National Institute for Health and Care Excellence

Suspected sepsis: recognition, diagnosis and early management

[F] Evidence reviews for indicators of organ hypoperfusion in people with suspected sepsis.

NICE guideline NG253

Evidence reviews underpinning recommendations 1.8.4; 1.8.20 to 1.8.21 in the NICE guideline

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Guideline version (Final)

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1.1 In people aged 16 or over with suspected sepsis, what indicators of organ hypoperfusion should be used (in addition to the NEWS2 score) to guide the administration of intravenous (IV) fluids for resuscitation?

1.2 In people aged 16 or over with suspected sepsis, what indicators of organ hypoperfusion should be used (in addition to the NEWS2 score) to guide the urgency of referral to, or discussion with, a critical care specialist or team?

1.1.1 Introduction

The incorporation of the NEWS2 scoring system to stratify someone's risk of illness or death from sepsis may have an impact on early management strategies of someone with suspected sepsis in acute settings. It is important to determine what range of indicators should be considered (when making decisions about referring someone to critical care or giving them IV fluids) in addition to their NEWS2 score. This evidence review searched for evidence on a range of different indicators of organ hypoperfusion as presented in the review protocol and appendix A.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	• Adults aged 16 or over with suspected or confirmed sepsis
Prognostic indicator	• Oliguria (defined as urine output less than 0.5 ml/kg/hour) • Peripheral shutdown (defined as cool, mottled extremities, prolonged capillary refill time, weak and thready peripheral pulse) • Development of acute kidney injury (high serum creatinine measured by SOFA criteria or KDIGO)) • Increasing lactate (rise above normal level, range can be >1.6, 1.8 or >2 mmol/l) • Base deficit (low base excess) • Delayed capillary refill
Outcomes	• Length of Hospital stay

	• Mortality • Administration of IV fluids • Admission to ICU • Length of stay in ICU • Change in NEWS2 score • Renal replacement therapy • Administration of vasopressors • Invasive ventilation
Study type	• Systematic reviews of prospective cohort studies • Prospective cohort studies • Retrospective cohort studies

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document in appendix H.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 26 03 2024. The following databases were searched: MEDLINE (Ovid), Embase (Ovid), the Cochrane Database of Systematic Reviews (Wiley), and Epistemonikos. Full search strategies for each database are provided in Appendix B.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. The QA procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.3.2 Protocol deviations

At full text sifting it became clear that no studies had propensity score matched or adjusted for the specific confounding factors outlined in the review protocol. A decision was made to include studies that did not adjust for these specific factors but had adjusted for other confounding factors as outlined by the study authors. The risk of bias assessment takes into account the adjustment for or matching for confounding factors.

1.1.4 Prognostic evidence

1.1.4.1 Included studies

A systematic search was carried out to identify potentially relevant studies for both review protocols given their similarity and found 2040 references (see appendix B for the literature search strategy).

These 2040 references were screened at title and abstract level against the review protocols, with 1969 excluded at this level. 10% of references were screened separately by one reviewer with 99.5% agreement. Discrepancies were resolved by discussion.

4 records from a separate systematic review were identified and in total, the full texts of 75 prospective and retrospective cohort studies were ordered for closer inspection. 10 of these studies met the criteria specified in the review protocol (appendix A). For a summary of the 10 included studies see table 2.

All included studies contained evidence for lactate or lactate clearance as an indicator of organ hypoperfusion. One study also included evidence on skin mottling and another on capillary refill time. No studies were included that contained evidence on oliguria, AKI or base deficit to guide the administration of intravenous (IV) fluids for resuscitation or referral to, or discussions with, a critical specialist or team. Most studies included populations aged >18 years, with one study including people >14 years and another >15 years.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.14 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix G.

1.1.5 Summary of studies included in the prognostic evidence

Table 2 Summary of studies included in the prognostic evidence

Study details	Setting and Location	Population	Prognostic factor	Outcome	Confounding adjusted for	Time of measurement (pre/post fluid)	Risk of bias
Amir et al 2016 n= 218 Prospective cohort	Setting: Emergency department, hospital Location: Uganda	Age> 14 years Severe sepsis defined as: (1) A clinically suspected infection; (2) at least 2 systemic inflammatory response syndrome criteria including an axillary temperature of at least 38°C or less than 36°C, heart rate higher than 90 beats/min, respiratory rate higher than 20 breaths/min, or white blood cell concentration greater than 12 000 cells/μL or less than 4000 cells/μL; and (3) signs of end-organ dysfunction including a systolic blood	Lactate clearance	In-hospital mortality	Unclear	Initial measurement and then 6 hours following fluids	High

Study details	Setting and Location	Population	Prognostic factor	Outcome	Confounding adjusted for	Time of measurement (pre/post fluid)	Risk of bias
		pressure (SBP) of 90 mm Hg or lower, thrombocytopenia (b100000 cells/μL), or a Glasgow Coma Scale (GCS) score lower than 15					
Chertoff et al 2016 N= 229 Retrospective cohort	Setting: hospital Location: USA	Sepsis, severe sepsis and/or septic shock (roughly 1/3 each respectively) Age: Adult	Lactate clearance vs non clearance	30-day mortality Administration of IV fluids Administration of Vasopressors	Adjusted for SOFA score, EGFR and MELD	Measured before treatment and post treatment 24-48 hrs	High
Drumheller et al 2016 N=378 Retrospective cohort	Setting: Emergency department, hospital Location: USA	Severe sepsis and serum lactate ≥4.0 mmol/L OR septic shock. Severe sepsis was defined as a suspected source of infection, presence of 2 or more systemic inflammatory response syndrome (SIRS) criteria, and evidence of	Lactate clearance	Mortality	Age, Cancer, DNR, Temperature > 100.4 degrees F; Glucose <60mg/dL; Intubation;	Post fluids – timepoint unclear	High

Study details	Setting and Location	Population	Prognostic factor	Outcome	Confounding adjusted for	Time of measurement (pre/post fluid)	Risk of bias
		acute organ dysfunction. Age: Adult					
Ha et al 2016 n=770 Prospective cohort study	Setting: tertiary hospital Location: Korea	Age >18 years Severe sepsis or septic shock: Severe sepsis was defined as sepsis associated with acute organ dysfunction. Septic shock was defined as sepsis with acute circulatory failure characterised by persistent arterial hypotension (systolic arterial pressure <90 mmHg, mean arterial pressure <60 mmHg, or a reduction in systolic blood pressure >40 mmHg from baseline)	Lactate clearance at 6 and 24 hours	In-hospital mortality	Adjusted for age, gender and initial lactate level, SOFA, infection site, bundle compliance, total fluids administered within 6h, creatinine, prothrombin time, pH, base excess, need for mechanical ventilation, and need for vasopressor within 24h	Post fluid 6 and 24 hrs	High

Study details	Setting and Location	Population	Prognostic factor	Outcome	Confounding adjusted for	Time of measurement (pre/post fluid)	Risk of bias
		despite adequate volume resuscitation					
Jagan et al 2021 n=8173 Retrospective cohort	Setting: Hospitals (6 sites) Location: USA	Adults Diagnosis of sepsis, severe sepsis (with or without septic shock)	Lactate increase per mmol/l	In-hospital mortality ICU discharge	Age, facility (6 different hospitals), temperature, Bilirubin, History of heart failure, Diabetes, MAP, Heart rate	Initial measurement taken pre-fluids	High
Lee et al 2021 n=363 Retrospective cohort	Setting: ED - hospital Location: Korea	Adults >19 years An initial positive qSOFA result, presence of infection, and a Sequential Organ Failure Assessment (SOFA) score increase of ≥2 Or: Sepsis-3 definitions and the 2016 Surviving Sepsis Campaign (SSC) guidelines	Lactate clearance at 6 hours	30 day mortality	Age, SOFA score, Initial lactate	Post fluids 6 hours	High
Londono et al 2018	Setting: Critical care	Adults ≥18 years	Lactate – non clearance	In-hospital mortality	SOFA, APACHE 11, Charleson Index, and	Pre and post fluid	High

Study details	Setting and Location	Population	Prognostic factor	Outcome	Confounding adjusted for	Time of measurement (pre/post fluid)	Risk of bias
n=884 Prospective cohort study	hospitals x3 Location: Columbia	Systolic blood pressure <90 mmHg after a bolus of crystalloid of at least 20 mL/kg, OR a serum lactate >4 mmol/L. Suspected or confirmed diagnosis of infection, sepsis, severe sepsis or septic shock; at least two criteria of systemic-inflammatory-response-syndrome			pneumonia diagnosis on admission		
Morocho et al 2022 n=175 Prospective cohort	Setting: ER and ICU – hospital Location: Ecuador	Septic shock diagnosis – Sepsis 3 guidelines Age >18 years	Lactate >2/<2 Capillary refill time	28 day mortality	SOFA score, lactate at 6 hours and CRT on entry	Pre and post 6 hours after resuscitation	High
Prachanukool et al 2022 n=460 Retrospective cohort	Setting: ED hospital Location: Thailand	Age >15 years Sepsis as defined: Surviving sepsis 2012 guideline: sepsis-induced tissue	Lactate	28-day mortality	venous lactate, qSOFA score, SIRS, hypertension, active malignancy and septic shock	Pre fluids	High

Study details	Setting and Location	Population	Prognostic factor	Outcome	Confounding adjusted for	Time of measurement (pre/post fluid)	Risk of bias
		hypoperfusion or organ dysfunction (any of the following thought to be due to the infection): (1) sepsis-induced hypotension; (2) blood lactate level above the upper limits of the normal laboratory; (3) urine output <0.5 mL/(kg·h) for more than 2 h despite adequate fluid resuscitation; (4) acute lung injury with PaO2/FiO2 <250 mmHg (1 mmHg=0.133 kPa) in the absence of pneumonia as the infection source; (5) acute lung injury with PaO2/FiO2 <200 mmHg in the presence of pneumonia as the infection source; (6) creatinine >2.0 mg/dL; (7) total					

Study details	Setting and Location	Population	Prognostic factor	Outcome	Confounding adjusted for	Time of measurement (pre/post fluid)	Risk of bias
		bilirubin >2 mg/dL; (8) platelet count <100,000/cumm; and (9) coagulopathy (international normalized ratio >1.5).					
Sanderson et al 2018 n=455 Prospective cohort study	Setting: Critical care/ICU Location: UK	Sepsis: Penultimate consensus definition for severe sepsis, with presence of two or more signs of the systemic inflammatory response syndrome (SIRS) and one or more signs of organ dysfunction or tissue hypoperfusion with a background of proven or suspicion of infection Age range: 17-95	Lactate Mottling	30-day mortality	Age, temperature, thrombocytopenia, hospital acquired sepsis, lactate, fluid refractory hypotension, remain in hypotensive state, surgical ward at time 0, mottling	Unclear	High

SOFA = sequential organ failure assessment
qSOFA = quick sequential organ failure assessment
eGFR = estimated glomerular filtration rate
APACHE = acute physiology and chronic health evaluation
CRT = capillary refill time
MELD = model for end stage liver disease
DNR = do not resuscitate

See Appendix D for full evidence tables

1.1.6 Summary of the prognostic evidence

Interpreting the effectiveness evidence

For mortality outcomes the line of no effect (represented by 1.0 as mortality is a dichotomous outcomes) was used as a clinical decision threshold. The following criteria were used to interpret the effect (column of 'Interpretation of effect' below) in the summary GRADE tables with results divided into 2 groups as follows:

- The evidence showed that there is an effect if the 95% CI does not cross the line of no effect. Where there is an effect, we have stated the direction of the effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect. Where this is the case we have stated 'could not differentiate'.

Where default MIDs have been used (0.8 and 1.25) the following criteria were used to interpret the effect (column of 'Interpretation of effect' below) in the summary GRADE tables. The results were divided into 4 groups as follows:

- Where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect. (Where there is an effect, we will state the direction of the effect.)
- Where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.

- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.

- In all other cases, we state that the evidence could not differentiate between the comparator.

Lactate

Prognostic factor and outcome	No. studies	Sample size	Effect size adjusted odds ratios, or hazard ratios (95% CI)	Certainty	Interpretation of effect
Lactate increase per 1 mmol/l association with 30-day mortality	1[1]	n=455	aOR 1.16 (1.06, 1.27)	Very low[12]	Effect -Increased odds of 30 day mortality with higher lactate
Lactate increase per 1 mmol/l association with in-hospital mortality	1[2]	n=8173	aOR 1.21 (1.17,1.24)	Very low[11]	Effect - Increased odds of in-hospital mortality with higher lactate
Lactate increase per 1mmol/l association with ICU discharge	1[2]	n=8173	aOR 0.96 (0.95, 0.98)	Very low[11]	No meaningful difference
Lactate at 6 hours ≥2mmol/L association with 30-day mortality	1[3]	n=363	aOR 1.72 (1.19, 3.83)	Very low[12]	Effect - Increased odds of 30 day mortality with lactate ≥2mmol/L at 6 hours
Lactate at 6 hours ≥2mmol/L association with overall mortality	1[4]	n=175	HR 2.03 (1.16, 3.53)	Very low[12]	Effect - Increased hazard of overall mortality with lactate ≥2mmol/L at 6 hours
Lactate clearance <10% association with 30 day mortality	1[3]	n=363	aOR 1.82 (0.97, 3.42)	Very low[12]	Could not differentiate
Lactate clearance <20% association with 30 day mortality	1[3]	n=363	aOR 1.97 (1.05, 3.96)	Very low[12]	Effect - Increased odds of 30 day mortality with lactate clearance <20%
Lactate clearance <30% association with 30 day mortality	1[3]	n=363	aOR 1.76 (1.00, 3.07)	Very low[12]	Could not differentiate
Lactate measured in ER ≥4 mmol/L association with in-hospital mortality	1[5]	n=884	aOR 1.20 (1.10, 1.30)	Very low[12]	Effect - Increased odds of in-hospital mortality with lactate ≥4 mmol/L in ER
Lactate measured on ICU admission ≥4 mmol/L	1[5]	n=884	aOR 1.30 (1.15,1.47)	Very low[12]	Effect - Increased odds of in-hospital mortality

Prognostic factor and outcome	No. studies	Sample size	Effect size adjusted odds ratios, or hazard ratios (95% CI)	Certainty	Interpretation of effect
association with in-hospital mortality					with lactate ≥4 mmol/L in ICU
Initial lactate (higher/lower) association with 28-day mortality	1[10]	n=460	aOR 1.17 (1.09, 1.24)	Very low[11]	Effect - Increased odds of 28-day mortality with higher initial lactate
Lactate clearance of >10% after 6 hours association with in-hospital mortality	1[6]	n=218	aOR 1.39 (0.64, 3.18)	Very low[12]	Could not differentiate
Lactate clearers vs non-clearers association with 30 day mortality	1[7]	n= 229	aOR 0.39 (0.20,0.76)	Very low[11]	Effect - Decreased odds of mortality for 'lactate clearers'
Lactate clearers vs non-clearers association with receipt of IV fluids	1[7]	n= 229	aOR 0.81 (0.48,1.39)	Very low[12]	Could not differentiate
Lactate clearers vs non-clearers association with receipt of vasopressors	1[7]	n= 229	aOR 0.41 (0.21, 0.79)	Very low[11]	Effect - Decreased odds of vasopressor receipt for lactate clearers
Low lactate clearance (<10%) at 6 hours and in-hospital mortality	1[8]	n=770	aOR 4.94 (1.76, 13.85)	Very low[11]	Effect - Increased odds of in hospital mortality for lactate clearance <10% at 6 hours
Low lactate clearance (<10%) at 24 hours and in-hospital mortality	1[8]	n=770	aOR 6.00 (2.15, 16.74)	Very low[11]	Effect - Increased odds of in-hospital mortality for lactate clearance <10% at 24 hours

Prognostic factor and outcome	No. studies	Sample size	Effect size adjusted odds ratios, or hazard ratios (95% CI)	Certainty	Interpretation of effect
Lactate clearance vs decreased lactate clearance association with in-hospital mortality	1[9]	n=378	aOR 0.992 (0.986, 0.998)	Very low[11]	Effect - Decreased odds of in-hospital mortality for normal lactate clearance compared with decreased lactate clearance

1. Sanderson et al 2018
2. Jagan et al 2021
3. Lee et al 2021
4. Morocho et al 2022
5. Londono et al 2018
6. Amir et al 2016
7. Chertoff et al 2016
8. Ha et al 2016
9. Drumheller et al 2016
10. Prachanukool et al 2022
11. Rated down for high risk of bias and inconsistency
12. Rated down for high risk of bias, inconsistency and imprecision
13. Rated down for high risk of bias, inconsistency, imprecision and indirectness

Capillary refill time

Prognostic factor and outcome	No. studies	Sample size	Effect size (95% CI) adjusted odds ratios or hazard ratios	Certainty	Interpretation of effect
CRT > 4.5 seconds on arrival and mortality	1[1]	n=175	HR 1.03 (0.60, 1.77)	Very Low[2]	Could not differentiate
CRT > 3.5 seconds at 6 hours and mortality	1[1]	n=175	HR 8.73 (4.79, 15.91)	Very low[3]	Effect - Increased hazard of mortality with CRT >3.5 seconds at 6 hours

1. Morocho et al 2022
2. Rate down for high risk of bias, inconsistency and imprecision
3. Rated down for high risk of bias and inconsistency

Skin mottling

Prognostic factor and outcome	No. studies	Sample size	Effect size (95% CI) adjusted odds ratios or hazard ratios	Certainty	Interpretation of effect
Mottled skin association with 30-day mortality	1[1]	n=455	OR 3.80 (1.06, 13.55)	Very Low[2]	Effect - Increased odds of 30-day mortality with mottled skin

1. Sanderson et al 2018
2. Rated down for high risk of bias and inconsistency and imprecision

See appendix F for full GRADE tables

1.1.7 Economic evidence

Economic evidence was not considered for these review questions because they are focussing on prognostic factors of organ hypoperfusion to guide care, such as administration of fluids. The cost-effectiveness of administering fluids is discussed in evidence review G.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee considered mortality (both in-hospital and at specific time points) to be the most important outcome when looking at prognostic indicators of organ hypoperfusion.

1.1.12.2 The certainty of the evidence

The committee noted that the evidence was rated as very low confidence due to the high risk of bias found in the studies, imprecision and inconsistency. Risk of bias was high mainly due to studies not having adjusted for the confounding factors specified in the review protocol in their analyses, inconsistency due to all outcomes being reported from single studies and imprecision because the confidence intervals for some outcomes crossed the minimum important difference threshold. Although mortality was reported for lactate clearance across a number of studies, meta-analysis was not appropriate due to the differences in time points this outcome were measured at (for example, 30-day mortality vs in hospital mortality), different timepoints of indicator measurement (e.g. measured on arrival vs after the administration of fluids etc), and different definitions of indicators used (e.g. lactate >2mmol/l or lactate clearance). In addition, different definitions of sepsis were used for the studies' inclusion criteria. The committee noted most of the evidence was found for lactate and mortality, with a small amount of evidence for capillary refill time and skin mottling. No evidence was found for the other indicators specified by the committee in the review protocol. The committee noted that most studies included populations aged ≥ 18 years meaning they excluded a relevant population of people 16-17 years. One study included people aged >14 years and another >15 years. Overall, the committee did not feel this difference in age ranges from the review protocol affected the applicability of the evidence.

1.1.12.3 Benefits and harms

The committee agreed that while raised blood lactate levels, mottled skin and delayed capillary refill time could be signs of organ hypoperfusion and illness, they should not be used in isolation to make decisions about giving someone IV fluids or escalating their care. It is important to consider a range of factors including the other indicators of hypoperfusion as listed in the review protocol, person's NEWS2 score and their history when making decisions about intravenous (IV) fluids for resuscitation or escalating care. They also noted that mottled skin might be a difficult indicator to measure in practice given a lack of clear assessment criteria for it, and that it should be interpreted with caution particularly in black and brown skinned populations.

The committee discussed the recommendation for giving IV fluids to people who were assessed as at high risk of severe illness or death from sepsis (NEWS ≥7). They agreed that this group of patients would usually be given fluids for resuscitation regardless of their lactate levels or systolic blood pressure (SBP), therefore it was agreed that these indicators could be removed from the recommendation. They also noted that SBP would already have been measured as part of the NEWS2 assessment. They agreed that further indicators of organ hypoperfusion would not need be assessed before giving fluids or escalating someone's care for this group and therefore didn't make any additions to this recommendation.

When discussing the recommendation on escalating someone's care, they agreed that it was important to note any decisions relating to this need to consider the individual, the context of someone's illness, or if the person and their family/carers had made a prior decision not to actively continue treatment as part of advanced care or treatment escalation plans. They therefore added this clarification to that recommendation.

The committee did agree that indicators of organ hypoperfusion, specifically lactate and acute kidney injury, were important clinical indicators for guiding treatment in people assessed as being at moderate risk of illness or death from sepsis in addition

to their NEWS2 score. For these reasons they amended the existing recommendation on treating people at moderate risk as being at high risk to include an assessment of these indicators. They also agreed that people at moderate risk regardless of these indicators may still require IV fluids and that this should still be considered as an option.

Although giving fluids or escalating to critical care were not recommended for people assessed as being at low risk of severe illness or death from sepsis, the committee reiterated the importance of clinical cause for concern being considered when reassessing someone's risk level and deciding to escalate to a clinician with core competencies in the care of acutely ill patients.

1.11.12.4 Cost effectiveness and resource use

Economic evidence was not considered for this review question. For the committee's discussion of the cost effectiveness and resource use associated with giving fluids, see evidence review G.

Overall, there is not anticipated to be a resource impact as a result of these recommendations, as they reflect current practice.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.4 and 1.8.20 to 1.8.21. Other evidence supporting these recommendations can be found in the evidence review H on intravenous (IV) fluids for resuscitation.

1.1.14 References – included studies

1.1.14.1 prognostic evidence

Amir A, Saulters KJ, Olum S, Pitts K, Parsons A, Churchill C, Taseera K, Muhindo R MC (2016) Outcomes of patients with severe sepsis after the first 6 hours of

resuscitation at a regional referral hospital in Uganda. Journal of Clinical Care 33: 78-83

Chertoff J, Chisum M, Simmons L, King B, Walker M LJ (2016) Prognostic utility of plasma lactate measured between 24 and 48 h after initiation of early goal-directed therapy in the management of sepsis, severe sepsis, and septic shock. Journal of Intensive Care: 13

Drumheller BC, Agarwal A, Mikkelsen ME, Sante SC, Weber AL, Goyal M GD (2016) Risk factors for mortality despite early protocolized resuscitation for severe sepsis and septic shock in the emergency department. Journal of Clinical Care 1(31): 13-20

Ha TS, Shin TG, Jo IJ, Hwang SY, Chung CR, Suh GY JK (2016) Lactate clearance and mortality in septic patients with hepatic dysfunction. The American Journal of Emergency Medicine 6(34): 1011-1015

Jagan, Nikhil, Morrow, Lee E, Walters, Ryan W et al. (2021) Sympathetic stimulation increases serum lactate concentrations in patients admitted with sepsis: implications for resuscitation strategies. Annals of intensive care 11(1): 24

Lee, Seong Geun, Song, Juhyun, Park, Dae Won et al. (2021) Prognostic value of lactate levels and lactate clearance in sepsis and septic shock with initial hyperlactatemia: A retrospective cohort study according to the Sepsis-3 definitions. Medicine 100(7): e24835

Londono, Jessica, Nino, Cesar, Archila, Andrea et al. (2018) Antibiotics has more impact on mortality than other early goal-directed therapy components in patients with sepsis: An instrumental variable analysis. Journal of critical care 48: 191-197

Morocho, J Pablo, Martinez, A Fernando, Cevallos, M Monica et al. (2022) Prolonged Capillary Refilling as a Predictor of Mortality in Patients With Septic Shock. Journal of intensive care medicine 37(3): 423-429

Prachanukool, T., Sanguanwit, P., Yuksen, K.S.C. et al. (2022) Initial venous lactate levels as a predictor of mortality in severe sepsis: a single-center retrospective cohort study. World Journal of Emergency Medicine 13(5): 363-399

Sanderson, Miriam, Chikhani, Marc, Blyth, Esme et al. (2018) Predicting 30-day mortality in patients with sepsis: An exploratory analysis of process of care and patient characteristics. Journal of the Intensive Care Society 19(4): 299-304

Appendices

Appendix A – Review protocols

Review protocols for indicators of organ hypoperfusion

ID	Field	Content
1.	Review title	Indicators of organ hypoperfusion used to guide the administration of intravenous fluids for resuscitation.
2.	Review question	In people aged 16 or over with suspected sepsis, what indicators of organ hypoperfusion should be used (in addition to the NEWS2 score) to guide the administration of intravenous fluids for resuscitation?
3.	Objective	To determine which indicators of organ hypoperfusion should be used to guide the administration of intravenous fluids for resuscitation?
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE in process Searches will be restricted by: • Studies from 2014 • English Language • Human studies • Conference abstracts excluded Other searches: • Reference searching The full search strategies for MEDLINE database will be published in the final review.

5.	Condition or domain being studied	Suspected or confirmed sepsis
6.	Population	Inclusion: • Adults aged 16 or over with suspected or confirmed sepsis Exclusion: • Children under the age of 16 • People who are of have recently been pregnant
7.	Prognostic indicator	The following indicators of organ hypoperfusion (in addition to NEWS2): • Oliguria (defined as urine output less than 0.5 ml/kg/hour) • Peripheral shutdown (defined as cool, mottled extremities, prolonged capillary refill time, weak and thready peripheral pulse) • Development of acute kidney injury (high serum creatinine measured by SOFA criteria or KDIGO)) • Increasing lactate (rise above normal level, range can be >1.6, 1.8 or >2 mmol/l) • Base deficit (low base excess) • Delayed capillary refill
8.	Comparator	The prognostic indicator compared against people without that indicator/other indicator/NEWS2 score
9.	Types of study to be included	• Systematic reviews of prospective cohort studies • Prospective cohort studies • Retrospective cohort studies
10.	Other exclusion criteria	• All other study types. • Studies reporting data without confidence intervals or data that cannot be used to calculate confidence intervals. • Studies that haven't controlled/matched for pre-existing comorbidities, age, sex, BMI, ethnicity
11.	Context	During the last update of the sepsis guideline which published in January 2024, committee members highlighted that the current focus on raised blood lactate levels and low systolic blood

		pressure as indicators of organ hypoperfusion to treat and manage people was too narrow. They agreed that waiting for someone's lactate or blood pressure to reach a certain level before giving them fluids or escalating their care could not be justified in all circumstances and that instead a range of indicators should be considered.
12.	Primary outcomes (critical outcomes)	• Length of Hospital stay • Mortality • Administration of IV fluids • Admission to ICU • Length of stay in ICU • Change in NEWS2 score • Renal replacement therapy • Administration of vasopressors • Invasive ventilation
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.2). Study investigators may be contacted for missing data where time and resources allow. Where appropriate, this review will make use of the priority screening functionality within the EPPI-reviewer software. At least 50% of the data set will be screened and we will stop screening after that if we screen more than 250 records without an include

15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	**Approach to meta-analysis** Association data will be defined as measures of association between one or more factors (which could be either a single variable or a group of variables) and an outcome variable, where the data are not reported in terms of outcome classification (i.e. diagnostic/predictive accuracy). Examples could include (but were not limited to) data assessing the association between variables and diagnosis (diagnostic association studies) or data assessing the association between variables and a future outcome (prognostic association studies). Data will be reported as hazard ratios (if measured over time) or odds ratios or risk ratios (if measured at a specific time-point). Where appropriate, hazard ratios will be pooled using the generic inverse-variance method. Adjusted odds ratios, hazard ratios and risk ratios from multivariate models will only be pooled if the same set of factors are used across multiple studies and if the same thresholds to measure factors are used across studies. Random effects models will be fitted when significant between-study heterogeneity in methodology, population, intervention or comparator is identified by the reviewer in advance of data analysis. This decision will be made and recorded before any data analysis is undertaken. For all other syntheses, fixed- and random-effects models will be fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean

		for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results will be presented. Fixed-effects models are deemed to be inappropriate if there is significant statistical heterogeneity in the meta-analysis, defined as I2≥50%. However, in cases where the results from individual pre-specified subgroup analyses is less heterogeneous (with I2 < 50%) the results from these subgroups will be reported using fixed effects models. This may lead to situations where pooled results are reported from random-effects models and subgroup results are reported from fixed-effects models. **Approach to GRADE** A modified approach will be applied using the GRADE framework. Data from cohort studies will be initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point. These criteria will be used to apply preliminary ratings, but will be overridden in cases where, in the view of the analyst or committee the uncertainty identified is unlikely to have a meaningful impact on decision making.
17.	Analysis of sub-groups	Where data allows, subgroup analysis may be conducted considering: • Age • People who are immunosuppressed
18.	Type and method of review	☐ Intervention ☐ Diagnostic ☒ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)

19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	January 2024		
22.	Anticipated completion date	tbc		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** sepsisupdate@nice.org.uk		

		5b Named contact e-mail sepsisupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and Guideline Development Team B
25.	Review team members	From the Centre for Guidelines: • Guideline lead: Emma McFarlane • Technical analyst: Anthony Gildea • Senior Technical analyst: James Jagroo • Health Economist: Lindsay Claxton • Information specialist: Lynda Ayiku
26.	Funding sources/sponsor	This systematic review is being completed by the guideline development team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: tbc
29.	Other registration details	N/A
30.	Reference/URL for published protocol	tbc
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication

		• publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Sepsis, Organ Hypoperfusion, critical care, IV Fluids
33.	Details of existing review of same topic by same authors	This is a new review question that will update Sepsis: recognition, diagnosis and early management NG51
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review. The searches were run on 26 03 2024.

This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search terms for the sepsis population from '(A) Evidence reviews for stratifying risk of severe illness or death from sepsis' in NG51 (Jan 2024) were used to inform the population terms for the search strategy.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice and the review protocol to exclude:

- Animal studies
- Conference abstracts and posters
- Registry entries for ongoing clinical trials or those that contain no results
- Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

> Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Date limits

A date limit of 2014 to 2024 was applied, as stated in the review protocol.

Search filters and classifiers

Effectiveness searches

Systematic reviews filters:

Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. BMC Medical Research Methodology, 12(1), 51.

- In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.
- In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Cohort studies terms:

Terms for cohort studies were used from the observational studies filters. The terms used for observational studies are standard NICE practice that have been developed in house.

OECD countries geographic search filters:

The OECD countries filters were used without modification:

Ayiku, L., Hudson, T., Williams, C., Levay, P., & Jacob, C. (2021). The NICE OECD countries' geographic search filters: Part 2 - Validation of the MEDLINE and Embase (Ovid) filters. *Journal of the Medical Library Association*, 109(4), 583–589.

Effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	26th March 2024	Wiley	Issue 2 of 12, February 2024	302
Embase	26th March 2024	Ovid	Embase <1974 to 2024 March 25>	1536
Epistemonikos	26th March 2024	Epistemonikos	Searched 26th March 2024	161
MEDLINE ALL	26th March 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to March 25, 2024>	784

Search strategy history

Database name: MEDLINE ALL

Searches
1 exp sepsis/ (145047)
2 sepsis.ti,ab. (123023)
3 blood-borne pathogens/ (3045)
4 (blood* adj2 (pathogen* or poison*)).ti,ab. (3426)
5 exp systemic inflammatory response syndrome/ (153223)
6 'systemic inflammatory response syndrome*'.tw. (5991)
7 sirs.ti,ab. (6733)
8 (septicaemi* or septicemi*).ti,ab. (22507)
9 ((septic or cryptic) adj2 shock).ti,ab. (28164)
10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (267)
11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (73727)
12 or/1-11 (289895)
13 (hypoperfusi* or perfusi* or microperfusi*).tw,kf. (198857)
14 ((blood or circulat*) adj3 (reduc* or restrict* or decreas* or poor* or low*)).ti,ab. (185024)
15 13 or 14 (374835)
16 12 and 15 (7231)

Searches
17 (MEDLINE or pubmed).tw. (352982)
18 systematic review.tw. (295724)
19 systematic review.pt. (256341)
20 meta-analysis.pt. (197669)
21 intervention$.ti. (211921)
22 or/17-21 (735178)
23 16 and 22 (226)
24 exp Cohort Studies/ (2587344)
25 (cohort adj (study or studies)).tw. (345433)
26 cohort analy$.tw. (12839)
27 (follow up adj (study or studies)).tw. (57856)
28 longitudinal.tw. (341595)
29 prospective.tw. (749357)
30 retrospective.tw. (799987)
31 or/24-30 (3272394)
32 16 and 31 (1565)
33 23 or 32 (1752)
34 limit 33 to yr="2014 -Current" (915)
35 limit 34 to english language (867)
36 animals/ not humans/ (5172741)
37 35 not 36 (839)
38 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ (1332835)
39 "organisation for economic co-operation and development"/ (599)

Searches
40 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ (3539424)
41 european union/ (17941)
42 developed countries/ (21508)
43 or/39-42 (3555685)
44 38 not 43 (1242226)
45 37 not 44 (784)

Database name: Embase

Searches
1 exp sepsis/ (349378)
2 sepsis.ti,ab. (192355)
3 bloodborne bacterium/ (2174)
4 (blood* adj2 (pathogen* or poison*)).ti,ab. (4465)
5 exp systemic inflammatory response syndrome/ (363129)
6 'systemic inflammatory response syndrome*'.ti,ab. (8861)
7 sirs.ti,ab. (11951)
8 (septicaemi* or septicemi*).ti,ab. (26388)
9 ((septic or cryptic) adj2 shock).ti,ab. (45986)
10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (134)
11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (102032)
12 or/1-11 (483779)
13 exp perfusion/ (239028)
14 (hypoperfusi* or perfusi* or microperfusi*).tw,kf. (276403)
15 ((blood or circulat*) adj3 (reduc* or restrict* or decreas* or poor* or low*)).tw. (259468)
16 or/13-15 (629037)
17 12 and 16 (15182)
18 (MEDLINE or pubmed).tw. (437452)
19 exp systematic review/ or systematic review.tw. (543720)
20 meta-analysis/ (310312)
21 intervention$.ti. (278247)
22 or/18-21 (1024376)
23 17 and 22 (524)
24 Case control study/ (215011)
25 Cohort analysis/ (1137939)
26 cross-sectional study/ (623045)

Searches
27 cohort analy$.tw. (20719)
28 Longitudinal study/ (209424)
29 Retrospective study/ (1590773)
30 Prospective study/ (910762)
31 (Cohort adj (study or studies)).tw. (497256)
32 (Case control$ adj (study or studies)).tw. (178101)
33 (follow up adj (study or studies)).tw. (75631)
34 longitudinal.tw. (461614)
35 (cross sectional adj (study or studies)).tw. (366453)
36 prospective.tw. (1147147)
37 retrospective.tw. (1327133)
38 or/24-37 (4857710)
39 17 and 38 (3425)
40 23 or 39 (3844)
41 limit 40 to yr="2014 -Current" (2638)
42 limit 41 to english language (2560)
43 nonhuman/ not human/ (5410504)
44 42 not 43 (2510)
45 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5876720)
46 44 not 45 (1640)
47 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or

Searches
vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1753897)
48 exp "organisation for economic co-operation and development"/ (2906)
49 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ (3851691)
50 european union/ (31998)
51 developed country/ (36125)
52 or/48-51 (3886132)
53 47 not 52 (1596539)
54 46 not 53 (1536)

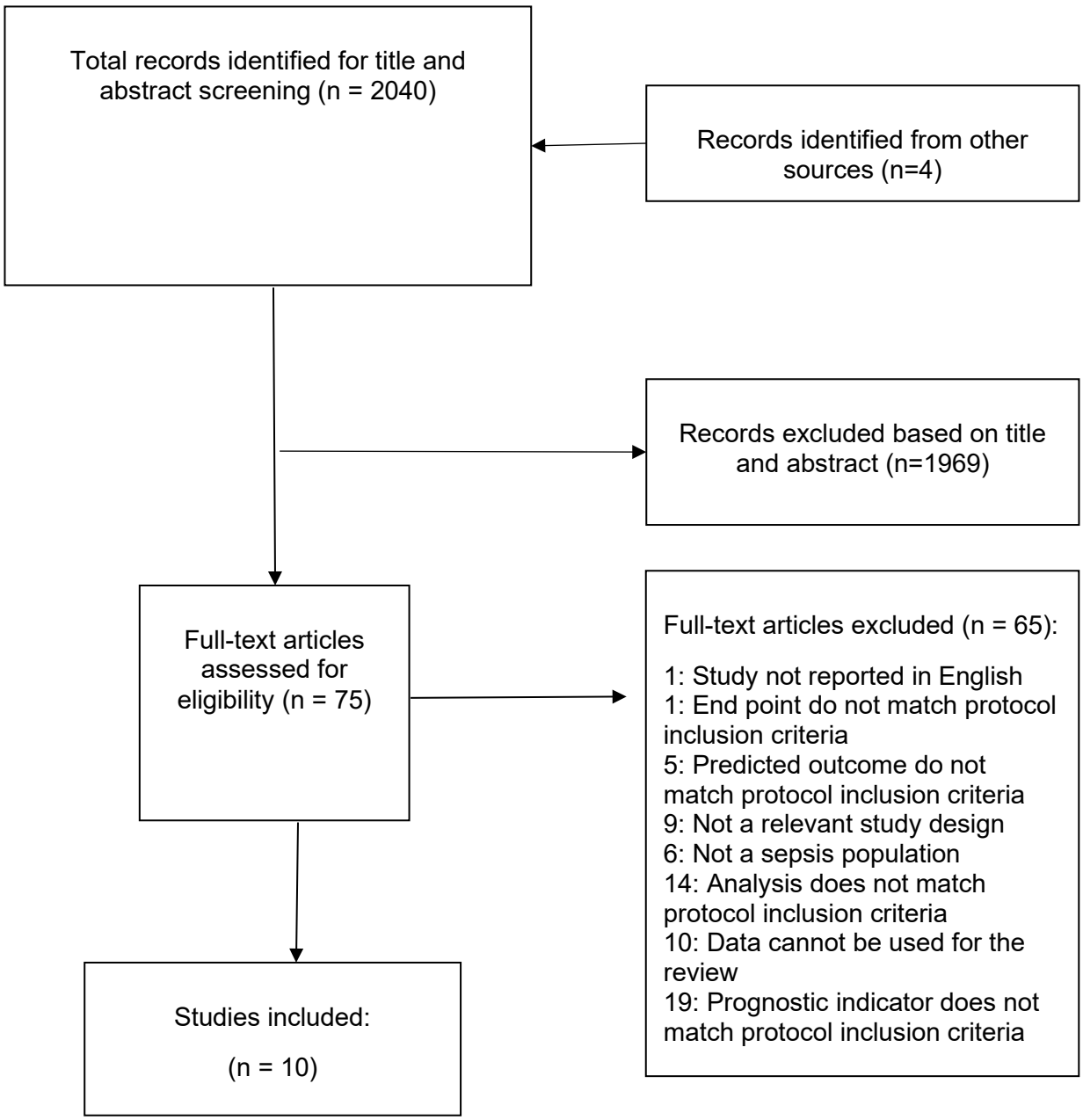
Database name: CDSR

Searches
#1 MeSH descriptor: [Sepsis] explode all trees 6463
#2 sepsis:ti,ab,kw 13946
#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 38
#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 369
#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 6993
#6 systemic inflammatory response syndrome*:ti,ab,kw 1768
#7 sirs:ti,ab,kw 914
#8 (septicaemi* or septicemi*):ti,ab,kw 1052
#9 ((septic or cryptic) near/2 shock):ti,ab,kw3986
#10 (pyaemi* or pyemi* or pyohemi*):ti,ab,kw 9
#11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw 6726
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 24503
#13 (hypoperfusi* or perfusi* or microperfusi*):ti,ab,kw 15063
#14 ((blood or circulat*) near/3 (reduc* or restrict* or decreas* or poor* or low*)):ti,ab,kw 42782
#15 #13 or #14 56796
#16 #12 and #15 with Publication Year from 2014 to 2024, with Cochrane Library publication date Between Jan 2014 and Mar 2024, in Trials 709
#17 "conference":pt or (clinicaltrials or trialsearch):so 733322
#18 #16 not #17 302

Database name: Epistemonikos

Searches
(title:((title:(sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasitaemi* OR viremi* OR viraemi* OR pathogen* OR poison*) OR abstract:(sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasitaemi* OR viremi* OR viraemi* OR pathogen* OR poison*)) AND (title:((hypoperfusi* OR perfusi* OR microperfusi* OR ((blood OR circulat*) AND (reduc* OR restrict* OR decreas* OR poor* OR low*)))) OR abstract:((hypoperfusi* OR perfusi* OR microperfusi* OR ((blood OR circulat*) AND (reduc* OR restrict* OR decreas* OR poor* OR low*)))))) OR abstract:((title:(sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasitaemi* OR viremi* OR viraemi* OR pathogen* OR poison*) OR abstract:(sepsis OR systemic inflammatory response syndrome* OR sirs OR septi* OR crypti* OR pyaemi* OR pyemi* OR pyohemi* OR bacteremi* OR bacteraemi* OR fungemi* OR fungaemi* OR parasitemi* OR parasitaemi* OR viremi* OR viraemi* OR pathogen* OR poison*)) AND (title:((hypoperfusi* OR perfusi* OR microperfusi* OR ((blood OR circulat*) AND (reduc* OR restrict* OR decreas* OR poor* OR low*)))) OR abstract:((hypoperfusi* OR perfusi* OR microperfusi* OR ((blood OR circulat*) AND (reduc* OR restrict* OR decreas* OR poor* OR low*)))))))) = 161 (date 2014-2024, limited to SRs)

Appendix C – Prognostic evidence study selection



Appendix D- Prognostic evidence

Amir 2016

Bibliographic Reference	Amir A, Saulters KJ, Olum S, Pitts K, Parsons A, Churchill C, Taseera K, Muhindo R MC; Outcomes of patients with severe sepsis after the first 6 hours of resuscitation at a regional referral hospital in Uganda; Journal of Clinical Care; 2016; vol. 33; 78-83

Study Characteristics

Study type	Prospective cohort study
Study details	Study location Uganda Study setting ED - hospital Study dates October 2014 and May 2015. Sources of funding Funding for the study was provided by the Pfizer Initiative in International Health and the Center for Global Health at the University of Virginia
Inclusion criteria	Sepsis Severe sepsis was defined by: (1) a clinically suspected infection; (2) at least 2 systemic inflammatory response syndrome criteria including an axillary temperature of at least 38°C or less than 36°C, heart rate higher than 90 beats/min, respiratory rate higher than 20 breaths/min, or white blood cell concentration greater than 12 000 cells/μL or less than 4000 cells/μL; and (3) signs of end-organ dysfunction including a systolic blood pressure (SBP) of 90 mm Hg or lower, thrombocytopenia (b100000 cells/μL), or a Glasgow Coma Scale (GCS) score lower than 15 At least 14 years age or over
Exclusion criteria	Patients were excluded if they required triage to a surgical or obstetrics and gynecology ward, had received any antibiotics or intravenous fluids prior to recruitment, or had a history suggestive of other diagnoses associated with lactic acidosis such as diabetic ketoacidosis, acute coronary syndrome, or chronic liver disease.

Number of participants	n=218
Loss to follow-up	Had data at 6 hours for 202 patients implying 16 patients loss to follow-up/missing
Duration of follow-up	Until discharge from ED
Predictive factor(s)	Lactate Lactate clearance
Outcome(s)	In hospital death

Population baseline characteristics

Study-level characteristics

Characteristic	Study (N = 218)
% Female Custom value	49%
Age Median (IQR)	35 (26 to 50)
HIV infected Custom value	57%
Infection - chest Custom value	44%
Infection - Gastrointestinal Custom value	30%
Infection - central nervous system Custom value	20%
Lactate on admission Median (IQR)	3.4 (2.2 to 5.2)
time to antibiotics (mins) Median (IQR)	30 (14 to 60)

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Data prospectively collected from general medical ward hospital. Sample potentially included populations (14 to 17 year olds) excluded from the review; Lactate clearance of at least 10% was the predictive factor. Data collected for 202/218 participants at 6 hours (7% attrition) which is still > than the sample size calculation of n=199 - no information regarding those that dropped out or the impact on regression analysis. Multivariable logistic regression did not consider sex and BMI and ethnicity. The definition of confounding factors is limited but the conditions for consideration in the regression are outlined (but no rationale). Method of the measurement of all confounding factors not specified but were undertaken in the emergency department. No evidence of selective reporting with data provided for all prognostic indicators. Analytical and model development strategies are brief but adequate in outlining approach.)*
Overall risk of bias and directness	Directness	Partially applicable *(Sample contains participants potentially outside the review protocol)*

Chertoff 2016

Bibliographic Reference	Chertoff J, Chisum M, Simmons L, King B, Walker M LJ; Prognostic utility of plasma lactate measured between 24 and 48 h after initiation of early goal-directed therapy in the management of sepsis, severe sepsis, and septic shock; Journal of Intensive Care; 2016; (no. 4); 13

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location USA, Florida Study setting Hospital Study dates

	during 2013 Sources of funding No details but ran by the University of Florida so likely to be funded by them
Inclusion criteria	Adult Sepsis Severe sepsis and/or septic shock An initial lactate measurement followed by one or more lactate measurements taken 24–48 h after resuscitation efforts started.
Exclusion criteria	Exclusion of patients admitted for non-infectious SIRS
Number of participants	n=229
Loss to follow-up	none
Duration of follow-up	30 days
Predictive factor(s)	Lactate 'lactate clearers' vs 'non-clearers'
Outcome(s)	30 day mortality Administration of IV fluids Administration of Vasopressors

Population baseline characteristics

Study-level characteristics

Characteristic	Study (N = 229)
% Female Custom value	Clearers (C) – 38.1%, Non-clearers (NC) – 46.67%
Mean age (SD) Custom value	C - 60.2, NC - 61.3
Severe Sepsis	C -55%, NC - 45%

Characteristic	Study (N = 229)
Custom value	
Septic shock Custom value	C - 45.52%, NC - 54.48%
eGFR Custom value	C - 47.4, NC - 45.9

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Retrospective analysis of hospital records data. Adult nonsurgical patients with admission diagnoses of sepsis, severe sepsis, and/or septic shock, admitted to University of Florida-Health during 2013; patients and diagnoses data obtained via database query using ICD coding and confirmed via chart review. No sample size calculation outlined. Data available and analysed for 229/229 patients (0% attrition). The age, diagnosis, EGFR, and MELD score of the patient groups (clearers and non-clearers) were compared to ensure similarity at baseline. Age, BMI, ethnicity and sex are not controlled for in the multiple logistic regression analysis. No evidence of selective reporting. Information on the analytical and model development strategy are adequately outlined.)*
Overall risk of bias and directness	Directness	Directly applicable

Drumheller 2016

Bibliographic Reference	Drumheller BC, Agarwal A, Mikkelsen ME, Sante SC, Weber AL, Goyal M GD; Risk factors for mortality despite early protocolized resuscitation for severe sepsis and septic shock in the emergency department; Journal of Clinical Care; 2016; vol. 1 (no. 31); 13-20

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location

	USA Study setting ED Study dates January 1, 2005, to December 31, 2009. Sources of funding University of Pennsylvania
Inclusion criteria	Sepsis severe sepsis and serum lactate ≥4.0 mmol/L OR septic shock. Severe sepsis was defined as a suspected source of infection, presence of 2 or more systemic inflammatory response syndrome (SIRS) criteria, and evidence of acute organ dysfunction. Septic shock was defined as arterial hypotension (systolic blood pressure <90 mm Hg) despite adequate fluid resuscitation (>1500 mL) or use of vasopressors
Exclusion criteria	Patients were excluded if they presented with concomitant trauma, pregnancy, acute myocardial infarction requiring immediate revascularization, or exsanguination as the primary cause for shock; left against medical advice; were transferred to another institution; or had previously been enrolled in the study
Number of participants	n=411 (378 in multivariable analysis)
Loss to follow-up	A total of 378 of 411 patients had complete data for all of the variables/predictive factors and were included in the regression model
Duration of follow-up	Until discharge or in-hospital death
Predictive factor(s)	Lactate lactate clearance
Outcome(s)	in-hospital mortality

Population baseline characteristics

Study-level characteristics

Characteristic	Study (N = 378)
% Female Custom value	43%
Mean age (SD) Mean (SD)	59.5 (16.3)
Race Custom value	White 45%, African American 49%, Other 6%
Immunosuppression Custom value	35%
Cancer Custom value	21%
Current smoker Custom value	8%
Diabetes Custom value	28%
Septic shock Custom value	51%
SOFA score Mean (SD)	6.9 (3.1)
Lactate Median (IQR)	4.8 (3.5 to 6.7)

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Data analysed retrospectively from visit logs and medical records for patients admitted via emergency department that received early protocolized resuscitation for severe sepsis or septic shock which is a potential source of bias due lack of detail regarding quality assurance regarding data measurement and recording. Exclude/inclusion criteria outlined. Baseline*

Section	Question	Answer
		characteristics outlined. Sample size calculation not outlined and n=411 patients included in the study. Data available for 378/411 participants (8% attrition). Definition of prognostic factors outlined. In-hospital mortality was the primary outcome. Information on the analytical and model development strategy are adequately outlined.)
Overall risk of bias and directness	Directness	Directly applicable

Ha 2016

Bibliographic Reference	Ha TS, Shin TG, Jo IJ, Hwang SY, Chung CR, Suh GY JK; Lactate clearance and mortality in septic patients with hepatic dysfunction; The American Journal of Emergency Medicine; 2016; vol. 6 (no. 34); 1011-1015

Study Characteristics

Study type	Prospective cohort study
Study details	Study location Korea Study setting Tertiary hospital Study dates August 2008 to March 2012 Sources of funding This study was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea
Inclusion criteria	Sepsis Severe sepsis was defined as sepsis associated with acute organ dysfunction. Septic shock was defined as sepsis with acute circulatory failure characterized by persistent arterial hypotension (systolic arterial pressure <90

	mmHg, mean arterial pressure <60 mmHg, or a reduction in systolic blood pressure >40 mmHg from baseline) despite adequate volume resuscitation. Adults 18 years +
Exclusion criteria	Poor performance with metastatic cancer unresponsive to chemotherapy or radiation therapy were excluded from this study. Under 18 Transferred from another hospital Limitations on decision making regarding care
Number of participants	n=770
Loss to follow-up	none
Duration of follow-up	until discharge or death
Predictive factor(s)	Lactate Lactate clearance at 6 and 24 hours
Outcome(s)	in-hospital mortality

Population baseline characteristics

Study-level characteristics

Characteristic	Study (N = 770)
Age - hepatic dysfunction group Median (IQR)	63 (52 to 70)
Age - non hepatic dysfunction group Median (IQR)	66 (55 to 73)
Male Custom value	Hepatic dysfunction 61%, non hepatic dysfunction 55%
Liver cirrhosis Custom value	Hepatic dysfunction 25%, non-hepatic dysfunction 3%

Characteristic	Study (N = 770)
Infection - abdomen Custom value	HD - 61%, non-HD 29%
Infection - respiratory tract Custom value	HD - 17%, Non-HD 33%
Infection - soft tissue Custom value	HD 3 %, Non-HD 4%
Infection - genitourinary tract Custom value	HD - 6%, Non HD - 18%
Infection - device related Custom value	HD - 1%. Non HD - 3%
Infection- other Custom value	HD - 12%, non HD - 14%

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Data retrospectively analysed from a hospital sepsis registry from patients presenting at the emergency department - potential source of bias due to quality assurance regarding collection and entry of data to hospital database. Baseline characteristic outlined. No sample size calculation present but data from n=770 used; Inclusion/exclusion criteria outlined. Data present for 770/770 participants - 0% attrition. Serum lactate concentration (mmol/L) was measured with a serum-based enzymatic colorimetry method, using a Modulator DDP analyser.. Multiple logistic regression does not consider BMI or ethnicity. No evidence of selective reporting with data provided for all prognostic indicators. Analytical and model development strategies are brief but adequate outlining approach and methods for model calibration (Hosmer-Lemeshow test).)*
Overall risk of bias and directness	Directness	Directly applicable

Jagan, 2021

Bibliographic Reference	Jagan, Nikhil; Morrow, Lee E; Walters, Ryan W; Plambeck, Robert W; Patel, Tej M; Moore, Douglas R; Malesker, Mark A; Sympathetic stimulation increases serum lactate concentrations in patients admitted with sepsis: implications for resuscitation strategies.; Annals of intensive care; 2021; vol. 11 (no. 1); 24

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location Nebraska, USA Study setting Six Catholic Health Initiative hospitals Study dates October 1, 2015, to June 30, 2018 Sources of funding Unclear - likely Creighton University, Nebraska
Inclusion criteria	Sepsis Diagnosis code of sepsis, severe sepsis (with or without septic shock) Adults
Exclusion criteria	Missing data Repeat sepsis admission
Number of participants	n=8173
Loss to follow-up	Retrospective analysis
Duration of follow-up	until discharge, or death
Predictive factor(s)	Serum lactate Mean Arterial Pressure

	Heart rate
Outcome(s)	Serum lactate In hospital death ICU discharge

Population baseline characteristics

Study-level characteristics

Characteristic	**Study (N = 8173)**
% Female Nominal	50.3
Median age (IQR Median (IQR)	67 (55 to 79)
BMI (Median and IQR) Median (IQR)	27.9 (23.5 to 33.9)
Lactate (mmol/L) Median (IQR)	2 (1.3 to 2.9)
Diabetes (%) Custom value	35.6%

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	**Question**	**Answer**
Overall risk of bias and directness	Risk of Bias	High *(Baseline characteristics lacked details on some characteristics (e.g. pregnancy) so study sample may have included participants that are not of interest. The study makes reference to geographical variations and multiple sites and does not specify exactly how serum lactate was measured indicating that variation in measurement could have occurred. For the outcome of interest (in-hospital death) it is unclear how this was measured and across what time point. Age and BMI not measured at baseline and are not controlled for in the analysis. The severity of sepsis is not accounted for within the analysis)*

Section	Question	Answer
Overall risk of bias and directness	Directness	Directly applicable

Lee, 2021

Bibliographic Reference	Lee, Seong Geun; Song, Juhyun; Park, Dae Won; Moon, Sungwoo; Cho, Han-Jin; Kim, Joo Yeong; Park, Jonghak; Cha, Jae Hyung; Prognostic value of lactate levels and lactate clearance in sepsis and septic shock with initial hyperlactatemia: A retrospective cohort study according to the Sepsis-3 definitions.; Medicine; 2021; vol. 100 (no. 7); e24835

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location Korea Study setting Emergency department - hospital Study dates January 2016 to December 2019 Sources of funding This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT)
Inclusion criteria	An initial positive qSOFA result, presence of infection, and a Sequential Organ Failure Assessment (SOFA) score increase of ≥2 Sepsis Sepsis-3 definitions and the 2016 Surviving Sepsis Campaign (SSC) guidelines Adults ≥19 years old

Exclusion criteria	Patients who visit ED for trauma care, patients with trauma, drug intoxication, drowning, vigorous exercises or animal bite are originally excluded. Patients who did not undergo a repeat 6-hour lactate measurement, and those with unknown 30-day mortality and initial lactate levels of less than 2mmol/L.
Number of participants	n=363
Loss to follow-up	retrospective
Duration of follow-up	30 days
Predictive factor(s)	Lactate Lactate at 6 hours, lactate clearance at <10%, <20%, <30%
Outcome(s)	30 day mortality

Population baseline characteristics

Study-level characteristics

Characteristic	Study (N = 363)
% Female Nominal	43.8
Mean age (SD) Median (IQR)	76 (64 to 82)
Septic shock Custom value	62.5%
SOFA score Median (IQR)	9 (6 to 11)
Positive blood culture Custom value	42.7

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Target population, method of recruitment and recruitment period adequately described with baseline characteristics outlined. Retrospective data so potential bias from recording and measurement. Inclusion/exclusion criteria align with the review protocol. Power calculation indicates that study sample is adequately powered. Study focused on lactate as a prognostic indicator and this is well defined. Data collected retrospectively from annual hospital census of 50,000 patients. 30-day mortality was the primary outcome. The regression analysis only accounts for age, SOFA score and initial lactate and does not consider other confounding factors including sex, BMI or ethnicity.)*
Overall risk of bias and directness	Directness	Directly applicable

Londono, 2018

Bibliographic Reference	Londono, Jessica; Nino, Cesar; Archila, Andrea; Valencia, Marta; Cardenas, Diana; Perdomo, Mayla; Moncayo, Giovanny; Vargas, Cesar; Vallejo, Carlos E; Hincapie, Carolina; Ascuntar, Johana; Leon, Alba; Jaimes, Fabian; Antibiotics has more impact on mortality than other early goal-directed therapy components in patients with sepsis: An instrumental variable analysis.; Journal of critical care; 2018; vol. 48; 191-197

Study Characteristics

Study type	Prospective cohort study
Study details	Study location Columbia Study setting Critical care - 3 hospitals Study dates June 2014 - February 2016 Sources of funding Funded by COLCIENCIAS – Science, Technology and Innovation Agency of Colombia (Departamento Administrativo de Ciencia, Tecnologia e Innovación-

	COLCIENCIAS) (Code 111556933362) and the University of Antioquia (code 2582)
Inclusion criteria	systolic blood pressure <90 mmHg after a bolus of crystalloid of at least 20 mL/kg, OR a serum lactate >4 mmol/L. Sepsis Suspected or confirmed diagnosis of infection, sepsis, severe sepsis or septic shock; at least two criteria of systemic-inflammatory-response-syndrome Adults ≥18 years
Exclusion criteria	Refusal by the patient, family or attending physician to participate; pregnancy, myocardial infarction, stroke, asthmatic crisis, arrhythmia, trauma, gastrointestinal bleeding, seizure not due to meningitis, psychoactive substance overdose, surgery <24 h, burns, CD4 count <50 cells/mm3 , hyperosmolar status, diabetic ketoacidosis or cirrhosis; released or referred in the first 24 h, prior participation in the study, referral from another institution where the patient has been hospitalized >24 h, or a Do-Not Resuscitate (DNR) order.
Number of participants	n=884
Loss to follow-up	Individual variables for calculation of APACHE-II or SOFA scores were missing in 4% of the patients and these values were assumed as normal.
Duration of follow-up	Unclear but likely until discharge or death occurred
Predictive factor(s)	Lactate Non-depuration 10%
Outcome(s)	In hospital death

Population baseline characteristics

Study-level characteristics

Characteristic	Study (N = 884)
% Female Nominal	51.7
Age Median (IQR)	62 (49 to 74)

Characteristic	Study (N = 884)
Infection - pneumonia Custom value	25.6%
Infection - UTI Custom value	24.1%
Infection- intra-abdominal Custom value	13.7%
Infection - not identified by fulfilled criteria for sepsis/septic shock Custom value	10.1%
Bloodstream infection Custom value	7.7%
Infection - skin and soft tissue Custom value	6.6%
Infection - other Custom value	12.3%
Kidney disease Custom value	20.1%
Congestive heart failure Custom value	8%
Diabetes with chronic complications Custom value	9.8%
Diabetes without chronic complications Custom value	9.8%
SOFA score Median (IQR)	5 (3 to 7)
Admission to ICU Custom value	61.9%

Characteristic	Study (N = 884)
Hospital length of stay Median (IQR)	11 (6-19) (*empty data* to *empty data*)

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Population derived prospectively from ER admissions of three university hospitals (Colombia); Inclusion/Exclusion criteria outlined; Baseline characteristics outlined; Estimated sample (method not specified) of n=650 achieved (n=884). The regression analysis considered participants with both initial and second lactate measure and there were no losses to follow-up but total numbers for lactate outcomes is unclear. The regression does not control for BMI, age, sex or ethnicity. The estimation of the effect of lactate clearance on hospital mortality, different cut off points were defined. Trained research nurses carried out the entire process of screening, selection and collection of information by means of a standardized form which was checked by co-investigators. Data for lactate outcomes was derived from participants with initial and second readings but it is unclear how many that was but the study outlines there were no losses to follow-up because of this. Instrumental variable analysis used was performed but its unclear what has been controlled for. Data presented and study narrative indicate adequate analytical strategy and model strategy. No evidence of selective reporting and a priori outcomes are reported.)*
Overall risk of bias and directness	Directness	Directly applicable

Morocho, 2022

Bibliographic Reference	Morocho, J Pablo; Martinez, A Fernando; Cevallos, M Monica; Vasconez-Gonzalez, Jorge; Ortiz-Prado, Esteban; Barreto-Grimaldos, Alejandra; Velez-Paez, Jorge Luis; Prolonged Capillary Refilling as a Predictor of Mortality in Patients With Septic Shock.; Journal of intensive care medicine; 2022; vol. 37 (no. 3); 423-429

Study Characteristics

Study type	Prospective cohort study
Study details	Study location Ecuador Study setting ICU - Hospital Study dates August 1, 2018, to May 31, 2019. Sources of funding This work did not receive a formal grant; however, it received financial support associated with the publication fee from the University of the Americas in Quito, Ecuador
Inclusion criteria	Sepsis Diagnosed with septic shock according to sepsis 3 guidelines Adults 18 years +
Exclusion criteria	Under 18 Pregnant Oncoproliferative disease CKD or under renal replacement therapy as well as having a diagnosis of hepatic cirrhosis
Number of participants	n=175
Loss to follow-up	none
Duration of follow-up	28 days
Predictive factor(s)	Capillary refill time Lactate
Outcome(s)	28 day mortality

Population baseline characteristics

Study-level characteristics

Characteristic	Study (N = 175)
Male Nominal	N= 106
Female Nominal	69
APACHE II score Mean (SD)	19.78 (6.79)
Charleson Mean (SD)	1.19 (1.92)
SOFA Mean (SD)	9.25 (3.47)

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Directness	Directly applicable *(Study is based in an Ecuadorian hospital. Ecuador is not an OECD country so its findings may not be wholly applicable but as the review considers physiological markers and their impact on outcomes this was not considered to impact the findings applicability.)*

Prachanukool, 2022

Bibliographic Reference	Prachanukool, T.; Sanguanwit, P.; Yuksen, K.S.C.; Vichiensanth, P.; Initial venous lactate levels as a predictor of mortality in severe sepsis: a single-center retrospective cohort study; World Journal of Emergency Medicine; 2022; vol. 13 (no. 5); 363-399

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location Thailand Study setting ED - hospital Study dates August 2015 to March 2017 Sources of funding 'None' - presumably funded by the hospital
Inclusion criteria	Sepsis Surviving sepsis 2012 guideline: sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection): (1) sepsis-induced hypotension; (2) blood lactate level above the upper limits of the normal laboratory; (3) urine output <0.5 mL/(kg·h) for more than 2 h despite adequate fl uid resuscitation; (4) acute lung injury with PaO2/ FiO2 <250 mmHg (1 mmHg=0.133 kPa) in the absence of pneumonia as the infection source; (5) acute lung injury with PaO2/FiO2 <200 mmHg in the presence of pneumonia as the infection source; (6) creatinine >2.0 mg/dL; (7) total bilirubin >2 mg/dL; (8) platelet count <100,000/cumm; and (9) coagulopathy (international normalized ratio >1.5). >15 years old
Exclusion criteria	not following the sepsis protocol DNR Incomplete records
Number of participants	n=460
Loss to follow-up	retrospective
Duration of follow-up	28 day
Predictive factor(s)	Initial lactate
Outcome(s)	28 day mortality

Population baseline characteristics

Study-level characteristics

Characteristic	Study (N = 460)
% Female Nominal	49.3
Age Median (IQR)	70 (59 to 81)
Diabetes mellitus Custom value	29.6%
Endstage renal disease Custom value	2.8%
Systemic hypertension Custom value	48.5%
Neuromuscular disease Custom value	28.5%
Infection - respiratory Custom value	53.7%
Infection - Gastrointestinal system Custom value	20%
Infection - Urinary system Custom value	13.7%
Infection - Skin Custom value	3.9%
Infection - blood stream Custom value	3.7%
SOFA score Median (IQR)	6 (4 to 10)

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Retrospective data from an emergency department of a university-affiliated tertiary care hospital (Thailand) was used in this study. Inclusion/exclusion outlined. Baseline characteristics outlined. No estimate of adequate sample size but data on 460 patients used. Data for venous lactate (n=460) and arterial lactate (n=433) analysed. Methods for serum lactate assessment not specified but undertaken by an emergency department physician. The multivariate analysis does not account for key confounders age, ethnicity, sex or BMI. Analytical and model development strategies are brief but adequate, outlining approach and methods for model calibration (Hosmer-Lemeshow test and observed-to-expected (O/E) ratio) and indicated good calibration and the ability to predict 7-d and 28-d hospital mortality and vasopressor administration within 24 h. No evidence of selective reporting with data provided for all prognostic indicators.)*
Overall risk of bias and directness	Directness	Directly applicable

Sanderson, 2018

Bibliographic Reference	Sanderson, Miriam; Chikhani, Marc; Blyth, Esme; Wood, Sally; Moppett, Iain K; McKeever, Tricia; Simmonds, Mark Jr; Predicting 30-day mortality in patients with sepsis: An exploratory analysis of process of care and patient characteristics.; Journal of the Intensive Care Society; 2018; vol. 19 (no. 4); 299-304

Study Characteristics

Study type	Prospective cohort study
Study details	Study location UK Study setting Hospital

	Study dates November 2011 and March 2014 Sources of funding The author(s) received no financial support for the research, authorship, and/or publication of this article.
Inclusion criteria	Sepsis Penultimate consensus definition for severe sepsis, with presence of two or more signs of the systemic inflammatory response syndrome (SIRS) and one or more signs of organ dysfunction or tissue hypoperfusion with a background of proven or suspicion of infection
Exclusion criteria	Transferred from another hospital with pre-existing sepsis.
Number of participants	n=455
Loss to follow-up	15 patients with missing data on hypotensive state - not relevant for this analysis
Duration of follow-up	30 days
Predictive factor(s)	Lactate Mottling
Outcome(s)	30 day mortality

Population baseline characteristics

Study-level characteristics

Characteristic	Study (N = 455)
% Female Nominal	42
Mean age (SD) Mean (SD)	64 (16.6)

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Population, setting and period of study outlined. Inclusion criteria met review protocol parameters but the exclusion criteria were vague and may mean some excluded populations (e.g. pregnant) could have been included. Patient baseline characteristics are not fully documents and are brief. Primary outcome (30-day mortality) measured via hospital administrative system. Data was provided for 455/455 study participants (0% attrition). Other potential confounding factors have not been accounted (ethnicity or BMI) but this is outlined in the study limitations. The a priori factors outlined accounted for in both univariate and multivariate analysis. The multivariate model accounted for variables that were identified as significant predictors of 30-day mortality ($p<0.05$) in the corresponding univariate analysis.)*
Overall risk of bias and directness	Directness	Directly applicable

Appendix E – Forest plots

As no meta-analyses were conducted forest plots have not been produced.

Appendix F – GRADE tables

Lactate

No of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
Lactate increase per 1 mmol/l association with 30-day mortality								
1[1]	Cohort	n=455	aOR 1.16 (1.06, 1.27)	Very serious[2]	Serious[3]	Not serious	Serious[11]	Very low
Lactate increase per 1 mmol/l association with in-hospital mortality								
1[4]	Cohort	n=8173	aOR 1.21 (1.17,1.24)	Very serious[2]	Serious[3]	Not serious	Not serious	Very low
Lactate increase per 1mmol/l association with ICU discharge								
1[4]	Cohort	n=8173	aOR 0.96 (0.95, 0.98)	Very serious[2]	Serious[3]	Not serious	Not serious	Very Low
Lactate at 6 hours ≥2mmol/L association with 30-day mortality								
1[5]	Cohort	n=363	aOR 1.72 (1.195-3.832)	Very serious[2]	Serious[3]	Not serious	Serious[11]	Very low

Lactate at 6 hours ≥2mmol/L association with overall mortality								
1[6]	Cohort	n=175	HR 2.03 (1.16, 3.53)	Very serious[2]	Serious[3]	Not serious	Serious[11]	Very low
Lactate clearance <10% association with 30 day mortality								
1[5]	Cohort	n=363	aOR 1.82 (0.97, 3.42)	Very serious[2]	Serious[3]	Not serious	Serious[11]	Very low
Lactate clearance <20% association with 30 day mortality								
1[5]	Cohort	n=363	aOR 1.97 (1.05, 3.96)	Very serious[2]	Serious[3]	Not serious	Serious[11]	Very low
Lactate clearance <30% association with 30 day mortality								
1[5]	Cohort	n=363	aOR 1.76 (1.00, 3.07)	Very serious[2]	Serious[3]	Not serious	Serious[11]	Very low
Lactate measured in ER ≥4 mmol/L association with in-hospital mortality								
1[7]	Cohort	n=884	aOR 1.20 (1.10, 1.30)	Very serious[2]	Serious[3]	Not serious	Serious[11]	Very low
Lactate measured on ICU admission ≥4 mmol/L association with in-hospital mortality								

1[7]	Cohort	n=884	aOR 1.30 (1.15,1.47)	Very serious[2]	Serious[3]	Not serious	Serious[11]	Very low
Initial lactate (higher/lower) association with 28-day mortality								
1[8]	Cohort	n=460	aOR 1.17 (1.09, 1.24)	Very serious[2]	Serious[3]	Not serious	Not serious	Very low
Lactate clearance of >10% after 6 hours association with in-hospital mortality								
1[9]	Cohort	n=218	aOR 1.39 (0.64, 3.018)	Very serious[2]	Serious[3]	Serious[10]	Very serious[15]	Very low
Lactate clearers vs non-clearers association with 30 day mortality								
1[12]	Cohort	n= 229	aOR 0.39 (0.20,0.76)	Very serious[2]	Serious[3]	Not serious	Not Serious	Very low
Lactate clearers vs non-clearers association with receipt of IV fluids								
1[12]	Cohort	n= 229	aOR 0.81 (0.48,1.39)	Very serious[2]	Serious[3]	Not serious	Very serious[15]	Very low
Lactate clearers vs non-clearers association with receipt of vasopressors								
1[12]	Cohort	n= 229	aOR 0.41 (0.21, 0.79)	Very serious[2]	Serious[3]	Not serious	Not serious	Very low

Low lactate clearance (<10%) at 6 hours and in-hospital mortality								
1[13]	Cohort	n=770	aOR 4.94 (1.76, 13.85)	Very serious[2]	Serious[3]	Not serious	Not serious	Very low
Low lactate clearance (<10%) at 24 hours and in-hospital mortality								
1[13]	Cohort	n=770	aOR 6.00 (2.15, 16.74)	Very serious[2]	Serious[3]	Not serious	Not serious	Very low
Lactate clearance vs decreased lactate clearance association with in-hospital mortality								
1[14]	Cohort	n=378	aOR 0.992 (0.986, 0.998)	Very serious[2]	Serious[3]	Not serious	Not serious	Very low

1 Sanderson et al 2018
2 Rated down twice for high risk of bias
3 Evidence from single study rated down once as per agreed guidelines methodology
4 Jagan et al 2021
5 Lee et al 2021
6 Morocho et al 2022
7 Londono et al 2018
8 Prachanukool et al 2022
9 Amir et al 2016
10 Rated as partially applicable due to sample containing some people <16 years
11 95% confidence interval crosses one end of the default MID (0.8-1.25)
12 Chertoff et al 2016

13	Ha et al 2016
14	Drumheller et al 2016
15	95% confidence interval crosses both ends of the default MID (0.8-1.25)

Capillary refill time

No of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
CRT > 4.5 seconds on arrival and mortality								
1[1]	Cohort	n=175	HR 1.03 (0.60, 1.77)	Very serious[2]	Serious[3]	Not serious	Very serious[4]	Very Low
CRT > 3.5 seconds at 6 hours and mortality								
1[1]	Cohort	n=175	HR 8.73 (4.79, 15.91)	Very serious[2]	Serious[3]	Not serious	Not serious	Very Low

1	Morocho et al 2022
2	Rated down twice for high risk of bias
3	Evidence from single study rated down once as per agreed guidelines methodology.
4	95% confidence interval crosses both ends of the default MID (0.8-1.25)

Mottled skin

No of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
Mottled skin association with 30-day mortality								
1[1]	Cohort	n=455	OR 3.80 (1.06, 13.55)	Very serious[2]	Serious[3]	Not serious	Serious[3]	Very low

1 Sanderson et al 2018

2 Rate down twice for high risk of bias

3 95% confidence interval crosses end of the default MID (0.8-1.25)

Appendix G – Excluded studies

Study	Reason for exclusion
Ait-Oufella, H, Bige, N, Boelle, P Y et al. (2014) Capillary refill time exploration during septic shock. Intensive care medicine 40(7): 958-64	- Analysis does not meet inclusion criteria (univariate analysis)
Alegria, Leyla, Vera, Magdalena, Dreyse, Jorge et al. (2017) A hypoperfusion context may aid to interpret hyperlactatemia in sepsis-3 septic shock patients: a proof-of-concept study. Annals of intensive care 7(1): 29	- Prognostic indicator not in protocol
Bjerregaard, MR; Hjortrup, PB; Perner, A (2019) Indications for fluid resuscitation in patients with septic shock: post-hoc analyses of the CLASSIC trial. Acta anaesthesiologica Scandinavica 63(3): 337-343	- Not a relevant study design
Blum, Arnon, Zoubi, Abd Almajid, Kuria, Shiran et al. (2015) High serum lactate level may predict death within 24 hours. Open medicine (Warsaw, Poland) 10(1): 318-322	- Population - not Sepsis
Bourcier, Simon, Pichereau, Claire, Boelle, Pierre-Yves et al. (2016) Toe-to-room temperature gradient correlates with tissue perfusion and predicts outcome in selected critically ill patients with severe infections. Annals of intensive care 6(1): 63	- Prognostic indicator not in protocol
Brunauer, Andreas, Kokofer, Andreas, Bataar, Otgon et al. (2016) Changes in peripheral perfusion relate to visceral organ perfusion in early septic shock: A pilot study. Journal of critical care 35: 105-9	- Prognostic indicator not in protocol
Cao, Bingbing, Chen, Qian, Tang, Tiantian et al. (2022) Non-linear relationship between baseline mean arterial pressure and 30-day mortality in patients with sepsis: a retrospective cohort study based on the MIMIC-III database. Annals of translational medicine 10(16): 872	- Prognostic indicator not in protocol
Ceylan, P.; Sencan, A.; Ece, C. (2020) The effect of the diagnostic criteria on the prognosis of patients diagnosed with sepsis at the intensive care unit. International	- Outcomes do not match that specified in the protocol

Study	Reason for exclusion
Journal of Academic Medicine and Pharmacy 2(3): 241-246	
Contreras, R., Hernandez, G., Valenzuela, E.D. et al. (2023) Exploring the relationship between capillary refill time, skin blood flow and microcirculatory reactivity during early resuscitation of patients with septic shock: a pilot study. Journal of Clinical Monitoring and Computing 37(3): 839-845	- Outcome to be predicted do not match that specified in the protocol
de Miranda, Ana Carolina, de Menezes, Igor Alexandre Cortes, Junior, Hipolito Carraro et al. (2020) Monitoring peripheral perfusion in sepsis associated acute kidney injury: Analysis of mortality. PloS one 15(10): e0239770	- Outcome to be predicted do not match that specified in the protocol
Dhumale, A.J., Balamkar, R., Jain, A. et al. (2023) EVALUATING THE ASSOCIATION OF INITIAL BLOOD LACTATE LEVELS WITH MORTALITY AND RESULTANT SEPTIC SHOCK IN NON- SHOCK SEPTIC SUBJECTS. Journal of Cardiovascular Disease Research 14(3): 1269-1276	- No adjusting or matching for any confounding factors
Dubee, Vincent, Hariri, Geoffroy, Joffre, Jeremie et al. (2022) Peripheral tissue hypoperfusion predicts post intubation hemodynamic instability. Annals of intensive care 12(1): 68	- Population - not Sepsis
Ferraris, Arnaud, Bouisse, Camille, Mottard, Nicolas et al. (2018) Mottling score and skin temperature in septic shock: Relation and impact on prognosis in ICU. PloS one 13(8): e0202329	- No adjusting or matching for any confounding factors
Ferraris, Arnaud, Bouisse, Camille, Thiolliere, Fabrice et al. (2020) Mottling Incidence and Mottling Score According to Arterial Lactate Level in Septic Shock Patients. Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine 24(8): 672-676	- No adjusting or matching for any confounding factors
Fotopoulou, G., Poularas, I., Kokkoris, S. et al. (2022) Renal Resistive Index on Intensive Care Unit Admission Correlates with Tissue Hypoperfusion Indices and Predicts Clinical Outcome. Shock 57(4): 501-507	- Population - not Sepsis

Study	Reason for exclusion
Galbois, Arnaud, Bige, Naike, Pichereau, Claire et al. (2015) Exploration of skin perfusion in cirrhotic patients with septic shock. Journal of hepatology 62(3): 549-55	- No adjusting or matching for any confounding factors
Gomez-Ramos, Jose Juan, Marin-Medina, Alejandro, Prieto-Miranda, Sergio Emilio et al. (2018) Determination of plasma lactate in the emergency department for the early detection of tissue hypoperfusion in septic patients. The American journal of emergency medicine 36(8): 1418-1422	- Data cannot be used for the review question
Gutierrez-Zarate, Damian; Rosas-Sanchez, Karina; Zaragoza, Jose J (2023) Clinical evaluation of peripheral tissue perfusion as a predictor of mortality in sepsis and septic shock in the intensive care unit: Systematic review and meta-analysis. Medicina intensiva 47(12): 697-707	- Outcome to be predicted do not match that specified in the protocol
Hasanin, Ahmed, Fekry, Radwa, Mostafa, Maha et al. (2024) The use of thermal imaging for evaluation of peripheral tissue perfusion in surgical patients with septic shock. BMC anesthesiology 24(1): 109	- Data cannot be used for the review question *Diagnostic measures*
Holley, Anthony D, Dulhunty, Joel, Udy, Andrew et al. (2021) Early Sequential Microcirculation Assessment In Shocked Patients as a Predictor of Outcome: A Prospective Observational Cohort Study. Shock (Augusta, Ga.) 55(5): 581-586	- Population - not Sepsis
Ikonomidis, I., Makavos, G., Nikitas, N. et al. (2014) Coronary flow reserve is associated with tissue ischemia and is an additive predictor of intensive care unit mortality to traditional risk scores in septic shock. International Journal of Cardiology 172(1): 103-108	- Outcome to be predicted do not match that specified in the protocol
Ilias, I., Apollonatou, S., Vassiliadi, D.-A. et al. (2018) Adipose tissue lactate clearance but not blood lactate clearance is associated with clinical outcome in sepsis or septic shock during the post-resuscitation period. Metabolites 8(2): 28	- No adjusting or matching for any confounding factors
Jog, Sameer Arvind, Narasimhan, Vikram L, Rajhans, Prasad Anant et al. (2023) Mottling in Septic Shock: Ethnicity and Skin Color Matter. Indian journal of critical care	- No adjusting or matching for any confounding factors

Study	Reason for exclusion
medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine 27(12): 902-909	
Jouffroy, Romain, Gilbert, Basile, Gueye, Papa-Ngalgou et al. (2021) Prehospital hemodynamic optimisation is associated with a 30-day mortality decrease in patients with septic shock. The American journal of emergency medicine 45: 105-111	- Prognostic indicator not in protocol
Kabil, Gladis, Frost, Steven A, McNally, Stephen et al. (2022) Identifying factors associated with intravenous fluid administration in patients with sepsis presenting to the emergency department: a retrospective cohort study. BMC emergency medicine 22(1): 98	- Prognostic indicator not in protocol
Kataria, Sahil, Singh, Omender, Juneja, Deven et al. (2023) Hypoperfusion context as a predictor of 28-d all-cause mortality in septic shock patients: A comparative observational study. World journal of clinical cases 11(16): 3765-3779	- No adjusting or matching for any confounding factors
Kazune, S., Caica, A., Volceka, K. et al. (2019) Relationship of mottling score, skin microcirculatory perfusion indices and biomarkers of endothelial dysfunction in patients with septic shock: An observational study. Critical Care 23(1): 311	- Data cannot be used for the review question
Kazune, Sigita, Piebalga, Anda, Strike, Eva et al. (2019) Impaired vascular reactivity in sepsis - a systematic review with meta-analysis. Archives of medical sciences. Atherosclerotic diseases 4: e151-e161	- Not a relevant study design *Systematic review containing wrong study designs and indicators not relevant to protocol*
Ko, Byuk Sung, Kim, Kyuseok, Choi, Sung-Hyuk et al. (2018) Prognosis of patients excluded by the definition of septic shock based on their lactate levels after initial fluid resuscitation: a prospective multi-center observational study. Critical care (London, England) 22(1): 47	- No adjusting or matching for any confounding factors
Lamontagne, Francois, Day, Andrew G, Meade, Maureen O et al. (2018) Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock. Intensive care medicine 44(1): 12-21	- Not a relevant study design

Study	Reason for exclusion
Lara, Barbara, Enberg, Luis, Ortega, Marcos et al. (2017) Capillary refill time during fluid resuscitation in patients with sepsis-related hyperlactatemia at the emergency department is related to mortality. PloS one 12(11): e0188548	- No adjusting or matching for any confounding factors
Lokhandwala, S., Patel, P., Cocchi, M.N. et al. (2015) Serial absolute lactate value < 4 versus relative 10% reduction as a predictor of mortality in severe sepsis and septic shock. Intensive Care Medicine Experimental 3(supplement1): a359	- Conference abstract *poster presentation only*
Lokhandwala, Sharukh, Moskowitz, Ari, Lawniczak, Rebecca et al. (2015) Disease heterogeneity and risk stratification in sepsis-related occult hypoperfusion: A retrospective cohort study. Journal of critical care 30(3): 531-6	- No adjusting or matching for any confounding factors
Mahajan, Rubina Khullar, Peter, John Victor, John, George et al. (2015) Patterns of central venous oxygen saturation, lactate and veno-arterial CO2 difference in patients with septic shock. Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine 19(10): 580-6	- No adjusting or matching for any confounding factors
Maheshwari, Kamal, Nathanson, Brian H, Munson, Sibyl H et al. (2018) The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients. Intensive care medicine 44(6): 857-867	- Prognostic indicator not in protocol
Massey, Michael J, Hou, Peter C, Filbin, Michael et al. (2018) Microcirculatory perfusion disturbances in septic shock: results from the ProCESS trial. Critical care (London, England) 22(1): 308	- Not a relevant study design *Intervention study*
Menezes, Igor Alexandre Cortes de, Cunha, Claudio Leinig da, Junior, Hipolito Carraro et al. (2019) Increase of Perfusion Index During Vascular Occlusion Test is Paradoxically Associated With Higher Mortality in Septic Shock After Fluid Resuscitation: A Prospective Study. Shock (Augusta, Ga.) 51(5): 605-612	- Prognostic indicator not in protocol

Study	Reason for exclusion
Momcicevic, D, Kovacevic, T, Dragic, S et al. (2020) Predictive significance of tissue hypoperfusion markers in different shock types in low income countries. Medizinische Klinik, Intensivmedizin und Notfallmedizin 115(4): 307-311	- Population - not Sepsis
Permpikul, C.; Sringam, P.; Tongyoo, S. (2014) Therapeutic goal achievements during severe sepsis and septic shock resuscitation and their association with patients' outcomes. Journal of the Medical Association of Thailand 97(3suppl3): 176-s183	- Analysis does not meet inclusion criteria (univariate analysis when sufficient studies with multivariate analysis are available)
Putowski, Zbigniew, Goldyn, Mateusz, Pluta, Michal P et al. (2023) Correlation Between Mean Arterial Pressure and Capillary Refill Time in Patients with Septic Shock: A Systematic Review and Meta-analysis. Journal of intensive care medicine 38(9): 838-846	- Data cannot be used for the review question
Rasmy, I., Nabil, N., Mohamed, H. et al. (2015) The evaluation of perfusion index as a predictor of vasopressor requirement in patient with sever sepsis and septic shock. Intensive Care Medicine Experimental 3(supplement1): a230	- Prognostic indicator not in protocol
Rasmy, Islam, Mohamed, Hossam, Nabil, Nashwa et al. (2015) Evaluation of Perfusion Index as a Predictor of Vasopressor Requirement in Patients with Severe Sepsis. Shock (Augusta, Ga.) 44(6): 554-9	- Prognostic indicator not in protocol
Ruangchan, S., Chusri, S., Saengsanga, P. et al. (2016) Clinical outcomes of community-acquired severe sepsis after implementation of a simple severe sepsis fast track. Journal of the Medical Association of Thailand 99(8): 877-885	- Prognostic indicator not in protocol
Sadjadi, Mahan, Porschen, Christian, von Groote, Thilo et al. (2023) Implementation of Nephroprotective Measures to Prevent Acute Kidney Injury in Septic Patients: A Retrospective Cohort Study. Anesthesia and analgesia 137(6): 1226-1232	- Prognostic indicator not in protocol
Sansone, Claudia M, Prendin, Fabiano, Giordano, Greta et al. (2017) Relationship	- Population - not Sepsis

Study	Reason for exclusion
between Capillary Refill Time at Triage and Abnormal Clinical Condition: A Prospective Study. The open nursing journal 11: 84-90	
Santos, D.M.D., Quintans, J.S.S., Quintans-Junior, L.J. et al. (2019) Association between peripheral perfusion, microcirculation and mortality in sepsis: a systematic review. Brazilian Journal of Anesthesiology 69(6): 605-621	- Data cannot be used for the review question *systematic review with no extractable data and mix of study designs*
Sereeyotin, J.; Nutthirameth, N.; Kumwilaisak, K. (2022) Correlation between Perfusion Index and Lactate Level in Critically Ill Patients. Journal of the Medical Association of Thailand 105(12): 1246-1253	- Data cannot be used for the review question
Shaker, Ahmed, Hasanin, Ahmed, Nagy, Mostafa et al. (2022) The Use of Lactate-Capillary Refill Time Product as Novel Index for Tissue Perfusion in Patients with Abdominal Sepsis: A Prospective Observational Study. International journal of general medicine 15: 7443-7448	- Data cannot be used for the review question *AUC data*
Shalman, Anna, Klein, Yoram, Toledano, Ronen et al. (2020) The Clinical Significance of Fluctuations in the Minute-to-minute Urine Flow Rate and in its Minute-to-minute Variability During Septic Events in Critically Ill Patients. Romanian journal of anaesthesia and intensive care 27(2): 1-5	- Prognostic indicator not in protocol *And wrong outcome*
Sharawy, Nivin, Mahrous, Reham, Whynot, Sara et al. (2018) Clinical relevance of early sublingual microcirculation monitoring in septic shock patients. Clinical hemorheology and microcirculation 68(4): 347-359	- Prognostic indicator not in protocol
Shin, Jikyoung, Hwang, Sung Yeon, Jo, Ik Joon et al. (2018) Prognostic Value of The Lactate/Albumin Ratio for Predicting 28-Day Mortality in Critically ILL Sepsis Patients. Shock (Augusta, Ga.) 50(5): 545-550	- Prognostic indicator not in protocol *Regression model doesn't include indicators from protocol*
Szakmany, Tamas, Lundin, Robert M, Sharif, Ben et al. (2016) Sepsis Prevalence and Outcome on the General Wards and Emergency Departments in Wales: Results of a Multi-Centre, Observational, Point Prevalence Study. PloS one 11(12): e0167230	- Not a relevant study design *Prevalence study*

Study	Reason for exclusion
Tarui, T., Yamaguchi, Y., Suzuki, K. et al. (2017) Early evaluation of severity in patients with severe sepsis: a comparison with "septic shock" - subgroup analysis of the Japanese Association for Acute Medicine Sepsis Registry (JAAM-SR). Acute Medicine and Surgery 4(4): 426-431	- No adjusting or matching for any confounding factors
Vanmassenhove, J, Glorieux, G, Hoste, E et al. (2014) AKI in early sepsis is a continuum from transient AKI without tubular damage over transient AKI with minor tubular damage to intrinsic AKI with severe tubular damage. International urology and nephrology 46(10): 2003-8	- Outcome to be predicted do not match that specified in the protocol
Verhaeghe, M. and Hachimi-Idrissi, S. (2020) Blood lactate and lactate kinetics as treatment and prognosis markers for tissue hypoperfusion. Acta Clinica Belgica: International Journal of Clinical and Laboratory Medicine 75(1): 1-8	- Data cannot be used for the review question *P values only reported*
Vincent, Jean-Louis, Quintairos E Silva, Amanda, Couto, Lucio Jr et al. (2016) The value of blood lactate kinetics in critically ill patients: a systematic review. Critical care (London, England) 20(1): 257	- Data cannot be used for the review question
Wang, T, Xia, Y, Hao, D et al. (2014) The significance of lactic acid in early diagnosis and goal-directed therapy of septic shock patients. Zhonghua wei zhong bing ji jiu yi xue 26(1): 51-55	- Study not reported in English
Ward, Michael A, Kuttab, Hani I, Tuck, Nicholas et al. (2022) The Effect of Fluid Initiation Timing on Sepsis Mortality: A Meta-Analysis. Journal of intensive care medicine 37(11): 1504-1511	- Not a relevant study design *SR on fluid timing*
Watchorn, James, Huang, Dean, Bramham, Kate et al. (2022) Decreased renal cortical perfusion, independent of changes in renal blood flow and sublingual microcirculatory impairment, is associated with the severity of acute kidney injury in patients with septic shock. Critical care (London, England) 26(1): 261	- Prognostic indicator not in protocol
Wittayachamnankul, Borwon, Chentanakij, Boriboon, Sruamsiri, Kamphee et al. (2016) The role of central venous oxygen	- Not a relevant study design *Review not systematic review*

Study	Reason for exclusion
saturation, blood lactate, and central venous-to-arterial carbon dioxide partial pressure difference as a goal and prognosis of sepsis treatment. Journal of critical care 36: 223-229	
Wong, Benjamin T, Chan, Matthew J, Glassford, Neil J et al. (2015) Mean arterial pressure and mean perfusion pressure deficit in septic acute kidney injury. Journal of critical care 30(5): 975-81	- Prognostic indicator not in protocol
Yang, Xuebing, Zhou, Yaqing, Liu, Aiming et al. (2022) Relationship between Dynamic Changes of Microcirculation Flow, Tissue Perfusion Parameters, and Lactate Level and Mortality of Septic Shock in ICU. Contrast media & molecular imaging 2022: 1192902	- Prognostic indicator not in protocol
Yumoto, Tetsuya, Kuribara, Tomoki, Yamada, Kohei et al. (2023) Clinical parameter-guided initial resuscitation in adult patients with septic shock: A systematic review and network meta-analysis. Acute medicine & surgery 10(1): e914	- Not a relevant study design *SR of intervention RCTs*
Zhao, Lina, Fan, Yan, Wang, Zhiwei et al. (2022) The blood pressure targets in sepsis patients with acute kidney injury: An observational cohort study of multiple ICUs. Frontiers in immunology 13: 1060612	- Data cannot be used for the review question
Zhong, Xiaoxin, Li, Haifeng, Chen, Qian et al. (2023) Association between different MAP levels and 30-day mortality in sepsis patients: a propensity-score-matched, retrospective cohort study. BMC anesthesiology 23(1): 116	- Prognostic indicator not in protocol