and management of sepsis and what is the evidence level for these?
- What if any, are the differences between key current guidelines?

The following additional review questions are also addressed:

- How is sepsis defined and what are the diagnostic criteria?
- What are the risk factors for sepsis and for a recurrent septic episode?
- Are there any clinical conditions, patient characteristics or procedures that are associated with a higher incidence of sepsis?
- What is the evidence regarding timing of initiating antimicrobials in sepsis?
- What is the evidence regarding fluid resuscitation in sepsis?
- What factors contribute to poor outcomes in sepsis management?
- What factors contribute to better outcomes in sepsis management?
- What is the evidence for timely review of antimicrobials (after the first dose) in sepsis management?

Given the large proportion of low and very low quality reviews identified, we have responded to each of the questions defined for the review using the highest quality evidence available for that question. Critically low quality reviews have been excluded from discussion and analysis in the main report but are described in full at Appendix 2 and Appendix 3 for completeness.

How is sepsis defined and what are the diagnostic criteria?

Different definitions of sepsis are used by different guideline developers of included guidelines and by authors of included systematic reviews and meta-analyses in this review.

Adult and general definitions

In 2001, the Surviving Sepsis Campaign (SSC) was formed by the Society of Critical Care Medicine (SCCM), European Society of Intensive Care Medicine (ESICM), and the International Sepsis Forum. A primary aim of the SSC was to develop evidenced-based guidelines and recommendations for the resuscitation and management of patients with sepsis. The initial guidelines were published in 2004 and have been reviewed and updated every four years thereafter. Following the 2016 edition, SCCM and ESICM formed separate task forces dedicated to guidelines for adults and children. As part of the work of SSC, international consensus definitions for sepsis have been developed. These have evolved over time.

According to the most recent Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3):

- **sepsis** is defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection.” (Rhodes et al, 2017).

- **septic shock** is defined as “a subset of sepsis in which the underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality” (Shankar-Hari et al., 2016).

The Sepsis-3 definition defines organ dysfunction as in increase of two or more points in the SOFA (Sequential Organ Failure Assessment) score (see Figure 2).

According to the consensus definition, septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or higher and a serum lactate level greater than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

Figure 2: Sequential Organ Failure Assessment Score

Lung: Respiration

- PaO_2/FiO_2 >400 (0 points)
- PaO_2/FiO_2 301 to 400 (1 point)
- PaO_2/FiO_2 ≤300 (2 points)
- PaO_2/FiO_2 101 to 200 with ventilatory support (3 points)
- PaO_2/FiO_2 ≤100 with ventilatory support (4 points)

Coagulation: Platelets

- >150 $x10^3/mm^3$ (0 points)
- 101 to 150 $x10^3/mm^3$ (1 point)
- 51 to 100 $x10^3/mm^3$ (2 points)
- 21 to 50 $x10^3/mm^3$ (3 points)
- ≤20 $x10^3/mm^3$ (4 points)

Liver: Bilirubin

- <1.2 mg/dL (20 mcmol/L) (0 points)
- 1.2 to 1.9 mg/dL (20 to 32 mcmol/L) (1 point)
- 2 to 5.9 mg/dL (33 to 101 mcmol/L) (2 points)
- 6 to 11.9 mg/dL (102 to 204 mcmol/L) (3 points)
- >12 mg/dL (>204 mcmol/L) (4 points)

Cardiovascular: Blood pressure

- Hypotension absent (0 points)
- Mean arterial pressure <70 mmHg (1 point)
- On dopamine ≤5 mcg/kg/min or any dobutamine (2 points)
- On dopamine >5 mcg/kg/min, epinephrine ≤0.1 mcg/kg/min, or norepinephrine ≤0.1 mcg/kg/min (3 points)
- On dopamine >15 mcg/kg/min, epinephrine >0.1 mcg/kg/min, or norepinephrine >0.1 mcg/kg/min (4 points)

Brain: Glasgow coma score

- 15 (0 points)
- 13 to 14 (1 point)
- 10 to 12 (2 points)
- 6 to 9 (3 points)

- <6 (4 points)

Kidney: Renal function

- Creatinine <1.2 mg/dL (110 mcmol/L) (0 points)
- Creatinine 1.2 to 1.9 mg/dL (110 to 170 mcmol/L) (1 point)
- Creatinine 2 to 3.4 mg/dL (171 to 299 mcmol/L) (2 points)
- Creatinine 3.5 to 4.9 mg/dL (300 to 440 mcmol/L) or urine output 200 to 500 mL/day (3 points)
- Creatinine >5 mg/dL (440 mcmol/L) or urine output <200 mL/day (4 points)

Earlier definitions of sepsis included categories for Systemic Inflammatory Response Syndrome (SIRS), sepsis and severe sepsis. These definitions are described in many of the systematic reviews included in our review as systematic reviews include studies that pre-date the Sepsis-3 definition being introduced. However, SIRS is no longer included in the international definition of sepsis since it is not always caused by infection. Further, the international definition of sepsis is not unanimously accepted. For example, the Center for Medicare and Medicaid Services (CMS) continues to support the previous definition of SIRS, sepsis, and severe sepsis (Rhodes et al., 2017; Weiss et al., 2020). Also, the National Institute for Health and Care Excellence (NICE), the highest quality guidelines identified in this review, question the value of the Sepsis-3 definition. Terminology when the NICE guideline was being developed included terms SIRS (systematic inflammatory response syndrome), severe sepsis and septic shock but the guidelines acknowledge the Sepsis-3 definition suggests using terms sepsis and septic shock only. NICE guideline authors state that Sepsis-3 definitions are not useful in early identification of people at risk and the guideline therefore recommends actions according to clinical parameters that stratify risk of severe illness or death from sepsis rather than definitions per se. Particular emphasis has been placed in the NICE guidelines on early sepsis recognition and the initial treatments prior to escalation of care or moving onto a more specific clinical pathway.

Paediatric definitions

The SSC taskforce has developed separate sepsis definitions for paediatric populations. In 2005, the International Pediatric Sepsis Consensus Conference published definitions and criteria for sepsis, severe sepsis, and septic shock in children based on prevailing views of adult sepsis at the time with modifications for physiology based on age and maturational considerations.

According to the authors of the 2020 SSC International Guidelines for the management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children (Weiss et al., 2020), although application of Sepsis-3 to children has been attempted formal revisions to the 2005 paediatric sepsis definitions remain pending. Therefore, the majority of studies used to establish evidence for the SSC 2020 paediatric sepsis guidelines refer to the 2005 nomenclature in which severe sepsis is defined as:

- greater than or equal to 2 age-based systemic inflammatory response syndrome (SIRS) criteria;
- confirmed or suspected invasive infection; and
- cardiovascular dysfunction, acute respiratory distress syndrome (ARDS), or greater than or equal to 2 noncardiovascular organ system dysfunctions.

Septic shock is defined in these guidelines in children as severe infection leading to cardiovascular dysfunction (including hypotension, need for treatment with a vasoactive medication, or impaired perfusion) and “sepsis associated organ dysfunction” in children as severe infection leading to cardiovascular and/or non-cardiovascular organ dysfunction.

In 2017 the American College of Critical Care Medicine published a revised definition of septic shock in children. “The inflammatory triad of fever, tachycardia, and vasodilation is common in children with benign infections (Davis et al., 2017). Septic shock is suspected when children with this triad have a change in mental status manifested as irritability, inappropriate crying, drowsiness, confusion, poor interaction with parents, lethargy, or becoming unarousable. The clinical diagnosis of septic shock is made in children who:

- have a suspected infection manifested by hypothermia or hyperthermia; and
- have clinical signs of inadequate tissue perfusion including any of the following: decreased or altered mental status, prolonged capillary refill greater than 2 seconds, diminished pulses, mottled cool extremities, or flash capillary refill, bounding peripheral pulses and wide pulse pressure or decreased urine output less than 1 mL/kg/hr.

Hypotension is not necessary for the clinical diagnosis of septic shock; however, its presence in a child with clinical suspicion of infection is confirmatory.”

Term neonatal septic shock is defined in the same guidelines as follows:

“Septic shock should be suspected in any newborn with tachycardia, respiratory distress, poor feeding, poor tone, poor colour, tachypnoea, diarrhea, or reduced perfusion, particularly in the presence of a maternal history of chorioamnionitis or prolonged rupture of membranes.”

Maternal definitions

The Society of Obstetric Medicine Australia and New Zealand (SOMANZ) provides definitions of sepsis and septic shock. Sepsis is broadly defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. It is this dysregulated response and subsequent organ dysfunction that differentiates sepsis from infection. Sepsis can occur at any time during pregnancy or in the early postpartum period. Septic shock is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities substantially increase mortality risk (Bonet et al., 2017).

What are the risk factors for sepsis and for a recurrent septic episode?

Are there any clinical conditions, patient characteristics or procedures that are associated with a higher incidence of sepsis?

Risk factors for sepsis are comprehensively described in the highest quality guidelines included in our review (NICE guidelines for sepsis). Other included guidelines did not comprehensively describe risk factors for sepsis. According to the results of very low quality evidence from risk factor studies included in the NICE guidelines, the groups below are at higher risk of developing sepsis:

- the very young (under 1 year) and older people (over 75 years) or people who are very frail
- people who have impaired immune systems because of illness or drugs, including people being treated for cancer with chemotherapy, people who have impaired immune function (for example, people with diabetes, people who have had a splenectomy, or people with sickle cell disease), people taking long-term steroids and people taking immunosuppressant drugs to treat non-malignant disorders such as rheumatoid arthritis
- people who have had surgery, or other invasive procedures, in the past 6 weeks, people with any breach of skin integrity (for example, cuts, burns, blisters or skin infections)
- people who misuse drugs intravenously
- people with indwelling lines or catheters.

In women who are pregnant, have given birth or had a termination of pregnancy or miscarriage in the past 6 weeks, those that are in a high risk group for sepsis include women who:

- have impaired immune systems because of illness or drugs
- have gestational diabetes or diabetes or other co-morbidities
- needed invasive procedures (for example, caesarean section, forceps delivery, removal of retained products of conception)
- had prolonged rupture of membranes
- have or have been in close contact with people with group A streptococcal infection, for example, scarlet fever
- have continued vaginal bleeding or an offensive vaginal discharge.

Risk factors for early-onset neonatal infection include:

- invasive group B streptococcal infection in a previous baby
- maternal group B streptococcal colonisation, bacteriuria or infection in the current pregnancy
- prelabour rupture of membranes
- preterm birth following spontaneous labour (before 37 weeks' gestation)
- suspected or confirmed rupture of membranes for more than 18 hours in a preterm birth
- intrapartum fever higher than 38°C, or confirmed or suspected chorioamnionitis
- parenteral antibiotic treatment given to the woman for confirmed or suspected invasive bacterial infection (such as septicaemia) at any time during labour, or in the 24-hour periods before and after the birth (this does not refer to intrapartum antibiotic prophylaxis)
- suspected or confirmed infection in another baby in the case of a multiple pregnancy.

Australian guidelines authored by Kanhutu et al. (2017) identify patients with asplenia or hyposplenism as being at increased risk of sepsis.

We identified seven systematic reviews (five in adults, two in children) that described risk factors for sepsis. Four studies are critically low quality systematic reviews and are not discussed further here[2] [3].

The three remaining studies were all conducted in adults.

- A moderate quality systematic review by Tsertsvadze (2016) combined data from 14 observational studies. The authors reported an excess risk for sepsis in participants with some chronic conditions (immunosuppression, lung disease and peripheral artery disease). In one cohort study, higher risk of sepsis was associated with being a nursing home resident (OR 2.60, 95 % CI 1.20-5.60) and in the other cohort study with being physically inactive (OR 1.33, 95 % CI 1.13-1.56) and smoking tobacco (OR 1.85, 95 % CI 1.54-2.22). The evidence on sex, ethnicity, statin use and body mass index as risk factors was inconclusive.
- A moderate quality systematic review by Upala et al. (2015) reported results of a meta-analysis of 10 observational studies. Pooled analysis demonstrated vitamin D deficiency in adults is associated with an increased susceptibility of sepsis.
- A low quality systematic review and meta-analysis by Plaeke et al. (2020) pooled results from 193 prospective and retrospective studies, comprising over 30 million patients, to identify risk factors for postoperative sepsis. The patient-related risk factors associated with post-operative sepsis included male gender (odds ratio, OR 1.41), pre-existing heart failure (OR 2.53), diabetes (OR 1.41), and chronic kidney disease (OR 1.26). The surgery-related risk factors identified included emergency surgery (OR 3.38), peri-operative blood transfusion (OR 1.90), inpatient hospital stay (OR 2.31), and open surgery (OR 1.80). The adjusted overall incidence of surgical sepsis was 1.84%.

What is the evidence regarding the diagnosis and investigation of sepsis?

Diagnosis and investigation of sepsis – guidelines

NICE guidance documents and International Consensus Guidelines (Rhodes et al. 2017 and Weiss et al. 2020) are relevant to the Australian health system and describe a broad range of recommendations for the diagnosis and investigation of sepsis[4].

The following tables document key recommendations in each guideline relevant to diagnosis and investigation of sepsis. A complete list of all recommendations in each guideline is provided at Appendix 2.

[2] Critically low quality meta-analyses included in this review relevant to this review question – Li et al. 2020 (exploring the relationship between vitamin D deficiency and sepsis in adults) and Fathi et al. 2019 (describing risk factors for sepsis in patient admitted to medical, surgical, neurologic, trauma and general ICU wards).

[3] In paediatric populations we identified two meta-analyses that examined the relationship between vitamin D deficiency and sepsis (Wang et al. 2019b and Xiao et al. 2019).

[4] Guidelines specific to resuscitation in paediatric and neonatal septic shock produced by the ACCM (Davis et al.) do not focus on sepsis diagnosis and investigation.

Interpreting NICE guidelines

NICE recommendations for investigation and management of sepsis are based on stratification of patient groups according to risk of severe illness of death (high, moderate to high and low. Stratification is also according to patient age group.

Adults, children and young people aged 12 years and over

High risk:

- objective evidence of new altered mental state
- respiratory rate of 25 breaths per minute or above, or new need for 40% oxygen or more to maintain oxygen saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease)
- heart rate of more than 130 beats per minute
- systolic blood pressure of 90 mmHg or less, or systolic blood pressure more than 40 mmHg below normal
- not passed urine in previous 18 hours (for catheterised patients, passed less than 0.5 ml/kg/hour)
- mottled or ashen appearance
- cyanosis of the skin, lips or tongue
- non-blanching rash of the skin.

Moderate to high risk:

- history of new-onset changed behaviour or change in mental state, as reported by the person, a friend or relative
- history of acute deterioration of functional ability
- impaired immune system (illness or drugs, including oral steroids)
- trauma, surgery or invasive procedure in the past 6 weeks
- respiratory rate of 21–24 breaths per minute
- heart rate of 91–130 beats per minute or new-onset arrhythmia, or if pregnant heart rate of 100–130 beats per minute
- systolic blood pressure of 91–100 mmHg
- not passed urine in the past 12–18 hours (for catheterised patients, passed 0.5–1 ml/kg/hour)
- tympanic temperature less than 36°C
- signs of potential infection, including increased redness, swelling or discharge at a surgical site, or breakdown of a wound.

Low risk

Consider adults, children and young people aged 12 years and over with suspected sepsis who do not meet any high or moderate to high risk criteria to be at low risk of severe illness or death from sepsis.

Children aged 5–11 years

High risk:

- has objective evidence of altered behaviour or mental state, or appears ill to a healthcare professional, or does not wake (or if roused, does not stay awake)
- respiratory rate:
    - aged 5 years, 29 breaths per minute or more
    - aged 6-7 years, 27 breaths per minute or more
    - aged 8-11 years, 25 breaths per minute or more
    - oxygen saturation of less than 90% in air or increased oxygen requirement over baseline
- heart rate
    - aged 5 years, 130 beats per minute or more
    - aged 6–7 years, 120 beats per minute or more
    - aged 8-11 years, 115 beats per minute or more
    - or heart rate less than 60 beats per minute at any age
- mottled or ashen appearance
- cyanosis of the skin, lips or tongue
- non-blanching rash of the skin.

Moderate to high risk:

- not responding normally to social cues or decreased activity, or parent or carer concern that the child is behaving differently from usual
- respiratory rate:
    - aged 5 years, 24-28 breaths per minute
    - aged 6-7 years, 24-26 breaths per minute
    - aged 8-11 years, 22-24 breaths per minute
    - oxygen saturation of less than 92% in air or increased oxygen requirement over baseline
- heart rate:
    - aged 5 years, 120-129 beats per minute
    - aged 6-7 years, 110-119 beats per minute
    - aged 8-11 years, 105-114 beats per minute
    - or capillary refill time of 3 seconds or more
- reduced urine output, or for catheterised patients passed less than 1 ml/kg of urine per hour
- tympanic temperature less than 36°C
- have leg pain or cold hands and feet.

Low risk:

Consider children aged 5-11 years with suspected sepsis who do not meet any high or moderate to high risk criteria to be at low risk of severe illness or death from sepsis.

Children aged under 5 years

High risk:

- behaviour
    - no response to social cues
    - appears ill to a healthcare professional
    - does not wake, or if roused does not stay awake
    - weak, high-pitched or continuous cry
- heart rate:
    - aged under 1 year, 160 beats per minute or more
    - aged 1-2 years, 150 beats per minute or more
    - aged 3-4 years, 140 beats per minute or more
    - heart rate less than 60 beats per minute at any age
- respiratory rate:
    - aged under 1 year, 60 breaths per minute or more
    - aged 1-2 years, 50 breaths per minute or more
    - aged 3-4 years, 40 breaths per minute or more
    - grunting
    - apnoea
    - oxygen saturation of less than 90% in air or increased oxygen requirement over baseline
- mottled or ashen appearance
- cyanosis of the skin, lips or tongue
- non-blanching rash of the skin
- aged under 3 months and temperature 38°C or more
- temperature less than 36oC.

Moderate to high risk:

- behaviour
    - not responding normally to social cues
    - no smile
    - wakes only with prolonged stimulation
    - decreased activity
    - parent or carer concern that the child is behaving differently from usual
- respiratory rate:
    - aged under 1 year, 50-59 breaths per minute
    - aged 1-2 years, 40-49 breaths per minute
    - aged 3-4 years, 35-39 breaths per minute
    - oxygen saturation less than 92% in air or increased oxygen requirement over baseline
    - nasal flaring
- heart rate:
    - aged under 1 year, 150-159 beats per minute
    - aged 1-2 years, 140-149 beats per minute
    - aged 3-4 years, 130-139 beats per minute
- capillary refill time of 3 seconds or more

- reduced urine output, or for catheterised patients passed less than 1 ml/kg of urine per hour
- pallor of skin, lips or tongue reported by parent or carer
- aged 3–6 months and temperature 39°C or over
- have leg pain or cold hands or feet.

Low risk:

Consider children aged under 5 years with suspected sepsis who do not meet any high or moderate to high risk criteria to be at low risk of severe illness or death from sepsis.

Guidelines for the diagnosis and investigation of sepsis

Recommendations for the diagnosis (Table 2) and investigation (Table 3) of sepsis are largely derived from the NICE guidelines as International Consensus Guidelines (Rhodes et al. 2017 and Weiss et al. 2020) mainly focus on sepsis management. Evidence supporting recommendations is of very low quality for those recommendations where quality scores are reported by guideline developers. For other recommendations, only the level of evidence identified was reported.

Diagnosis of paediatric and neonatal septic shock

We note the ACCM guidelines, although specific to paediatric and neonatal septic shock, recommend health services use a recognition bundle to optimise identification of paediatric patients at risk for septic shock. Recognition bundles were not recommended in other guidelines.

Diagnosis of maternal sepsis

SOMANZ guidelines (Bowyer et al. 2017) make the following recommendations:

- Screen for sepsis using the omqSOFA: respiratory rate ≥25min, mental status (any non-alert state) and systolic blood pressure <90mmHg. Assess for any evidence of end organ dysfunction by reviewing for signs such as oliguria or by using omSOFA (increase >2) (moderate quality evidence).
- Blood cultures and appropriate microbiological specimens should be obtained ideally prior to commencement of antimicrobial therapy; however, this should NOT delay administration of antibiotics or antivirals. Imaging should not be withheld just because the patient is pregnant or breast feeding. Be aware of pregnancy-appropriate normal ranges for investigations and observations (high quality evidence).

The level of evidence and quality of source literature supporting each recommendation was not comprehensively described. Therefore, the basis for the rating of evidence as moderate and high quality is unclear.

Table 2: Diagnosis of sepsis – guideline recommendations

Recommendation	NICE	International Consensus Guidelines	Quality / level of evidence[5]
A specific anatomic diagnosis of infection requiring emergent source control should be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention should be implemented as soon as medically and logistically practical after the diagnosis is made		√	Best practice statement (no evidence)
In children who present as acutely unwell, we suggest implementing systematic screening for timely recognition of septic shock and other sepsis-associated organ dysfunction		√	Weak recommendation (very low quality evidence)
Pay particular attention to concerns expressed by the person and their family or carers, for example changes from usual behaviour.	√		Not informed by evidence review
Assess people who might have sepsis with extra care if they cannot give a good history (for example, people with English as a second language or people with communication problems).	√		Not informed by evidence review
Assess people with any suspected infection to identify possible source of infection, factors that increase risk of sepsis and any indications of clinical concern, such as new onset abnormalities of behaviour, circulation or respiration.	√		Not informed by evidence review
Identify factors that increase risk of sepsis or indications of clinical concern such as new onset abnormalities of behaviour, circulation or respiration when deciding during a remote assessment whether to offer a face-to-face assessment and if so, on the urgency of face-to-face assessment.	√		Not informed by evidence review
Use a structured set of observations to assess people in a face-to-face setting to stratify risk	√		Very low quality evidence (III-2)
Use the person's history and physical examination results to grade risk of severe illness or death from sepsis using criteria based on age	√		Very low quality evidence
Consider using an early warning score to assess people with suspected sepsis in acute hospital settings.	√		Very low quality evidence (III-2)
Suspect neutropenic sepsis in patients having anticancer treatment who become unwell.	√		Not informed by evidence review
Examine people with suspected sepsis for mottled or ashen appearance, cyanosis of the skins, lips or tongue, non-blanching rash of the skin, any breach of skin integrity (for example, cuts, burns or skin infections) or other rash indicating potential infection	√		Not informed by evidence review

[5] Level of evidence provided if cited in guideline

Recommendation	NICE	International Consensus Guidelines	Quality / level of evidence[5]
Assess temperature, heart rate, respiratory rate, blood pressure, level of consciousness and oxygen saturation in young people and adults with suspected sepsis.	√		Very low quality evidence
Measure oxygen saturation in community settings if equipment is available and taking a measurement does not cause a delay in assessment or treatment.	√		Very low quality evidence
Interpret blood pressure in the context of a person's previous blood pressure, if known. Be aware that the presence of normal blood pressure does not exclude sepsis in children and young people.	√		Very low quality evidence
Measure blood pressure of children under 5 years if heart rate or capillary refill time is abnormal and facilities to measure blood pressure, including a correctly-sized blood pressure cuff, are available. Measure blood pressure of children aged 5 to 11 years who might have sepsis if facilities to measure blood pressure, including a correctly-sized cuff, are available. Only measure blood pressure in children under 12 years in community settings if facilities to measure blood pressure, including a correctly-sized cuff, are available and taking a measurement does not cause a delay in assessment or treatment.	√		Very low quality evidence
Ask the person, parent or carer about frequency of urination in the past 18 hours.	√		Very low quality evidence
Do not use a person's temperature as the sole predictor of sepsis. Do not rely on fever or hypothermia to rule sepsis either in or out. Some groups of people with sepsis may not develop a raised temperature.	√		Very low quality evidence (III-3)
Interpret the heart rate of a person with suspected sepsis in context, taking into account that baseline heart rate may be lower in young people and adults who are fit; baseline heart rate in pregnancy is 10-15 beats per minute more than normal; older people with an infection may not develop an increased heart rate; older people may develop a new arrhythmia in response to infection rather than an increased heart rate; and heart rate response may be affected by medicines such as beta-blockers	√		Very low quality evidence (III-3)

Table 3: Investigation of sepsis – guideline recommendations

Recommendation	NICE	International Consensus Guidelines	Quality / level of evidence[6]
In all adult and paediatric patients who have suspected sepsis and 1 or more high risk criteria carry out a venous blood test for blood gas including glucose and lactate measurement; blood culture; full blood count; C-reactive protein; urea and electrolytes; creatinine; a clotting screen.	√	-	Very low quality evidence (III-2)[7]
We were unable to issue a recommendation about using blood lactate values to stratify children with suspected septic shock or other sepsis-associated organ dysfunction into low-versus high-risk of having septic shock or sepsis (paediatric).		√	Insufficient evidence to assess
Clotting screen is not recommended in adult or paediatric patients with suspected sepsis and 2 or more moderate to high risk criteria, or in adult or paediatric patients aged 12 years and over with systolic blood pressure 91–100 mmHg.	√		Very low quality evidence (no RCTs identified)
For adults and children with suspected sepsis who meet only 1 moderate to high risk criterion perform blood tests if indicated.	√		Not stated in guideline
Arrange clinical assessment of adults and children who have suspected sepsis and no high risk or moderate to high risk criteria and manage according to clinical judgement.	√		Not stated in guideline
Take microbiological samples before prescribing an antimicrobial. For people with suspected sepsis take blood cultures before antibiotics are given.	√		Not informed by evidence review
Appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis or septic shock if doing so results in no substantial delay in the start of antimicrobials (adult and paediatric)		√	Best practice statement (no evidence)
Consider urine analysis and chest X-ray in all people with suspected sepsis.	√		Not informed by evidence review
Consider imaging of the abdomen and pelvis if no likely source is identified after clinical examination and initial tests.	√		Not informed by evidence review
Do not perform a lumbar puncture without consultant instruction if any of the following contraindications are present: signs suggesting raised intracranial pressure or reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 points or more); relative bradycardia and hypertension; focal neurological signs; abnormal posture or posturing; unequal, dilated or poorly responsive pupils; papilloedema; abnormal 'doll's eye' movements; shock; extensive or spreading purpura; after convulsions until stabilized; coagulation abnormalities or coagulation results outside the normal range or platelet count below 100x109/litre or receiving anticoagulant therapy; local superficial infection at the lumbar puncture site; respiratory insufficiency in children.	√		Not informed by evidence review

[6] Highest level of evidence provided if cited in guidelines

[7] No evidence was found for the following blood tests; blood gas (arterial, venous or capillary), pH, bicarbonates, base deficit, electrolytes (sodium, potassium), renal and liver function, and haematocrit.

Recommendation	NICE	International Consensus Guidelines	Quality / level of evidence[6]
Perform lumbar puncture in the following children with suspected sepsis unless contraindicated: infants younger than 1 month; all infants aged 1–3 months who appear unwell; infants aged 1–3 months with a white blood cell count less than 5×109/litre or greater than 15×109/litre.	√		Not informed by evidence review
Measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients		√	Weak recommendation (low quality evidence)
Procalcitonin levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection		√	Weak recommendation (low quality evidence)

Diagnosis and investigation of sepsis in adults – included studies

We identified the following systematic reviews and meta-analysis of studies relevant to the diagnosis and investigation of sepsis in adults (Table 4).

Table 4: Studies for diagnosis and investigation of sepsis in adults

	Number of studies	Quality of evidence	Study ID (Study described at Appendix 3)
Procalcitonin / presepsin	17	High (2) Moderate (1) Low (5) Critically low (9)	Andriolo 2017; Iankova 2018; Kondo 2019; Lam 2018; Liu 2015; Peng 2019a; Tan 2019; Tong 2015; Wirz 2018; Wu 2017; Wu 2015; Xin 2015; Yang 2018; Zhang 2015a; Zhang 2015c; Zheng 2015; Zhu 2019b
Sepsis calculators / shock indices / early warning scores	8	High (3) Moderate (1) Low (1) Critically low (3)	Fernando 2018; Hamilton 2018; Maitra 2018; Middleton 2019; Roney 2015; Serafim 2018; Song 2018; Tan 2018
Automated systems for sepsis detection from medical records	7	High (1) Moderate (1) Critically low (5)	Despins 2017; Fleuren 2020; Islam 2019; Joshi 2019; Makam 2015; Warttig 2018; Wulff 2019
Serum lactate measurement	4	Low (2) Critically low (2)	Khodashahi 2020; Liu 2017b; Morris 2017; Pan 2019
Interleukin 6	2	High (1) Critically low (1)	Franco 2019; Hou 2015
Infrared spectroscopy	1	Critically low	MacDonald 2015
Measurement of pCO2 delta	1	Critically low	Diaztagle 2017

Procalcitonin and presepsin

We identified eight studies of sufficient quality that assessed procalcitonin (Andriolo 2017; Iankova 2018; Peng 2019a; Wirz 2018), presepsin (Tong 2015; Wu 2015) or assessed either procalcitonin or presepsin (Kondo 2019; Wu 2017) measurement in patients with sepsis.

Studies published by Andriolo 2017 and Kondo 2019 were high quality systematic reviews and the study by Wirz 2018 was of moderate quality. The other studies were low quality systematic reviews.

These studies failed to conclusively demonstrate a role for procalcitonin or presepsin in the diagnosis or investigation of sepsis in adults.

Procalcitonin

Andriolo included 10 randomised controlled trials (RCTs) (23,378 patients) in a Cochrane review that assessed effectiveness and safety of procalcitonin evaluation for reducing mortality in adults with sepsis, severe sepsis or septic shock. Low-quality evidence showed no significant differences in mortality. However, mean time receiving

antimicrobial therapy was reduced. No primary study was identified that analysed the change in antimicrobial regimen from a broad to a narrower spectrum.

Iankova 2018, Peng 2019a and Wirz 2018 also conducted meta-analyses of RCTs that assessed outcomes associated with procalcitonin measurement in adults with sepsis. The RCTs included in each systematic review are reported below (Table 5). Only one additional included RCT was identified (Daubin 2018) after the publication date of the systematic review by Andriolo 2017. This was included in the systematic review by Peng et al. 2019a. This low quality systematic review by Peng et al. assessed procalcitonin-guided antibiotic therapy in critically ill patients. The authors concluded procalcitonin-guided antibiotic therapy fails to decrease mortality or length of stay of critically ill patients with suspected or confirmed sepsis.

Table 5: Included RCTs in systematic reviews of procalcitonin and sepsis in adults

Included RCTs	Andriolo 2017	Iankova 2018	Peng 2019a	Wirz 2018
Annane 2013	X	X	x	X
Bloos 2016			X	X
Bouadma 2010		X	X	X
Daubin 2018			X	
De Jong 2016		X	X	X
Deliberato 2013	X	X	X	X
Dharaniyadewi 2013	X			
Hochreiter 2009	X	X	X	X
Jensen 2011			X	
Layios 2012		X	X	X
Liu 2013	X			
Najafi 2015		X	X	
Nobre 2008	X	X	X	X
Oliveira 2013	X		X	X
Schroeder 2009	X	X	X	X
Shehabi 2014	X	X	X	X
Stolz 2009			X	
Svoboda 2007	X			
Wang 2016			X	

Presepsin

Tong et al. (2015) pooled results from 11 observational studies to assess presepsin as a diagnostic marker for sepsis. The pooled sensitivity and specificity were 0.83 (95% CI 0.77–0.88) and 0.81 (95% CI 0.74–0.87) respectively.

Wu et al. (2015) pooled results from 10 observational studies to assess accuracy of presepsin in sepsis diagnosis in adults. All trials had high risk of bias. The authors pooled results any way and found the pooled sensitivity of presepsin for sepsis was 0.78 (95% CI 0.76–0.80) and pooled specificity was 0.83 (95% CI 0.80–0.85).

Procalcitonin and presepsin – pooled observational studies

Kondo 2019 included 19 observational studies (3,012 critically ill adults with sepsis) in a pooled analysis to assess the diagnostic value of procalcitonin and presepsin. The pooled sensitivities and specificities were 0.80 (95% CI 0.75-0.84) and 0.75 (95% CI 0.67-0.81) for procalcitonin. For presepsin, these values were 0.84 (95% CI 0.80-0.88) and 0.73 (95% CI 0.61-0.82), respectively. There were no statistically significant

differences in both pooled sensitivities (p = 0.48) and specificities (p = 0.57) between procalcitonin and presepsin.

Wu et al. (2017) also pooled observational studies in a lower quality systematic review of 18 observational studies. There was no significant difference between presepsin and procalcitonin or CRP. However, for studies conducted in ICU, the pooled sensitivity of presepsin was found to be higher than procalcitonin (0.88, 95% CI 0.82–0.92 vs. 0.75, 95% CI 0.68–0.81), while the pooled specificity of presepsin was lower than procalcitonin (0.58, 95% CI 0.42–0.73 vs. 0.75, 95% CI 0.65–0.83).

Systematic reviews authored by Lam 2018, Liu 2015, Tan 2019, Xin 2015, Yang 2018, Zhang 2015a, Zhang 2015c, Zheng 2015 and Zhu 2019b were assessed as critically low quality and are not considered further here.

Sepsis calculators and scores

We identified five studies of sufficient quality that assessed sepsis calculators and scoring tools for the assessment of sepsis.

- Results from three studies suggest SIRS criteria (now no longer part of the international consensus definition of sepsis) has sensitivity superior to that of qSOFA, supporting their use for screening of patients and as a prompt for treatment initiation in sepsis.
- Early Warning Scores (EWS) are not predictive of sepsis outcomes.
- Evidence regarding the prognostic accuracy of shock index was insufficient to determine its role in shock assessment.

Fernando 2018 (high quality meta-analysis) summarized and compared the prognostic accuracy of qSOFA and the systemic inflammatory response syndrome (SIRS) criteria for prediction of mortality in adult patients with suspected infection. Thirty-eight studies were included (n = 385,333). qSOFA was associated with a pooled sensitivity of 60.8% (95% CI 51.4%-69.4%) and a pooled specificity of 72.0% (CI 63.4%-79.2%) for mortality whereas the SIRS criteria were associated with a pooled sensitivity of 88.1% (CI, 82.3% to 92.1%) and a pooled specificity of 25.8% (CI, 17.1%-36.9%). The pooled sensitivity of qSOFA was higher in the ICU population. The pooled specificity of qSOFA was higher in the non-ICU population.

Serafim 2018 (moderate quality meta-analysis) also performed a systematic review and meta-analysis with the aim of comparing the qSOFA and SIRS. The focus of this review was patients outside the ICU. Across 10 studies that were pooled (229,480 participants) the meta-analysis of sensitivity for the diagnosis of sepsis comparing the qSOFA and SIRS was in favour of SIRS whereas qSOFA demonstrated better specificity.

Song 2018 (low quality meta-analysis) also assessed the performance of qSOFA as a prognostic tool in infected patients outside the ICU. The authors also concluded a positive qSOFA score had high specificity outside the ICU in early detection of in-hospital mortality, acute organ dysfunction, and ICU admission, but low sensitivity may have limitations as a predictive tool for adverse outcomes.

Hamilton 2018 (high quality meta-analysis) pooled results of six studies (4,298 participants) that assessed the utility of early warning scores to predict mortality in sepsis. Five studies assessed the Modified Early Warning Score and one assessed the National Early Warning Score. Results suggest that EWS cannot be used to predict which

patients with sepsis will (positive likelihood ratio 1.79, 95% CI 1.53-2.11) or will not die (negative likelihood ratio 0.59, 95% CI 0.45-0.78).

Middleton 2019 (high quality meta-analysis) assessed the prognostic accuracy of shock index (heart rate divided by systolic blood pressure) and its modifications in patients with sepsis. There was marked inter-study heterogeneity in criteria used to identify cohorts and in disease severity. Eight studies (n = 7,181) assessed the prognostic utility of shock index, though there was considerable variation in the threshold values used, ranging from ≥ 0.7 to ≥ 1.0. Results were unable to be pooled due to heterogeneity. Shock index at the time of ED admission may predict mortality and pre-hospital shock index may predict ICU admission.

Systematic reviews authored by Maitra 2018, Roney 2015 and Tan 2018 were assessed as critically low quality and are not considered further here.

Automated detection from medical records

One high quality (Warttig et al. 2018) and one moderate quality (Fleuren et al. 2020) systematic review was identified relevant to automated detection systems for the detection of sepsis.

Evidence was insufficient to determine the role of automated detection systems in improving outcomes in adults with sepsis.

Warttig et al. evaluated 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. The authors included three very low quality RCTs in the review. Results were unable to be pooled. They concluded it is unclear what effect automated systems for monitoring sepsis have on any relevant outcome.

Fleuren et al. conducted a systematic review to assess the effectiveness of machine learning for the prediction of sepsis. A total of 28 papers were eligible for synthesis, from which 130 models were extracted. Varying sepsis definitions limited pooling of the performance across studies. However, from the limited available data for the prediction of sepsis, diagnostic test accuracy assessed by the AUROC ranged from 0.68-0.99 in the ICU, to 0.96-0.98 in-hospital and 0.87 to 0.97 in the ED.

Systematic reviews authored by Despins 2017, Islam 2019, Joshi 2019, Makam 2015 and Wulff 2019 were assessed as critically low quality and are not considered further here.

Serum lactate measurement

Two low quality meta-analyses were identified relevant to lactate measurement for sepsis.

Studies suggest serum lactate can be useful to identify patients at increased risk of mortality and can guide clinical management decisions regarding resuscitation in sepsis.

Liu et al. (2017b) conducted a meta-analysis of eight prospective observational studies and fourteen retrospective observational studies including a total of 28,429 patients. Elevated early lactate levels were significantly associated with increased risk of mortality (OR 2.92, 95% CI 2.40-3.55). The association was consistent for cut-off point of about 2 mmol/L (OR 3.21, 95% CI 2.07-4.97) and cut-off point of 4 mmol/L (OR 2.79, 95% CI

2.24-3.47). The overall sensitivity and specificity were 0.56 (95% CI 0.48-0.64) and 0.70 (95% CI 0.64-0.75) respectively.

Pan et al. (2019) conducted a meta-analysis of seven randomized controlled trials encompassing 1,301 cases. Compared with guided ScvO2 (central venous oxygen saturation) therapy, early lactate clearance-directed therapy (as a specific indicator of resuscitation outcome) was associated with decreased in-hospital mortality (RR 0.68, 95% CI 0.56-0.82), shorter ICU stay (MD -1.64 days, 95% CI -3.23 to -0.05), shorter mechanical ventilation time (MD -10.22 hours, 95% CI -15.94 to -4.5), and lower APACHE-II scores (MD -4.47, 95% CI -7.25 to -1.69). However, patients undergoing early lactate clearance-guided therapy had similar lengths of hospital stay and similar SOFA scores.

Systematic reviews authored by Khodashahi 2020 and Morris 2017 were assessed as critically low quality and are not considered further here.

Serum Interleukin-6

Franco 2019 (high quality meta-analysis) reported results from 23 studies (4,192 patients) to determine the diagnostic accuracy of plasma interleukin-6 (IL-6) concentration for the diagnosis of bacterial sepsis in critically ill adults. All studies were judged to be at high risk of bias and considerable heterogeneity between studies prevented formal accuracy estimates to be calculated. This prevented robust conclusions being drawn from the published literature.

The systematic review authored by Hou 2015 was assessed as critically low quality and is not considered further here.

Other topics

We could only identify critically low quality studies assessing infrared spectroscopy (MacDonald 2015) and pCO2 delta (Diaztagle 2017).

Diagnosis and investigation of sepsis in paediatric patients – included studies

We identified the following systematic reviews and meta-analysis of studies relevant to the diagnosis and investigation of sepsis in paediatric patients (Table 6).

Table 6: Studies for diagnosis and investigation of sepsis in paediatric patients

	Number of studies	Quality of evidence	Study ID (Study described at Appendix 3)
Procalcitonin / presepsin	8	Moderate (1) Low (2) Critically low (5)	Bellos 2018; Chiesa 2015; Liu 2019; Parri 2019; Pontrelli 2017; Ruan 2018; Shabuj 2017; Xu 2016
Interleukins	4	Low (1) Critically low (3)	Boskabadi 2018; Qiu 2018; Sun 2019; Zhou 2015b
Neonatal early onset sepsis calculators	4	Low (2) Critically low (2)	Achten 2019; Deshmukh 2019; Helmbrecht 2019; Pettinger 2020;
Role of parental concerns	1	Critically low (1)	Harley 2019
Screening	1	Low (1)	Li 2020d

Procalcitonin and presepsin

We identified three studies of sufficient quality that assessed procalcitonin (Chiesa 2015; Pontrelli 2017) and presepsin (Parri 2019) in paediatric populations.

These studies failed to conclusively demonstrate a role for procalcitonin in the diagnosis or investigation of sepsis in neonates. Low quality evidence suggests presepsin may have a role supporting diagnosis of sepsis in neonates. There is insufficient evidence for procalcitonin or presepsin in the diagnosis of sepsis in children.

Pontrelli 2017 (moderate quality systematic review) pooled results from 17 observational studies (1,408 patients – 1,086 neonates and 322 children). Studies in neonates with early onset sepsis (EOS) and late onset sepsis (LOS) were grouped together. In the neonatal group, sensitivity of 0.85 (95% CI 0.76-0.90) and specificity of 0.54 (95%CI 0.38-0.70) was calculated at the procalcitonin cut-off value of 2.0-2.5 ng/ml. In the paediatric group it was not possible to undertake a pooled analysis due to the paucity of studies.

Chiesa 2015 (low quality systematic review) reported results of 18 observational studies (6,547 neonates, 680 of whom had early onset neonatal sepsis). Studies were too heterogeneous to pool. The authors identified poor quality of reporting of results for included studies, limiting the ability for firm conclusions to be drawn from the available literature.

Parri 2019 (low quality systematic review) identified 15 observational studies (9 studies including 712 neonates from which pooled analysis could be conducted). Pooled sensitivity and specificity of presepsin for diagnosis of neonatal sepsis were 0.90 and 0.90 respectively.

Five critically low quality systematic reviews authored by Bellos 2018, Liu 2019, Ruan 2018, Shabuj 2017 and Xu 2016b are not considered further here.

Interleukins

Only one low quality study (Qiu 2018) was identified that assessed interleukin-6 (IL-6) for the early diagnosis of neonatal sepsis with premature rupture of the membranes. Pooled

analysis of nine studies (study designs not reported) including 694 participants demonstrated an overall pooled sensitivity and specificity of 0.85 (95% CI 0.81–0.91) and 0.88 (95% CI 0.86–0.91) respectively. Although the authors concluded IL-6 is a sensitive and specific diagnostic marker, the reference standard against which IL-6 was compared with blood culture, which is not diagnostic of sepsis.

Three critically low quality systematic reviews authored by Boskabadi 2018, Sun 2019 and Zhou 2015b are not considered further here.

Neonatal early onset sepsis calculators

Two low quality systematic reviews were identified that assessed early onset sepsis calculators. Neither produced conclusive results that support the use of neonatal early onset sepsis calculators.

Pettinger 2020 assessed the sensitivity of the Kaiser Permanente early onset sepsis calculator in 186,196 babies born at 34 weeks or above. There were a total of 75 EOS cases across the studies and a minimum of 14 (best case scenario), and a maximum of 22 (worst case scenario) cases where use of the calculator would have resulted in delayed or missed treatment, compared to if NICE guidelines had been followed. Results therefore were not supportive of the use of the calculator.

Deshmukh 2019 pooled results from 6 prospective studies involving 172,385 neonates aged over 34 weeks gestation. There was very substantial heterogeneity across studies but results were pooled anyway. The authors conclusions that use of the Centers for Disease Control and Prevention guidelines “Sepsis Calculator” was associated with reduce usage of antibiotics, laboratory tests and admission to neonatal units is therefore not supported by the results of the methodologically flawed pooled analyses.

Screening to prevent sepsis

Li 2020d reported results of a low quality meta-analysis of 18 cohort studies in newborns to assess screening-based versus risk-based strategies for the prevention of early onset sepsis. Screening-based strategies included molecular and microbiological methods for detecting colonisation with micro-organisms in the third trimester. Risk-based strategies were based on assessment of prenatal risk factors that increase risk of early onset sepsis. Pooled analysis yielded a 55% decreased risk of early onset Group B Streptococcus sepsis for screening-based versus risk-based strategies (RR = 0.45; 95% CI 0.34–0.59). There was no significant difference between strategies for early onset non-Group B Streptococcus sepsis (RR 0.91; 95% CI 0.74–1.11).

What is the evidence regarding the management of sepsis?

Management of sepsis – adult guidelines

The NICE guidance documents and the International Consensus Guidelines by Rhodes et al. 2017 provided recommendations for the management of sepsis in adults (Table 7).

The following table documents key recommendations in each guideline relevant to management of sepsis in adults. A complete list of all recommendations in each guideline is provided at Appendix 2.

NICE guidelines are formulated against assessment of patient risk. Scope includes initial out of hospital management. International Consensus Guidelines (Rhodes et al. 2017) have a stronger focus on recommendations for the intensive care management of patients with sepsis compared with NICE guidelines. There are few recommendations in common across both guidelines.

Levels of evidence supporting each recommendation cannot be derived from NICE guidelines for all recommendations nor can levels of evidence be confidently identified for each recommendation in the International Consensus Guidelines (Rhodes et al. 2017). As a result, the table below focuses on the levels of evidence or quality assessment that authors made to support each recommendation (depending on which was reported by the guideline developers).

SOMANZ guidelines for the management of sepsis in pregnancy and Australian guidelines for the prevention of sepsis in patients with asplenia and hyposplenism are described separately.

Table 7: Management of sepsis – guideline recommendations

Recommendation	NICE	International Consensus Guidelines (Rhodes 2017)[8]	Quality / level of evidence[9]
Outside hospital (includes children aged 12 years and over)			
Refer all people with suspected sepsis outside acute hospital settings for emergency medical care by the most appropriate means of transport if they meet any high risk criteria or they are aged under 17 years and their immunity is impaired by drugs or illness and they have any moderate to high risk criteria.	√		Not informed by evidence review
Provide people with suspected sepsis, who do not have any high or moderate to high risk criteria information about symptoms to monitor and how to access medical care if they are concerned.	√		Not informed by evidence review
Hospital – high risk patients (includes children aged 12 years and over)			
If lactate over 4 mmol/litre, or systolic blood pressure less than 90 mmHg give intravenous fluid bolus without delay (within 1 hour of identifying that they meet any high risk criteria) and refer to critical care for review of management including need for central venous access and initiation of inotropes or vasopressors.	√		Very low quality evidence
If lactate between 2 and 4 mmol/litres give intravenous fluid bolus without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting)	√		Very low quality evidence
If lactate below 2 mmol/litre consider giving intravenous fluid bolus	√		Very low quality evidence
Monitor people with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all adult patients in acute hospital settings.	√		Very low quality evidence (III-3)
Monitor the mental state of people with suspected sepsis. Consider using a scale such as the Glasgow Coma Scale (GCS) or AVPU ('alert, voice, pain, unresponsive') scale.	√		Very low quality evidence (III-3)
Alert a consultant to attend in person if patient with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of: - systolic blood pressure persistently below 90 mmHg - reduced level of consciousness despite resuscitation - respiratory rate over 25 breaths per minute or a new need for mechanical ventilation	√		Very low quality evidence III-2)

[8] Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system principles guided assessment of quality of evidence from high to very low. Level of evidence supporting each recommendation not explicitly described.

[9] Highest level of evidence provided if cited in guidelines

Recommendation	NICE	International Consensus Guidelines (Rhodes 2017)[8]	Quality / level of evidence[9]
- lactate not reduced by more than 20% of initial value within 1 hour.			
Hospital – moderate risk patients (includes children aged 12 years and over)			
For people who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre or evidence of acute kidney injury, treat as high risk	√		Not informed by evidence review
For people with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition cannot be identified: - repeat structured assessment at least hourly - ensure review by a senior clinical decision maker within 3 hours of meeting 2 or more moderate to high risk criteria in an acute hospital setting for consideration of antibiotics.	√		Very low quality evidence (III-2)
For people with suspected sepsis who meet 2 moderate to high risk criteria, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition or infection can be identified and treated: - manage the definitive condition - if appropriate, discharge with information depending on the setting	√		Very low quality evidence
For people with suspected sepsis who meet only 1 moderate to high risk criterion arrange clinician review within 1 hour of meeting criterion for clinical assessment in an acute hospital setting, manage the definitive condition and if appropriate, discharge with information depending on the setting	√		Not stated in guideline
For people with suspected sepsis who meet only 1 moderate to high risk criterion, have lactate of less than 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition cannot be identified, repeat structured assessment at least hourly and ensure review by a senior clinical decision maker within 3 hours of meeting moderate to high criterion in an acute hospital setting for consideration of antibiotics.	√		Very low quality evidence (III-2)
Hospital – low risk patients (includes children aged 12 years and over)			
Arrange clinical assessment of people who have suspected sepsis and no high risk or moderate to high risk criteria and manage according to clinical judgement.	√		Not stated in guideline
Antimicrobials			
For all people with suspected sepsis where the source of infection is clear use existing local antimicrobial guidance.	√		Not informed by evidence review
For high risk patients (includes children aged 12 years and over) give a broad-spectrum antimicrobial at the maximum recommended dose without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting)	√		Very low quality evidence (III-2)
We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 hour for both sepsis and septic shock		√	Strong recommendation (moderate quality evidence)

Recommendation	NICE	International Consensus Guidelines (Rhodes 2017)[8]	Quality / level of evidence[9]
Ensure GPs and ambulance services have mechanisms in place to give antibiotics for people with high risk criteria in pre-hospital settings in locations where transfer time is more than 1 hour.	√		Very low quality evidence (III-2)
For people aged 18 years and above who need an empirical intravenous antimicrobial for a suspected infection but who have no confirmed diagnosis, use an intravenous antimicrobial from the agreed local formulary and in line with local (where available) or national guidelines.	√		Not informed by evidence review
We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage)		√	Strong recommendation (moderate quality evidence)
We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted		√	Best practice statement (no evidence)
We recommend that dosing strategies of antimicrobials be optimized based on accepted pharmacokinetic / pharmacodynamic principles and specific drug properties in patients with sepsis or septic shock		√	Best practice statement (no evidence)
We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock		√	Weak recommendation (low quality evidence)
We suggest that combination therapy not be routinely used for ongoing treatment of most other serious infections, including bacteremia and sepsis without shock		√	Weak recommendation (low quality evidence)
We recommend against combination therapy for the routine treatment of neutropenic sepsis/bacteremia		√	Strong recommendation (moderate quality evidence)
If combination therapy is used for septic shock, we recommend de-escalation with discontinuation of combination therapy within the first few days in response to clinical improvement and/or evidence of infection resolution. This applies to both targeted (for culture-positive infections) and empiric (for culture-negative infections) combination therapy		√	Best practice statement (no evidence)
We suggest that an antimicrobial treatment duration of 7 to 10 days is adequate for most serious infections associated with sepsis and septic shock		√	Weak recommendation (low quality evidence)
We suggest that longer courses are appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with Staphylococcus aureus, some fungal and viral infections, or immunologic deficiencies, including neutropenia		√	Weak recommendation (low quality evidence)
We suggest that shorter courses are appropriate in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis		√	Weak recommendation (low quality evidence)
We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock		√	Best practice statement (no evidence)
Fluids			

Recommendation	NICE	International Consensus Guidelines (Rhodes 2017)[8]	Quality / level of evidence[9]
We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock		√	Weak recommendation, low quality evidence)
We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock		√	Strong recommendation (moderate quality evidence)
We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock		√	Weak recommendation, low quality evidence)
If patients over 16 years need intravenous fluid resuscitation, use crystalloids that contain sodium in the range 130–154 mmol/litre with a bolus of 500 ml over less than 15 minutes.	√		Low quality evidence (I)
We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours		√	Strong recommendation (low quality evidence)
Reassess the patient after completion of the intravenous fluid bolus, and if no improvement give a second bolus. If there is no improvement after a second bolus alert a consultant to attend.	√		Very low quality evidence (II)
We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status		√	Best practice statement (No evidence)
We suggest that dynamic over static variables be used to predict fluid responsiveness, where available		√	Weak recommendation, low quality evidence)
We recommend that a fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve		√	Best practice statement (no evidence)
If using a pump or flow controller to deliver intravenous fluids for resuscitation to people over 12 years with suspected sepsis who need fluids in bolus form ensure device is capable of delivering fluid at required rate for example at least 2000 ml/hour in adults.	√		Not informed by evidence review
Do not use starch based solutions/hydroxyethyl starches for fluid resuscitation for people with sepsis.	√	√	Very low quality evidence (I) (NICE) Strong recommendation (high quality evidence) (International Guidelines)
Consider human albumin solution 4–5% for fluid resuscitation only in patients with sepsis and shock.	√		Moderate quality evidence (I)
We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock, when patients require substantial amounts of crystalloids		√	Weak recommendation, low quality evidence)
Oxygen			
Give oxygen to achieve a target saturation of 94-98% for adult patients or 88-92% for those at risk of hypercapnic respiratory failure.	√		No studies identified
Vasopressors			

Recommendation	NICE	International Consensus Guidelines (Rhodes 2017)[8]	Quality / level of evidence[9]
We recommend an initial target mean arterial pressure (MAP) of 65 mm Hg in patients with septic shock requiring vasopressors		√	Strong recommendation (moderate quality evidence)
We recommend norepinephrine as the first-choice vasopressor		√	Strong recommendation (moderate quality evidence)
We suggest adding either vasopressin (up to 0.03 U/min) to norepinephrine with the intent of raising mean arterial pressure to target or adding vasopressin (up to 0.03 U/min) to decrease norepinephrine dosage.		√	Weak recommendation (low to moderate quality evidence)
We suggest using dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia)		√	Weak recommendation, low quality evidence)
We recommend against using low-dose dopamine for renal protection		√	Strong recommendation (high quality evidence)
We suggest using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents		√	Weak recommendation, low quality evidence)
We suggest that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available		√	Weak recommendation, very low quality evidence)
Steroids			
We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200mg per day		√	Weak recommendation, low quality evidence)
Blood products			
We recommend that red blood cell (RBC) transfusion occur only when hemoglobin concentration decreases to < 7.0g/dL in adults in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage		√	Strong recommendation (high quality evidence)
We recommend against the use of erythropoietin for treatment of anemia associated with sepsis		√	Strong recommendation (moderate quality evidence)
We suggest against the use of fresh frozen plasma to correct clotting abnormalities in the absence of bleeding or planned invasive procedures		√	Weak recommendation, very low quality evidence)
We suggest prophylactic platelet transfusion when counts are < 10,000/mm^3 (10×10^9/L) in the absence of apparent bleeding and when counts are < 20,000/mm^3 (20×10^9/L) if the patient has a significant risk of bleeding. Higher platelet counts (≥ 50,000/mm^3 [50 x 10^9/L]) are advised for active bleeding, surgery, or invasive procedures		√	Weak recommendation, very low quality evidence)
Immunoglobulins			
We suggest against the use of IV immunoglobulins in patients with sepsis or septic shock		√	Weak recommendation, low quality evidence)
Anticoagulants			

Recommendation	NICE	International Consensus Guidelines (Rhodes 2017)[8]	Quality / level of evidence[9]
We recommend against the use of antithrombin for the treatment of sepsis and septic shock		√	Strong recommendation (moderate quality evidence)
Resuscitation			
We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion		√	Weak recommendation (low quality evidence)
Mechanical ventilation			
We recommend using a target tidal volume of 6mL/kg predicted body weight compared with 12mL/kg in adult patients with sepsis-induced acute respiratory distress syndrome		√	Strong recommendation (high quality evidence)
We recommend using an upper limit goal for plateau pressures of 30cm H_2O over higher plateau pressures in adult patients with sepsis-induced severe acute respiratory distress syndrome (ARDS)		√	Strong recommendation (moderate quality evidence)
We suggest using higher positive end-expiratory pressure (PEEP) over lower PEEP in adult patients with sepsis-induced moderate to severe ARDS		√	Weak recommendation, moderate quality evidence)
We suggest using recruitment maneuvers in adult patients with sepsis-induced, severe ARDS		√	Weak recommendation, moderate quality evidence)
We recommend using prone over supine position in adult patients with sepsis-induced ARDS and a Pao2/Fio2 ratio < 150		√	Strong recommendation (moderate quality evidence)
We recommend against using high-frequency oscillatory ventilation in adult patients with sepsis-induced ARDS		√	Strong recommendation (moderate quality evidence)
We suggest using neuromuscular blocking agents for ≤ 48 hours in adult patients with sepsis-induced ARDS and a Pao2/Fio2 ratio < 150mm Hg		√	Weak recommendation, moderate quality evidence)
We recommend a conservative fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion		√	Strong recommendation (moderate quality evidence)
We recommend against the use of ß-2 agonists for the treatment of patients with sepsis-induced ARDS without bronchospasm		√	Strong recommendation (moderate quality evidence)
We recommend against the routine use of the pulmonary artery catheter for patients with sepsis-induced ARDS		√	Strong recommendation (high quality evidence)
We suggest using lower tidal volumes over higher tidal volumes in adult patients with sepsis-induced respiratory failure without ARDS		√	Weak recommendation (low quality evidence)
We recommend that mechanically ventilated sepsis patients be maintained with the head of the bed elevated between 30 and 45 degrees to limit aspiration risk and to prevent the development of ventilator-associated pneumonia		√	Strong recommendation (low quality evidence)
We recommend using spontaneous breathing trials in mechanically ventilated patients with sepsis who are ready for weaning		√	Strong recommendation (high quality evidence)
We recommend using a weaning protocol in mechanically ventilated patients with sepsis-induced respiratory failure who can tolerate weaning		√	Strong recommendation (moderate quality evidence)

Recommendation	NICE	International Consensus Guidelines (Rhodes 2017)[8]	Quality / level of evidence[9]
Sedation and analgesia			
We recommend that continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration end points		√	Best practice statement (no evidence)
We recommend a protocolized approach to blood glucose management in ICU patients with sepsis, commencing insulin dosing when two consecutive blood glucose levels are > 180mg/dL. This approach should target an upper blood glucose level ≤ 180mg/dL rather than an upper target blood glucose level ≤ 110mg/dL		√	Strong recommendation (high quality evidence)
We recommend that blood glucose values be monitored every 1 to 2 hours until glucose values and insulin infusion rates are stable, then every 4 hours thereafter in patients receiving insulin infusions		√	Best practice statement (no evidence)
We recommend that glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution because such measurements may not accurately estimate arterial blood or plasma glucose values		√	Best practice statement (no evidence)
We suggest the use of arterial blood rather than capillary blood for point-of-care testing using glucose meters if patients have arterial catheters		√	Weak recommendation (low quality evidence)
Renal replacement therapy			
We suggest that either continuous or intermittent renal replacement therapy (RRT) be used in patients with sepsis and acute kidney injury		√	Weak recommendation (moderate quality evidence)
We suggest using continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients		√	Weak recommendation (very low quality evidence)
We suggest against the use of RRT in patients with sepsis and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis		√	Weak recommendation (low quality evidence)
Bicarbonate therapy			
We suggest against the use of sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥ 7.15		√	Weak recommendation (moderate quality evidence)
Venous thromboembolism prophylaxis			
We recommend pharmacologic prophylaxis (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]) against venous thromboembolism (VTE) in the absence of contraindications to the use of these agents		√	Strong recommendation (moderate quality evidence)
We recommend LMWH rather than UFH for VTE prophylaxis in the absence of contraindications to the use of LMWH		√	Strong recommendation (moderate quality evidence)
We suggest combination pharmacologic VTE prophylaxis and mechanical prophylaxis, whenever possible		√	Weak recommendation (low quality evidence)
We suggest mechanical VTE prophylaxis when pharmacologic VTE is contraindicated		√	Weak recommendation (low quality evidence)

Recommendation	NICE	International Consensus Guidelines (Rhodes 2017)[8]	Quality / level of evidence[9]
Stress ulcer prophylaxis			
We recommend that stress ulcer prophylaxis be given to patients with sepsis or septic shock who have risk factors for gastrointestinal (GI) bleeding		√	Strong recommendation (low quality evidence)
We suggest using either proton pump inhibitors or histamine-2 receptor antagonists when stress ulcer prophylaxis is indicated		√	Weak recommendation (low quality evidence)
We recommend against stress ulcer prophylaxis in patients without risk factors for GI bleeding		√	Best practice statement (no evidence)
Nutrition			
We recommend against the administration of early parenteral nutrition alone or parenteral nutrition in combination with enteral feedings (but rather initiate early enteral nutrition) in critically ill patients with sepsis or septic shock who can be fed enterally		√	Strong recommendation (moderate quality evidence)
We recommend against the administration of parenteral nutrition alone or in combination with enteral feeds (but rather to initiate IV glucose and advance enteral feeds as tolerated) over the first 7 days in critically ill patients with sepsis or septic shock for whom early enteral feeding is not feasible		√	Strong recommendation (moderate quality evidence)
We suggest the early initiation of enteral feeding rather than a complete fast or only IV glucose in critically ill patients with sepsis or septic shock who can be fed enterally		√	Weak recommendation (low quality evidence)
We suggest either early trophic/hypocaloric or early full enteral feeding in critically ill patients with sepsis or septic shock; if trophic/hypocaloric feeding is the initial strategy, then feeds should be advanced according to patient tolerance		√	Weak recommendation (moderate quality evidence)
We recommend against the use of omega-3 fatty acids as an immune supplement in critically ill patients with sepsis or septic shock		√	Strong recommendation (low quality evidence)
We suggest against routinely monitoring gastric residual volumes in critically ill patients with sepsis or septic shock (weak recommendation, low quality of evidence). However, we suggest measurement of gastric residuals in patients with feeding intolerance or who are considered to be at high risk of aspiration		√	Weak recommendation (very low quality evidence)
We suggest the use of prokinetic agents in critically ill patients with sepsis or septic shock and feeding intolerance		√	Weak recommendation (low quality evidence)
We suggest placement of post-pyloric feeding tubes in critically ill patients with sepsis or septic shock with feeding intolerance or who are considered to be at high risk of aspiration		√	Weak recommendation (low quality evidence)
We recommend against the use of IV selenium to treat sepsis and septic shock		√	Strong recommendation (moderate quality evidence)
We suggest against the use of arginine to treat sepsis and septic shock		√	Weak recommendation (low quality evidence)
We recommend against the use of glutamine to treat sepsis and septic shock		√	Strong recommendation (moderate quality evidence)

Recommendation	NICE	International Consensus Guidelines (Rhodes 2017)[8]	Quality / level of evidence[9]
Information and support			
Ensure a care team member is nominated to give information to families and carers. Ensure information is given without using medical jargon. Check regularly that people understand the information and explanations they are given. Give people with sepsis and their family members and carers opportunities to ask questions about diagnosis, treatment options, prognosis and complications. Be willing to repeat any information as needed. Give people with sepsis and their families and carers information about national charities and support groups that provide information about sepsis and the causes of sepsis.	√		Low quality evidence (IV)
Give people who have been assessed for suspected sepsis but have been discharged without a diagnosis of sepsis (and their family or carers, if appropriate) verbal and written information. Confirm that people understand the information they have been given, and what actions they should take to get help if they need it.	√		Low quality evidence (IV)
Ensure people who are at increased risk of sepsis (for example after surgery) are told before discharge about symptoms that should prompt them to get medical attention and how to get it.	√		Not informed by evidence review
Ensure people and their families and carers if appropriate have been informed that they have had sepsis. Ensure discharge notifications to GPs include the diagnosis of sepsis. Give people who have had sepsis (and their families and carers, when appropriate) opportunities to discuss their concerns. Give people who have had sepsis and their families and carers information about national charities and support groups that provide information about sepsis and causes of sepsis. Advise carers they have a legal right to have a carer's assessment of their needs and give them information on how they can get this.	√		High quality evidence (IV)
We recommend that goals of care and prognosis be discussed with patients and families		√	Best practice statement (no evidence)
We recommend that goals of care be incorporated into treatment and end-of-life care planning, utilizing palliative care principles where appropriate		√	Strong recommendation (moderate quality evidence)
We suggest that goals of care be addressed as early as feasible, but no later than within 72 hours of ICU admission		√	Weak recommendation (low quality evidence)
Training and education			
Ensure all healthcare staff and students involved in assessing people's clinical condition are given regular, appropriate training in identifying people who might have sepsis. Ensure all healthcare professionals involved in triage or early management are given regular appropriate training in identifying, assessing and managing sepsis.	√		Low quality evidence (II)
Performance improvement			

Recommendation	NICE	International Consensus Guidelines (Rhodes 2017)[8]	Quality / level of evidence[9]
We recommend that hospitals and hospital systems have a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients		√	Best practice statement (no evidence)
Source control			
We recommend prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established		√	Best practice statement (no evidence)

SOMANZ guidelines

Bowyer et al. (2017) provide a series of recommendations for the assessment and management of sepsis in pregnancy. The authors provide quality ratings for each recommendation derived from GRADE. Quality scoring methods were not described in full. Levels of evidence associated with each statement in the guidelines are not described.

Assessment of sepsis (moderate quality evidence)

- Numerous measures can be used to screen for sepsis. In addition, assessment for end organ dysfunction should be undertaken. Consideration needs to be given to the altered physiology of pregnancy.
- Screen for sepsis using the obstetrically modified qSOFA (omqSOFA). This modifies the qSOFA criteria for the obstetric population: respiratory rate ≥25/min (instead of ≥22/min in non-pregnant population), mental status (any non-alert state instead of Glasgow Coma Scale < 15 in non-pregnant population) and systolic blood pressure ≤90mmHg (instead of ≤100 in non-pregnant population).
- Assess for any evidence of end organ dysfunction by reviewing for signs such as oliguria or by using omSOFA (increase >2)
- Septic shock is a complication of sepsis and is diagnosed when, despite adequate fluid resuscitation, there is hypotension and a requirement for vasopressors. It is associated with an elevated serum lactate and has increased mortality.

Investigations in sepsis (high quality evidence)

- The type of investigations undertaken to establish the cause of sepsis are important. However, what is more important is that they occur in a timely manner.
- Blood cultures and appropriate microbiological specimens should be obtained ideally prior to commencement of antimicrobial therapy; however this should NOT delay administration of antibiotics or antivirals.
- Imaging should not be withheld just because the patient is pregnant or breast feeding
- Be aware of pregnancy-appropriate normal ranges for investigations and observations

Treatment in the golden hour (moderate quality evidence)

- All women with suspected sepsis require prompt treatment, ideally within the first hour of presentation.
- Commence fluid resuscitation immediately to stabilize the mother.
- Administer empiric therapy immediately and preferably within one hour
- Where the source of sepsis is identified, de-escalate to appropriate antibiotics
- Consider the impact of the antibiotics on pregnancy and breast feeding

These guidelines also describe specific recommendations regarding fever in pregnancy, the aetiology of sepsis, fetal surveillance and intensive care issues. These are described in full at Appendix 2.

Spleen Australia guidelines

Kanhutu et al. (2017) provided the following recommendations in patients with asplenia or hyposplenism. Levels of evidence and quality ratings of evidence that underpins each recommendation were not described.

- Patients should receive information about the risk of sepsis and strategies to minimise risk
- Patients should receive antibiotic prophylaxis
- Patients should have an emergency antibiotic supply
- Patients should be vaccinated against pathogens associated with OPSI
- Patients who travel overseas should receive specialist advice
- Patients who are scratched or bitten by animals should receive antibiotics
- Systems should exist to improve adherence to preventive measures

Management of sepsis in adult patients – included studies

We identified the following systematic reviews and meta-analysis of studies relevant to the management of sepsis in adult patients (Table 8).

Table 8: Studies for management of sepsis in adult patients

	Number of studies	Quality of evidence	Study ID (Study described at Appendix 3)
Antibiotics	7	Moderate (3) Low (3) Critically low (1)	Johnston 2017; Roberts 2016; Shiber 2015; Sjovall 2017; Sterling 2015; Vardakas 2018; Xantus 2019
Fluids	11	High (3) Moderate (3) Low (3) Critically low (2)	Li 2020a; Li 2018; Meyhoff 2020; Orbegozo 2019; Quinn 2018; Rochwerg 2015; Scully 2020; Seccombe 2019; Silversides 2017; Tigabu 2018; Zou 2018
Steroids	15	High (8) Low (4) Critically low (3)	Aletreby 2019; Annane 2019; Fang 2019; Gibbison 2017; Lian 2019; Lin 2019; Lyu 2018; Ni 2019; Rochwerg 2018; Rygard 2018; Volbeda 2015; Wen 2019; Wu 2020a; Xu 2018; Zhou 2018
Vasopressors	24	High (1) Moderate (3) Low (6) Critically low (14)	Avni 2015; Belletti 2017; Bhattacharjee 2017; Chang 2018; Chen 2019a; Cheng 2019; Chidambaram 2019; D'Aragon 2015; Duclos 2019; Feng 2019; Hammond 2019; Huang 2020; Huang 2019a and 2019b; Jiang 2019; Nagendran 2019; Ping 2018; Song 2020; Tan 2016; Wu 2020b; Yin 2018; Zangrillo 2015; Zhou 2015a; Zhu 2019a
Anticoagulants	4	High (1) Moderate (1) Critically low (2)	Fan 2016; Umemura 2016; Zarychanski 2015; Zhang 2017
Hemofiltration / hemoperfusion	4	High (1) Moderate (1) Low (1)	Borthwick 2017; Fujii 2018; Terayama 2017; Tzu 2017

	Number of studies	Quality of evidence	Study ID (Study described at Appendix 3)
		Critically low (1)	
Immunoglobulins / immune modulators	10	Low (3) Critically low (7)	Busani 2016; Fang 2016; Feng 2016; Gu 2018; Han 2015; Li 2015; Liu 2017a; Wang 2016; Wang 2019a; Yang 2019
Beta blockers	6	Critically low (6)	Chacko 2015; Lee 2019; Li 2020b; Liu 2018; Sanfilippo 2015b; Shi 2018
Statins	4	Moderate (1) Low (2) Critically low (1)	Chen 2018; Deshpande 2015; Pertzov 2019; Quinn 2016
Antipyretics	2	High (1) Critically low (1)	Drewry 2017; Zhang 2015d
Transfusion	2	High (1) Low (1)	Dupuis 2017; Hirano 2019
Other	2	Low (1) Critically low (1)	Wang 2017; Zamani 2016

Antimicrobials

We identified six systematic reviews of sufficient quality that examined antimicrobials for sepsis in adults. Three moderate quality reviews (Sjovall 2017, Vardakas 2018 and Xantus 2019) and three low quality reviews (Johnston 2017, Roberts 2016, Sterling 2015) were identified.

Two questions specific to antimicrobials and sepsis were described for this review:

- What is the evidence regarding timing of initiating antimicrobials in sepsis?
- What is the evidence for timely review of antimicrobials (after the first dose) in sepsis management?

Regarding timing of initiating antimicrobials in sepsis, two low quality reviews demonstrated a positive association between shorter times to administration of antibiotics and mortality in most patient groups (Johnston 2017; Sterling 2015). The association was not statistically significant in Sterling 2015. One moderate quality review concluded evidence is equivocal regarding administration of antibiotics within one hour of ED presentation (Xantus 2019). We also identified moderate quality evidence for an association between prolonged versus short-term antimicrobial infusion and survival (Vardakas 2018). Available evidence did not demonstrate any survival benefit from antibiotic combination versus monotherapy in adults with sepsis in ICU. We identified no studies of sufficient quality that assessed the relationship between timely review of antimicrobials and sepsis outcomes.

Sjovall 2017 compared empirical monotherapy versus combination antibiotic therapy in adults with severe sepsis in ICU. Pooled analysis of 13 RCTs (2,633 patients) showed carbapenems were the most frequently used mono-antibiotic (8 of 13 trials). There was no difference in mortality (RR 1.11, 95% CI 0.95-1.29) or in any other patient-important outcomes (secondary infection, length of stay, duration of mechanical ventilation) between mono- vs. combination therapy.

Vardakas 2018 compared prolonged versus short-term IV infusion of antipseudomonal beta lactams for patients with sepsis. Across 22 RCTs (1,876 patients) prolonged infusion (defined as three or more hours or 24 hours continuous infusion) was associated with lower all-cause mortality than short-term infusion (defined as bolus or up to 60 minutes) (RR 0·70, 95% CI 0·56–0·87). This was also the topic of the lower quality systematic review by Roberts et al. (2016).

Xantus 2019 reported results from seven observational studies (48,104 adults presenting to ED screening positive for sepsis) that examined patient outcomes associated with antibiotic administration within one hour of ED presentation. Heterogeneity between studies prevented pooling of results. Three of the seven studies demonstrated survival benefit for patients who screened positive for sepsis who were administered antibiotics ≤1 h after presentation to the ED. Four studies reported no statistically significant improvement in survival associated with administration of antibiotics within 1 h of ED presentation. Two studies reported worse outcomes associated with early administration of antibiotics in patients with low acuity sepsis.

Johnston 2017 pooled results from 10 studies (9 observational) including 23,696 participants that assessed the effect of immediate administration of antibiotics (within one hour of presentation) on mortality. The pooled results suggest a significant 33% reduction in mortality odds for immediate (within 1 hour) compared with later (41 hours) antibiotic administration (OR 0.67, 95% CI 0.59–0.75) in patients with sepsis.

Sterling 2015 also examined the relationship between timing of antibiotics and mortality. A total of 16,178 patients (11 studies, study design not specified) were evaluable for antibiotic administration from ED triage. Patients who received antibiotics more than 3 hours after ED triage (< 3 hours reference), had a pooled OR for mortality of 1.16 (95% CI 0.92-1.46). A total of 11,017 patients were evaluable for antibiotic administration from severe sepsis/septic shock recognition. Patients who received antibiotics more than 1 hour after severe sepsis/shock recognition (< 1 hour reference) had a pooled OR for mortality of 1.46 (95% CI 0.89-2.40). There was no increased mortality in the pooled ORs for each hourly delay from <1 to >5 hours in antibiotic administration from severe sepsis/shock recognition.

One critically low quality systematic review authored by Shiber 2015 is not considered further here.

Antibiotic discontinuation initiatives are considered separately at Question 4.

Fluids

We identified 11 systematic reviews of sufficient quality that examined fluid management of sepsis. Three high quality reviews (Li 2018, Meyhoff 2020, Tigabu 2018), three moderate quality reviews (Scully 2020, Seccombe 2019, Silversides 2017) and three low quality reviews (Li 2020a, Orbegozo 2019, Quinn 2018) were identified.

Our review methods defined the following question specific to fluid management of sepsis: What is the evidence regarding fluid resuscitation in sepsis?

We found conflicting evidence regarding the relationship between volume strategies for fluid resuscitation in adults.

- Li 2018 conducted a Cochrane review that included three RCTs that assessed liberal versus conservative fluid therapy in adults and children with sepsis or septic shock. Importantly, the authors identified no studies in adults that met the inclusion criteria. The authors concluded there was insufficient evidence to recommend an appropriate volume strategy for fluid resuscitation in adults.
- Meyhoff (2020) also examined higher versus lower fluid volumes during initial management of sepsis. Nine studies including 637 participants were pooled and showed no difference between strategies in all cause mortality. The authors note the quality of the evidence was very low.
- Tigabu (2018) pooled cohort studies (31,443 patients with severe sepsis and septic shock) and observed patients with a high fluid balance have a 70% increased risk of mortality (RR 1.70, 95% CI 1.20-2.41).

To examine the impacts of fluid overload on patient outcomes, Silversides (2017) explored conservative versus liberal fluid strategies after initial fluid resuscitation in patients with sepsis or SIRS. Conservative fluid strategies were associated with a lower mortality than liberal strategies. However, the result was not statistically significant (RR0.86, 95% CI 0.62-1.17).

Evidence was also insufficient to identify evidence-based strategies for patient monitoring of fluid management in sepsis.

- Scully et al. (2020) summarised results from nine prospective parallel trials (894 patients) of static versus dynamic measurement using transpulmonary thermodilution devices for patient monitoring. The authors found both dynamic and static parameters derived from transpulmonary thermodilution devices appear to lead to a reduction in positive fluid balance in septic shock patients compared to measurements of central venous pressure and early goal-directed therapy. However, very high levels of heterogeneity across included studies was described.
- Seccombe et al. (2019) described results from 14 studies (594 patients) of tests for fluid assessment in patients with sepsis who are not mechanically ventilated. Five categories of index test were identified: inferior vena cava collapsibility index (IVCCI), haemodynamic change with passive leg raise, haemodynamic change with respiration, haemodynamic change with intravenous fluid administration, and static assessment tools. Due to the high level of clinical heterogeneity affecting all aspects of study design, quantitative analysis was not feasible.

Comparisons of different types of fluid for resuscitation were of limited scope. One included review showed no clinically significant difference in patient outcomes with hypertonic saline versus isotonic fluids. Another included study demonstrated adverse renal outcomes associated with the use of high molecular weight hydroxyethl starch (H-HES).

- Li (2020a) conducted a network meta-analysis of 13 RCTs (8,616 patients). This low quality systematic review found that no significant differences were detected in the outcomes of 28-day mortality and 90-day mortality among various resuscitation fluids. Analysis of acute kidney injury outcomes demonstrated that H-HES use was associated with increased risk of kidney injury and increased need for renal replacement therapy.

- A low quality meta-analysis by Orbegozo (2019) pooled results from eight RCTs to examine the relationship between hypertonic saline versus isotonic solutions and sepsis outcomes. Hypertonic saline administration was associated with a transient increase in sodium and chloride concentrations without adverse effects on renal function (moderate-quality evidence). Mortality rates were not significantly different with hypertonic saline than with other fluids (OR 0.946, 95% CI 0.688–1.301; low-quality evidence).

Two critically low quality systematic reviews authored by Rochwerg 2015 and Zou 2018 are not considered further here.

Steroids

We identified eight high quality systematic reviews of steroid use in adults with sepsis (Annane 2019, Fang 2019, Gibbison 2017, Lin 2019, Rochwerg 2018, Rygard 2018, Volbeda 2015, Wu 2020a). Low quality reviews by Lian 2019, Ni 2019, Wen 2019 and Zhou 2018 were also identified.

Steroid use was associated with positive impacts on patient survival in the short term but not in the long term. ICU length of stay was improved with steroid use but a significantly increased risk of some complications (hypernatraemia, hyperglycaemia, muscle weakness) was observed. There was insufficient evidence to recommend one steroid type, dose or duration over any other.

The highest quality study of corticosteroids for treating sepsis is a Cochrane review by Annane et al. (2019). Studies published at the same time or after this study (Fang 2019, Wu 2020a) did not identify any RCTs published after the date of last searches in the Annane review. Therefore, the most recent, highest quality evidence for the purposes of this review is the Annane 2019 systematic review and meta-analysis.

Authors combined results from 61 RCTs (55 RCTs that included adult patients). They found that compared with placebo or usual care, corticosteroids:

- probably slightly reduce 28-day mortality (RR 0.91, 95% CI 0.84-0.99; 11,233 participants; 50 studies; moderate-certainty evidence).
- may result in little to no difference in long-term mortality (RR 0.97, 95% CI 0.91-1.03; 6,236 participants; 7 studies; low-certainty evidence) and probably slightly reduce hospital mortality (RR 0.90, 95% CI 0.82-0.99; 8,183 participants; 26 trials; moderate-certainty evidence).
- reduce length of ICU stay for all participants (MD -1.07 days, 95% CI -1.95 to -0.19; 7,612 participants; 21 studies; high certainty evidence) and resulted in a large reduction in length of hospital stay for all participants (MD -1.63 days, 95% CI -2.93 to -0.33; 8,795 participants; 22 studies; high-certainty evidence).
- increase the risk of muscle weakness (RR 1.21, 95% CI 1.01 to 1.44; 6,145 participants; 6 studies; high-certainty evidence).
- probably do not increase the risk of superinfection (RR 1.06, 95% CI 0.95 to 1.19; 5,356 participants; 25 studies; moderate-certainty evidence).
- increase the risk of hypernatraemia (high certainty evidence) and probably increase the risk of hyperglycaemia (moderate-certainty evidence).

The authors reported that moderate-certainty evidence shows there is probably little or no difference in gastroduodenal bleeding, stroke, or cardiac events, and low-certainty evidence suggests that corticosteroids may result in little to no difference in neuropsychiatric events. The authors were unable to draw any conclusions about the difference between continuous infusion versus intermittent boluses due to the paucity of studies identified.

Comparisons of different steroids were reported by Gibbison et al. (2017) and yielded mixed results. Gibbison (2017) conducted a network meta-analysis of 23 RCTs (3,287 participants – 135 paediatric) that examined the association between corticosteroids and outcomes in patients with septic shock. Network meta-analysis provided no clear evidence that any intervention or treatment regimen was better than any other across the spectrum of outcomes except for in shock reversal, where there was strong evidence hydrocortisone boluses and infusions were more likely than methylprednisolone boluses and placebo to result in shock reversal.

Mixed evidence was identified regarding appropriate duration or dosage of steroid treatment.

- Lin 2019 compared long course (7 days or more), low dose corticosteroid therapy with sort course, high dose steroids in patients with sepsis. Long course low-dose corticosteroid therapy was associated with improved 28-day mortality (RR 0.90, 95% CI 0.84–0.97; high quality), intensive care unit mortality (RR 0.87; 95% CI 0.79–0.95; moderate quality) and in-hospital mortality (RR 0.88, 95% CI 0.79–0.997; high quality) but not 90-day, 180-day or 1-year mortality. Limited data were available to assess impacts in patients with septic shock; however, authors concluded long course, low dose corticosteroids were associated with marginal reductions in 28-day mortality.
- Volbeda 2015 pooled results from 35 RCTs (4,682 participants) and found no statistically significant difference in mortality in subgroups of trials stratified according to high (500 mg or more) or low (<500 mg) dose hydrocortisone (or equivalent) (RR 0.87, 95% CI 0.38–1.99; and RR 0.90, 95% CI 0.49–1.67, respectively).
- A low quality review by Ni et al. (2019) pooled results from 19 RCTs and found no significant difference in reoccurrence of septic shock (RR 1.08, 95% CI 1.00–1.16).

Critically low quality systematic reviews authored by Aletreby 2019, Lyu 2018 and Xu 2018 are not considered further here.

Vasopressors

There were 24 systematic reviews we identified that explored vasopressors in managing sepsis. One was a high quality review (Jiang 2019), three were moderate quality reviews (Huang 2020, Huang 2019a and Zhu 2019a) and six were low quality reviews (Belletti 2017, Bhattacharjee 2017, Cheng 2019, D'Aragon 2015, Nagendran 2019, Zhou 2015a).

Overall, vasopressor use is associated with improved mortality. There is insufficient evidence to recommend any one vasopressor alone or in combination over any other vasopressor. There is insufficient evidence to define blood pressure targets for vasopressor use in adults with septic shock.

Jiang 2019 pooled results from 20 RCTs (2,250 patients) that assessed vasopressin receptor agonists in adults with septic shock. Vasopressin receptor agonist use

(vasopressin, terlipressin or selepressin) was associated with reduced mortality (RR 0.92; 95% CI 0.84-0.99). There was no significant effects on ICU length of stay, duration of mechanical ventilation, total adverse events, cardiovascular events, arrhythmia, mesenteric ischemia, diarrhoea, cerebrovascular events or hyponatremia but vasopressin receptor agonists administration increased the risk of digital ischemia (RR 4.85, 95% CI 2.81- 8.39). Huang (2020), published after Jiang 2019, did not include any additional RCTs published after Jiang et al.'s date of last search. Results from other lower quality reviews on the same topic are not discussed further here.

Some included reviews described comparisons between different medication strategies. These showed conflicting results:

- Huang 2019a compared terlipressin and norepinephrine in adults with septic shock. Pooled analysis of six RCTs (756 patients) showed no clinically significant difference between groups.
- Belletti 2017 conducted a network meta-analysis of 33 RCTs (3,470 patients) comparing different inotrope or vasopressor combinations. Authors of this low quality review found that use of inodilators was associated with the highest survival probability in adults with sepsis. As compared with placebo, levosimendan (OR 0.17, 95% CI 0.05-0.60), dobutamine (OR 0.30, 95% CI 0.09-0.99), epinephrine (OR 0.35, 95% CI 0.13-0.96), vasopressin (OR 0.37, 95% CI 0.16-0.89) and norepinephrine plus dobutamine (OR 0.4, 95% CI 0.11-0.96) were significantly associated with survival. Norepinephrine improved survival compared with dopamine (OR 0.81, 95% CI 0.66-1.00). Rank analysis showed that levosimendan had the highest probability of being the best treatment.
- In contrast, Bhattacharjee 2017 pooled results from seven RCTs (122 patients) comparing levosimendan with dobutamine in adults with septic shock in ICU and found no benefit of levosimendan in terms of mortality and length of ICU stay.
- Cheng 2019 also conducted a network meta-analysis. This study included 43 RCTs (5,767 participants) comparing vasoactive medications in patients with septic shock. These authors found the combination of norepinephrine and dobutamine was associated with the lowest 28-day mortality and was superior to levosimendan or any other agent.
- Zhou 2015a, in a network meta-analysis of 21 RCTs (3,189 patients) concluded norepinephrine was superior to dopamine in terms of survival in adults with septic shock. Otherwise there is insufficient evidence to suggest any vasopressor agent or combination is superior to any other.

D'Aragon 2015 reported results from 12 studies (two RCTs and 10 crossover trials) that examined blood pressure targets for vasopressor therapy. The authors concluded there is a paucity of evidence to guide the administration of vasopressors in terms of blood pressure target in critically ill patients with septic shock.

Critically low quality systematic reviews authored by Avni 2015, Chang 2018, Chen 2019a, Chidambaram 2019, Duclos 2019, Feng 2019, Hammond 2019, Huang 2019b, Ping 2018, Song 2020, Tan 2016, Wu 2020b, Yin 2018 and Zangrillo 2015 are not considered further here.

Anticoagulants

We identified two systematic reviews of sufficient quality that assessed anticoagulants in sepsis management in adults. The impact of anticoagulants on mortality in adults with sepsis was conflicting across these two studies.

Zarychanski 2015 conducted a high quality systematic review that pooled results of nine RCTs (2,637 patients) that examined the efficacy and safety of heparin in patients with sepsis. The authors concluded heparin in patients with sepsis, septic shock and DIC may be associated with decreased mortality. However, safety outcomes have been under-reported. The risk ratio for death associated with heparin was 0.88 (95% CI 0.77–1.00). In trials comparing heparin to other anticoagulants, the risk ratio for death was 1.30 (95% CI 0.78–2.18). In trials comparing heparin to placebo or usual care, major haemorrhage was not statistically significantly increased (RR 0.79, 95% CI 0.53–1.17).

In contrast, Umemura 2016, in a moderate quality systematic review pooled results from 24 RCTs (14,767 patients), found no significant reductions in mortality in the overall sepsis population or in the population with sepsis induced coagulopathy. The authors did, however, observe a significant reduction in mortality in patients with sepsis-induced DIC (RR 0.72, 95% CI 0.62–0.85).

Critically low quality systematic reviews by Fan 2016 and Zhang 2017 are not considered further in this review.

Haemofiltration / haemoperfusion

We identified three systematic reviews of sufficient quality that assessed haemofiltration / haemoperfusion in sepsis management in adults. The impact of haemofiltration and haemoperfusion on outcomes in adults with sepsis is unknown as there is insufficient evidence.

Borthwick 2017 conducted a Cochrane review of high volume haemofiltration for sepsis in adults. Pooled analysis of four RCTs (201 patients with sepsis in critical care units) was conducted and showed no significant association between high volume haemofiltration and 28 day mortality. The authors concluded there was insufficient evidence to determine whether the therapy was effective.

Fujii 2018 (moderate quality review, six RCTs, 857 participants) compared Polymyxin B-immobilised haemoperfusion (PMX-HP) with usual care or placebo in adults with sepsis or septic shock. The pooled risk ratio for 28-day mortality associated with PMX-HP was 1.03 (95% CI 0.78–1.36). The pooled RR for adverse events was 2.17 (95% CI 0.68–6.94). Organ dysfunction scores over 24–72 h after PMX-HP treatment did not change significantly. The certainty of the body of evidence was judged as low for both benefit and harm using the GRADE methodology. Terayama 2017 conducted a lower quality review on the same topic which is not discussed further here.

Tzu et al. 2017 authored a critically low quality systematic review that is not considered further here.

Immunoglobulins / immune modulators

Three low quality reviews were identified that were authored by Feng 2016, Wang 2019 and Yang 2019 and that examined immunoglobulins and immune modulators in the

management of adults with sepsis. Because studies are of low quality and results are in some cases conflicting, we cannot confidently say immunoglobulins are associated with improved outcomes in adults with sepsis.

Wang 2019a pooled results from 15 RCTs (1,358 patients) that examined ulinastatin treatment in adults with sepsis. Ulinastatin was associated with significantly lower all-cause mortality (OR 0.48, 95% CI 0.35-0.66). APACHE II scores were significant improved and incidence of multiple organ dysfunction syndrome was significantly reduced.

Feng 2016, in an earlier review, pooled results of 12 RCTs (526 participants) that examined ulinastatin +/- thymosin alpha 1 for severe sepsis. Ulinastatin combined with thymosin alpha 1 was associated with lower 28-day mortality (RR 0.67, 95% CI 0.57-0.80) whereas ulinastatin alone was not associated with lower 28-day mortality. The authors concluded that, because of obvious heterogeneity, the impacts of either therapy on APACHE II scores cannot be determined.

Yang 2019 pooled results from 13 RCTs (1,041 patients) that examined IV immunoglobulin (IVIG) treatment in adults with sepsis. Compared with the control treatment, the IVIG treatment reduced the all-cause mortality of patients with sepsis (OR 0.61, 95% CI 0.41-0.92). Regarding the IVIG dosage regimens, the highest total dose range (1.5-2 g/kg) was the optimal dose of administration.

Critically low quality systematic reviews authored by Busani 2016, Fang 2016, Gu 2018, Han 2015, Li 2015, Liu 2017a and Wang 2016 are not considered further here.

Beta blockers

No systematic reviews of sufficient quality were identified that assessed beta blockers in the management of adults with sepsis. We identified six critically low quality systematic reviews relevant to this topic (Chacko 2015; Lee 2019; Li 2020b; Liu 2018; Sanfilippo 2015b; Shi 2018).

Statins

There were three systematic reviews of sufficient quality that explored the relationship between statin use and outcomes in adults with sepsis (Deshpande 2015, Pertzov 2019, Quinn 2016). Available evidence suggest statins do not improve outcomes in adults with sepsis.

The highest quality review by Deshpande 2015 (moderate quality systematic review and meta-analysis) pooled results from seven RCTs (1,720 patients). Statin therapy did not significantly decrease in-hospital mortality (RR 1.04, 95% CI 0.87-1.24) or 28-day mortality (RR 0.93, 95% CI 0.46-1.89) in patients with sepsis.

More recent, low quality reviews were conducted by Pertzov 2019 and Quinn 2016. The most recent review by Pertzov 2019 pooled 14 RCTs (2,628 patients) and also found statins did not reduce mortality.

A critically low quality systematic review authored by Chen et al. 2018 was identified that is not considered further here.

Antipyretics

Antipyretics have no impact on outcomes, either positive or negative, in adults with sepsis. Drewry 2017 conducted a high quality systematic review that included 16 studies (8 RCTs, 8 observational studies) of antipyretics in the management of sepsis. Antipyretic therapy did not reduce 28-day/hospital mortality in the randomized studies (RR 0.93, 95% CI 0.77–1.13) or observational studies (OR 0.90, 95% CI 0.54–1.51). Shock reversal and acquisition of nosocomial infections were also unchanged.

The critically low quality systematic review by Zhang 2015d is not considered further here.

Transfusion

Hirano 2019 conducted a high quality systematic review of three RCTs (1,516 patients) comparing liberal versus restrictive transfusion practices in sepsis management. Significant heterogeneity between studies, together with the small body of research identified, limits the ability for firm conclusions to be drawn.

A low quality systematic review was reported by Dupuis 2017 that examined the impact of transfusion on patients with sepsis admitted to the ICU. One RCT and 12 observational studies were included. The authors also concluded the data on transfusion in patients with sepsis are sparse and there is high heterogeneity between studies.

Other

Zamani 2016 (low quality review) examined the survival benefits of dexmedetomidine for sedating patients with sepsis in intensive care settings. Evidence of sufficient quality is lacking to determine the association between dexmedetomidine and outcomes in adults with sepsis. Six studies (242 patients) were pooled (study design not described). The authors reported the risk ratio for 28-day mortality was 0.49 (95% CI 0.24-0.99) in favour of dexmedetomidine.

A critically low quality review by Wang 2017 was identified and is not considered further.

Management of sepsis – paediatric guidelines

Three high quality guidelines (NICE guidance documents, the International Consensus Guidelines by Weiss et al. and ACCM guidelines by Davis et al.) are relevant to the Australian health system and describe a broad range of recommendations for the management of sepsis in paediatric patients[10]. Note, the previous section ***Management of Sepsis – Adult Guidelines*** describes NICE recommendations for sepsis management which are inclusive of children aged 12 years and above.

Table 9 and Table 10 describe recommendations from NICE guidelines and the International Consensus Guidelines (Weiss et al. 2020). The ACCM guidelines are specific to the management of paediatric septic shock and did not include recommendations for the general management of sepsis. These are described at Table 11.

[10] Guidelines specific to resuscitation in paediatric and neonatal septic shock produced by the ACCM (Davis et al.) do not focus on sepsis diagnosis and investigation.

There are few recommendations in common across guidelines.

- NICE guidelines are formulated against assessment of patient risk, described at Question 1 and in Appendix 2.
- NICE guidelines are inclusive of out of hospital assessment and management of patients with suspected sepsis.
- International Consensus Guidelines (Weiss et al. 2020) have a stronger focus on recommendations for the intensive care management of patients with sepsis compared with NICE guidelines.

Levels of evidence supporting each recommendation cannot be derived from NICE guidelines for all recommendations nor can levels of evidence be confidently identified for each recommendation in the International Consensus Guidelines (Weiss et al. 2020) or ACCM guidelines. As a result, the table below focuses on the quality assessment that authors make to support each recommendation in respective guidelines.

We identified specific guideline recommendations for managing sepsis in paediatric patients using antimicrobials, fluids, steroids, immunoglobulins, prophylaxis, oxygen, endocrine / metabolic management and nutrition. Guideline recommendations for these are described at Table 10.

Table 11 describes recommendations specific to the management of paediatric and newborn patients with septic shock (including children with sepsis-related organ dysfunction). Some broad recommendations in the Tables 9 and 10 are also inclusive of, but are not limited to, children with septic shock.

Table 9: Management of sepsis – guideline recommendations in paediatric patients

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	Quality / level of evidence
We recommend implementing a protocol/guideline for management of children with septic shock or other sepsis-associated organ dysfunction		√	Best practice statement (no evidence)
We were unable to issue a recommendation about using blood lactate values to stratify children with suspected septic shock or other sepsis-associated organ dysfunction into low-versus high-risk of having septic shock or sepsis		√	No evidence identified
We suggest using trends in blood lactate levels, in addition to clinical assessment, to guide resuscitation of children with septic shock and other sepsis-associated organ dysfunction		√	Weak recommendation (very low quality evidence)
Children aged 5-11 years – high risk			
For children aged 5-11 years who have suspected sepsis and 1 or more high risk criteria give a broad-spectrum antimicrobial at the maximum recommended dose without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting) and discuss with a consultant.	√		Very low quality evidence (III-3)
If any high risk criteria and lactate over 4 mmol/litre give intravenous fluid bolus without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting) and refer to critical care for review of central access and initiation of inotropes or vasopressors.	√		Very low quality evidence
If any high risk criteria and lactate between 2 and 4 mmol/litre give intravenous fluid bolus as soon as possible (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting).	√		Very low quality evidence
If any high risk criteria and lactate below 2 mmol/litre consider giving intravenous fluid bolus.	√		Very low quality evidence
Monitor children with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all children in acute hospital settings.	√		Very low quality evidence (III-3)
Monitor the mental state of children aged 5-11 years with suspected sepsis. Consider using the Glasgow Coma Scale (GCS) or AVPU ('alert, voice, pain, unresponsive') scale.	√		Very low quality evidence (III-3)
Alert a consultant to attend in person if a child aged 5-11 years with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of reduced level of consciousness despite resuscitation; heart rate or respiratory rate fulfil high risk criteria or lactate remains over 2 mmol/litre after 1 hour.	√		Very low quality evidence (III-3)
Children aged 5-11 years – moderate risk			
For children aged 5-11 years with suspected sepsis and 2 or more moderate to high risk criteria arrange for a clinician to review the person's condition and venous lactate results within 1 hour of meeting criteria in an acute hospital setting.	√		Not stated in guideline
For children aged 5-11 years with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre, treat as high risk.	√		Very low quality evidence

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	Quality / level of evidence
For children aged 5-11 years with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, and in whom a definitive condition cannot be identified repeat structured assessment at least hourly and ensure review by a senior clinical decision maker within 3 hours of meeting 2 or more moderate to high risk criteria in an acute hospital setting for consideration of antibiotics.	√		Very low quality evidence III-3)
For children aged 5-11 years with suspected sepsis who meet 2 or more moderate to high risk criteria, have lactate of less than 2 mmol/litre, and in whom a definitive condition or infection can be identified and treated manage the definitive condition, and if appropriate, discharge with information depending on the setting.	√		Very low quality evidence
For children aged 5-11 years with suspected sepsis who meet only 1 moderate to high risk criterion arrange clinician reviews within 1 hour of meeting 1 moderate to high risk criterion in an acute hospital setting for clinical assessment.	√		Not stated in guideline
For children aged 5-11 years with suspected sepsis who meet only 1 moderate to high risk criterion and in whom a definitive condition can be identified and treated manage the definitive condition and if appropriate, discharge with information depending on the setting.	√		Not stated in guideline
For children aged 5-11 years with suspected sepsis who meet only 1 moderate to high risk criterion, and in whom a definitive condition cannot be identified repeat structured assessment at least hourly and ensure review by a senior clinical decision maker within 3 hours of meeting a moderate to high risk criterion in an acute hospital setting for consideration of antibiotics.	√		Not stated in guideline
Arrange clinical assessment of children aged 5-11 years who have suspected sepsis and no high risk or moderate to high risk criteria and manage according to clinical judgement.	√		Not stated in guideline
In children with septic shock, we recommend starting antimicrobial therapy as soon as possible, within 1 hour of recognition		√	Strong recommendation (very low quality evidence)
Children aged under 5 years – high risk			
For children aged under 5 years who have suspected sepsis and 1 or more high risk criteria arrange for immediate review by the senior clinical decision maker to assess the child and think about alternative diagnoses to sepsis (for example bronchiolitis) and give a broad-spectrum antimicrobial at the maximum recommended dose without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting) and discuss with a consultant.	√		Very low quality evidence (III-3)
In children with septic shock, we recommend starting antimicrobial therapy as soon as possible, within 1 hour of recognition		√	Strong recommendation (very low quality evidence)
If any high risk criteria and lactate over 4 mmol/litre give intravenous fluid bolus without delay and refer to critical care for review of central access and initiation of inotropes or vasopressors.	√		Very low quality evidence
If any high risk criteria and lactate between 2 and 4 mmol/litre give intravenous fluid bolus without delay (within 1 hour of identifying that they meet any high risk criteria in an acute hospital setting).	√		Very low quality evidence

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	Quality / level of evidence
If any high risk criteria and lactate below 2 mmol/litre, consider giving intravenous fluid bolus.	√		Very low quality evidence
Monitor children aged under 5 years with suspected sepsis who meet any high risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all children in acute hospital settings.	√		Very low quality evidence (III-3)
Monitor the mental state of children under 5 years with suspected sepsis. Consider using the Glasgow Coma Scale (GCS) or AVPU ('alert, voice, pain, unresponsive') scale.	√		Very low quality evidence (III-3)
Alert a consultant to attend in person if a child aged under 5 years with suspected sepsis and any high risk criteria fails to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation. Failure to respond is indicated by any of reduced level of consciousness despite resuscitation, heart rate or respiratory rate fulfil high risk criteria or lactate over 2 mmol/litre after 1 hour.	√		Very low quality evidence (III-3)
Give parenteral antibiotics to infants aged under 3 months as follows: infants younger than 1 month with fever; all infants aged 1–3 months with fever who appear unwell; and infants aged 1–3 months with white blood cell count less than 5×109/litre or greater than 15×109/litre.	√		Not stated in guideline
Children aged under 5 years – moderate risk			
For children aged under 5 years with suspected sepsis and 2 or more moderate to high risk criteria arrange for a clinician to review the person's condition and venous lactate results within 1 hour of meeting 2 or more moderate to high risk criteria in an acute hospital setting.	√		Very low quality evidence (III-3)
For children aged under 5 years with suspected sepsis who meet 2 or more moderate to high risk criteria and have lactate over 2 mmol/litre, treat as high risk.	√		Very low quality evidence
If 2 or more moderate to high risk criteria, lactate of less than 2 mmol/litre, and in whom a definitive condition cannot be identified repeat structured assessment at least hourly and ensure review by a senior clinical decision maker within 3 hours of meeting 2 or more moderate to high risk criteria in an acute hospital setting for consideration of antibiotics.	√		Very low quality evidence
If 2 moderate to high risk criteria, lactate of less than 2 mmol/litre, and in whom a definitive condition or infection can be identified and treated manage the definitive condition and if appropriate, discharge with information depending on the setting.	√		Very low quality evidence
If only 1 moderate to high risk criterion arrange clinician review within 1 hour of meeting a moderate to high risk criterion for clinical assessment.	√		Not stated in guideline
If only 1 moderate to high risk criterion and in whom a definitive condition can be identified and treated manage the definitive condition and if appropriate, discharge with information depending on the setting.	√		Not stated in guideline
If only 1 moderate to high risk criterion and in whom a definitive condition cannot be identified repeat structured assessment at least hourly and ensure review by a senior clinical decision maker within 3 hours of meeting a moderate to high risk criterion in an acute hospital setting for consideration of antibiotics.	√		Not stated in guideline
Children aged under 5 years – low risk			

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	Quality / level of evidence
If no high risk or moderate to high risk criteria arrange clinical assessment of children aged under 5 years who have suspected sepsis and no high risk or moderate to high risk criteria and manage according to clinical judgement.	√		Not stated in guideline
Information and support			
Ensure a care team member is nominated to give information to families and carers. Ensure information is given without using medical jargon. Check regularly that people understand the information and explanations they are given. Give people with sepsis and their family members and carers opportunities to ask questions about diagnosis, treatment options, prognosis and complications. Be willing to repeat any information as needed. Give people with sepsis and their families and carers information about national charities and support groups that provide information about sepsis and the causes of sepsis.	√		High quality evidence (IV)
Give people who have been assessed for suspected sepsis but have been discharged without a diagnosis of sepsis (and their family or carers, if appropriate) verbal and written information. Confirm that people understand the information they have been given, and what actions they should take to get help if they need it.	√		High quality evidence (IV)
Ensure people who are at increased risk of sepsis (for example after surgery) are told before discharge about symptoms that should prompt them to get medical attention and how to get it.	√		No studies identified
Ensure people and their families and carers if appropriate have been informed that they have had sepsis. Ensure discharge notifications to GPs include the diagnosis of sepsis. Give people who have had sepsis (and their families and carers, when appropriate) opportunities to discuss their concerns. Give people who have had sepsis and their families and carers information about national charities and support groups that provide information about sepsis and causes of sepsis. Advise carers they have a legal right to have a carer's assessment of their needs, and give them information on how they can get this.	√		High quality evidence (IV)
Training and education			
Ensure all healthcare staff and students involved in assessing people's clinical condition are given regular, appropriate training in identifying people who might have sepsis. Ensure all healthcare professionals involved in triage or early management are given regular appropriate training in identifying, assessing and managing sepsis.	√		Low quality evidence (II)
Source control			
We recommend removal of intravascular access devices that are confirmed to be the source of sepsis or septic shock after other vascular access has been established and depending on the pathogen and the risks/benefits of a surgical procedure		√	Strong recommendation (low quality of evidence)
We recommend that emergent source control intervention be implemented as soon possible after a diagnosis of an infection amenable to a source control procedure is made		√	Best practice statement (no evidence)

Table 10: Management of sepsis – therapy-specific guideline recommendations in paediatric patients

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	Quality of evidence cited
Antimicrobials			
For people aged up to 17 years (excluding neonates) with suspected community acquired sepsis of any cause give ceftriaxone 80 mg/kg once a day with a maximum dose of 4 grams daily at any age.	√		Not informed by evidence review
For people aged up to 17 years with suspected sepsis who are already in hospital, or who are known to have previously been infected with or colonised with ceftriaxone-resistant bacteria, consult local guidelines for choice of antibiotic	√		Not informed by evidence review
For children younger than 3 months, give an additional antibiotic active against listeria (for example, ampicillin or amoxicillin).	√		Not informed by evidence review
Treat neonates presenting in hospital with suspected sepsis in their first 72 hours with intravenous benzylpenicillin and gentamicin.	√		Not informed by evidence review
Treat neonates who are more than 40 weeks corrected gestational age who present with community acquired sepsis with ceftriaxone 50 mg/kg unless already receiving an intravenous calcium infusion at the time. If 40 weeks corrected gestational age or below or receiving an intravenous calcium infusion use cefotaxime 50 mg/kg every 6 to 12 hours, depending on the age of the neonate.	√		Not informed by evidence review
In children with sepsis-associated organ dysfunction but without shock, we suggest starting antimicrobial therapy as soon as possible after appropriate evaluation, within 3 hours of recognition		√	Weak recommendation (very low quality evidence)
We recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens		√	Best practice statement (no evidence)
Once the pathogen(s) and sensitivities are available, we recommend narrowing empiric antimicrobial therapy coverage		√	Best practice statement (no evidence)
If no pathogen is identified, we recommend narrowing or stopping empiric antimicrobial therapy according to clinical presentation, site of infection, host risk factors, and adequacy of clinical improvement in discussion with infectious disease and/or microbiological expert advice		√	Best practice statement (no evidence)
In children without immune compromise and without high risk for multidrug-resistant pathogens, we suggest against the routine use of empiric multiple antimicrobials directed against the same pathogen for the purpose of synergy		√	Weak recommendation (very low quality evidence)
In children with immune compromise and/or at high risk for multidrug-resistant pathogens, we suggest using empiric multi-drug therapy when septic shock or other sepsis-associated organ dysfunction is present/suspected		√	Weak recommendation (very low quality evidence)
We recommend using antimicrobial dosing strategies that have been optimized based on published pharmacokinetic/ pharmacodynamic principles and with consideration of specific drug properties		√	Best practice statement (no evidence)
In children with septic shock or sepsis-associated organ dysfunction who are receiving antimicrobials, we recommend daily assessment (e.g., clinical, laboratory assessment) for de-escalation of antimicrobial therapy		√	Best practice statement (no evidence)

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	Quality of evidence cited
We recommend determining the duration of antimicrobial therapy according to the site of infection, microbial aetiology, response to treatment, and ability to achieve source control		√	Best practice statement (no evidence)
Fluids			
If children and young people up to 16 years need intravenous fluid resuscitation, use glucose-free crystalloids that contain sodium in the range 130–154 mmol/litre, with a bolus of 20 ml/kg over less than 10 minutes. Take into account pre-existing conditions (for example, cardiac disease or kidney disease), because smaller fluid volumes may be needed.	√		Moderate quality evidence (II)
If neonates need intravenous fluid resuscitation, use glucose-free crystalloids that contain sodium in the range 130–154 mmol/litre, with a bolus of 10–20 ml/kg over less than 10 minutes.	√		No studies identified
Reassess the patient after completion of the intravenous fluid bolus, and if no improvement give a second bolus. If there is no improvement after a second bolus alert a consultant to attend	√		No studies identified
Use a pump, or syringe if no pump is available, to deliver intravenous fluids for resuscitation to children under 12 years with suspected sepsis who need fluids in bolus form.	√		No studies identified
In healthcare systems with availability of intensive care, we suggest administering up to 40-60 mL/kg in bolus fluid (10-20 mL/ kg per bolus) over the first hour, titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction		√	Weak recommendations (low quality evidence)
In healthcare systems with no availability of intensive care and in the absence of hypotension, we recommend against bolus fluid administration while starting maintenance fluids		√	Strong recommendation (high quality evidence)
In healthcare systems with no availability of intensive care, if hypotension is present, we suggest administering up to 40 mL/kg in bolus fluid (10-20 mL/kg per bolus) over the first hour with titration to clinical markers of cardiac output and discontinued if signs of fluid overload develop		√	Weak recommendations (low quality evidence)
We suggest using crystalloids, rather than albumin, for the initial resuscitation of children with septic shock or other sepsis associated organ dysfunction		√	Weak recommendation (moderate quality evidence)
We suggest using balanced/buffered crystalloids, rather than 0.9% saline, for the initial resuscitation of children with septic shock or other sepsis-associated organ dysfunction		√	Weak recommendations (very low quality evidence)
We recommend against using starches in the acute resuscitation of children with septic shock or other sepsis-associated organ dysfunction		√	Strong recommendation (moderate quality evidence)
We suggest against using gelatin in the resuscitation of children with septic shock or other sepsis-associated organ dysfunction		√	Weak recommendations (low quality evidence)
Steroids			
We suggest against using intravenous hydrocortisone to treat children with septic shock if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability		√	Weak recommendations (low quality evidence)

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	Quality of evidence cited
We suggest that either intravenous hydrocortisone or no hydrocortisone may be used if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability		√	Weak recommendations (low quality evidence)
Immunoglobulins			
We suggest against the routine use of intravenous immune globulin in children with septic shock or other sepsis associated organ dysfunction		√	Weak recommendations (low quality evidence)
Prophylaxis			
We suggest against the routine use of stress ulcer prophylaxis in critically ill children with septic shock or other sepsis-associated organ dysfunction, except for high-risk patients		√	Weak recommendations (very low quality evidence)
We suggest against routine deep vein thrombosis prophylaxis (mechanical or pharmacologic) in critically ill children with septic shock or other sepsis-associated organ dysfunction, but potential benefits may outweigh risks and costs in specific populations		√	Weak recommendations (low quality evidence)
Oxygen			
Oxygen should be given to children with suspected sepsis who have signs of shock or oxygen saturation (SpO2) of less than 92% when breathing air. Treatment with oxygen should also be considered for children with an SpO2 of greater than 92%, as clinically indicated	√		No studies identified
Endocrine / metabolic			
We recommend against insulin therapy to maintain glucose target at or below 140 mg/dL (7.8 mmol/L)		√	Strong recommendations (moderate quality evidence)
We suggest against the routine use of levothyroxine in children with septic shock and other sepsis-associated organ dysfunction in a sick euthyroid state		√	Weak recommendations (low quality evidence)
We suggest either antipyretic therapy or a permissive approach to fever in children with septic shock or other sepsis-associated organ dysfunction		√	Weak recommendations (moderate quality evidence)
We were unable to issue a recommendation regarding what blood glucose range or as to whether to target normal blood calcium levels in children with septic shock or sepsis-associated organ dysfunction.		√	No evidence
Nutrition			
We suggest not withholding enteral feeding solely on the basis of vasoactive-inotropic medication administration		√	Weak recommendations (low quality evidence)
We suggest enteral nutrition as the preferred method of feeding and that parenteral nutrition may be withheld in the first 7 days of PICU admission in children with septic shock or other sepsis-associated organ dysfunction		√	Weak recommendations (moderate quality evidence)
We suggest against supplementation with specialized lipid emulsions in children with septic shock or other sepsis-associated organ dysfunction		√	Weak recommendations (very low quality evidence)

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	Quality of evidence cited
We suggest against the routine measurements of gastric residual volumes in children with septic shock or other sepsis associated organ dysfunction		√	Weak recommendations (low quality evidence)
We suggest administering enteral feeds through a gastric tube, rather than a post-pyloric feeding tube, to children with septic shock or other sepsis-associated organ dysfunction who have no contraindications to enteral feeding		√	Weak recommendations (low quality evidence)
We suggest against the routine use of prokinetic agents for the treatment of feeding intolerance in children with septic shock or other sepsis-associated organ dysfunction		√	Weak recommendations (low quality evidence)
We suggest against the use of selenium in children with septic shock or other sepsis-associated organ dysfunction		√	Weak recommendations (low quality evidence)
We suggest against the use of glutamine supplementation in children with septic shock or other sepsis-associated organ dysfunction		√	Weak recommendations (low quality evidence)
We suggest against the use of arginine in the treatment of children with septic shock or other sepsis-associated organ dysfunction		√	Weak recommendations (very low quality evidence)
We suggest against using zinc supplementation in children with septic shock and other sepsis-associated organ dysfunction		√	Weak recommendations (very low quality evidence)
We suggest against the use of ascorbic acid (vitamin C) in the treatment of children with septic shock or other sepsis-associated organ dysfunction		√	Weak recommendations (very low quality evidence)
We suggest against the use of thiamine to treat children with sepsis-associated organ dysfunction		√	Weak recommendations (low quality evidence)
We suggest against the acute repletion of vitamin D deficiency for treatment of septic shock or other sepsis-associated organ dysfunction		√	Weak recommendations (very low quality evidence)
We were unable to issue a recommendation regarding early hypocaloric/trophic enteral feeding followed by slow increase to full enteral feeding versus early full enteral feeding in children with septic shock or sepsis-associated organ dysfunction without contraindications to enteral feeding.		√	No evidence

Table 11: Recommendations for management of septic shock in paediatric patients

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	ACCM guidelines (Davis 2017)	Quality / level of evidence
In children with septic shock, we recommend starting antimicrobial therapy as soon as possible, within 1 hour of recognition		√		Strong recommendation (very low quality evidence)
Vasoactive medications				
We suggest using epinephrine, rather than dopamine, in children with septic shock		√		Weak recommendations (low quality evidence)
We suggest using norepinephrine, rather than dopamine, in children with septic shock		√		Weak recommendations (very low quality evidence)
We suggest either adding vasopressin or further titrating catecholamines in children with septic shock who require high-dose catecholamines		√		Weak recommendations (low quality evidence)
We were unable to issue a recommendation for a specific first-line vasoactive infusion for children with septic shock.		√		No evidence
We were unable to issue a recommendation about initiating vasoactive agents through peripheral access in children with septic shock.		√		No evidence
We were unable to issue a recommendation about adding an inodilator in children with septic shock and cardiac dysfunction despite other vasoactive agents.		√		No evidence
Plasma exchange, renal replacement and extracorporeal support				
We suggest against using plasma exchange in children with septic shock or other sepsis-associated organ dysfunction without thrombocytopenia-associated multiple organ failure (TAMOF)		√		Weak recommendations (very low quality evidence)
We cannot suggest for or against the use of plasma exchange in children with septic shock or other-sepsis-associated organ dysfunction with TAMOF.				No evidence
We suggest using renal replacement therapy to prevent or treat fluid overload in children with septic shock or other sepsis associated organ dysfunction who are unresponsive to fluid restriction and diuretic therapy		√		Weak recommendations (very low quality evidence)
We suggest against high-volume hemofiltration over standard hemofiltration in children with septic shock or other sepsis associated organ dysfunction who are treated with renal replacement therapy		√		Weak recommendations (low quality evidence)
We suggest using veno-venous (VV) extracorporeal membrane oxygenation (ECMO) in children with sepsis-induced PARDS and refractory hypoxia		√		Weak recommendations (very low quality evidence)

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	ACCM guidelines (Davis 2017)	Quality / level of evidence
We suggest using veno-arterial (VA) ECMO as a rescue therapy in children with septic shock only if refractory to all other treatments		√		Weak recommendations (very low quality evidence)
Haemodynamic monitoring				
We suggest not using bedside clinical signs in isolation to categorize septic shock in children as “warm” or “cold”		√		Weak recommendations (very low quality evidence)
We were unable to issue a recommendation about whether to target mean arterial blood pressure (MAP) at the 5th percentile for age in children with septic shock and other sepsis-associated organ dysfunction.		√		No evidence
We suggest using advanced hemodynamic variables, when available, in addition to bedside clinical variables to guide the resuscitation of children with septic shock or other sepsis-associated organ dysfunction		√		Weak recommendations (low quality evidence)
Blood products				
We suggest against transfusion of red blood cells if the blood haemoglobin concentration is ≥7 g/dL in hemodynamically stabilized children with septic shock or other sepsis-associated organ dysfunction		√		Weak recommendations (low quality evidence)
We cannot make a recommendation regarding haemoglobin transfusion thresholds for critically ill children with unstable septic shock.		√		No evidence
We suggest against prophylactic platelet transfusion based solely on platelet levels in non-bleeding children with septic shock or other sepsis-associated organ dysfunction and thrombocytopenia		√		Weak recommendations (very low quality evidence)
We suggest against prophylactic plasma transfusion in non-bleeding children with septic shock or other sepsis-associated organ dysfunction and coagulation abnormalities		√		Weak recommendations (very low quality evidence)
Ventilation				
We suggest not to use etomidate when intubating children with septic shock or other sepsis-associated organ dysfunction		√		Weak recommendations (low quality evidence)
We suggest a trial of non-invasive mechanical ventilation (over invasive mechanical ventilation) in children with sepsis-induced pediatric ARDS (PARDS) without a clear indication for intubation and who are responding to initial resuscitation		√		Weak recommendations (very low quality evidence)
We suggest using high positive end-expiratory pressure (PEEP) in children with sepsis-induced PARDS		√		Weak recommendations (very low quality evidence)

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	ACCM guidelines (Davis 2017)	Quality / level of evidence
We suggest a trial of prone positioning in children with sepsis and severe PARDS		√		Weak recommendations (low quality evidence)
We recommend against the routine use of inhaled nitric oxide (iNO) in all children with sepsis-induced PARDS		√		Strong recommendations (low quality evidence)
We suggest using iNO as a rescue therapy in children with sepsis-induced PARDS and refractory hypoxemia after other oxygenation strategies have been optimized		√		Weak recommendations (moderate quality evidence)
We suggest using neuromuscular blockade in children with sepsis and severe PARDS		√		Weak recommendations (very low quality evidence)
We were unable to issue a recommendation about whether to intubate children with fluid-refractory, catecholamine-resistant septic shock.		√		No evidence
We cannot suggest for or against the use of recruitment manoeuvres in children with sepsis-induced PARDS and refractory hypoxemia.		√		No evidence
We were unable to issue a recommendation to use high-frequency oscillatory ventilation (HFOV) versus conventional ventilation in children with sepsis-induced PARDS.		√		No evidence
Septic shock bundles				
Activate a sepsis resuscitation bundle within 15 minutes for patients with suspected septic shock.			√	1c
Adopt a first hour stabilization bundle.			√	1c
Develop or adopt a performance bundle to identify barriers to attaining the recognition, resuscitation, and stabilization bundle goals			√	1c
Managing the first hour of resuscitation for septic shock (paediatric)				
In the first hour of resuscitation the goals are to maintain or restore airway, oxygenation, and ventilation; maintain or restore circulation, defined as normal perfusion and blood pressure; and maintain or restore threshold HR.			√	1c
In the first hour of resuscitation the therapeutic endpoints are capillary refill less than or equal to 2 seconds, normal pulses with no differential between the quality of peripheral and central pulses, warm extremities, urine output greater than 1 mL/kg/hr, normal mental status, normal blood pressure for age (only reliable when pulses palpable), normal glucose concentration, normal ionized calcium concentration.			√	1c

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	ACCM guidelines (Davis 2017)	Quality / level of evidence
In the first hour of resuscitation monitoring includes pulse oximeter, continuous electrocardiogram (ECG), blood pressure and pulse pressure, temperature, urine output, glucose and ionized calcium			√	1c
Airway and breathing should be rigorously monitored and maintained. Supplemental oxygen or high-flow nasal cannula oxygen is titrated as initial therapy to avoid hypoxia and hyperoxia (Spo2 100%). Lung compliance and work of breathing may change precipitously. In early sepsis, patients often have a respiratory alkalosis from centrally mediated hyperventilation. As sepsis progresses, patients may have hypoxemia as well as metabolic acidosis and are at high risk to develop respiratory acidosis secondary to a combination of parenchymal lung disease and/or inadequate respiratory effort due to altered mental status. The decision to intubate and ventilate is based on clinical assessment of increased work of breathing, hypoventilation, or impaired mental status. Waiting for confirmatory laboratory tests is discouraged. If possible, volume loading and peripheral or central inotropic/vasoactive drug support is recommended before and during intubation because of relative or absolute hypovolemia, cardiac dysfunction, and the risk of suppressing endogenous stress hormone response with agents that facilitate intubation. Etomidate is not recommended. Ketamine with atropine pre-treatment should be considered the induction combination of choice during intubation, to promote cardiovascular integrity during the procedure. A short-acting neuromuscular blocking agent can facilitate intubation if the provider is confident and skilled.			√	1c
Vascular access should be rapidly attained. In addition to direct visualization and/or palpation, portable near-infrared imaging devices may assist in peripheral vascular access. Establish intraosseous access if reliable peripheral intravenous line (PIV) access cannot be attained in minutes. Powered intraosseous devices (i.e., intraosseous drill) can facilitate successful intraosseous placement but should be reserved for use in children greater than 3 kg (device not approved below this size). Fluid resuscitation should commence immediately unless hepatomegaly, rales, or a cardiac gallop are present. In the fluid-refractory patient, begin a peripheral inotrope if a second PIV/intraosseous is in place, while establishing a central venous catheter. When administered through a PIV/intraosseous, the inotrope should be infused either as a dilute solution (peripheral epinephrine dilution may be 10 × central) or with a second carrier solution running at a flow rate to assure that it reaches the heart in a timely fashion. Care must be taken to reduce dosage if evidence of peripheral infiltration/ischemia occurs as α-adrenergic receptor mediated effects occur at higher concentrations for epinephrine and dopamine. Central dopamine, epinephrine, or norepinephrine can be administered as a first-line drug as indicated by hemodynamic state when a central line is in place. It is generally appropriate to begin central venous			√	1c

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	ACCM guidelines (Davis 2017)	Quality / level of evidence
infusion and wait until a pharmacologic effect is observed before stopping the peripheral infusion. Establishing a central venous catheter during the initial resuscitation may be dependent upon the availability of skilled personnel and appropriate equipment and should not delay or compromise ongoing resuscitation efforts. Utilization of bedside vascular imaging modalities such as ultrasound guidance can facilitate successful central venous access for skilled personnel familiar with such technologies. High frequency (7.5–13 MHz) probes should be used for infants and children, with higher frequencies yielding better resolution for the smallest patients (< 15 kg).				
Rapid fluid boluses of 20 mL/kg (isotonic crystalloid or 5% albumin) can be administered by push or rapid infusion device (pressure bag) while observing for signs of fluid overload (i.e., the development of increased work of breathing, rales, cardiac gallop rhythm, or hepatomegaly). In the absence of these clinical findings, children can require 40–60 mL/kg in the first hour. Fluid can be pushed with the goal of attaining normal perfusion and blood pressure. Hypoglycemia and hypocalcemia should be corrected. A 10% dextrose containing isotonic IV solution can be run at maintenance IV fluid rates to provide age appropriate glucose delivery and to prevent hypoglycemia.			√	1c
Central dopamine can be titrated to a maximum of 10 µg/kg/min through central access; however, epinephrine or norepinephrine is more likely to be beneficial. Central epinephrine can be started for “cold shock” (0.05–0.3 µg/kg/min) or norepinephrine can be titrated for “warm shock” to restore normal perfusion and blood pressure.			√	1c
If a child is “at risk of absolute adrenal insufficiency or adrenal pituitary axis failure” (e.g., purpura fulminans, congenital adrenal hyperplasia, prior steroid exposure, hypothalamic/pituitary abnormality, intubation with etomidate induction) and remains in shock despite epinephrine or norepinephrine infusion, then hydrocortisone can be administered ideally after attaining a blood sample for subsequent determination of baseline cortisol concentration.			√	1c
Recommendations beyond the first hour of resuscitation (paediatric)				
Goals beyond the first hour are normal perfusion, capillary refill less than or equal to 2 seconds, threshold HRs; perfusion pressure (MAP-CVP or MAP-IAP) appropriate for age. Scvo2 greater than 70%; and cardiac index (CI) greater than 3.3 and less than 6.0 L/min/m2			√	1c
Therapeutic endpoints beyond the first hour are capillary refill less than or equal to 2 seconds, threshold heart rates (HRs), normal pulses with no differential between the quality of the peripheral and central pulses, warm extremities, urine output greater than 1 mL/kg/hr, normal mental status, CI greater than 3.3 and less than 6.0 L/min/m2 with normal perfusion pressure (MAP-CVP, or MAP-IAP) for age, Scvo2 greater than 70%.			√	1c

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	ACCM guidelines (Davis 2017)	Quality / level of evidence
Maximize preload in order to maximize CI, MAP-CVP. Normal INR, anion gap, and lactate.				
Monitoring beyond the first hour includes pulse oximetry, continuous ECG, continuous intra-arterial blood pressure, temperature (core), urine output, CVP/oxygen saturation and/or pulmonary artery pressure/oxygen saturation, cardiac output (CO), serial limited echocardiogram, glucose and calcium, INR, lactate and anion gap			√	1c
Fluid losses and persistent hypovolemia secondary to diffuse capillary leak can continue for days. Ongoing fluid replacement should be directed at clinical endpoints including perfusion, PAOP (pulmonary artery occlusion pressure)/global end-diastolic volume (when available), and CO. Crystalloid is the fluid of choice in patients with haemoglobin greater than 10 g/dL. RBC transfusion can be given to children with haemoglobin less than 10 g/dL. Fresh frozen plasma (FFP) is recommended for patients with prolonged INR but as an infusion, not a bolus. Following shock resuscitation, diuretics/peritoneal dialysis/high flux continuous renal replacement therapy (CRRT) can be used to remove fluid in patients who are 10% fluid overloaded and unable to maintain fluid balance with negative urine output/extra-renal losses. Elevated lactate concentration and anion gap measurements can be treated by assuring both adequate oxygen delivery and glucose utilization. Adequate oxygen delivery (indicated by a Scvo2 > 70%) can be achieved by attaining haemoglobin greater than 10 g/dL and CO greater than 3.3 L/min/m2 using adequate volume loading and inotrope/vasodilator support when needed (as described below). Appropriate glucose delivery can be attained by giving a D10% containing isotonic IV solution at fluid maintenance rate. Appropriate glucose uptake can be attained in subsequently hyperglycemic patients by titrating a glucose/insulin infusion to prevent hyperglycemia (keep glucose concentration ≤ 150 mg/dL) and hypoglycemia (keep glucose concentration > 80 mg/dL). The use of lesser glucose infusion rates (e.g., Dextrose 5% or lower volumes of Dextrose 10%) will not provide glucose delivery requirements.			√	1c
Hemodynamic support can be required for days. Children with “catecholamine-resistant shock” can present with low CO/high systemic vascular resistance (SVR), high CO/low SVR, or low CO/low SVR shock. Although children with persistent shock commonly have worsening cardiac failure, hemodynamic states may completely change with time. Titration of vasoactive infusion(s) may be guided by clinical examination (blood pressure, HR, and capillary refill/skin perfusion analysis) and laboratory data (arterial blood gas and Scvo2 analysis). For patients with persistent shock (reduced urine output, poor perfusion, metabolic/lactic acidosis, or hypotension), a more accurate assessment of CO may be warranted. Many modalities for CO assessment currently exist and include pulmonary artery, pulse index contour continuous cardiac output,			√	1c

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	ACCM guidelines (Davis 2017)	Quality / level of evidence
femoral artery or thermodilution catheters, and/or CO estimated by Doppler ultrasound. These additional data may justify further changes in the vasoactive regimen with resolution of shock. Therapies should be directed to maintain mixed venous/Scvo2 greater than 70%, CI greater than 3.3 less than 6.0 L/min/m2, and a normal perfusion pressure for age (MAP-CVP).				
In shock with low CI, normal BP and high SVR milrinone is considered by the authors to be the first-line inodilator in patients with epinephrine-resistant shock and normal blood pressure. Nitroprusside or nitroglycerin may be considered as second-line vasodilators. Monitoring is needed to avoid cyanide or isothiocyanate toxicity. Levosimendan and enoximone may have a role in recalcitrant low CO syndrome. Thyroid replacement with triiodothyronine is warranted for thyroid insufficiency, and hydrocortisone replacement can be warranted for adrenal or HPA axis insufficiency.			√	1d
In shock with low CI, low BP and low SVR norepinephrine can be added to/or substituted for epinephrine to increase DBP and SVR. Once an adequate blood pressure is achieved, dobutamine, type III phosphodiesterase inhibitors such as milrinone or enoximone (which is more cardioselective than milrinone) or levosimendan can be added to norepinephrine to improve CI and Scvo2. Thyroid replacement with triiodothyronine is warranted for thyroid insufficiency, and hydrocortisone replacement is warranted for adrenal or hypothalamo-pituitary axis insufficiency.			√	1d
For shock with high CI and low SVR, when titration of norepinephrine and fluid does not resolve hypotension, then low-dose vasopressin, angiotensin, or terlipressin can be helpful in restoring blood pressure; however, these potent vasoconstrictors can reduce CO, therefore it is recommended that “these drugs are used with CO/Scvo2 monitoring.” In this situation, additional inotropic therapies will be required such as low-dose epinephrine or dobutamine. Terlipressin is a longer acting drug than angiotensin or vasopressin, so toxicities are more long-acting. As with other forms of severe shock, thyroid hormone or adrenocortical replacement therapy may be added for appropriate indications. We recommend frequent reevaluation of hemodynamic parameters when a patient requires the use of vasopressors, especially in relation to CO, SVR, and peripheral perfusion so as to choose the appropriate combination with inotropic or vasodilator drugs ± fluids.			√	1d
Children with refractory shock must be suspected to have unrecognized morbidities (treatment in parenthesis), including inappropriate source control of infection (remove nidus and use antibiotics with the lowest minimum inhibitory concentration possible, preferably < 1, use IV immunoglobulin for toxic shock), pericardial effusion (pericardiocentesis), pneumothorax (thoracentesis), hypoadrenalism (adrenal hormone replacement), hypothyroidism (thyroid hormone replacement), ongoing blood loss			√	2c

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	ACCM guidelines (Davis 2017)	Quality / level of evidence
(blood replacement/hemostasis), increased IAP (peritoneal catheter or abdominal release), necrotic tissue (nidus removal), excessive immunosuppression (wean immunosuppressants), or immunocompromise (restore immune function; e.g., white cell growth factors/transfusion for neutropenic sepsis). When these potentially reversible causes are addressed, ECMO becomes an important alternative to consider. The expected survival with ECMO for septic shock is no greater than 50% in children, although some centers have recently reported survival rates as high as 75% by using high flow, goal-directed central ECMO where the right atrium and ascending aorta are cannulated directly. This approach mitigates any differential cyanosis and allows the highest possible flow rates, which may facilitate faster resolution of shock. If high flow rates are necessary to resolve shock, it is important to monitor for, and prevent, hemolysis. Maintaining plasma free hemoglobin concentration less than 0.05 g/L by using adequate catheter, circuit, and oxygenator sizes for age. Monitor the inlet pressure as close to the patient as possible (at the connection between the venous cannula and the tubing) and maintain this pressure between zero and the expected pressure drop for the cannula size and the pump flow that is employed. At pressures below these points, there is an increased risk for creating negative pressure in the vessel leading to vessel damage. Thus, the cannula size should be chosen to stay below this limit at the peak expected flow. If these limits are approached, the pump speed should be temporarily reduced while the cause is urgently sought out and corrected. Aside from unnecessarily high circuit flow targets, causes of extremely negative inlet pressures include hypovolemia, inadequate cannula size, partial cannula obstruction or kinking, or high intrathoracic pressure (e.g., cardiac tamponade, excessive positive end-expiratory pressure, pneumothorax, abdominal compartment syndrome). Adequate cannula placement can be confirmed using both chest x-ray and ultrasound guidance. Use of CRRT should be considered for management of potential or actual fluid overload and in patients with purpura. CRRT dosing of 20–25 mL/kg/hr is adequate. High flux CRRT dosing (> 35 mL/kg/hr) can be used, but benefits are theoretical. Consideration should be given to use of CRRT on ECMO primarily for improvement of fluid balance. Therapeutic plasma exchange (TPE) should not be used during the initial septic shock resuscitation. Once shock resuscitation is addressed, TPE could be considered as a strategy to reverse multiple organ dysfunction, especially in patients with significant coagulopathy. Titration of medications will be needed during the procedure to prevent hemodynamic changes because TPE will also remove inotropes, vasopressors, and sedatives. Citrate, a calcium chelator, is used as an anticoagulant for the TPE circuit; therefore, calcium levels will need to be monitored and replenished during the procedure.				

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	ACCM guidelines (Davis 2017)	Quality / level of evidence
Recommendations in the first hour of resuscitation (newborn)				
Goals of resuscitation are to maintain airway, oxygenation, and ventilation; restore and maintain circulation, defined as normal perfusion and blood pressure; maintain neonatal circulation; and maintain threshold HRs.			√	1c
Therapeutic endpoints of resuscitation are capillary refill less than or equal to 2 seconds, normal pulses with no differential in quality between peripheral and central pulses, warm extremities, urine output greater than 1 mL/kg/hr, normal mental status, normal blood pressure for age, normal glucose, and calcium concentrations; difference in preductal and postductal oxygen saturation less than 5%; and 95% Sao2			√	1c
Monitoring requirements include temperature, preductal and postductal pulse oximetry; intra-arterial (umbilical or peripheral) blood pressure; continuous ECG; blood pressure; arterial pH; urine output; glucose and ionized calcium concentration			√	1c
Airway patency and adequate oxygenation and ventilation should be rigorously monitored and maintained. Supplemental or high-flow nasal cannula oxygen is the first choice for respiratory support. The decision to intubate and ventilate is based on clinical diagnosis of increased work of breathing or inadequate respiratory effort or marked hypoxemia. Volume loading and inotrope infusion are often necessary prior to intubation and ventilation because analgesia, sedation, and positive-pressure ventilation can reduce preload, precipitating severe hemodynamic instability or arrest. Critically ill neonates may have rapid decline in systolic and diastolic ventricular function, which implies the need for close reassessment as resuscitation progresses. Expertly timed and performed intubation and mechanical ventilation will enhance physiologic performance at all levels by obviating work of breathing and ensuring the best possible oxygenation and perfusion. Pharmacologic management of intubation includes, in addition to adequate fluid resuscitation, the use of atropine to prevent hemodynamically significant bradycardia, and judicious analgesia, which can be accomplished in many cases with small doses of fentanyl, given slowly as 1–2 μg/kg aliquots. The use of NMDA-receptor antagonists such as ketamine is discouraged by many experts, given concerns regarding neurotoxicity despite it being the only hemodynamically stable drug. Etomidate is associated with adrenal suppression and is generally discouraged, although the agent has been used successfully by some experts in this setting with adjunctive hydrocortisone. Morphine, propofol, barbiturates, high-dose benzodiazepines, and dexmedetomidine are likely to cause hemodynamic instability in the septic neonate and should not be used as first-line agents to secure the airway in this setting.			√	1d

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	ACCM guidelines (Davis 2017)	Quality / level of evidence
Vascular access can be rapidly attained according to NRP (neonatal resuscitation program) /PALS (paediatric advanced life support) guidelines. Placement of an umbilical arterial and venous catheter is preferred. Intraosseous access, particularly in preterm newborns, is not the preferred route of drug administration.			√	1d
Fluid boluses of 10 mL/kg can be administered, observing for the development of hepatomegaly and increased work of breathing. Up to 60 mL/kg may be required in the first hour. Fluid should be infused with a goal of attaining normal perfusion and blood pressure. A D10 containing isotonic IV solution run at maintenance rate will provide age appropriate glucose delivery to prevent hypoglycemia.			√	1c
Patients with severe shock uniformly require cardiovascular support during fluid resuscitation. Although dopamine can be used as the first-line agent, its effect on pulmonary vascular resistance should be considered. A combination of dopamine at low dosage (< 8 µg/kg/min) and dobutamine (up to 10 µg/kg/min) is initially recommended. If the patient does not adequately respond to these interventions, then epinephrine (0.05–0.3 µg/kg/min) can be infused to restore normal blood pressure and perfusion.			√	1c
Hyper oxygenate initially with 100% oxygen and institute metabolic alkalinisation (up to pH 7.50) with NaHCO3 or tromethamine unless and until inhaled NO is available. Mild hyperventilation to produce a respiratory alkalosis can also be instituted until 100% oxygen saturation and less than 5% difference in preductal and postductal saturations are obtained. Inhaled nitric oxide should be administered as the first treatment when available. Back-up therapies include milrinone and inhaled iloprost.			√	1b
Recommendations beyond the first hour (newborn)				
Goals of resuscitation beyond the first hour include • Restore and maintain threshold HR. • Maintain normal perfusion and blood pressure. • Maintain neonatal circulation. • Scvo2 greater than 70% • CI greater than 3.3 L/min/m2 • SVC flow greater than 40 mL/kg/min			√	1c
Therapeutic endpoints beyond the first hour are: • Capillary refill less than or equal to 2 seconds, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output greater than 1 mL/kg/hr, normal mental status, and normal blood pressure for age • greater than 95% Sao2 • less than 5% difference in preductal and postductal Sao2			√	1c

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	ACCM guidelines (Davis 2017)	Quality / level of evidence
• Scvo2 greater than 70% • Absence of right-to-left shunting, tricuspid regurgitation, or right ventricular failure on echocardiographic analysis. • Normal glucose and ionized calcium concentrations • SVC flow greater than 40 mL/kg/min • CI greater than 3.3 L/min/m2 • Normal INR • Normal anion gap, and lactate Fluid overload less than 10%				
Monitoring required beyond the first hour is pulse oximetry, arterial pH, continuous ECG, continuous intra-arterial blood pressure, temperature, glucose and calcium concentration, urine output, CVP/oxygen saturation CO, SVC flow, INR, anion gap and lactate			√	1c
Fluid losses and persistent hypovolemia secondary to diffuse capillary leak can continue for days. Ongoing fluid replacement should be directed at clinical endpoints, including perfusion and CVP. Crystalloid is the fluid of choice in patients with haemoglobin greater than 12 g/dL. Packed RBCs can be transfused in newborns with haemoglobin less than 12 g/dL. Diuretics are recommended in newborns who are 10% fluid overloaded and unable to attain fluid balance with native urine output/extra-renal losses. A Dextrose 10% containing isotonic IV solution run at maintenance rate can provide age appropriate glucose delivery to prevent hypoglycemia. Insulin infusion can be used to correct hyperglycemia. Diuretics are indicated in hypervolemic patients to prevent fluid overload.			√	1c
A 5-day, 6 hour/d course of IV pentoxifylline can be used to reverse septic shock in VLBW babies. In term newborns with persistent pulmonary hypertension of the newborn, inhaled nitric oxide is often effective. Its greatest effect is usually observed at 20 ppm. In newborns with poor left ventricle function and normal blood pressure, the addition of nitroso-vasodilators or type III PDEIs to epinephrine (0.05–0.3 µg/kg/min) can be effective but must be monitored for toxicities. It is important to volume load based on clinical examination and blood pressure changes when using these systemic vasodilators. Triiodothyronine is an effective inotrope in newborns with thyroid insufficiency. Norepinephrine can be effective for refractory hypotension, but Scvo2 should be maintained greater than 70%. An additional inotrope therapy should be added if warranted. Hydrocortisone therapy can be added if the newborn has adrenal insufficiency (defined by a peak cortisol after adreno-corticotrophic hormone < 18 µg/dL, or basal cortisol < 4 mg/dL, or basal cortisol < 18 with the need for inotropic support). An additional inotrope therapy should be added if warranted.			√	1c

Recommendation	NICE	International Consensus Guidelines (Weiss 2020)	ACCM guidelines (Davis 2017)	Quality / level of evidence
The total duration of umbilical catheterization should not exceed 5 days for an umbilical artery catheter (UAC) or 14 days for an umbilical vein catheter. Low doses of heparin (0.25–1.0 U/mL) should be added to the fluid infused through UACs. Prophylactic use of heparin for peripherally inserted silastic percutaneous central venous catheters increases the likelihood that they will complete their intended use (complete therapy) and reduces catheter occlusion.				
Newborns with refractory shock must be suspected to have unrecognized morbidities (requiring specific treatment) including cyanotic or obstructive heart disease (responsive to prostaglandin E1), a critically large patent ductus arteriosus (PDA) (PDA closure), inborn errors of metabolism (responsive to glucose and insulin infusion or ammonia scavengers), pericardial effusion (pericardiocentesis), pneumothorax (thoracentesis), ongoing blood loss (blood replacement/hemostasis), hypoadrenalism (hydrocortisone), and/or hypothyroidism (triiodothyronine). When these causes have been excluded, ECMO becomes an important therapy to consider in term newborns. The current ECMO survival rate for newborn sepsis is 80%. Most centers accept refractory shock or a Pao2 less than 40 mm Hg after maximal therapy to be sufficient indication for ECMO support. When on venovenous ECMO, persistent hypotension and/or shock should be treated with inotropic and/or vasopressor therapy, or conversion to venoarterial support. For newborns with refractory shock related to PPHN-induced right ventricular failure, venovenous ECMO can unload the right ventricle, reduce septal bowing, and improve left ventricle output. However, for newborns with primary left ventricle or biventricular failure refractory to inotropic and vasodilator support, venoarterial ECMO is required to reverse shock. Inotrope requirements can diminish when venoarterial ECMO is used but may persist. Calcium concentration should be normalized in the RBC pump prime (usually requires 300 mg CaCl2 per unit of RBCs). In newborns with inadequate urine output and 10% fluid overload despite diuretics, CRRT is best performed while on the ECMO circuit. No specific recommendations for CRRT can be made in neonatal sepsis. Venous access for CRRT in neonates can be problematic, but in patients on ECMO, CRRT can be provided in tandem. It is a technical challenge to perform TPE in a neonate weighing less than 5 kg. TPE should not be used during the initial septic shock resuscitation. Once the shock resuscitation is addressed, TPE could be considered as a strategy to reverse multiple organ dysfunction, especially in patients with significant coagulopathy. Titration of medications and calcium replenishment will be needed during the procedure to prevent hemodynamic changes.			√	1c

Management of sepsis in paediatric patients – included studies

We identified the following systematic reviews and meta-analysis of studies relevant to the management of sepsis in paediatric patients (Table 12).

Table 12: Studies for management of sepsis in paediatric patients

	Number of studies	Quality of evidence	Study ID (Study described at Appendix 4)
Antimicrobials	2	High (1) Critically low (1)	Dona 2019; Rao 2016b
Fluids	3	High (1) Low (1) Critically low (1)	Gelbart 2015; Li 2018; Medeiros 2015
Steroids	1	High (1)	Annane 2019
Vasopressors	1	Critically low (1)	Wen 2020
Probiotics and prebiotics	5	Moderate (4) Low (1)	Aceti 2017; Chi 2019; Rao 2016a; Sun 2017; Zhang 2016
Lactoferrin	3	High (1) Low (2)	He 2018; Pammi 2017; Razak 2019
Immunotherapy	1	Low (1)	Li 2019
Pentoxifylline	3	High (1) Low (1) Critically low (1)	Pammi 2015; Peng 2019b; Tian 2019
Antibiotic prophylaxis in pregnancy	1	High (1)	Thinkhamrop 2015

Antimicrobials

We identified one systematic review of sufficient quality that examined antimicrobials for sepsis in neonates. Rao 2016b conducted a Cochrane review of 11 RCTs (574 newborns) that examined one dose compared with multiple doses per day of gentamycin in neonates with suspected or proven sepsis. The authors concluded there is insufficient evidence from the currently available RCTs to conclude whether a 'once a day' or a 'multiple doses a day' regimen of gentamicin is superior in treating proven neonatal sepsis. However, data suggest that pharmacokinetic properties of a 'once a day' gentamicin regimen are superior to a 'multiple doses a day'.

Two questions specific to antimicrobials and sepsis were described for this review:

- What is the evidence regarding timing of initiating antimicrobials in sepsis?
- What is the evidence for timely review of antimicrobials (after the first dose) in sepsis management?

Neither question could be answered by studies included in this review. The critically low quality review by Dona 2019 is not considered further in our review.

Fluids

We identified 2 systematic reviews of sufficient quality that examined fluid management of sepsis. Li 2018 conducted a high quality review and meta-analysis and Gelbart 2015 reported results from a low quality review.

Our review methods defined the following question specific to fluid management of sepsis: What is the evidence regarding fluid resuscitation in sepsis? We found some evidence that a liberal fluid strategy may increase mortality compared with a conservative

fluid strategy. There were no other studies of sufficient quality identified in this review from which firm conclusions could be drawn regarding fluid management of paediatric patients with septic shock.

The highest quality, most recent review by Li et al. (2018) pooled results from three RCTs (3,288 children aged between 1 month and 12 years with sepsis or septic shock) investigating liberal versus conservative fluid therapy. The authors concluded that liberal fluid therapy might increase mortality among children with sepsis or septic shock in hospital and at four-week follow-up. All three included trials investigated liberal versus conservative fluid therapy, although definitions of liberal and conservative fluid therapy varied slightly across included studies. Liberal fluid therapy was associated with increased risk of in-hospital mortality by 38% (2 studies; N = 3,288; RR 1.38, 95% CI 1.07-1.77) and may increase risk of mortality at follow-up (at four weeks) by 39% (1 study; N = 3141; RR 1.39, 95% CI 1.11-1.74).There was insufficient evidence to determine risk of adverse events with either strategy.

Gelbart 2015 examined fluid bolus resuscitation for people aged between 28 days and 18 years with severe sepsis or septic shock. This low quality review reported results from 11 studies (three RCTs, 8 non-randomised studies). Heterogeneity between studies precluded meta-analysis. No randomized controlled trials compared fluid bolus therapy with alternative interventions, such as vasopressors. The nonrandomized studies were heterogeneous in populations, methodology, and outcome measures. No observed physiological differences were identified based on volume of fluid bolus therapy.

The critically low quality review by Medeiros 2015 is not considered further here.

Steroids

We only identified one study on this topic. Annane 2018 published a high quality Cochrane review that examined corticosteroids for treating sepsis in children and adults. Of the 61 included studies, six were performed in children and two included both children and adults. In the discussion section of the review the authors report “subgroup analyses based on factors related to participants suggest that age (children vs adults) did not influence patients' response to corticosteroids”. However, data from these subgroup analyses are not published in the review.

Vasopressors

We did not identify any studies of sufficient quality on this topic. There was one critically low quality review (Wen 2020) which is not considered further here.

Probiotics and prebiotics

Four moderate quality reviews (Aceti 2017, Chi 2019, Rao 2016a, Sun 2017) and one low quality review (Zhang 2016) were identified that are relevant to this topic. Studies demonstrated positive sepsis-related outcomes associated with both probiotics and prebiotics in premature and very premature infants.

Regarding probiotic supplementation:

- Aceti 2017 examined probiotics to prevent late onset sepsis in very low birth weight preterm infants that are milk fed. Pooled results from 25 RCTs (5,866 infants of gestational age less than 37 weeks) who received any probiotic within one month of birth showed significantly lower incidence of late onset sepsis (RR 0.79, 95% CI 0.71–

0.88). only probiotic mixtures, and not single-strain products, were effective in reducing late onset sepsis incidence (RR 0.68, 95% CI 0.57–0.80).

- Rao 2016a examined probiotic supplementation and late onset sepsis in 9,415 preterm neonates aged < 37 weeks, with birth weight < 2,500 grams or both. Pooled analysis of 37 RCTs showed that probiotics were associated with significantly lower risk of late onset sepsis (RR 0.86, 95% CI 0.78-0.94).
- The focus of the review by Sun 2017 was very preterm infants (weight < 1,500 grams or gestational age < 32 weeks). Pooled results from 32 RCTs (8,998 infants) showed incidence of sepsis was reduced by 37% (95% CI 0.72%-0.97%), mortality by 20% (95% CI 0.67%-0.95%), necrotising enterocolitis was reduced by 37% (95% CI 0.51%-0.78%) and length of hospital stay reduced by 3.77 days (95% CI 25.94-21.60) in favour of patient groups receiving probiotics.

Probiotic supplementation was also the topic of the low quality review by Zhang 2016.

Chi 2019 examined prebiotics rather than probiotics to prevent sepsis in preterm infants. The authors pooled 18 RCTs (1,322 infants of birth weight <2,500 grams or < 36 weeks) that included various prebiotic preparations (short or long chain galactooligosaccharides, pectin oligosaccharides, oligosaccharides, fructans, inulin or oligofructose). Participants who took prebiotics showed significant decreases in the incidence of sepsis (RR 0.64, 95% CI 0.51-0.78), mortality (RR 0.58, 95% CI 0.36-0.94), length of hospital stay (MD −5.18, 95% CI: −8.94 to −1.11), and time to full enteral feeding (MD −0.99, 95% CI −1.15 to 0.83). The pooled effects showed no significant differences between intervention and control groups in relation to the morbidity rate of necrotising enterocolitis or feeding intolerance.

Lactoferrin

We identified three systematic reviews of sufficient quality that examined lactoferrin in the management of paediatric patients with sepsis. The review by Pammi et al. (2017) was a high quality Cochrane review. Reviews by He 2018 and Razak 2019 are low quality reviews. Results across included studies demonstrated a positive association between lactoferrin supplementation and sepsis outcomes in premature infants.

Pammi 2017 pooled results from six RCTs (886 premature infants < 37 weeks gestation) that examined lactoferrin supplementation of enteral feeds at any dosage or duration. Supplementation was associated with decreased late onset sepsis (RR 0.59, 95% CI 0.40-0.87). There was no association with all-cause mortality (RR 0.65, 95% CI 0.37-1.11). Incidence of necrotising enterocolitis was also reduced. There were no adverse effects observed associated with supplementation.

He 2018 and Razak 2019, although lower quality reviews than Pammi 2017, included RCTs published after the date of last search in Pammi 2017. They are therefore described here for completeness.

- He 2018 pooled results from nine RCTs (1,834 preterm infants < 37 weeks or birth weight < 2,500 grams). Pooled analysis showed that prophylactic lactoferrin was associated with a reduced incidence of culture-proven late onset sepsis (RR 0.47, 95% CI 0.33–0.67).
- Razak 2019 pooled results from 10 RCTs (3,679 infants <37 weeks gestation age admitted to neonatal intensive care units). Bovine or recombinant human lactoferrin

were compared with placebo or no intervention. In this study lactoferrin supplementation with or without probiotics decreased late onset sepsis (RR 0.56, 95% CI 0.36-0.86).

Immunotherapy

One study of sufficient quality assessed immunotherapy in the management of sepsis (Li 2019). This low quality review pooled results from 27 RCTs in neonates with suspected or proven sepsis. All-cause mortality was not significantly different between patients who received the immunoglobulin (IgG), IgM-enriched immunoglobulin (IgGAM), granulocyte-colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) immunotherapies and those who received placebo. Compared with placebo, none of the interventions showed statistically significant differences in the duration of hospital stay.

Pentoxifylline

Two studies of sufficient quality assessed pentoxifylline in the management of sepsis. Pammi 2015 conducted a Cochrane review that pooled results from six RCTs (416 neonates with sepsis). Pentoxifylline used as an adjunct to antibiotics in neonates with sepsis was associated with decreased all-cause mortality during hospital stay (RR 0.57, 95% CI 0.35- 0.93) and decreased length of hospital stay (MD -7.59 days, 95% CI -11.65 to -3.52). Pentoxifylline did not change the risk of development of necrotising enterocolitis, chronic lung disease, severe intraventricular haemorrhage, retinopathy of prematurity or periventricular leukomalacia in neonates with sepsis.

Pentoxifylline therapy compared to pentoxifylline and immunoglobulin M-enriched intravenous immunoglobulin or immunoglobulin M-enriched intravenous immunoglobulin alone did not change mortality or development of necrotising enterocolitis in neonates with sepsis (one study, very low-quality evidence). There were no adverse effects due to pentoxifylline.

Peng 2019b conducted a low quality review on the same topic. No studies were included that were identified after the date of last search by Pammi 2015.

The critically low quality review by Tian 2019 is not considered further here.

Antibiotic prophylaxis in pregnancy

One high quality Cochrane review (Thinkhamrop 2015) assessed the relationship between antibiotic prophylaxis in pregnancy and sepsis outcomes. Pooled analysis of 7 RCTs (2,100 women in the second or third trimester of pregnancy) compared prophylactic prenatal antibiotic administration with placebo or no treatment. There was no difference in neonatal sepsis (RR 11.31; 95% CI 0.64 to 200.79); and blood culture confirming sepsis was not reported in any of the studies. The authors concluded there is not enough evidence to recommend the use of routine antibiotics during pregnancy to prevent infectious adverse effects on pregnancy outcomes.

What factors contribute to better or poorer outcomes in sepsis management?

There were nine systematic reviews that addressed this review question (Table 13). Only two studies were of sufficient quality to warrant further discussion here. One study presented evidence that overweight or obese BMI may be associated with reduced mortality in adults admitted to the ICU with sepsis. Another study reported an association between mortality and worse global longitudinal strain (measured with strain echocardiographic assessment) but not worse left ventricular ejection fraction in adults with severe sepsis and / or septic shock. Both reviews were tentative in their conclusions and reported more studies are needed.

Table 13: Studies of factors that contribute to sepsis outcomes

	Number of studies	Levels of evidence	Study ID (Study described at Appendices 3 and 4)
Gender	1	Critically low (1)	Failla 2017
Ethnicity	1	Critically low (1)	Galiatsatos 2019
BMI	1	Moderate (1)	Pepper 2016
Fever	1	Critically low (1)	Rumbus 2017
Cardiac function	2	High (4) Critically low (1)	Sanfilippo 2015a, Sanfilippo 2018
Facility case volume	1	Critically low (1)	Gu 2016
Early Goal Directed Therapy-associated factors	1	Critically low (1)	Kalil 2017
Etomidate use	1	Critically low (1)	Gu 2015

Pepper 2016 conducted a review of six observational studies in adults admitted to ICU for sepsis, severe sepsis or septic shock. Compared with normal BMI, across five studies each, overweight or obese BMIs was associated with reduced mortality (OR 0.83, 95% CI 0.75-0.91 and OR 0.82, 95% CI 0.67-0.99 respectively). Across three studies each, morbidly obese BMI and underweight BMI did not alter OR (0.90, 95% CI 0.59-1.39 and 1.24 (95% CI 0.79-1.95 respectively). Only one study clearly defined how and when height and weight measurements were calculated. The authors concluded more studies are needed.

Sanfilippo 2018 assessed left ventricular systolic function in patients with severe sepsis or septic shock. Eight studies (794 patients with severe sepsis or septic shock) were pooled. The authors found a significant association between worse left ventricular function and global longitudinal strain values and mortality (SMD − 0.26, 95% CI − 0.47 to − 0.04). No significant association was found between left ventricular ejection fraction and mortality in the same population of patients. The authors concluded more research is warranted.

What are the differences between key current guidelines?

Diagnosis of sepsis

How should people with sepsis be identified?

Screening of patients, early warning scores and recognition bundles were proposed in various guidelines to aid in the identification of patients with sepsis. Recommendations across guidelines are inconsistent.

- NICE guidelines recommend the reader considers using an early warning score to assess people with suspected sepsis.
- International Consensus Guidelines (Weiss et al. 2020) recommend systematic screening of acutely unwell children for sepsis but do not prescribe how patients are screened. These guidelines do not explicitly recommend the use of an early warning score.
- ACCM guidelines recommend the use of a 'recognition bundle' to identify patients at risk of sepsis. Recognition bundles were not recommended in other guidelines.
- SOMANZ guidelines recommended patients are screened for sepsis using a modified SOFA (omqSOFA / omSOFA).

Included studies did not support the use of early warning scores (Hamilton 2018) or qSOFA (Fernando 2018, Serafim 2018, Song 2018) in the identification of people with sepsis. The qSOFA was not examined in pregnant women in studies included in our review.

Should patients be risk stratified?

NICE guidelines recommend the use of a structured set of observations to stratify their risks associated with sepsis. This stratification directly influences recommendations regarding subsequent investigation and management of the patient. Other guidelines do not stratify patients according to risk criteria.

Investigation of sepsis

Should serum lactate be used in the investigation of sepsis in children?

NICE guidelines recommend the use of serum lactate in the investigation of patients with sepsis. International Consensus Guidelines (Rhodes et al. 2017) recommend "guiding resuscitation to normalise lactate" – specific guidance about how lactate is used to guide resuscitation is not provided. Paediatric International Consensus Guideline authors stated they were unable to make a recommendation about lactate measurement. The guideline text did, however, note that "if lactate levels can be rapidly obtained, we often measure blood lactate in children when evaluating for septic shock and other sepsis-associated organ dysfunction".

Included systematic reviews in this review suggest serum lactate can be useful to identify adult patients at increased risk of mortality and can guide clinical management decisions regarding resuscitation in sepsis (low quality evidence).

Management of sepsis in adults

Antibiotics

Should antibiotics be administered within one hour of presentation?

NICE guidelines recommended antibiotic administration within one hour only for patients who meet high risk criteria. In comparison, International Consensus Guidelines (Rhodes et al. 2017) recommend antibiotics for both sepsis and septic shock within one hour and do not stratify according to risk criteria.

Most included studies in our review demonstrated a positive association between shorter times to administration of antibiotics and sepsis outcomes. However, one moderate quality review (Xantus 2019) reported some included studies where outcomes were worse with early administration of antibiotics.

NICE guidelines, International Consensus Guidelines (Rhodes et al. 2017) and SOMANZ guidelines all recommended microbiological specimens be collected before antimicrobial therapy is commenced but only if this does not delay administration of antimicrobials.

Should combination therapy be used? Should antibiotic spectrum be narrowed?

Both NICE and International Consensus Guidelines in adults (Rhodes et al. 2017) recommend initial IV treatment with broad spectrum antibiotics.

NICE guidelines make no specific recommendations regarding empirical combination antibiotic therapy. International Consensus Guidelines (Rhodes et al. 2017) recommend:

- Empiric combination therapy of at least two antibiotics of two different classes aimed at the most likely pathogens is used in initial treatment of septic shock
- empiric antibiotic therapy is narrowed once a pathogen is identified and sensitivities are established.
- Empiric combination therapy is de-escalated / discontinued within the first few days in response to clinical improvement / infection resolution in septic shock.
- empiric combination therapy of at least two antibiotics of two different classes should not be used for ongoing treatment or for sepsis without shock.

Available evidence from included studies in our review did not demonstrate any survival benefit from antibiotic combination versus monotherapy in adults with sepsis in ICU.

How long should antibiotics be continued?

NICE guidelines make no specific recommendations regarding antibiotic duration. International Consensus Guidelines (Rhodes et al. 2017) recommend daily assessment for de-escalation of antimicrobial therapy and duration of 7 to 10 days is adequate for most serious infections.

Should procalcitonin be used to guide antibiotic administration including discontinuation?

International Consensus Guidelines (Rhodes et al. 2017) provide a recommendation regarding the measurement of procalcitonin to guide antimicrobial usage. NICE guidelines did not provide recommendations regarding procalcitonin.

Systematic reviews included in our review failed to conclusively demonstrate a role for procalcitonin or presepsin in the diagnosis or investigation of sepsis in adults.

Fluids

NICE guidelines recommend fluid resuscitation within one hour based on high risk criteria and serum lactate levels (> 2 mmol/L). International Consensus Guidelines (Rhodes et al. 2017) do not base resuscitation guidance on risk stratification or lactate levels.

Both sets of guidelines recommend crystalloids (isotonic solution) as the preferred fluid for resuscitation. NICE recommend a fluid bolus of 500mL over <15 minutes. International Consensus Guidelines (Rhodes et al. 2017) recommend a 30mL/kg IV crystalloid bolus be given over 3 hours.

Included studies in our review reported conflicting evidence regarding the relationship between volume strategies for fluid resuscitation in adults with sepsis. A Cochrane review on the subject concluded there is insufficient evidence to recommend an appropriate volume strategy for fluid resuscitation in adults.

NICE guidelines recommend use of albumin 4-5% but do not specify which patient groups. International Consensus Guidelines (Rhodes et al. 2017) recommend albumin use in addition to crystalloids for initial resuscitation and subsequent volume replacement in patients who require 'substantial amounts of crystalloids'. 'Substantial' is not defined. Included studies in our review did not identify a substantial literature from which recommendations can be drawn regarding different types of fluids for resuscitation.

Vasopressors

NICE guidelines recommend patient assessment for initiation of inotropic support based on serum lactate levels and meeting high risk criteria.

NICE guidelines made no specific recommendation for use of inotropes or vasopressors. The authors conducted a comprehensive review of the literature and concluded the clinical evidence did not show any clinically important difference between different types of inotropic agents or vasopressors.

International guidelines provide a series of recommendations regarding vasopressor use. The authors recommend norepinephrine as the first choice vasopressor, with addition of vasopressin to norepinephrine if required to achieve target mean arterial pressure. Dopamine is only recommended in highly selected patient groups. Dobutamine is recommended in patients with persistent hypoperfusion despite adequate fluid loading and use of other vasopressors.

Overall, studies included in our review demonstrated improved patient outcomes associated with vasopressor use but insufficient evidence to recommend any one vasopressor alone or in combination over any other vasopressor.

Topics not covered in all guidelines

Only NICE guidelines make recommendations regarding oxygen and training and education.

Only International Consensus Guidelines (Rhodes et al. 2017) make recommendations regarding steroids, blood products, immunoglobulins, anticoagulants, mechanical ventilation, sedation and analgesia, renal replacement therapy, bicarbonate therapy,

venous thrombo-embolism prophylaxis, stress ulcer prophylaxis, nutrition, performance improvement and source control.

Included studies in our review demonstrated steroid use is associated with short-term positive impacts on patient survival and reduced ICU length of stay but not improved long-term survival. There was a significantly increased risk of some complications associated with steroid use. We found studies of sufficient quality that examined the association between both statin use and antipyretic use and sepsis outcomes. Statins and antipyretics have no impact on outcomes, either positive or negative, in adults with sepsis.

We found insufficient evidence from which recommendations can be drawn regarding anticoagulant use, haemofiltration / haemoperfusion, immunoglobulins and immune modulators, beta blockers or transfusions.

Management of sepsis in paediatric / neonatal patient groups

Antibiotics

Should antibiotics be administered within one hour of presentation?

Guidelines generally recommended the administration of antibiotics within one hour of presentation in paediatric patients.

- In children aged 5-11 years and in children aged under 5 years NICE guidelines recommend antibiotic administration within one hour only for patients who meet high risk criteria, except in infants aged under 3 months where antibiotics are recommended for all infants younger than 1 month with fever, all infants 1-3 months with fever and who appear unwell and infants aged 1-3 months with a white blood cell count < 5x109 or >15x109 / litre.
- International Consensus Guidelines (Weiss et al. 2020) recommend antibiotics in children with septic shock within one hour of recognition. In children with sepsis-associated organ dysfunction but no shock, antibiotics are recommended within 3 hours of recognition.

NICE guidelines for children aged 12 years and above recommended microbiological specimens be collected before antimicrobial therapy is commenced but only if this does not delay administration of antimicrobials. No recommendations were provided in the paediatric International Consensus Guidelines (Weiss et al. 2020) or for children aged less than 12 years in NICE guidelines.

Should combination therapy be used? Should antibiotic spectrum be narrowed?

Both NICE and International Consensus Guidelines (Weiss et al. 2020) recommend initial IV treatment with broad spectrum antibiotics.

NICE guidelines specifically recommend ceftriaxone for people aged up to 17 years with suspected community acquired sepsis. In children younger than 3 months, an additional antibiotic active against listeria is recommended.

NICE guidelines for neonates are to administer ceftriaxone if more than 40 weeks gestation and presenting with community acquired sepsis and not receiving calcium infusion. Neonates presenting with suspected sepsis in their first 72 hours are treated

with IV benzylpenicillin and gentamycin. Neonates less than 40 weeks gestation or receiving calcium infusion are recommended to receive cefotaxime.

International Consensus Guidelines (Weiss et al. 2020) make no specific recommendations regarding which antibiotic to use. Instead, these guidelines recommend:

- Empiric combination therapy of at least two antibiotics to cover all likely pathogens
- empiric antibiotic therapy is narrowed once a pathogen is identified and sensitivities are established
- if no pathogen is identified, empiric antimicrobial therapy is narrowed or stopped according to clinical features
- do not routinely use multiple empiric antimicrobials directed against the same pathogen in children without immune compromise or at high risk of multi-resistant pathogens
- use empiric multi-drug therapy in children with immune compromise and / or at high risk for multi-resistant organisms only if septic shock or other sepsis-associated organ dysfunction is present.

Only one systematic review of sufficient quality was included in our review that was broadly relevant to this topic. This review compared multiple versus single daily dosing of gentamycin in newborns with suspected or proven sepsis. The authors concluded there is insufficient evidence to recommend one strategy over another.

How long should antibiotics be continued?

International Consensus Guidelines (Weiss et al. 2020) recommend daily assessment of children receiving antimicrobials to guide de-escalation of therapy. NICE guidelines make no specific recommendations regarding antibiotic duration.

Should procalcitonin be used to guide antibiotic administration including discontinuation?

Systematic reviews included in our review failed to conclusively demonstrate a role for procalcitonin in the diagnosis or investigation of sepsis in neonates. Low quality evidence suggests presepsin may have a role supporting diagnosis of sepsis in neonates. There is insufficient evidence for procalcitonin or presepsin in the diagnosis of sepsis in children.

Fluids

NICE guidelines recommend fluid resuscitation within one hour based on high risk criteria and serum lactate levels (> 2 mmol/L). International Consensus Guidelines (Weiss et al. 2020) do not base resuscitation guidance on risk stratification or lactate levels.

Both NICE and International Consensus Guidelines (Weiss et al. 2020) recommend crystalloids (isotonic solution) as the preferred fluid for resuscitation. Both guidelines state albumin is not used as an initial fluid for resuscitation.

- NICE recommend a glucose free crystalloid is used. A fluid bolus of 20mL/kg over <10 minutes is recommended. In neonates a bolus of 10-20mL/kg over <10 minutes is recommended.
- International Consensus Guidelines (Weiss et al. 2020) recommend administering up to 40-60mL/kg in bolus fluid (10-20mL/kg per bolus) over the first hour. Boluses are

titrated to clinical markers of cardiac output. Balanced / buffered crystalloids are recommended rather than normal saline.

- ACCM guidelines for septic shock recommend rapid fluid boluses of 20mL/kg of isotonic crystalloid or 5% albumin by push or rapid infusion. These guidelines state children can require 40-60mL/kg in the first hour. They also state a 10% dextrose containing IV solution can be run at maintenance IV fluid rates in the first hour.

We identified two systematic reviews of sufficient quality that examined fluid management of sepsis. The highest quality review reported that a liberal fluid strategy may be associated with increased mortality compared with a conservative fluid strategy.

Vasopressors

NICE guidelines recommend patient assessment for initiation of vasopressors inotropic support based on serum lactate levels and meeting high risk criteria.

NICE guidelines made no specific recommendation for use of inotropes or vasopressors. The authors conducted a comprehensive review of the literature and concluded the clinical evidence did not show any clinically important difference between different types of inotropic agents or vasopressors.

International Consensus Guidelines (Weiss et al. 2020) provide a series of recommendations regarding vasopressor use. The authors recommend epinephrine or norepinephrine in preference to dopamine in children with septic shock. Vasopressin is recommended as additional therapy. They were unable to recommend a specific first-line vasoactive infusion, provide guidance regarding initiating vasoactive medication through peripheral access or about adding an inodilator in children with septic shock.

ACCM guidelines for septic shock make recommendations regarding administering inotropes through a peripheral IV – the inotrope should be infused either as a dilute solution or with a second carrier solution with care to reduce dosage if evidence of peripheral infiltration or ischaemia. Guidelines state dopamine, epinephrine or norepinephrine can be administered first line.

Oxygen

NICE guidelines recommend giving oxygen to children with septic shock or Ox saturation less than 92% on room air. The guidelines also state ‘treatment with oxygen should also be considered for children with an SpO2 of greater than 92% as clinically indicated’ but do not describe in which circumstances this may be clinically applied.

ACCM guidelines for septic shock recommend supplemental oxygen or high-flow nasal cannula oxygen titrated as initial therapy to avoid hypoxia and hyperoxia in patients with septic shock.

Steroids

International Consensus Guidelines (Weiss et al. 2020) recommend against using IV hydrocortisone to treat children with septic shock if adequate fluid and vasopressor management have restored haemodynamic stability. If haemodynamically unstable in spite of fluid and vasopressors, IV hydrocortisone or no hydrocortisone may be used.

ACCM guidelines for septic shock recommend that, if a child is at risk of absolute adrenal insufficiency or adrenal pituitary access failure and remains in shock in spite of epinephrine or norepinephrine infusion then hydrocortisone can be administered.

Blood products

International Consensus Guidelines (Weiss et al. 2020) recommend against transfusion of RBCs if haemoglobin is 7g/dL or over or if the child is haemodynamically stable. Guidelines suggest against prophylactic plasma transfusion or platelet transfusion in non-bleeding children.

ACCM guidelines for septic shock state RBC transfusion can be given to children with haemoglobin < 10g/dL. Fresh frozen plasma infusion is recommended for patients with prolonged INR.

Renal replacement therapy

International Consensus Guidelines (Weiss et al. 2020) suggest using renal replacement therapy to prevent or treat fluid overload in children with septic shock or other sepsis associated organ dysfunction who are unresponsive to fluid restriction and diuretics. These guidelines suggest against high-volume haemofiltration over standard haemofiltration.

ACCM guidelines for septic shock recommend continuous renal replacement therapy (inclusive of high flux therapy) to remove fluid in patients who are 10% fluid overloaded and unable to maintain fluid balance.

Ventilation

International Consensus Guidelines (Weiss et al. 2020) recommend against using etomidate to intubate children with septic shock / organ dysfunction. A neuromuscular blocking agent is suggested in children with sepsis and severe paediatric acute respiratory distress syndrome.

ACCM guidelines also recommend against use of etomidate. Ketamine with atropine pre-treatment should be considered as the combination of choice according to these guidelines. A short-acting neuromuscular blocking agent can be used if the provider is confident and skilled.

Monitoring

International Consensus Guidelines (Weiss et al. 2020) were unable to issue a recommendation about whether to target mean arterial blood pressure (MAP) at the 5th percentile for age in children with septic shock and other sepsis-associated organ dysfunction. ACCM guidelines for septic shock recommend therapeutic endpoints beyond the first hour that include normal perfusion pressure (MAP-CVP, or MAP-IAP) for age.

Topics not covered in all guidelines

Only NICE guidelines make recommendations regarding information and support and training and education.

Only International Consensus Guidelines (Weiss et al. 2020) make recommendations regarding endocrine / metabolic treatment, nutrition and source control.

Only ACCM guidelines provide recommendations specific to management of newborns with septic shock.

Included studies in our systematic review examined the association between probiotics and prebiotics, lactoferrin, pentoxifylline and immunotherapy and sepsis outcomes. These topics were not the subject of specific recommendations in included guidelines.

Question 3

This section addresses the following review questions:

- How is variation in sepsis outcomes measured?
- What evidence is available to indicate that health care delivery for sepsis in Australia is not in line with best available evidence?

How is variation in sepsis outcomes measured?

We identified seven systematic reviews (six adult and one paediatric) that were of direct relevance to this review question. We found that measuring variation in sepsis outcomes is problematic because there is no valid, standard approach for defining sepsis. Further, coded hospital administrative data lack validity in identifying patients with sepsis. Most studies that measure outcomes use some form of mortality metric as their primary outcome measure.

Public health burden associated with sepsis was described in a moderate quality review by Tsertsvadze et al. (2016). These authors measured variation in incidence of community onset sepsis using the number of cases per 100,000 people per year as the preferred measure. A total of 14 observational studies (10 cohort, four case-control) were discussed. Differences in case ascertainment contributed to wide variations in incidence. Differences in how sepsis was defined contributed to this wide variation. This review highlights the urgent need for an accurate and standard method for identifying sepsis.

The relationship between ICD coding and accurate sepsis diagnosis was examined in a low quality review by Jolley et al. (2015). The authors identified 12 studies conducted using health administration data. They demonstrated issues associated with the validity of ICD-coded sepsis diagnosis codes when used in studies to identify patients with sepsis. A total of 38 sepsis case definitions were tested by the authors, including over 130 different ICD codes. Sensitivity ranged from 5.9% to 82.3%, specificity from 78.3% to 100%, positive predictive value ranged from 5.6% to 100% and negative predictive value from 62.1% to 99.7% depending on codes used.

Five studies (four adult and one paediatric) used mortality as a measure of variation in sepsis outcomes. Across the five included studies that directly examined variation in mortality, two were low quality reviews (Bauer 2020 and Fleischmann 2018) and three were critically low quality reviews (de Grooth 2018, Fleischmann 2016 and Vincent 2019). We note that mortality is also the main outcome measure defined across most other included systematic reviews in our review.

The review by Bauer et al. (2020) pooled results from 170 RCTs and cohort studies that included 371,937 adults with sepsis or septic shock. Measures that were described in the review include:

- 30-day septic shock mortality;
- 90-day septic shock mortality;
- 30-day sepsis mortality;
- 90-day sepsis mortality.

Rates varied between regions, with 30-day septic shock mortality being 33.7% (95% CI 31.5–35.9) in North America, 32.5% (95% CI 31.7–33.3) in Europe and 26.4% (95% CI

18.1–34.6) in Australia. A statistically significant decrease of 30-day septic shock mortality rate was found between 2009 and 2011, but not after 2011.

The review by Fleischmann et al. (2018) pooled results from 23 observational studies conducted high and middle income countries and including children (aged < 20 years) with sepsis and severe sepsis. This study measured variation in outcomes through measurement of sepsis cases and severe sepsis cases per 100,000 person years. There was an aggregate estimate of 48 (95% CI 27–86) sepsis cases and 22 (14–33) severe sepsis cases in children per 100,000 person-years. Mortality ranged from 1% to 5% for sepsis and 9% to 20% for severe sepsis.

What evidence is available to indicate that health care delivery for sepsis in Australia is not in line with best available evidence?

We found one systematic review that included evidence from which this question could be answered. The low quality review by Bauer et al. (2020), described in the previous section, found that 30-day septic shock mortality in Australia is lower than mortality in North America and Europe.

Sources other than guidelines and systematic reviews / meta-analyses may better address this question.

Question 4

This section addresses the following review question:

- What programs or interventions have been used to improve health care delivery and outcomes for sepsis and what were their outcomes?

We identified 24 systematic reviews of a range of programs and interventions specifically designed to improve care delivery and outcomes for sepsis (Table 14).

Table 14: Studies of programs or interventions that improve health care delivery and outcomes for sepsis

	Number of studies	Quality of evidence	Study ID (Study described at Appendices 3 ad 4)
Early goal-directed therapy	15	High (2) Low (6) Critically low (7)	Angus 2015; Chelkeba 2015; Chen 2017; Coccolini 2016; Ding 2018; PRISMA Investigators 2017; Lang 2017; Lee 2016; Liu 2016; Lu 2016; Lu 2018; Park 2017; Xu 2016a; Yu 2016; Zhang 2015b
Performance improvement programs	1	Low (1)	Damiani 2015
Sepsis bundles	2	Moderate (1) Critically low (1)	Kramer 2015; Pepper 2019
Pre-hospital emergency management interventions	2	Moderate (1) Critically low (1)	Lane 2016; Smyth 2016
Guideline implementation strategies	1	Low (1)	Sungkar 2018
Screening programs	1	Critically low (1)	Alberto 2017
Antibiotic discontinuation strategies	2	Low (1) Critically low (1)	Arulkumaran 2020; Guo 2016

Early goal-directed therapy

Early goal-directed therapy (EGDT) refers to a protocol-driven approach to diagnosis and treatment of sepsis at time of presentation that involves intensive monitoring and aggressive management. Eight reviews of sufficient quality were identified that examined EGDT and sepsis outcomes. All studies were in adult populations. Two reviews were high quality (Angus 2015 and PRISMA investigators 2017) and six were low quality (Lang 2017, Lee 2016, Liu 2016, Park 2017, Xu 2016a, Yu 2016). Overall, early goal directed therapy did not have a positive impact on sepsis outcomes compared with usual care.

The review by the PRISMA Investigators was a high quality meta-analysis of individual patient data pooled from the ProCESS, ARISE and ProMISe trials. The authors examined 3,723 patients at 138 hospitals in seven countries. Mortality at 90 days was similar for EGDT (462 of 1852 patients [24.9%]) and usual care (475 of 1871 patients [25.4%]); the adjusted odds ratio was 0.97 (95% CI 0.82-1.14). EGDT was associated with greater mean (±SD) use of intensive care (5.3±7.1 vs. 4.9±7.0 days, P = 0.04) and cardiovascular support (1.9±3.7 vs. 1.6±2.9 days, P = 0.01) than was usual care; other

outcomes did not differ significantly, although average costs were higher with EGDT. Subgroup analyses showed no benefit from EGDT for patients with worse shock (higher serum lactate level, combined hypotension and hyperlactatemia, or higher predicted risk of death) or for hospitals with a lower propensity to use vasopressors or fluids during usual resuscitation.

The other high quality review by Angus et al. (2015) was also from the PRISMA investigators. A systematic review was conducted that identified 11 RCTs, five of which were included in the meta-analysis. The authors again found no effect on the primary mortality outcome with EGDT versus control (23.2 % [495/2134] versus 22.4 % [582/2601]; pooled OR 1.01 [95 % CI 0.88–1.16]. EGDT was associated with increased vasopressor use (OR 1.25 [95 % CI 1.10–1.41]) and ICU admission [OR 2.19 (95 % CI 1.82–2.65)].

The lower quality reviews by Lang 2017, Liu 2016, Park 2017, Xu 2016a and Yu 2016 addressed the same research question and are not described further here.

Lee 2016 compared goal-directed protocol-based resuscitation for septic shock in a meta-analysis of 24 studies (12 RCTs, 12 observational studies, 13,269 adults). The overall mortality odds ratio for goal-directed, protocol-based resuscitation versus conventional care was 0.746 (95% CI 0.631–0.883). However, in RCTs only, there was no statistically significant difference between patient groups (OR 0.93, 95% CI 0.75–1.16). The beneficial effect of GDT decreased as more recent studies were added in an alternative, cumulative meta-analysis.

Critically low quality systematic reviews by Chelkeba 2015, Chen 2017, Coccolini 2016, Ding 2018, Lu 2016, Lu 2018 and Zhang 2015b are not considered further here.

Performance improvement programs

One low quality review (Damiani 2015) examined the effect of performance improvement programs on compliance with sepsis bundles and mortality. Performance improvement programs were defined as ‘any intervention aimed at improving compliance to one or more components of the 6-hour resuscitation bundle or 24-hour sepsis management bundles as based on the 2004 SSC guidelines’.

Very high levels of heterogeneity were observed across included studies. However, the authors pooled results from 50 observational studies (434,447 adults with sepsis, severe sepsis or septic shock) and found that performance improvement programs were associated with increased compliance with the complete 6-hour bundle (OR 4.12, 95% CI 2.95-5.76) and the complete 24-hour bundle (OR 2.57, 95% CI 1.74-3.77) and with a reduction in mortality (OR 0.66, 95% CI 0.61-0.72).

For studies that assessed compliance with the 6-hour bundle, studies on patients with higher illness severity consistently showed a larger increase in compliance compared with studies on patients with a lower risk of death. Ten studies that implemented both educational and process change programs yielded a higher increase in compliance compared with studies that implemented educational or process change interventions alone. Subgroup analyses performed according to geographical location showed larger effect sizes in studies performed in North America and Asia compared with other geographical regions (Europe and South America).

For studies that assessed compliance with the 24-hour sepsis bundle, studies that implemented both educational and process change programs showed higher increase in compliance with the 24-hour bundle compared with only educational or process change interventions. The largest improvements were observed in centres that reported the lowest compliance at baseline. Larger effect sizes were observed in studies performed in North America compared with other geographical regions (Asia, Europe and South America).

Sepsis bundles

One moderate quality review by Pepper 2019 examined the association between sepsis bundles and sepsis outcomes. The authors pooled results from 17 observational studies (16,280 adults hospitalised with sepsis). They included studies that compared mortality between subjects receiving versus not receiving a focussed sepsis bundle that included antibiotic and fluid administration, with or without vasopressors.

Included study interventions were heterogeneous – different studies specified different antibiotic treatment times and fluid volumes. Antibiotics were required within 1 hour in seven studies, 3 hours in seven, within 3 hours in the emergency department or within 1 hour for inpatients in one study. Two studies did not report times. The fluid volume required was 30mL/kg in seven studies, greater than or equal to 2L in one, greater than or equal to 20mL/kg in two and 1.5 to 2L or 500mL in one study each.

Bundles were associated with increased odds of survival. Survival benefits were consistent in the five largest studies (1,697–12,486 patients per study) (OR 1.20, 95% CI 1.11–1.30) and six medium sized studies (167–1,029) (OR 2.03, 95% CI 1.52–2.71). No study had a low risk of bias or assessed potential adverse bundle effects.

Pre-hospital emergency management initiatives

A moderate quality review by Smyth 2016 reported results from a systematic review of nine studies (147,320 adult patients) that examined outcomes in people with suspected sepsis managed by emergency medical services out of hospital. Emergency medicine personnel used a pre-hospital screening tool to identify patients with suspected sepsis. Six pre-hospital screening tools were described – critical illness score, Prehospital Recognition of Severe Sepsis [PRESS] score, Prehospital Early Sepsis Detection [PRESEP] score, Robson tool, modified Robson tool and BAS 90-30-90 tool. Owing to considerable variation in the methodological approach adopted and outcome measures reported, a narrative approach to data synthesis was adopted.

The authors found there is little robust evidence addressing the impact of prehospital interventions on outcomes in sepsis. That which is available is of low quality and indicates that prehospital interventions have limited impact on outcomes in sepsis beyond improving process outcomes and expediting the patient's passage through the emergency care pathway. Evidence indicating that prehospital antibiotic therapy and fluid resuscitation improve patient outcomes is currently lacking.

The authors also reported that recognition of sepsis by ambulance clinicians is poor. The use of screening tools, based on the Surviving Sepsis Campaign diagnostic criteria, improved prehospital sepsis recognition. Screening tools derived from EMS data have been developed, but they have not yet been validated in clinical practice. There is a need

to undertake validation studies to determine whether prehospital sepsis screening tools confer any clinical benefit.

Guideline implementation strategies

Sungkar 2018 reported results of a systematic review of 24 longitudinal cohort studies that assessed the impact of implementation of guidelines for sepsis management in emergency departments. Heterogeneity between studies prevented results from being pooled. The studies were of low-to-moderate methodological quality. Of the 24 studies included, 22 (92%) reported decreases in antibiotic administration times and two (8%) reported an increase in antibiotic administration time. All eight studies measuring compliance to completing all components of the sepsis guidelines, as well as all 12 studies measuring lactate sampling reported improvements in antibiotic administration times.

The impact of sepsis guideline implementation on inpatient mortality and 28 / 30 day mortality were reported for 14 and 4 studies respectively. Changes in inpatient mortality ranged between a 30.8% decrease and 6% increase with guideline implementation. Twelve studies reported a decrease in inpatient mortality and two reported an increase in mortality. All four studies reported a decrease in 28 / 30 day mortality with guideline implementation, ranging from a 9.1% decrease to an 18% decrease.

Antibiotic discontinuation strategies

Arulkumaran 2020 pooled results from 22 RCTs (6,046 critically ill adults receiving antibiotics for sepsis) to examine the effect of antibiotic discontinuation on outcomes. Strategies to minimize antibiotic use included procalcitonin (14 RCTs), clinical algorithms (two RCTs), and fixed-antibiotic duration (six RCTs).

Procalcitonin (RR –1.23, 95% CI –1.61 to –0.85), but not clinical algorithm–guided antibiotic therapy (RR –7.41, 95% CI–18.18 to 3.37), was associated with shorter duration of antibiotic therapy. The intended reduction in antibiotic duration ranged from 3 to 7 days in fixed-duration antibiotic therapy randomized clinical trials.

Neither procalcitonin-guided antibiotic treatment (RR 0.91, 95% CI 0.82–1.01), clinical algorithm–guided antibiotic treatment (RR 0.67, 95% CI 0.30–1.54) nor fixed-duration antibiotics (RR 1.21, 95% CI 0.90–1.63) were associated with reduction in mortality.

Question 5

This section addresses the following review question:

- What audits, indicators and data collection mechanisms have been developed or are in use to support the measurement of care improvement for sepsis?

Guidelines

Only the SOMANZ Guidelines provided specific advice and recommendations regarding indicators for measurement of care improvement. These guidelines propose the following indicators in maternal sepsis:

- What is the Incidence of sepsis as a proportion of all births?
- What proportion of patients diagnosed with sepsis where screened using qSOFA?
- What proportion of pregnant women presenting with fever were administered anti-pyretics?
- What is the prevalence of the different microorganisms causing sepsis?
- What proportion of all infections are caused by group A Streptococcus?
- What proportion of women with sepsis had blood cultures taken?
- What proportion of women were administered intravenous fluids within the first hour of the suspicion of sepsis?
- What proportion of women with sepsis were administered empiric antibiotics within the first hour?
- What proportion of fetuses of a suitable gestation (greater than 24 weeks) were assessed with electronic fetal monitoring whilst treating the woman with sepsis?
- What proportion of pregnant women with sepsis undergo anaesthetic consultation?
- What proportion of pregnant women with sepsis, having received neuraxial blockade develop complications, in particular hemodynamic and neurological complications?
- What proportion of women with sepsis required intensive care admission?
- What proportion of women with sepsis who had evidence of end-organ dysfunction were referred to intensive care?

Other guidelines included in this review did not provide specific recommendations to supporting measurement of care improvement.

Systematic reviews

We identified four reviews (two adult and two paediatric) that described results relevant to this review question. Only one review (Menon 2017) was of sufficient quality for results to be discussed here. Three critically low quality systematic reviews (Kramer 2015, Luhr 2019 and Odetola 2017) are described at Appendix 3 and 4.

The low quality review by Menon 2017 reported results from 19 RCTs that described primary outcome measures in paediatric trials of septic shock management. Studies were too heterogeneous for any pooling of results. According to the authors, mortality rate was the most commonly reported primary outcome used to measure care outcomes (57% of studies), followed by duration of shock (29% of studies) and organ failure (7% of studies).

References

International guidelines

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Appendix 1: Reasons for exclusion of full text publications

Full text articles that were excluded from this literature review are described below.

Excluded full text publications

Author year	Reason for exclusion
Aghai 2020	Letter to Editor
Allen 2019	Not all patients had sepsis
AHC Media 2018(a)	Commentary
AHC Media 2018(b)	Commentary
AHC Media 2019	Commentary
Anand 2019	Non-systematic review
Azevedo 2017	Impacts of sepsis on cerebral microcirculation
Barnes 2019	Sepsis as endpoint of perioperative care quality. Not specific to patients with sepsis.
Bourcier 2019	Methodology study
Cabral 2016	Specific to patients with burns
Casserly 2015	Commentary
Chebbo 2016	Non-systematic review
Chen 2019b	Case vignette
Chen 2020	Ventilation duration study
Colbert 2016	Non-systematic review
Dani 2015	Case reviews
Dong 2019	Non-systematic review
Dugar 2020	Non-systematic review
Gilfillan 2017	Non-systematic review
Guery 2019	Non-systematic review
Kaukonen 2018	Not systematic review
Lamontagne 2018a	Results for sepsis subgroup of patients with shock not reported separately
Lamontagne 2018b	Summary guideline
Lewis 2018	Results for sepsis subgroup of patients not reported or analysed separately
Long 2017a	Non-systematic review
Long 2017b	Non-systematic review
Menon 2015	Non-systematic review

Author year	Reason for exclusion
Mousavi 2016	Systematic review of alternative medicines
Murao 2019	Meta-review
Pepper 2018	Letter to the editor
Plante 2019	Summary guideline
Pourmand 2019	Non-systematic review
Putzu 2017	Results for sepsis subgroup of patients not reported separately to patients with ARDS
Russell 2018	Journal club article
Sherwin 2017	Non-systematic review
Simpson 2016	Meta-review
Thomas 2015	Included studies not systematically identified
Valeriani 2020	Coagulopathy management
Winters 2017a	Non-systematic review
Winters 2017b	Non-systematic review
Yamakawa 2019	Coagulopathy management