National Institute for Health and Care Excellence

Final

Sepsis: recognition, diagnosis, and early management

(C) Evidence review for early management of suspected sepsis (except antibiotic therapy) in the NEWS2 population, in acute hospital settings

NICE guidelines NG253, NG254 and NG255

Evidence reviews underpinning recommendations in the NICE guidelines

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Final

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2. In people with suspected sepsis how accurate is blood lactate to identify worsening sepsis?
3. In people with suspected sepsis how accurate is serum creatinine to identify worsening sepsis
4. When is the most appropriate time for care of people with suspected sepsis to be directed to a) a senior healthcare professional, and b) staff with critical care skills?

1.1.1 Introduction

The NICE guideline on Sepsis: recognition, diagnosis, and early management (NG51) was originally published in July 2016. In early 2023, NICE reviewed the recommendations on stratifying risk of severe illness or death from sepsis to incorporate the National Early Warning Score (NEWS2) for evaluating risk level in people with suspected sepsis. The recommendations on antibiotic treatment in people with suspected sepsis were also updated. We consulted on this update in March 2023 (the draft guideline that was consulted on can be viewed here).
A key next step in creating a cohesive sepsis guideline was to align risk stratification system in the recommendations on early non-antibiotic management sections in the updated March 2023 consultation version of the guideline to the NEWS2 risk strata.

This supporting document outlines the steps taken to update the recommendations on early non-antibiotic management.

1.1.2 Summary of the protocols

Table 1 - PICOS inclusion criteria RQ 1

Population	Adults aged 16 or over with suspected sepsis in acute hospital settings.
Test	• blood gas (arterial, venous, or capillary): pH, bicarbonates, base deficit • glucose • lactate • full blood count (haemoglobin, platelets or thrombocytopenia, white cell count or leucocyte (TLC) or neutrophil (ANC), Immature to Total Neutrophil Ratio (I/T ratio) bands or Toxic granulations, polymorph)

	• biochemical tests (urea/electrolytes (sodium, potassium)/renal/liver function, creatinine, haematocrit) • clotting screen; prothrombin time PT/INR, aPTT/aPTR, TT and fibrinogen • C-reactive protein (CRP).
Reference standard	• Blood culture proven infection. • American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM). Consensus Conference definition of SIRS, sepsis, severe sepsis, and septic shock. • Other composite definitions based on clinical biochemistry tests and signs and symptoms.
Outcomes	Diagnostic test accuracy data (i.e. TP, FP, TN, FN) that allows calculation of • Sensitivity and specificity • Positive and negative likelihood ratios We will also include area under the curve (AUC) data if reported in the studies.
Study type	Systematic reviews in the first instance. If insufficient systematic review evidence is identified, we will expand the scoping review to include the following primary evidence: • Prospective and retrospective cohort studies • Cross-sectional studies • Case-control studies

Table 2 – PICOS inclusions criteria RQ2

Population	Adults aged 16 or over with suspected sepsis in acute hospital settings.
Test	• Lactate
Reference standard	Reference standard measures that a worsening of sepsis had taken place: • all-cause mortality at 28 days (or nearest time point) • ICU admission • Hospitalisation • length of hospital stay
Outcomes	Diagnostic test accuracy data (i.e. TP, FP, TN, FN) that allows calculation of

	• Sensitivity and specificity
Study type	Systematic reviews in the first instance. If insufficient systematic review evidence is identified, we will expand the scoping review to include the following primary evidence: • Prospective and retrospective cohort studies • Cross-sectional studies • Case-control studies

Table 3 – PICOS inclusion criteria RQ3

Population	Adults aged 16 or over with suspected sepsis in acute hospital settings.
Test	• Serum creatinine
Reference standard	Reference standard measures that a worsening of sepsis had taken place: • all-cause mortality at 28 days (or nearest time point) • ICU admission • Hospitalisation • length of hospital stay
Outcomes	Diagnostic test accuracy data (i.e. TP, FP, TN, FN) that allows calculation of • Sensitivity and specificity • Positive and negative likelihood ratios • Odds ratios We will also include area under the curve (AUC) data if reported in the studies.
Study type	Systematic reviews in the first instance. If insufficient systematic review evidence is identified, we will expand the scoping review to include the following primary evidence: • Prospective and retrospective cohort studies • Cross-sectional studies • Case-control studies (if there is no other evidence)

Table 4 – PICOS inclusion criteria RQ4

Population	Adults aged 16 or over with suspected sepsis in acute hospital settings
Interventions	Early escalation (as defined in the studies)
Comparator	Late escalation (as defined in the studies)
Outcomes	• all-cause mortality at 28 days (or nearest time point) • health-related quality of life • admission to critical care Secondary outcomes: • duration of hospital stay • duration of critical care stay • adverse events (long-term disability; short-term heart failure)
Study type	Systematic reviews in the first instance. If insufficient systematic review evidence is identified, we will expand the scoping review to include the following primary evidence: • RCTs • Prospective and retrospective cohort studies

For the full protocols see Appendix B.

1.1.3 Methods and process

To support a timely update of the guideline recommendations, a proportionate approach was followed in line with the NICE guideline manual Appendix M: Interim principles for methods and processes for supporting digital living guideline recommendations and Appendix N: Multi-criteria decision framework for deciding whether to develop or update recommendations and which methods to use. This meant that a scoping review was conducted rather than a full evidence review, meta-analysis was not conducted, and Grading of Recommendations Assessment, Development and Evaluation (GRADE) was not applied.

1.1.3.1 Scoping search methods

The recommendations within the sections on early non-antibiotic management cover initial management strategies for people with suspected sepsis in acute hospital settings including blood tests, assessment and monitoring and escalation of care.

As these recommendations were developed in 2015, scoping searches were conducted to determine if there was any new evidence that indicated the current initial management strategies included in the recommendations (blood tests, assessment and monitoring and escalation of care) were out of date, or if there was evidence to suggest moving to the NEWS2 risk stratification system was incorrect. The approach for scoping searches was conducted in line with chapter 2 of the NICE guideline manual. One search was conducted to identify evidence relevant to all the questions on tests and a separate search was conducted for the question on escalation of care. A cut-off date of October 2015 was used to find new evidence published since NG51 was developed (see C for the search strategies). The searches focused on identifying systematic reviews of the evidence but were extended to include primary studies where review level evidence was deemed insufficient. Insufficient systematic review evidence was defined as a situation where evidence for an intervention or diagnostic test was lacking in volume or quality as agreed with the topic adviser for the guideline committee.

1.1.3.2 Evidence synthesis

As this was a scoping review, data was taken directly from included studies for presentation to the committee, but no meta-analyses were conducted. For the review areas on diagnostic test accuracy, sensitivity and specificity along with area under the curve (AUC) data has been presented (see section 1.1.5) Where systematic reviews have conducted their own meta-analysis, the pooled sensitivity, specificity, and AUC data has been presented. Where systematic reviews have not conducted meta-analysis, individual data from primary studies is reported. Cut-off points and thresholds for tests are included where systematic review authors have indicated these.

Risk of bias for systematic reviews has been assessed using the ROBIS checklist and can be found in Appendix E. Where review authors have conducted risk of bias assessments on primary studies, these have been reported in the summary of studies tables in section 1.1.4.

1.1.3.3 Mapping exercise and committee survey

As the evidence did not indicate that the currently recommended initial management strategies were out of date, a decision was made to draw upon the expertise of the committee to amend the recommendations by consensus using a modified nominal group technique. Full details of the methods used for formal consensus can be found in Appendix A. The original recommendations were presented in a table alongside proposed recommendations, in which the old risk stratification categories were amended to the NEWS2-based risk strata categories. This table formed a survey for the committee to elicit their views on the proposed changes to the recommendations. For each recommendation, the committee were invited to comment on whether they agreed or disagreed with the changes, and to provide a rationale for any disagreement. See Appendix F for the survey and results.

Formal consensus methods as outlined in Developing NICE guidelines: the manual were used to reach agreement on updating the recommendations.

1.1.3.4 Search methods

The searches for the effectiveness evidence were run between 20 06 2023 to 26 06 2023. The following databases were searched: MEDLINE ALL (Ovid,) Embase (Ovid), Cochrane Database of Systematic Reviews (Wiley), Cochrane Central Register of Controlled Trials (Wiley), and Epistemonikos, Full search strategies for each database are provided in Appendix C.

The searches for the cost effectiveness evidence were run on between 23 06 2023 to 27 06 2023. The following databases were searched: MEDLINE ALL (Ovid,) Embase (Ovid), EconLit (Ovid), and the International HTA Database (INAHTA). Full search strategies for each database are provided in Appendix C.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist. The procedure was adapted from the 2015 PRESS Guideline Statement.

1.1.3.5 Included studies

For review questions 1-3 which covered tests for suspected sepsis, after de-duplication,1825 references were screened at title and abstract with 41 studies included for screening at full text. From this, 6 systematic reviews which included diagnostic evidence relevant to review questions 1, 2 and 3 were identified.

As the 6 systematic reviews covered the main tests listed within the protocols, this was considered sufficient systematic review evidence and a decision was made not to include primary studies. This decision was validated by the topic adviser for the guideline committee.

For question 4 on escalation of care, after de-duplication, 1157 references were screened at title and abstract with 18 studies included for screening at full text. No systematic reviews were identified as relevant, and a decision was made to search for primary studies. After de-duplication of primary studies, 7314 references were screened at title and abstract, with 2 studies included for screening at full text. From these studies, none were identified as relevant.

See also the study selection flow chart in Appendix D and study evidence tables in Appendix E.

1.1.3.6 Excluded studies

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

1.1.4 Summary of studies included in the diagnostic evidence for review questions 1-3

Table 5 - Primary studies included in Kumar 2023 systematic review

Study details	Setting/Location	Population	Index test	Reference standard	Risk of bias[1]
Primary studies included in Kumar 2023[2]					
Ljungstrom 2017 N=1572	Setting: ED, Skaraborg Hospital Location: Sweden	Patients aged >18 years consecutively admitted to the emergency department with suspected community-onset sepsis	Neutrophil-lymphocyte count ratio (NLCR), C-reactive protein (CRP), and lactate	Sepsis-2 and Sepsis-3 criteria	Low to moderate[3]
Visveswari 2019 N = 126	Setting: tertiary care hospital Location: Asia	Patients >21 years with complaints suggestive of an infection	C-reactive protein, neutrophil-lymphocyte count ratio (NLCR), lactate, blood culture	SIRS	Low to moderate[3]
Karon 2017 N= 201	Setting: ED Location: Minnesota USA	Patients presenting at ED with suspected sepsis	Lactate, white blood cell (WBC) and neutrophil count, procalcitonin and immature granulocyte (IG)	SIRS	Low to moderate[3]

1. As appraised by the review authors
2. Primary studies that informed meta-analysis for C-reactive protein not included as review authors have not reported these.
3. Risk of bias not reported for individual studies – review authors state all studies included were at low to moderate risk of bias

Table 6 – Primary studies included in Li 2022 systematic review

Study details	Setting/Location	Population	Index test	Reference standard	Risk of bias[1]
Primary studies included in Li 2022					
Bergquist 2016 Sample size: N=8	Setting: Hospital Location: Sweden	>18 years, burns patients with suspected infection	White blood cell, C-reactive protein	American Burn Association 2007 Consensus Definition	High
Cakir Madenci 2014[2] Sample size: n=37	Setting: ICU, Burn centre Location: Turkey	Adult burn patients with suspected infection	White blood cell, C-reactive protein	American Burn Association 2007 Consensus Definition	High
Klein 2020 Sample size: N=90	Setting: Burn centre Location: Zurich	>18 years, burn patients with suspected infection	White blood cell, C-reactive protein	Sepsis-3 definition	High
Williams 2018 Sample size: N=72	Setting: ED Location: USA	>18 years burns patients with suspected sepsis	White blood cell, C-reactive protein	Custom[3]	High
Wineberg 2020 Sample size: N=178	Setting: ICU, Burns Location: Johannesburg	Adult burns patients – routine testing	White blood cell, C-reactive protein	American Burn Association 2007 Consensus Definition	High

1. As appraised by the review authors using QUADAS-2
2. Although prior to cut-off date of 2015, included here as it forms part of meta-analysis

Study details	Setting/Location	Population	Index test	Reference standard	Risk of bias[1]
3. Study authors own algorithm for diagnosing sepsis – although not an include in protocol, data from study informs meta-analysis.					

Table 7 – Primary studies included in Huang 2023 systematic review

Study details	Setting/Location	Population	Index test	Reference standard	Risk of bias[1]
Primary studies included in Huang 2023					
Ognibene 2022 Sample size: N=308	Setting: ED Location: Italy	Adult patients with suspected infection	C-reactive protein	Sepsis 3 criteria	High
Yu 2022 Sample size: N=1234	Setting: ED Location: Korea	Adult patients with suspected infection	C-reactive protein	Sepsis 3 criteria	Moderate
Poz 2022 Sample size: N=985	Setting: ED Location: Italy	Adult patients with suspected infection	C-reactive protein	Sepsis 2 criteria	Moderate
Hausfater 2021 Sample size: N=1517	Setting: ED Location: France	Adult patients with suspected infection	C-reactive protein	Sepsis 3 criteria	Low
Woo 2021 Sample size:	Setting: ED Location: Korea	Adult patients with suspected infection	C-reactive protein	Sepsis 3 criteria	Low

Study details	Setting/Location	Population	Index test	Reference standard	Risk of bias[1]
N=549					
1. As appraised by the review authors using QUADAS-2					

Table 8 – primary studies included in Tan 2019

Study details	Setting/Location	Population	Index test	Reference standard	Risk of bias
Primary studies included in Tan 2019					
Hongxiang Li 2014[2] Sample size: N=55	Setting: Hospital, ICU Location: China	Adult critically ill patients	C-reactive protein	ACCP or SCCM[3]	No information
B Jamali 2013[2] Sample size: N=64	Setting: malignant care centre Location: Iran	Febrile neutropenic patients who were above 14 years	C-reactive protein	ACCP or SCCM[3]	No information
Gian Paolo Castelli 2004[2]	Setting: ICU Location: Italy	Adult ICU patients	C-reactive protein	ACCP or SCCM[3]	No information

Study details	Setting/Location	Population	Index test	Reference standard	Risk of bias
Sample size: N= 49					
Karin SR Massaro 2007[2] Sample size: N=52	Setting: Hospital Location: São Paulo	Adult inpatients with neutropenia	C-reactive protein	ACCP or SCCM[3]	No information
Longxiang Su 2012[2] Sample size: N=52	Setting: ICU Location: China	Blood culture negative patients with fever	C-reactive protein	ACCP or SCCM[3]	No information
Kundan Kumar 2014[2] Sample size: N=40	Setting: Department of Gastroenterology Location: India	Males with alcoholic liver disease admitted to Department of Gastroenterology	C-reactive protein	ACCP or SCCM[3]	No information
Fabian A jamies 2013[2] Sample size: N=719	Setting: Emergency department Location: Columbia	>18 years with one of the following: any kind of infectious disease (confirmed or suspected), fever of unknown origin, delirium or any kind of encephalopathy of unknown	C-reactive protein	ACCP or SCCM[3]	No information

Study details	Setting/Location	Population	Index test	Reference standard	Risk of bias
		origin, acute hypotension not explained by hemorrhage, myocardial infarction, stroke or heart failure.			
Yi Yang 2016 Sample size: N=300	Setting: ICU Location: China	>18 years admitted to ICU	C-reactive protein	ACCP or SCCM[3]	No information
Ozlem Cakir Madenci 2014[2] Sample size: N=37	Setting: ICU, Burn centre Location: Turkey	Adult burn patients with suspected infection	C-reactive protein	ACCP or SCCM[3]	No information[1]

1. Although risk of bias was not assessed/reported in this systematic review, this study is included in another systematic review (Li 2022) who rated it as having a high risk of bias.
2. Primary studies that published before the October 2015 cut-off date reported as their data is pooled in a meta-analysis with data from post October 2015 studies.
3. American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) definition

Table 9 – Primary studies included in Wu 2017

Study details	Setting/Location	Population	Index test	Reference standard	Risk of bias[1]
Primary studies included in Wu 2017					
Brenner 2014[2] Sample size: N=120	Setting: ICU	Adults who presented to ICU with proven criteria of septic shock	C-reactive protein	ACCP/SCCM 2001	Moderate
Romualdo 2014[2] Sample size: N=226	Setting: ED	Presented to ED with SIRS and suspected infection	C-reactive protein	SSIDCM	Moderate
Kweon 2014[2] Sample size: N=118	Setting: ED	Presented to ED with ≥ 2 criteria for SIRS	C-reactive protein	ACCP/SCCM 1991	Moderate
Cakir Madenci 2014[2] Sample size: N=37	Setting: ED and ICU	Presented to ICU with burn	C-reactive protein	ABA[3]	Moderate
Godnic 2015[2]	Setting: ICU	Presented to ICU with ≥ 2 criteria for SIRS	C-reactive protein	Blood culture	High

Study details	Setting/Location	Population	Index test	Reference standard	Risk of bias[1]
Sample size: N=47					
Takahashi 2015[2] Sample size: N=456	Setting: ICU	Presented to ED with ≥ 1 criteria for SIRS	C-reactive protein	ACCP/SCCM 1991	Moderate
Romualdo 2016 Sample size: N=200	Setting: ED	Presented to ED with suspected infection	C-reactive protein	Sepsis 3	Moderate

1. As appraised by the review authors using QUADAS-2
2. Primary studies that published before the October 2015 cut-off date reported as their data is pooled in a meta-analysis with data from post October 2015 studies.
3. American Burns Association criteria. Although not in the protocol, this has been included as it forms part of a meta-analysis

Table 10 – Primary studies included in Yeh 2019

Study details	Setting/Location	Population	Index test	Reference standard	Risk of bias[1]
Primary studies included in Yeh 2019					
Davis 2006[2] Sample size:	Setting: ED Location: USA	Blood sample from patients being evaluated in an ED	C-reactive protein	Sepsis 2	Moderate

Study details	Setting/Location	Population	Index test	Reference standard	Risk of bias[1]
N= 100					
Dimoula 2014[2] Sample size: N=468	Setting: ICU Location: Belgium	>18 years admitted to ICU	C-reactive protein	Sepsis 2	Moderate
Righi 2014[2] Sample size: N=93	Setting: ICU Location: Italy	Adults admitted to ICU with suspected infection	C-reactive protein	Sepsis 2	Moderate
Godnic 2015[2] Sample size: N=47	Setting: ICU Location: Germany	Presented to ICU with ≥ 2 criteria for SIRS	C-reactive protein	Sepsis 2	High
Bauer 2016 Sample size: N=196	Setting: ICU Location: USA	Adults admitted to ICU with suspected sepsis	C-reactive protein	Sepsis 2	High
Muzlovic 2016 Sample size: N=32	Setting: ICU Location: Slovenia	Adults in ICU with ventilator associated pneumonia	C-reactive protein	Sepsis 2	High

1. As appraised by the review authors using QUADAS-2

Study details	Setting/Location	Population	Index test	Reference standard	Risk of bias[1]
2. Primary studies that published before the October 2015 cut-off date reported as their data is pooled in a meta-analysis with data from post October 2015 studies.					

See Appendix D for full evidence tables.

1.1.5 Summary of the diagnostic evidence

Table 11 – from Kumar 2023 systematic review

No. of studies	Sample size	Index test	Cut-off	Reference standard	Sensitivity (95%CI)	Specificity (95%CI)	AUC
From Kumar 2023 systematic review							
1[1]	n=1572	Serum Lactate	2.5mmol/l	Sepsis-3	0.295 (0.257-0.334)	0.842 (0.819-0.865)	0.646
1[1]	n=1572	Serum Lactate	3.5 mmol/l	Sepsis-3	0.149 (0.119-0.18)	0.953 (0.94-0.966)	0.666
1[2]	n=126	Serum Lactate	1.55 mmol/l	SIRS	0.672	0.470	0.557 [a]
1[3]	n=501	Point of care lactate	1.3 mmol/l	SIRS	0.551	0.627	0.63
63[4]	n=7463	CRP	<50 mg/l	No information	0.688 (0.25-1)	0.764 (0.22-1)	0.70 (0.41-0.90)
2[4]	N=218	CRP	≥ 50 - <100 mg/l	No information	61.6 (51.6-75.0)	62.25 (53.3-70.7)	0.670 (0.56-0.78)
6[4]	N=2270	CRP	≥ 100 mg/l	No information	43.93 (12.0-80.0)	77.03 (41-100)	0.64 (0.60-0.67)

1. Ljungstrom 2017 – *data taken directly from primary study as this was reported incorrectly in Kumar 2023 SR*
2. Visveswari, 2019 *a) AUC data taken directly from primary study as this was reported incorrectly in Kumar 2023 SR*
3. Karon, 2017
4. Taken from Kumar 2023 meta-analysis. Details of primary studies not reported in supplementary paper.

Table 12 – from Li 2022 systematic review

No. of studies	Sample size	Index test	Cut-off	Reference standard	Sensitivity (95%CI)	Specificity (95%CI)	AUC
From Li 2022 systematic review							
5[1]	N=257	White blood cell count	Ranged from 5.6-17 (10^9 cells/L) across studies.	Mixed definitions	0.47 (0.23–0.72)	0.65 (0.36–0.85)	0.57 (0.27–0.83)
4[2]	N=118	CRP	Range 115-241 mg/l across studies	Mixed definitions	0.86 (0.70–0.94)	0.54 (0.43–0.65)	0.79 (0.45 - 0.95)

1. Berquist 2016, Cakir Madenci 2014, Klein et al, 2020, Williams 2018, Wineberg 2020
2. Berquist 2016, Cakir Madenci 2014, Klein et al, 2020, Wineberg 2020

Table 13 – from Huang 2023 systematic review

No. of studies	Sample size	Index test	Cut-off	Reference standard	Sensitivity (95%CI)	Specificity (95%CI)	AUC
From Huang 2023 systematic review							
5[1]	N=4593	CRP	Range 5-31.75 mg/l across studies	Sepsis 2 or Sepsis 3	0.86 (76–92)	0.63 (44–79)	Not reported

1. Ognibene 2022, Yu2022, Poz 2022, Hausfater 2021, Woo 2021

Table 14 – from Tan 2019 systematic review

No. of studies	Sample size	Index test	Cut-off	Reference standard	Sensitivity (95%CI)	Specificity (95%CI)	AUC
From Tan 2019 systematic review							

No. of studies	Sample size	Index test	Cut-off	Reference standard	Sensitivity (95%CI)	Specificity (95%CI)	AUC
9[1]	N=1368	CRP	Range 12 – 90 mg/l across studies	ACCP or SCCM	0.80 (0.63-0.90)	0.61 (0.50-0.72)	0.73 (0.69-0.77)

1. Li 2014, Jamali 2013, Castelli 2004, Massaro 2007, Su 2012, Kumar 2014, Jamies 2013, Yi Yang 2016, Cakir Madenci 2014

Table 15 – from Wu 2017 systematic review

No. of studies	Sample size	Index test	Cut-off	Reference standard	Sensitivity (95%CI)	Specificity (95%CI)	AUC
From Wu 2017 systematic review							
7[1]	N=1204	CRP	Range not reported	Mixed definitions	0.77 (0.53–0.91)	0.79 (0.62–0.89)	0.85 (0.82–0.88)

1. Brenner 2014, Romualdo 2014, Kweon 2014, Cakir Madenci 2014, Godnic 2015, Takahashi 2015, Romualdo 2016

Table 16 – from Yeh 2019 systematic review

No. of studies	Sample size	Index test	Cut-off	Reference standard	Sensitivity (95%CI)	Specificity (95%CI)	AUC
From Yeh 2019 systematic review							
6[1]	N=936	CRP	Range not reported	Sepsis-2	0.83 (0.78–0.86	0.71 (0.56–0.85)	0.84 (0.80–0.88)
1. Davis 2006, Dimoula 2014, Righi 2014, Godnic 2015, Bauer 2016, Muzlovic 2016							

1.1.6 Economic evidence

A search was performed to identify published economic evaluations of relevance to this guideline update (see Appendix C – scoping search strategies). The search of evidence for review questions 1 to 3 returned 613 studies, and the search for review question 4 returned 275 studies.

For review questions 1 to 3, all 613 studies were excluded based on title and abstract screening. Similarly for review question 4, all 275 studies were excluded based on title and abstract screening. Therefore, there was no economic evidence identified for these review questions.

These questions were not prioritised for original economic analysis.

1.1.7 Evidence statements

1.1.7.1 Serum lactate

The data indicated that at higher cut-off thresholds for lactate (2.5 and 3.5 mmol/L) sensitivity was lower and specificity was higher. It should be noted that the primary study that reported these higher thresholds was looking for bacterial sepsis.

- Serum lactate 2.5 mmol/L: sensitivity 29.5% (29.5% with infection as defined by Sepsis-3 criteria had a serum lactate level of 2.5 mmol/L or above) and specificity 84.2% (84.2% without infection as defined by Sepsis-3 criteria had a serum lactate level below 2.5 mmol/L)

- Serum lactate 3.5 mmol/L: sensitivity 14.9% (14.9% with infection as defined by Sepsis-3 criteria had a serum lactate level of 3.5 mmol/L or above) and specificity 95.3% (95.3% without infection had a serum lactate level below 3.5 mmol/L)

- At a lower cut-off threshold for lactate (1.55 mmol/L) sensitivity was higher than at 2.5/3.5 mmol/l (67.2% with infection had a serum lactate level of 1.55 mmol/L or above) and specificity was lower (47% without infection had a serum lactate level below 1.55 mmol/L).

- Conversely, a point of care lactate test at a cut-off of 1.3 mmol/L had lower sensitivity than at 1.55mmol/L (55.1% with infection had a serum lactate level of 1.3 mmol/L or above) and higher specificity (62.7% without infection had a serum lactate level below 1.3 mmol/L).

In the original guideline, the data for lactate was inconclusive and there was no clear sense of whether sensitivity or specificity increased or decreased with increasing blood test thresholds. However, the evidence suggested that specificity was higher at higher lactate levels, indicating that those patients with higher lactate levels were more likely to have sepsis. A similar trend was observed in the evidence identified through this scoping review.

1.1.7.2 C-reactive protein (CRP)

Sensitivity and specificity for CRP between the reviews was inconsistent, with the only consistent pattern observed within Kumar 2023 which reported sensitivity and specificity at three different cut-off ranges and found that sensitivity was lower for higher cut-off thresholds. Summaries from Kumar 2023 are therefore reported separately below:

Kumar 2023:

- CRP at a cut-off of lower than 50 mg/l: sensitivity was 68.8% (68.8% with infection - as defined by study authors – had a CRP level at 50mg/l and above). Specificity was 76.4% (76.4% without infection – had a CRP level below 50mg/l).

- At cut-offs ranging between 50-100mg/l across studies: sensitivity was 61.6% (61.6% with infection – as defined by study authors – had a CRP level of 50-100mg/l or above, depending on the specific cut off in the primary study). Specificity was 62.25% (62.25% without infection – had a CRP level between 50-100mg/l depending on the specific cut-off in the study).

- At a range of 100mg/l or greater, sensitivity was 43.93% (43.93% with infection – as defined by study authors – had a CRP level of 100mg/l or

above). Specificity was 77.03% (77.03% without infection had a CRP level below 100mg/l).

Other systematic reviews:

- Sensitivity ranged from 77% to 86% across 5 systematic reviews that reported a CRP range (5mg/l - 241mg/l) and 2 studies that did not. Specificity ranged from 54% to 79% across the same studies.

Overall, because data was pooled combining studies that used different cut-off points, the diagnostic accuracy of CRP from this evidence is inconclusive. Evidence on CRP was also inconclusive in the original guideline NG51, however the committee recommended assessing it for people at high risk of sepsis as a useful marker of inflammation and for monitoring a patient's condition.

1.1.7.3 White blood cell count

At different cut-off points ranging from 5.6-17 (10^9 cells/L) across 5 studies, sensitivity was 47% (47% of people with infection had white blood cell count of 5.6-17 (10^9 cells/L) or above depending on the specific cut-off point used in the primary study). Specificity was 65% (65% of people without infection had a white blood cell count below 5.6-17 (10^9 cells/L) depending on the specific cut off point used in the primary study).

As with CRP, because data was pooled combining studies that used different cut-off points, the diagnostic accuracy of white blood cell counts for sepsis is inconclusive based on this evidence. In the original guideline, the committee discussed the difficulties in the clinical interpretation of white blood cell counts. A high WBC can indicate an infection, but a low WBC can also indicate a lack of response to severe infection. They felt however it was useful for monitoring a patient's condition and therefore recommended it be taken in patients at high risk of sepsis.

1.1.8 The committee's discussion and interpretation of the evidence

The committee did not discuss or interpret the diagnostic evidence for lactate, c-reactive protein and white blood cell count for reasons outlined in section 1.1.8.4.

The committee discussed their responses to the survey relative to the recommendations (see Appendix F for full survey and responses and Appendix A for survey methods). There was consensus among all committee members that the new risk strata based on NEWS2 scoring could be mapped onto the initial management of sepsis in hospital recommendations as proposed in the survey. The impact of making this change meant that some of the recommendation content around frequency of monitoring within the sections on early non-antibiotic management needed to be amended for internal consistency with new recommendations on NEWS2. The committee discussed and agreed these changes. The committee also discussed refreshing the wording of the recommendations in this section to keep them in line with current practice and to aid implementation.

1.1.8.1 Initial assessment and examination

The committee discussed the initial assessment and agreed this is an important opportunity to identify those most at risk of suspected sepsis. They noted that, because signs and symptoms of sepsis are not specific, it is a condition that is hard to recognise, especially in its initial stages. So when people present multiple times to a GP or hospital with non-specific signs and symptoms of being unwell, they may not initially be considered at risk of suspected sepsis. However, repeated presentations should be recognised as a flag of increased likelihood of sepsis. The committee therefore agreed, by consensus, to create a new recommendation to highlight this important risk factor, to provide further safety netting for people in this situation.

1.1.8.2 When to transfer immediately: people in acute mental health settings

The committee discussed the importance of people at high risk of severe illness or death from suspected sepsis being managed and treated appropriately in an acute hospital setting. They recognised that this could include people who are already being cared for in acute mental health

settings. No evidence was identified for acute mental health settings. The committee therefore made a consensus recommendation that people at the highest risk in the acute mental health setting are considered for treatment and transfer to an acute hospital setting.

1.1.8.3 Finding the source of infection

The committee acknowledged that the guideline includes guidance on investigating the source of infection, but its coverage of source control was limited to involving of the surgical and gynaecological teams early on if intra-abdominal or pelvic infection is suspected, in case surgical treatment is needed. The committee agreed, by consensus, that sepsis can be caused by surgically treatable infection at other sites of the body. So they broadened this recommendation to ensure that the relevant surgical team is involved early on if intervention is needed to control the source of infection.

The committee also wanted to emphasise the importance of thinking about source control early on in the care pathway. For that reason, the committee agreed to emphasise that investigations to identify the source of infection should start at the same time as suspected sepsis management in acute hospital settings. This is because prompt source control has greater potential to improve patient outcomes than any other intervention for the someone with suspected sepsis.

1.1.8.4 High risk of severe illness or death from sepsis

In recommendations for people at high risk of severe illness or death from sepsis the committee changed the following:

- Added that the initial urgent review be conducted by a clinician with core competencies in the care of acutely ill patients (FY2 or above),
- Added that referral be made to a senior clinical decision maker (ST3 or above)
- Added that clinical judgement be used regarding discussion with a consultant

- Removed examples of consultant speciality in the recommendation.
- Added liver function tests to the list of blood tests taken at initial assessment

The committee specified that for initial urgent assessment of someone at high risk of sepsis in hospital, a clinician with core competencies in the care of acutely ill patients (who they defined as an FY2 doctor or above) was appropriate given the requirement for the patient to be assessed in an urgent time frame. However, they specified that referral to a senior clinical decision maker (who they defined as an ST3 doctor or above) should be made urgently for a more detailed assessment and diagnosis, and that discussion with a consultant may also be required.

The committee agreed that there were a range of consultants this could be discussed with in this instance depending on the patient's illness or circumstances, therefore having an exhaustive list suggesting this would be either acute medicine or anaesthetic specialities was too restrictive.

The committee added liver function tests to the list of tests taken at initial assessment as these were routinely conducted in practice.

- Removing the necessity to refer to a critical care team after giving fluids if someone responds within 1 hour.
- Adding the requirement for a senior clinical decision maker to attend in person if someone was not responding to an intervention and to inform the responsible consultant.

The committee agreed that if a patient was responding well to fluids or any intervention and their condition was being managed, it was not necessary to refer them to a critical care team in every instance. Therefore, the recommendation was amended to reflect that a referral or discussion would only be required if a patient is not responding. Given the level of risk for this population, the committee also felt it was appropriate that a senior clinical

decision maker attended in person as well as the responsible consultant being informed.

- Aligning the section on monitoring to earlier recommendations 1.5.8 and 1.5.9 on monitoring of NEWS 2 score.

The committee agreed that as an earlier recommendation in NG51 covered the frequency of monitoring NEWS 2, and that NEWS 2 would supersede the 'physiological track and trigger systems' cited within the previous guideline, this recommendation could be aligned with 1.5.8 and 1.5.9 for internal consistency within the guideline.

- Removing the recommendation on monitoring the mental state of patients.

The committee agreed that there was no longer a requirement for a separate recommendation on monitoring someone's mental state, as this was already done as part of the NEWS 2 assessment.

1.1.8.5 Moderate risk of severe illness or death from sepsis

In recommendations for people at moderate risk of severe illness or death from sepsis, the committee changed the following:

- Added a clotting screen to the list of tests carried out at initial assessment for those at moderate risk.

The committee noted that a clotting screen was included for people in the high-risk category. They agreed that a clotting screen was still useful for looking at patient progression in those at moderate risk, and that it was done routinely.

- Removed discharge and added a separate recommendation on safe discharge which is no longer linked to someone's risk category.

The committee removed the recommendation on discharge for people at moderate risk as they felt that discharging people in relation to their risk level, particularly those at moderate risk, could be unsafe. They also felt that considering discharge during the initial management of a person with

suspected sepsis was not the right time within the pathway. They therefore created a new recommendation after the initial management section which outlines the considerations needed for discharge and signposts to the section on information that should be provided at discharge. This includes safety netting advice to ensure people seek medical attention if they experience certain symptoms that may be indicative of suspected sepsis.

1.1.8.6 Low and very low risk of severe illness or death from sepsis

In recommendations for people at low and very low risk of severe illness or death from sepsis, the committee changed the following:

- Align with review and monitoring times set out for this risk group in the Academy of Medical Royal College (AoMRC) statement on the initial antimicrobial treatment of sepsis V2.0 (2022).

To align with the AoMRC guidance, the timings for initial review of people at low risk of severe illness or death from sepsis at 1 hour remained the same. Further monitoring in line with recommendations on recalculating NEWS 2 (4-6 hours for this risk group) was added along with guidance on escalation of care if someone shows no improvement or their condition deteriorates. The requirement for an hourly structured assessment was also removed to align with the AoMRC guidance.

- Removed discharge and added a separate recommendation on safe discharge which is no longer linked to someone's risk category.

The committee removed the recommendation on discharge for people at low risk as they felt that discharging people in relation to their risk level could be unsafe. They also felt that considering discharge during the initial management of a person with suspected sepsis was not the right time within the pathway. They therefore created a new recommendation after the initial management section which outlines the considerations needed for discharge and signposts to the section on information that should be provided at discharge. This includes safety netting advice to ensure people seek medical

attention if they experience certain symptoms that may be indicative of suspected sepsis.

- Amended review within 1 hour for people at low and very low risk to be conducted by a registered nurse.

The committee agreed that initial assessment will have taken place by a clinician, but a registered nurse could conduct a review of a person at low or very low risk of suspected sepsis within one hour. This further aligns this recommendation with guidance from the Academy of Medical Royal Colleges.

1.1.8.7 The outcomes that matter most

While the committee recognised the importance of lactate, white blood cell count and CRP as indicators that help to provide an overall picture of someone's prognosis, they did not feel that using these as diagnostic measures for sepsis had any value.

The committee agreed that assessment and reassessment of someone's NEWS2 score, treating them according to which risk category they were in and escalating care when appropriate would improve severe illness and mortality outcomes for people with suspected sepsis. The committee also wanted to ensure patient safety by emphasising the importance of regular monitoring and providing people with enough information on discharge to spot signs or symptoms of sepsis.

1.1.8.8 The quality of the evidence

Serum Lactate

Data on lactate was limited and came from single studies reported in the Kumar 2023 systematic review which was assessed as having a high risk of bias based on inaccurate reporting of some data and underreporting of primary study details included in some of their meta-analyses for other outcomes. Primary studies were assessed as 'high quality' by the review authors; however, this was not assessed using GRADE as per NICE methods. The review authors stated that risk of bias was low to moderate across all included studies, however individual risk of bias ratings were not provided and

it is not clear if their assessment used the QUADAS risk of bias tool as per NICE methods.

C-reactive protein

Pooled data on C-reactive protein was reported in all of the systematic reviews identified through the scoping search, with the largest meta-analysis (63 studies) found in Kumar 2023. However, reference details of primary studies, their individual characteristics, what reference standard they used and risk of bias ratings were not reported in Kumar 2023. All systematic reviews reporting results for CRP were given a high risk of bias rating, details of which can be found in appendix D. Data had also been pooled in all systematic reviews comprising studies using different cut-off points, therefore only a threshold range across studies has been reported above.

White blood cell count

Data on white blood cell counts (WBC) came from one systematic review (Li 2022) rated as high risk of bias and specifically in burns populations. Data was pooled from 5 primary studies all assessed by review authors as having a high risk of bias. As with CRP, data was pooled combining studies that used different cut-off points.

1.1.8.9 Benefits and harms

Mapping the NEWS2 risk strata onto these initial management strategies creates a more cohesive pathway, where risk of illness or death from sepsis is defined by NEWS2, and people are then managed appropriately in hospital depending on their risk level. The further refresh of these recommendations adds greater clarity, it updates them in line with current practice and it aligns them with other national guidance from the AoMRC.

1.1.8.9.1 Cost effectiveness and resource use

The main purpose of this guideline update was to update the risk stratification system to the NEWS2 risk strata. Aside from any updates to recommendations within each risk strata, any impact on the overall level of resources required to manage people with suspected sepsis would only be

expected to occur if substantially more (or fewer) people end up in the higher risk category and are managed more intensively. The committee believed that the risk categories in the new update were broadly similar to the previous guideline, and therefore this will not have a significant resource impact.

The committee also discussed whether any of the recommendations within each of the risk strata should be updated. The majority of these were to improve the clarity and understanding of the recommendations, which should mean that the guideline is implemented more efficiently. Other minor updates to recommendations, e.g. including a clotting screen for assessing people with a moderate risk of severe illness or death from sepsis, align with the AoMRC report on managing sepsis and reflect current practice.

1.1.9 Recommendations supported by this evidence review

This evidence review supports recommendations in the sections on early non-antibiotic management.

1.1.10 References – included studies

1.1.10.1 Diagnostic evidence

Huang, Yu-Hsuan, Chen, Ching-Jung, Shao, Shih-Chieh et al. (2023) Comparison of the Diagnostic Accuracies of Monocyte Distribution Width, Procalcitonin, and C-Reactive Protein for Sepsis: A Systematic Review and Meta-Analysis. Critical care medicine 51(5): e106-e114

Kumar, Ashwani, Abbenbroek, Brett, Delaney, Anthony et al. (2023) Sepsis triggers and tools to support early identification in healthcare settings: An integrative review. Australian critical care : official journal of the Confederation of Australian Critical Care Nurses

Li, Andrew T, Moussa, Anthony, Gus, Eduardo et al. (2022) Biomarkers for the Early Diagnosis of Sepsis in Burns: Systematic Review and Meta-analysis. Annals of surgery 275(4): 654-662

Tan, Meichun, Lu, Yunxia, Jiang, Hao et al. (2019) The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: A systematic review and meta-analysis. Journal of cellular biochemistry 120(4): 5852-5859

Wu, C.-C., Lan, H.-M., Han, S.-T. et al. (2017) Comparison of diagnostic accuracy in sepsis between presepsin, procalcitonin, and C-reactive protein: a systematic review and meta-analysis. Annals of Intensive Care 7(1): 91

Yeh, Chun-Fu, Wu, Chin-Chieh, Liu, Su-Hsun et al. (2019) Comparison of the accuracy of neutrophil CD64, procalcitonin, and C-reactive protein for sepsis identification: a systematic review and meta-analysis. Annals of intensive care 9(1): 5

1.1.10.2 Economic evidence

No included studies.

Appendix A – Methods and Processes

To support a timely update of the guideline recommendations, a proportionate approach was followed in line with the NICE guideline manual Appendix M: Interim principles for methods and processes for supporting digital living guideline recommendations and Appendix N: Multi-criteria decision framework for deciding whether to develop or update recommendations and which methods to use. In addition, formal consensus methods were used as outlined below.

Rationale

The evidence did not indicate that the currently recommended initial management strategies were out of date. To assist with the update of the risk stratification categories in the recommendations, a mapping exercise and committee survey was conducted. This was done using a modified nominal group technique. The aim of this approach was to enable the committee to use their expertise and opinions to reach formal consensus on the updates to the recommendations.

Development and conduct of the survey

The original recommendations were presented in a table alongside proposed recommendations, in which the old risk stratification categories were amended to the NEWS2-based risk strata categories. This table formed a survey for the committee to elicit their views on the proposed changes to the recommendations. Free text boxes were included to generate discussion points to facilitate a structured discussion with the committee to update the recommendations.

The survey was distributed to all 15 committee members by email in July 2023; and they had 10 days to respond. For each recommendation, the committee were invited to comment on whether they agreed or disagreed with the changes, and to provide a rationale for any disagreement. Responses were received from 9 committee members and collated.

Data analysis and presentation to the committee

The level of agreement and discussion points were extracted from the collated survey responses per question. There was broad agreement with the proposed changes to the recommendations through the survey exercise and some suggestions for further changes to the recommendations to improve clarity and implementation.

The survey results were then presented to the committee. All committee members were given the opportunity to express their views, take part in the committee discussions and were involved in the final decision-making. Discussions continued on each recommendation until the full group were in agreement with the change. The committee concluded that:

- Replacing the risk strata with the relevant NEWS2 strata in the relevant recommendations within sections on initial management was appropriate.

- The implications of amending the risk strata meant that some of the currently recommended advice around frequency of monitoring and escalation of care for people in the low-risk strata doesn't align with NEWS2 and they agreed to amend this.

- The committee also agreed on some minor changes to advice on referral and discharge to make it clearer to end users around when those aspects of care should be considered.

- The committee also agreed on withdrawing a recommendation on monitoring the mental state of a person with suspected sepsis as this has been superseded by NEWS2 which includes this parameter.

See Appendix F for the survey and results.

Appendix B – Review protocols

Review protocol for blood tests to identify whether sepsis is present

ID	Field	Content
0.	PROSPERO registration number	Not applicable – scoping review therefore will not be registered on Prospero.
1.	Review title	Blood tests to identify whether sepsis is present
2.	Review question	In people with suspected sepsis how accurate are blood tests to identify whether sepsis is present?
3.	Objective	To identify the blood tests that would assist in the recognition and early assessment of people with suspected sepsis.
4.	Searches	The following databases will be searched: • Embase • MEDLINE • Cochrane library Relevant guidance on management of sepsis in acute hospital settings from other developers will also be searched for. The following databases will be searched: TRIP database, FERN (internal NICE grey lit resource), ECRI, relevant Royal College and UK professional organisation websites and SIGN. Searches will be restricted by: • English language • Human studies

		• From October 2015 The full scoping search strategies will be published in the final review. The search will focus on identifying systematic reviews of the evidence but will be extended to identify relevant primary studies if there is insufficient review level evidence.
5.	Condition or domain being studied	Suspected sepsis
6.	Population	Inclusion: • Adults aged 16 or over with suspected sepsis in acute hospital settings. Exclusion: • Children (15 and under) • Pregnant and recently pregnant people (People who have given birth in the past 4 weeks, or had a termination of pregnancy or miscarriage in the past 24 hours)
7.	Test	• blood gas (arterial, venous, or capillary): pH, bicarbonates, base deficit • glucose • lactate • full blood count (haemoglobin, platelets or thrombocytopenia, white cell count or leucocyte (TLC) or neutrophil (ANC), Immature to Total Neutrophil Ratio (I/T ratio) bands or Toxic granulations, polymorph) • biochemical tests (urea/electrolytes (sodium, potassium)/renal/liver function, creatinine, haematocrit) • clotting screen; prothrombin time PT/INR, aPTT/aPTR, TT and fibrinogen • C-reactive protein (CRP).

8.	Reference standard	• Blood culture proven infection. • American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM). Consensus Conference definition of SIRS, sepsis, severe sepsis, and septic shock. • Other composite definitions based on clinical biochemistry tests and signs and symptoms.
9.	Types of study to be included	We will focus on systematic reviews in the first instance. If insufficient systematic review evidence is identified, we will expand the scoping review to include the following primary evidence: • Prospective and retrospective cohort studies • Cross-sectional studies • Case-control studies (if there is no other evidence)
10.	Other exclusion criteria	• Non-English language studies • Primary care settings • Conference abstracts • Pre-prints • Procalcitonin (PCT) • Erythrocyte sedimentation rate (ESR) • Gram-stained gastric aspirate cytology (GAC) • Endotoxin • Interleukin (IL) • Activators adenosine diphosphate (ADP) • Arachidonic acid (AA) • Collagen (Col) • Thrombin receptor activating peptide (TRAP) • Tumour necrosis factor (TNF) • Microalbuminuria • Studies conducted in non-OECD countries.
11.	Context	This review question will partly update the following: Sepsis: recognition, diagnosis, and early management (NG 51)

12.	Primary outcomes (critical outcomes)	Diagnostic test accuracy data (i.e. TP, FP, TN, FN) that allows calculation of • Sensitivity and specificity • Positive and negative likelihood ratios We will also include area under the curve (AUC) data if reported in the studies.
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. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, study type and dates), participant characteristics, inclusion and exclusion criteria, details of index tests and reference standards, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews of diagnostic test accuracy studies

		• QUADAS-2 for diagnostic accuracy studies The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	To support a timely update of the guideline recommendations, a proportionate approach to data synthesis will be followed in line with Appendix M: Interim principles for methods and processes for supporting digital living guideline recommendations and Appendix N: Multi-criteria decision framework for deciding whether to develop or update recommendations and which methods to use. For this review, this means that meta-analysis will not be undertaken, and Grading of Recommendations Assessment, Development and Evaluation (GRADE) will not be applied. We will prioritise the evidence that is discussed with the committee and report it in full in the evidence review. This process of prioritisation will be applied to study includes identified after full text screening and will be undertaken for systematic reviews and also for primary studies if insufficient systematic reviews are identified and the search is expanded. Evidence that is not prioritised will be listed in an appendix in the evidence review with reasons explaining why it has not been prioritised. The final set of includes will undergo prioritisation based on the following criteria: For individual studies the first criterion used would be the quality of the study derived from study appraisal based on risk of bias. High and moderate quality evidence will be prioritised. The rationale being that the higher quality studies will provide the higher quality data to inform guideline development. If further prioritisation is necessary (for example, where there is a high volume of high and moderate quality studies) then we will apply additional prioritisation criteria.

		The additional criteria for prioritisation of individual studies will be the size of the study followed by being UK based/UK sample the rationale being that larger studies are more likely to be more representative and provide greater insights to inform guideline development; and a focus on UK-based population studies would increase the applicability of findings. For systematic reviews we will cross check included studies with those that had been identified within the reviews. We would subsequently exclude primary studies that featured in any included systematic review as they would have already been considered. When prioritising systematic reviews, we will use the most recent review in the instance there are two or more covering the same question. The second criterion for prioritisation of systematic reviews would be the quality of the study derived from study appraisal based on risk of bias. The rationale being that the higher quality studies will provide the higher quality data to inform guideline development. If multiple systematic reviews are identified that are all of the same quality, we will prioritise these based on the systematic review's comprehensiveness based on: • Number of primary studies • Date cut off of searches and identified studies with October 2015 as the measure; for example, if one review has more studies that are identified with a data cut off <October 2015 than another identified systematic review it would be deprioritised in favour of the other. • Number of databases searched (assessed using the ROBIS tool). Prioritised studies will be data extracted into evidence tables by index test, with diagnostic accuracy parameters obtained from the studies or calculated by the technical team for example, using data from the prioritised studies to generate a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not). Data extracted will include: • baseline characteristics • sensitivity and specificity data. • positive and negative predictive values; likelihood ratios

		• area under the receiver operator characteristic (ROC) curve (AUC) with 95% CIs used as outcomes for diagnostic test accuracy.
17.	Analysis of sub-groups	Not applicable for a scoping review.

Review protocol for blood lactate to identify worsening sepsis

ID	Field	Content
0.	PROSPERO registration number	Not applicable – scoping review therefore will not be registered on Prospero.
1.	Review title	Blood tests to identify whether sepsis is present
2.	Review question	In people with suspected sepsis how accurate is blood lactate to identify worsening sepsis?
3.	Objective	To determine the accuracy of initial blood lactate and blood lactate clearance in predicting worsening sepsis
4.	Searches	The following databases will be searched: • Embase • MEDLINE • Cochrane library Relevant guidance on management of sepsis in acute hospital settings from other developers will also be searched for. The following databases will be searched: TRIP database, FERN (internal NICE grey lit resource), ECRI, relevant Royal College and UK professional organisation websites and SIGN. Searches will be restricted by: • English language • Human studies

		• From October 2015 The full scoping search strategies will be published in the final review. The search will focus on identifying systematic reviews of the evidence but will be extended to identify relevant primary studies if there is insufficient review level evidence.
5.	Condition or domain being studied	Suspected sepsis
6.	Population	Inclusion: • Adults aged 16 or over with suspected sepsis in acute hospital settings. Exclusion: • Children (15 and under) • Pregnant and recently pregnant people (people who have given birth in the past 4 weeks, or had a termination of pregnancy or miscarriage in the past 24 hours)
7.	Test	• Lactate
8.	Reference standard	Reference standard measures that a worsening of sepsis had taken place: • all-cause mortality at 28 days (or nearest time point) • ICU admission • Hospitalisation • length of hospital stay
9.	Types of study to be included	We will focus on systematic reviews in the first instance. If insufficient systematic review evidence is identified, we will expand the scoping review to include the following primary evidence:

		• Prospective and retrospective cohort studies • Cross-sectional studies • Case-control studies (if there is no other evidence)
10.	Other exclusion criteria	• Non-English language studies • Primary care settings • Conference abstracts • Pre-prints • Studies conducted in non-OECD countries. • Studies published before 2015
11.	Context	This review question will partly update the following: Sepsis: recognition, diagnosis, and early management (NG 51)
12.	Primary outcomes (critical outcomes)	Diagnostic test accuracy data (i.e. TP, FP, TN, FN) that allows calculation of • Sensitivity and specificity
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. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion.

		A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of index tests and reference standards, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews of diagnostic test accuracy studies • QUADAS-2 for diagnostic accuracy studies The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	To support a timely update of the guideline recommendations, a proportionate approach to data synthesis will be followed in line with Appendix M: Interim principles for methods and processes for supporting digital living guideline recommendations and Appendix N: Multi-criteria decision framework for deciding whether to develop or update recommendations and which methods to use. For this review, this means that meta-analysis will not be undertaken, and Grading of Recommendations Assessment, Development and Evaluation (GRADE) will not be applied. We will prioritise the evidence that is discussed with the committee and report it in full in the evidence review. This process of prioritisation will be applied to study includes identified after full text screening and will be undertaken for systematic reviews and also for primary studies if insufficient systematic reviews are identified and the search is

		expanded. Evidence that is not prioritised will be listed in an appendix in the evidence review with reasons explaining why it has not been prioritised. The final set of includes will undergo prioritisation based on the following criteria: For individual studies the first criterion used would be the quality of the study derived from study appraisal based on risk of bias. High and moderate quality evidence will be prioritised. The rationale being that the higher quality studies will provide the higher quality data to inform guideline development. If further prioritisation is necessary (for example, where there is a high volume of high and moderate quality studies) then we will apply additional prioritisation criteria. The additional criteria for prioritisation of individual studies will be the size of the study followed by being UK based/UK sample the rationale being that larger studies are more likely to be more representative and provide greater insights to inform guideline development; and a focus on UK-based population studies would increase the applicability of findings. For systematic reviews we will cross check included studies with those that had been identified within the reviews. We would subsequently exclude primary studies that featured in any included systematic review as they would have already been considered. When prioritising systematic reviews, we will use the most recent review in the instance there are two or more covering the same question. The second criterion for prioritisation of systematic reviews would be the quality of the study derived from study appraisal based on risk of bias. The rationale being that the higher quality studies will provide the higher quality data to inform guideline development. If multiple systematic reviews are identified that are all of the same quality, we will prioritise these based on the systematic review's comprehensiveness based on: • Number of primary studies • Date cut off of searches and identified studies with October 2015 as the measure; for example, if one review has more studies that are identified with a data cut off <October 2015 than another identified systematic review it would be deprioritised in favour of the other.

		• Number of databases searched (assessed using the ROBIS tool). Prioritised studies will be data extracted into evidence tables by index test, with diagnostic accuracy parameters obtained from the studies or calculated by the technical team for example, using data from the prioritised studies to generate a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not). Data extracted will include: • baseline characteristics • sensitivity and specificity data;
17.	Analysis of sub-groups	Not applicable for a scoping review.

Review protocol for serum creatinine to identify worsening sepsis

ID	Field	Content
0.	PROSPERO registration number	Not applicable – scoping review therefore will not be registered on Prospero.
1.	Review title	Blood tests to identify whether sepsis is present
2.	Review question	In people with suspected sepsis how accurate is serum creatinine to identify worsening sepsis?
3.	Objective	To determine the accuracy of initial serum creatinine in predicting worsening sepsis
4.	Searches	The following databases will be searched: • Embase

		• MEDLINE • Cochrane library Relevant guidance on management of sepsis in acute hospital settings from other developers will also be searched for. The following databases will be searched: TRIP database, FERN (internal NICE grey lit resource), ECRI, relevant Royal College and UK professional organisation websites and SIGN. Searches will be restricted by: • English language • Human studies • From October 2015 The full scoping search strategies will be published in the final review. The search will focus on identifying systematic reviews of the evidence but will be extended to identify relevant primary studies if there is insufficient review level evidence.
5.	Condition or domain being studied	Suspected sepsis
6.	Population	Inclusion: • Adults aged 16 or over with suspected sepsis in acute hospital settings. Exclusion: • Children (15 and under) • Pregnant and recently pregnant people (people who have given birth in the past 4 weeks, or had a termination of pregnancy or miscarriage in the past 24 hours)

7.	Test	• Serum creatinine
8.	Reference standard	Reference standard measures that a worsening of sepsis had taken place: • all-cause mortality at 28 days (or nearest time point) • ICU admission • Hospitalisation • length of hospital stay
9.	Types of study to be included	We will focus on systematic reviews in the first instance. If insufficient systematic review evidence is identified, we will expand the scoping review to include the following primary evidence: • Prospective and retrospective cohort studies • Cross-sectional studies • Case-control studies (if there is no other evidence)
10.	Other exclusion criteria	• Non-English language studies • Primary care settings • Conference abstracts • Pre-prints • Studies conducted in non-OECD countries. • Studies published before 2015
11.	Context	This review question will partly update the following: Sepsis: recognition, diagnosis, and early management (NG 51)
12.	Primary outcomes (critical outcomes)	Diagnostic test accuracy data (i.e. TP, FP, TN, FN) that allows calculation of • Sensitivity and specificity • Positive and negative likelihood ratios • Odds ratios

		We will also include area under the curve (AUC) data if reported in the studies.
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. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of index tests and reference standards, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews of diagnostic test accuracy studies • QUADAS-2 for diagnostic accuracy studies • ROBINS-I for cohort studies

		The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	To support a timely update of the guideline recommendations, a proportionate approach to data synthesis will be followed in line with Appendix M: Interim principles for methods and processes for supporting digital living guideline recommendations and Appendix N: Multi-criteria decision framework for deciding whether to develop or update recommendations and which methods to use. For this review, this means that meta-analysis will not be undertaken, and Grading of Recommendations Assessment, Development and Evaluation (GRADE) will not be applied. We will prioritise the evidence that is discussed with the committee and report it in full in the evidence review. This process of prioritisation will be applied to study includes identified after full text screening and will be undertaken for systematic reviews and also for primary studies if insufficient systematic reviews are identified and the search is expanded. Evidence that is not prioritised will be listed in an appendix in the evidence review with reasons explaining why it has not been prioritised. The final set of includes will undergo prioritisation based on the following criteria: For individual studies the first criterion used would be the quality of the study derived from study appraisal based on risk of bias. High and moderate quality evidence will be prioritised. The rationale being that the higher quality studies will provide the higher quality data to inform guideline development. If further prioritisation is necessary (for example, where there is a high volume of high and moderate quality studies) then we will apply additional prioritisation criteria.

		The additional criteria for prioritisation of individual studies will be the size of the study followed by being UK based/UK sample the rationale being that larger studies are more likely to be more representative and provide greater insights to inform guideline development; and a focus on UK-based population studies would increase the applicability of findings. For systematic reviews we will cross check included studies with those that had been identified within the reviews. We would subsequently exclude primary studies that featured in any included systematic review as they would have already been considered. When prioritising systematic reviews, we will use the most recent review in the instance there are two or more covering the same question. The second criterion for prioritisation of systematic reviews would be the quality of the study derived from study appraisal based on risk of bias. The rationale being that the higher quality studies will provide the higher quality data to inform guideline development. If multiple systematic reviews are identified that are all of the same quality, we will prioritise these based on the systematic review's comprehensiveness based on: • Number of primary studies • Date cut off of searches and identified studies with October 2015 as the measure; for example, if one review has more studies that are identified with a data cut off <October 2015 than another identified systematic review it would be deprioritised in favour of the other. • Number of database searched (assessed using the ROBIS tool). Prioritised studies will be data extracted into evidence tables by index test, with diagnostic accuracy parameters obtained from the studies or calculated by the technical team for example, using data from the prioritised studies to generate a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not). Data extracted will include: • baseline characteristics • sensitivity and specificity data; • positive and negative predictive values; likelihood ratios

		area under the receiver operator characteristic (ROC) curve (AUC) with 95% CIs used as outcomes for diagnostic test accuracy.
17.	Analysis of sub-groups	Not applicable for a scoping review.

Review protocol for escalation of care

ID	Field	Content
0.	PROSPERO registration number	Not applicable – scoping review therefore will not be registered on Prospero.
1.	Review title	Escalation of care
2.	Review question	When is the most appropriate time for care of people with suspected sepsis to be directed to a) a senior healthcare professional, and b) staff with critical care skills?
3.	Objective	To determine when to escalate care to senior healthcare professionals and/or critical care providers.
4.	Searches	The following databases will be searched: • Embase • MEDLINE

		• Cochrane library Relevant guidance on management of sepsis in acute hospital settings from other developers will also be searched for. The following databases will be searched: TRIP database, FERN (internal NICE grey lit resource), ECRI, relevant Royal College and UK professional organisation websites and SIGN. Searches will be restricted by: • English language • Human studies • From October 2015 The full scoping search strategies will be published in the final review. The search will focus on identifying systematic reviews of the evidence but will be extended to identify relevant primary studies if there is insufficient review level evidence.
5.	Condition or domain being studied	Suspected sepsis
6.	Population	Inclusion:

		• Adults aged 16 or over with suspected sepsis in acute hospital settings. Exclusion: • Children (15 and under) • Pregnant and recently pregnant people (people who have given birth in the past 4 weeks, or had a termination of pregnancy or miscarriage in the past 24 hours)
7.	Intervention	• Early escalation (as defined in the studies)
8.	Comparator	• Late escalation (as defined in the studies)
9.	Types of study to be included	We will focus on systematic reviews in the first instance. If insufficient systematic review evidence is identified, we will expand the scoping review to include the following primary evidence: • RCTs • Prospective and retrospective cohort studies
10.	Other exclusion criteria	• Non-English language studies • Primary care settings • Conference abstracts • Pre-prints • Studies published before 2015 • Studies conducted in non-OECD countries.

11.	Context	This review question will partly update the following: Sepsis: recognition, diagnosis and early management (NG 51)
12.	Primary outcomes (critical outcomes)	• all-cause mortality at 28 days (or nearest time point) • health-related quality of life • admission to critical care
13.	Secondary outcomes (important outcomes)	• duration of hospital stay • duration of critical care stay • adverse events (long-term disability; short-term heart failure)
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. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates),

		participant characteristics, inclusion and exclusion criteria, details of interventions, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool (2.0) for RCTs • Cohort studies will be assessed using ROBINS-I The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	To support a timely update of the guideline recommendations, a proportionate approach to data synthesis will be followed in line with Appendix M: Interim principles for methods and processes for supporting digital living guideline recommendations and Appendix N: Multi-criteria decision framework for deciding whether to develop or update recommendations and which methods to use. For this review, this means that meta-analysis will not be undertaken, and Grading of Recommendations Assessment, Development and Evaluation (GRADE) will not be applied. We will prioritise the evidence that is discussed with the committee and report it in full in the evidence review. This process of prioritisation will be applied to study includes identified after full text screening and will be undertaken for systematic reviews and also for primary studies if insufficient systematic reviews are identified and the search is expanded. Evidence that is not prioritised will be listed in an appendix in the evidence review with reasons explaining why it has not been prioritised.

		The final set of includes will undergo prioritisation based on the following criteria: For individual studies the first criterion used would be the quality of the study derived from study appraisal based on risk of bias. High and moderate quality evidence will be prioritised. The rationale being that the higher quality studies will provide the higher quality data to inform guideline development. If further prioritisation is necessary (for example, where there is a high volume of high and moderate quality studies) then we will apply additional prioritisation criteria. The additional criteria for prioritisation of individual studies will be the size of the study followed by being UK based/UK sample the rationale being that larger studies are more likely to be more representative and provide greater insights to inform guideline development; and a focus on UK-based population studies would increase the applicability of findings. For systematic reviews we will cross check included studies with those that had been identified within the reviews. We would subsequently exclude primary studies that featured in any included systematic review as they would have already been considered. When prioritising systematic reviews, we will use the most recent review in the instance there are two or more covering the same question. The second criterion for prioritisation of systematic reviews would be the quality of the study derived from study appraisal based on risk of bias. The rationale being that the higher quality studies will provide the higher quality data to inform guideline development. If multiple systematic reviews are identified that are all of the same quality, we will prioritise these based on the systematic review's comprehensiveness based on: • Number of primary studies • Date cut off of searches and identified studies with October 2015 as the measure; for example if one review has more studies that are identified with a data cut off <October 2015 than another identified systematic review it would be deprioritised in favour of the other. • Number of database searched (assessed using the ROBIS tool).

		Prioritised studies will be data extracted into evidence tables by intervention. Data extracted will include: • baseline characteristics • population • intervention/comparator (early/late escalation of care) • study design outcomes
17.	Analysis of sub-groups	Not applicable for a scoping review.

Appendix C – Scoping literature search strategies

Background and development

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were run between 20th June 2023 to 27th June 2023. 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 strategy below was quality assured (QA) by a trained NICE information specialist. The procedure was 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 strategy was 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 Population and Intervention search terms for this review were based on the literature search strategies used for the original Sepsis guideline (NG51) that was last updated in 2017. Amendments to update subject headings and to increase the relevancy of the literature search were made.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

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

The search was limited from 2015 to 2023 as defined in the review protocol.

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.

Search filters and classifiers

Clinical/public health searches

Systematic reviews

The MEDLINE SR filter was “Health-evidence.ca Systematic review search filter” from Lee et al. (2012). The standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

The Embase SR filter was “Health-evidence.ca Systematic review search filter” from Lee et al. (2012). The standard NICE modifications were used: pubmed.tw added to line medline.tw.

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

RCTs

The MEDLINE RCT filter was McMaster Therapy – Medline - “best balance of sensitivity and specificity” version. The standard NICE modifications were used: the MeSH heading *randomized controlled trial/*, which is equivalent *to randomized controlled trial.pt* was exploded to capture newer, narrower *terms equivalence trial/*

and pragmatic clinical trial. The free-text term *randomized.mp* was also changed to the (more inclusive) alternative *randomi?ed.mp.* to capture both UK and US spellings.

Reference: Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

Reference: Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

Diagnosis studies

The 'optimal' version of the diagnosis filter was used.

Reference: Haynes RB, Wilczynski NL. Optimal search strategies for retrieving scientifically strong studies of diagnosis from MEDLINE: analytical survey. *BMJ*. 2004;328:1040-2.

Observational studies

The terms used for observational studies are standard NICE practice that have been developed in house.

Cost effectiveness searches

The following search filters (precise version/) were applied to the search strategies in MEDLINE and Embase to identify cost-utility studies:

Hubbard W, Walsh N, Hudson T, Heath A, Dietz J. & Rogers G. (2022) Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. *BMC Medical Research Methodology*, 22(1), 310.

Key decisions

One literature search approach was developed to identify evidence for review questions 1-3. Within this approach, the first search was conducted to identify systematic reviews, the second search was conducted to find RCTs, diagnosis studies and observational studies, and a third search was conducted to find cost-effectiveness studies. Broader versions of the Population and Intervention terms were used in the search for systematic reviews.

A separate literature search approach was developed to identify evidence for review question 4. Within this approach, the first search was conducted to identify systematic reviews, the second search was conducted to find RCTs, diagnosis studies and observational studies, and a third search was conducted to find cost-effectiveness studies. Broader versions of the Population and Intervention terms were used in the search for systematic reviews.

Effectiveness searches – review questions 1-3

Systematic reviews – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	20th June 2023	Wiley	Issue 6 of 12, June 2023	51
Embase	20th June 2023	Ovid	Embase <1974 to 2023 June 19>	778
Epistemonikos	20th June 2023	Epistemonikos	Searched 20th June 2023	843
MEDLINE	20th June 2023	Ovid	Ovid MEDLINE(R) ALL <1946 to June 19, 2023>	714

Search strategy history

Database name: MEDLINE

1 exp sepsis/ (141157)

2 sepsis.ti,ab. (117230)

3 blood-borne pathogens/ (3038)

4 (blood* adj2 (pathogen* or poison*)).ti,ab. (3304)

5 exp systemic inflammatory response syndrome/ (148946)

6 "systemic inflammatory response syndrome*".ti,ab. (5769)

7 sirs.ti,ab. (6445)

8 (septicaemi* or septicemi*).ti,ab. (22179)

9 ((septic or cryptic) adj2 shock).ti,ab. (26957)

10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (257)

11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (71531)

12 (hypotension adj3 induced adj3 hypoperfusion).ti,ab. (7)

13 or/1-12 (280059)

14 Biomarkers/ (348086)

15 (blood adj6 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (462926)

16 Blood Gas Analysis/ (22645)

17 ("blood gas*" or abg or vbg or cbg).ti,ab. (32281)

18 blood glucose/an, bl (60975)

19 lactic acid/an, bl (11535)

20 ((lactate or lactic) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (15501)

21 exp Blood Cell Count/ (151286)

22 blood culture/ (1714)

23 ((blood or serolog* or leukocyte* or leucocyte* or erythrocyte* or thrombocyte* or platelet* or wbc* or rbc*) adj2 (differential or count* or cultur*)).ti,ab. (145116)

24 (fbc or cbc or fbe).ti,ab. (6009)

25 (polymorph* or polymorphonucleocyte* or neutrophil*).ti,ab. (544613)

26 leukocytes/an, bl, di (1687)

27 neutrophils/an, bl, bs, di (752)

28 blood platelets/an (2247)

29 urea/an, bl (10390)

30 (urea adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (8693)

31 electrolytes/bl (5578)

32 (electrolyte* adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (5228)

33 u&e.ti,ab. (2688)

34 (blood urea nitrogen adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (900)

35 bun.ti,ab. (10499)

36 ((kidney or renal) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (85960)

37 creatinine/bl (36960)

38 (creatinine adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (12235)

39 ((liver or hepatic) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (117804)

40 limax.ti,ab. (591)

41 ((coagul* or anticoagul* or act) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (29008)

42 (partial thromboplastin time or ptt or aptt or pt or aptr).ti,ab. (83237)

43 ((prothrombin or bleed* or clot* or thrombin or blood) adj2 time*).ti,ab. (48361)

44 fibrinogen/bl, di (276)

45 (fibrinogen* adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (4965)

46 c-reactive protein/bl (156)

47 (c-reactive protein* adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (7767)

48 or/14-47 (1947610)

49 13 and 48 (58612)

50 (MEDLINE or pubmed).tw. (320600)

51 systematic review.tw. (265085)

52 systematic review.pt. (231378)

53 meta-analysis.pt. (182869)

54 intervention$.ti. (198410)

55 or/50-54 (676144)

56 49 and 55 (1126)

57 limit 56 to ed=20151001-20230620 (660)

58 limit 56 to dt=20151001-20230620 (691)

59 or/57-58 (749)

60 limit 59 to english language (719)

61 animals/ not humans/ (5099139)

62 60 not 61 (714)

Database name: Embase

1 exp sepsis/ (334492)

2 sepsis.ti,ab. (185824)

3 bloodborne bacterium/ (2155)

4 (blood* adj2 (pathogen* or poison*)).ti,ab. (4346)

5 exp systemic inflammatory response syndrome/ (347394)

6 "systemic inflammatory response syndrome*".ti,ab. (8638)

7 sirs.ti,ab. (11637)

8 (septicaemi* or septicemi*).ti,ab. (25958)

9 ((septic or cryptic) adj2 shock).ti,ab. (44535)

10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (133)

11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (99872)

12 (hypotension adj3 induced adj3 hypoperfusion).ti,ab. (8)

13 or/1-12 (466002)

14 *biological marker/ (127356)

15 (blood adj6 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (703183)

16 *blood gas analysis/ (2211)

17 ("blood gas*" or abg or vbg or cbg).ti,ab. (48045)

18 *glucose blood level/ (35813)

19 *lactic acid/ (22153)

20 ((lactate or lactic) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (20685)

21 exp *blood cell count/ (25323)

22 *blood culture/ (5439)

23 ((blood or serolog* or leukocyte* or leucocyte* or erythrocyte* or thrombocyte* or platelet* or wbc* or rbc*) adj2 (differential or count* or cultur*)).ti,ab. (243846)

24 (fbc or cbc or fbe).ti,ab. (16582)

25 (polymorph* or polymorphonucleocyte* or neutrophil*).ti,ab. (710824)

26 *leukocyte/ (26673)

27 *neutrophil/ (47835)

28 *thrombocyte/an (260)

29 *urea/ (14298)

30 (urea adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (12470)

31 *electrolyte/ (15393)

32 (electrolyte* adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (6896)

33 u&e.ti,ab. (4616)

34 (blood urea nitrogen adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (1293)

35 bun.ti,ab. (20318)

36 ((kidney or renal) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (131441)

37 *creatinine/ (12063)

38 (creatinine adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (21430)

39 ((liver or hepatic) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (181167)

40 limax.ti,ab. (694)

41 ((coagul* or anticoagul* or act) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (47625)

42 (partial thromboplastin time or ptt or aptt or pt or aptr).ti,ab. (138771)

43 ((prothrombin or bleed* or clot* or thrombin or blood) adj2 time*).ti,ab. (73288)

44 *fibrinogen/ (17416)

45 (fibrinogen* adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (7363)

46 *c reactive protein/ (28353)

47 (c-reactive protein* adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (11465)

48 or/14-47 (2353350)

49 13 and 48 (86229)

50 (MEDLINE or pubmed).tw. (414719)

51 exp systematic review/ or systematic review.tw. (519712)

52 meta-analysis/ (296507)

53 intervention$.ti. (266800)

54 or/50-53 (980810)

55 49 and 54 (1762)

56 limit 55 to dc=20151001-20230620 (1213)

57 limit 56 to english language (1176)

58 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5576317)

59 57 not 58 (796)

60 nonhuman/ not human/ (5322780)

61 59 not 60 (778)

Database name: CDSR

#1 MeSH descriptor: [Sepsis] explode all trees 6750

#2 sepsis:ti,ab,kw 13232

#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 36

#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 345

#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 7318

#6 systemic inflammatory response syndrome*:ti,ab,kw 1683

#7 sirs:ti,ab,kw 863

#8 (septicaemi* or septicemi*):ti,ab,kw 1103

#9 ((septic or cryptic) near/2 shock):ti,ab,kw 3765

#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 6522

#12 (hypotension near/3 induced near/3 hypoperfusion) 1

#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 23469

#14 MeSH descriptor: [Biomarkers] this term only 18063

#15 (blood near/6 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 120360

#16 MeSH descriptor: [Blood Gas Analysis] this term only 1493

#17 (blood gas* or abg or vbg or cbg):ti,ab,kw 36386

#18 MeSH descriptor: [Blood Glucose] this term only and with qualifier(s): [analysis - AN] 5472

#19 MeSH descriptor: [Lactic Acid] this term only and with qualifier(s): [blood - BL, analysis - AN] 1649

#20 ((lactate or lactic) near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 1761

#21 MeSH descriptor: [Blood Cell Count] explode all trees 9854

#22 MeSH descriptor: [Blood Culture] this term only 99

#23 ((blood or serolog* or leukocyte* or leucocyte* or erythrocyte* or thrombocyte* or platelet* or wbc* or rbc*) near/2 (differential or count* or cultur*)):ti,ab,kw 26009

#24 (fbc or cbc or fbe):ti,ab,kw 1919

#25 (polymorph* or polymorphonucleocyte* or neutrophil*):ti,ab,kw 25012

#26 MeSH descriptor: [Neutrophils] this term only 1580

#27 MeSH descriptor: [Blood Platelets] this term only 2196

#28 MeSH descriptor: [Urea] this term only and with qualifier(s): [blood - BL, analysis - AN] 519

#29 (urea near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 2335

#30 MeSH descriptor: [Electrolytes] this term only and with qualifier(s): [blood - BL] 350

#31 (electrolyte* near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 779

#32 u&e:ti,ab,kw 0

#33 (blood urea nitrogen near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 199

#34 bun:ti,ab,kw 2222

#35 ((kidney or renal) near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 11775

#36 MeSH descriptor: [Creatinine] this term only and with qualifier(s): [blood - BL] 2826

#37 (creatinine near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 3284

#38 ((liver or hepatic) near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 12786

#39 limax:ti,ab,kw 15

#40 ((coagul* or anticoagul* or act) near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 4867

#41 (partial thromboplastin time or ptt or aptt or pt or aptr):ti,ab,kw 20413

#42 ((prothrombin or bleed* or clot* or thrombin or blood) near/2 time*):ti,ab,kw 15663

#43 MeSH descriptor: [Fibrinogen] this term only 1347

#44 (fibrinogen* near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 1308

#45 MeSH descriptor: [C-Reactive Protein] this term only 5560

#46 (c-reactive protein* near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 3873

#47 {or #14-#46} 248311

#48 #13 and #47 with Cochrane Library publication date Between Oct 2015 and Jun 2023 4433

Database name: Epistemonikos

(advanced_title_en:((advanced_title_en:(blood OR abg OR vbg OR cbg OR lactate OR lactic OR serolog* OR leukocyte* OR leucocyte* OR erythrocyte* OR thrombocyte* OR platelet* OR wbc* OR rbc* OR fbc OR cbc OR fbe OR polymorph* OR polymorphonucleocyte* OR neutrophil* OR urea* OR electrolyte* OR creatinine OR limax OR thromboplastin OR ptt OR aptt OR pt OR aptr OR prothrombin OR bleed* OR clot* OR thrombin OR fibrinogen* OR c-reactive protein*) OR advanced_abstract_en:(blood OR abg OR vbg OR cbg OR lactate OR lactic OR serolog* OR leukocyte* OR leucocyte* OR erythrocyte* OR thrombocyte* OR platelet* OR wbc* OR rbc* OR fbc OR cbc OR fbe OR polymorph* OR polymorphonucleocyte* OR neutrophil* OR urea* OR electrolyte* OR creatinine OR limax OR thromboplastin OR ptt OR aptt OR pt OR aptr OR prothrombin OR bleed* OR clot* OR thrombin OR fibrinogen* OR c-reactive protein*))) OR advanced_abstract_en:((advanced_title_en:(blood OR abg OR vbg OR cbg OR lactate OR lactic OR serolog* OR leukocyte* OR leucocyte* OR erythrocyte* OR thrombocyte* OR platelet* OR wbc* OR rbc* OR fbc OR cbc OR fbe OR polymorph* OR polymorphonucleocyte* OR neutrophil* OR urea* OR electrolyte* OR creatinine OR limax OR thromboplastin OR ptt OR aptt OR pt OR aptr OR prothrombin OR bleed* OR clot* OR thrombin OR fibrinogen* OR c-reactive protein*) OR advanced_abstract_en:(blood OR abg OR vbg OR cbg OR lactate OR lactic OR serolog* OR leukocyte* OR leucocyte* OR erythrocyte* OR thrombocyte* OR platelet* OR wbc* OR rbc* OR fbc OR cbc OR fbe OR polymorph* OR polymorphonucleocyte* OR neutrophil* OR urea* OR electrolyte* OR creatinine OR limax OR thromboplastin OR ptt OR aptt OR pt OR aptr OR prothrombin OR bleed* OR clot* OR thrombin OR fibrinogen* OR c-reactive protein*)))) AND

(advanced_title_en:((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 parasiteami* viremi* OR vireami* OR hypoperfusion* OR pathogen* OR poison*)) OR advanced_abstract_en:((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 parasiteami* viremi* OR vireami* OR hypoperfusion* OR pathogen* OR poison*))) [Filters: classification=systematic-review, protocol=no, min_year=2015, max_year=2023]

RCTs, observational studies, diagnosis studies – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	22nd June 2023	Wiley	Issue 6 of 12, June 2023	1481
Embase	22nd June 2023	Ovid	Embase <1974 to 2023 June 21>	8883
MEDLINE	22nd June 2023	Ovid	Ovid MEDLINE(R) ALL <1946 to June 21, 2023>	8404

Search strategy history

Database name: MEDLINE

1 exp *sepsis/ (101110)

2 sepsis.ti,ab. (117237)

3 *blood-borne pathogens/ (1554)

4 (blood* adj2 (pathogen* or poison*)).ti,ab. (3305)

5 (septicaemi* or septicemi*).ti,ab. (22181)

6 ((septic or cryptic) adj2 shock).ti,ab. (26957)

7 (pyaemi* or pyemi* or pyohemi*).ti,ab. (257)

8 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (71511)

9 or/1-8 (247899)

10 *Biomarkers/ (46478)

11 (blood adj6 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (462908)

12 *Blood Gas Analysis/ (4782)

13 ("blood gas*" or abg or vbg or cbg).ti,ab. (32279)

14 *blood glucose/an, bl (15727)

15 *lactic acid/an, bl (3234)

16 ((lactate or lactic) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (15497)

17 exp *Blood Cell Count/ (18900)

18 *blood culture/ (789)

19 ((blood or serolog* or leukocyte* or leucocyte* or erythrocyte* or thrombocyte* or platelet* or wbc* or rbc*) adj2 (differential or count* or cultur*)).ti,ab. (145124)

20 (fbc or cbc or fbe).ti,ab. (6007)

21 (polymorph* or polymorphonucleocyte* or neutrophil*).ti,ab. (544601)

22 *leukocytes/an, bl, di (791)

23 *neutrophils/an, bl, bs, di (346)

24 *blood platelets/an (1224)

25 *urea/an, bl (2207)

26 (urea adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (8693)

27 *electrolytes/bl (1748)

28 (electrolyte* adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (5233)

29 u&e.ti,ab. (2689)

30 (blood urea nitrogen adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (903)

31 ((kidney or renal) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (85971)

32 *creatinine/bl (4458)

33 (creatinine adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (12240)

34 ((liver or hepatic) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (117800)

35 limax.ti,ab. (591)

36 ((coagul* or anticoagul* or act) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (28995)

37 (partial thromboplastin time or ptt or aptt or pt or aptr).ti,ab. (83246)

38 ((prothrombin or bleed* or clot* or thrombin or blood) adj2 time*).ti,ab. (48356)

39 *fibrinogen/bl, di (90)

40 (fibrinogen* adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (4963)

41 *c-reactive protein/bl (76)

42 (c-reactive protein* adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (7769)

43 or/10-42 (1526095)

44 9 and 43 (44764)

45 exp Randomized Controlled Trial/ (596476)

46 randomi?ed.mp. (1066533)

47 placebo.mp. (246973)

48 or/45-47 (1132126)

49 Observational Studies as Topic/ (8823)

50 Observational Study/ (142970)

51 exp Case-Control Studies/ (1423688)

52 exp Cohort Studies/ (2492443)

53 Cross-Sectional Studies/ (469626)

54 Controlled Before-After Studies/ (726)

55 Historically Controlled Study/ (227)

56 Comparative Study.pt. (1912688)

57 case control$.tw. (157752)

58 case series.tw. (102828)

59 (cohort adj (study or studies)).tw. (314671)

60 cohort analy$.tw. (11745)

61 (follow up adj (study or studies)).tw. (56175)

62 (observational adj (study or studies)).tw. (160350)

63 longitudinal.tw. (321233)

64 prospective.tw. (711781)

65 retrospective.tw. (741510)

66 cross sectional.tw. (510458)

67 or/49-66 (5489242)

68 (sensitiv: or predictive value:).mp. or accurac:.tw. (2562223)

69 48 or 67 or 68 (8075777)

70 44 and 69 (22487)

71 (MEDLINE or pubmed).tw. (320585)

72 systematic review.tw. (265090)

73 systematic review.pt. (231282)

74 meta-analysis.pt. (182807)

75 intervention$.ti. (198330)

76 or/71-75 (676020)

77 44 and 76 (805)

78 70 not 77 (22015)

79 limit 78 to ed=20151001-20230622 (7761)

80 limit 78 to dt=20151001-20230622 (8368)

81 79 or 80 (9185)

82 limit 81 to english language (8745)

83 animals/ not humans/ (5098411)

84 82 not 83 (8404)

Database name: Embase

1 exp *sepsis/ (118653)

2 sepsis.ti,ab. (185958)

3 bloodborne bacterium/ (2155)

4 (blood* adj2 (pathogen* or poison*)).ti,ab. (4348)

5 (septicaemi* or septicemi*).ti,ab. (25961)

6 ((septic or cryptic) adj2 shock).ti,ab. (44567)

7 (pyaemi* or pyemi* or pyohemi*).ti,ab. (133)

8 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (99922)

9 or/1-8 (349084)

10 *biological marker/ (127631)

11 (blood adj6 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (703599)

12 *blood gas analysis/ (2211)

13 ("blood gas*" or abg or vbg or cbg).ti,ab. (48064)

14 *glucose blood level/ (35830)

15 *lactic acid/ (22164)

16 ((lactate or lactic) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (20696)

17 exp *blood cell count/ (25342)

18 *blood culture/ (5441)

19 ((blood or serolog* or leukocyte* or leucocyte* or erythrocyte* or thrombocyte* or platelet* or wbc* or rbc*) adj2 (differential or count* or cultur*)).ti,ab. (244002)

20 (polymorph* or polymorphonucleocyte* or neutrophil*).ti,ab. (711102)

21 *leukocyte/ (26684)

22 *neutrophil/ (47854)

23 *thrombocyte/an (260)

24 *urea/ (14308)

25 (urea adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (12472)

26 *electrolyte/ (15406)

27 (electrolyte* adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (6899)

28 u&e.ti,ab. (4625)

29 (blood urea nitrogen adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (1293)

30 ((kidney or renal) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (131511)

31 *creatinine/ (12067)

32 (creatinine adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (21438)

33 ((liver or hepatic) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (181260)

34 limax.ti,ab. (694)

35 ((coagul* or anticoagul* or act) adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (47643)

36 (partial thromboplastin time or ptt or aptt or pt or aptr).ti,ab. (138861)

37 ((prothrombin or bleed* or clot* or thrombin or blood) adj2 time*).ti,ab. (73332)

38 *fibrinogen/ (17422)

39 (fibrinogen* adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (7366)

40 *c reactive protein/ (28367)

41 (c-reactive protein* adj3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)).ti,ab. (11473)

42 or/10-41 (2336205)

43 9 and 42 (74412)

44 random:.tw. (1979682)

45 placebo:.mp. (525177)

46 double-blind:.tw. (246155)

47 or/44-46 (2257200)

48 Clinical study/ (163461)

49 Case control study/ (207200)

50 Family study/ (25777)

51 Longitudinal study/ (195193)

52 Retrospective study/ (1483898)

53 comparative study/ (1010135)

54 Prospective study/ (883988)

55 Randomized controlled trials/ (263126)

56 54 not 55 (872881)

57 Cohort analysis/ (1050184)

58 cohort analy$.tw. (19694)

59 (Cohort adj (study or studies)).tw. (473453)

60 (Case control$ adj (study or studies)).tw. (173681)

61 (follow up adj (study or studies)).tw. (74088)

62 (observational adj (study or studies)).tw. (256584)

63 (epidemiologic$ adj (study or studies)).tw. (123019)

64 (cross sectional adj (study or studies)).tw. (341879)

65 case series.tw. (149450)

66 prospective.tw. (1108721)

67 retrospective.tw. (1264184)

68 or/48-53,56-67 (5428618)

69 (sensitiv: or predictive value:).mp. or accurac:.tw. (3207857)

70 56 or 68 or 69 (8015597)

71 43 and 70 (32680)

72 (MEDLINE or pubmed).tw. (415310)

73 exp systematic review/ or systematic review.tw. (520633)

74 meta-analysis/ (296955)

75 intervention$.ti. (267020)

76 or/72-75 (982021)

77 43 and 76 (1401)

78 71 not 77 (31975)

79 limit 78 to dc=20151001-20230622 (17507)

80 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5580097)

81 79 not 80 (10123)

82 limit 81 to english language (9592)

83 nonhuman/ not humans/ (5845073)

84 82 not 83 (8883)

Database name: CENTRAL

#1 MeSH descriptor: [Sepsis] explode all trees 6750

#2 sepsis:ti,ab,kw 13232

#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 36

#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 345

#5 (septicaemi* or septicemi*):ti,ab,kw 1103

#6 ((septic or cryptic) near/2 shock):ti,ab,kw 3765

#7 (pyaemi* or pyemi* or pyohemi*):ti,ab,kw 9

#8 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*):ti,ab,kw 6522

#9 {or #1-#8} 21963

#10 MeSH descriptor: [Biomarkers] this term only 18063

#11 (blood near/6 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 120360

#12 MeSH descriptor: [Blood Gas Analysis] this term only 1493

#13 (blood gas* or abg or vbg or cbg):ti,ab,kw 36385

#14 MeSH descriptor: [Blood Glucose] this term only and with qualifier(s): [analysis - AN] 5472

#15 MeSH descriptor: [Lactic Acid] this term only and with qualifier(s): [blood - BL, analysis - AN] 1649

#16 ((lactate or lactic) near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 1761

#17 MeSH descriptor: [Blood Cell Count] explode all trees 9854

#18 MeSH descriptor: [Blood Culture] this term only 99

#19 ((blood or serolog* or leukocyte* or leucocyte* or erythrocyte* or thrombocyte* or platelet* or wbc* or rbc*) near/2 (differential or count* or cultur*)):ti,ab,kw 26009

#20 (polymorph* or polymorphonucleocyte* or neutrophil*):ti,ab,kw 25012

#21 MeSH descriptor: [Neutrophils] this term only 1580

#22 MeSH descriptor: [Blood Platelets] this term only 2196

#23 MeSH descriptor: [Urea] this term only and with qualifier(s): [blood - BL, analysis - AN] 519

#24 (urea near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 2335

#25 MeSH descriptor: [Electrolytes] this term only and with qualifier(s): [blood - BL] 350

#26 (electrolyte* near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 779

#27 u&e:ti,ab,kw 0

#28 (blood urea nitrogen near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 199

#29 ((kidney or renal) near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 11775

#30 MeSH descriptor: [Creatinine] this term only and with qualifier(s): [blood - BL] 2826

#31 (creatinine near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 3284

#32 ((liver or hepatic) near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 12786

#33 limax:ti,ab,kw 15

#34 ((coagul* or anticoagul* or act) near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 4867

#35 (partial thromboplastin time or ptt or aptt or pt or aptr):ti,ab,kw 20413

#36 ((prothrombin or bleed* or clot* or thrombin or blood) near/2 time*):ti,ab,kw 15663

#37 MeSH descriptor: [Fibrinogen] this term only 1347

#38 (fibrinogen* near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 1308

#39 MeSH descriptor: [C-Reactive Protein] this term only 5560

#40 (c-reactive protein* near/3 (analys* or analyz* or test* or investigat* or evaluat* or examin* or check* or assess* or measur* or diagnos* or identif* or verif* or assay*)):ti,ab,kw 3873

#41 {or #10-#40} 246903

#42 #9 and #41 with Publication Year from 2015 to 2023, with Cochrane Library publication date Between Oct 2015 and Jun 2023, in Trials 3122

#43 "conference":pt or (clinicaltrials or trialsearch):so 687567

#44 #42 not #43 1481

Effectiveness searches – review question 4

Systematic reviews – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	23rd June 2023	Wiley	Issue 6 of 12, June 2023	96

Embase	23rd June 2023	Ovid	Embase <1974 to 2023 June 21>	395
Epistemonikos	27th June 2023	Epistemonikos	Searched 27th June 2023	909
MEDLINE	18th June 2023	Ovid	Ovid MEDLINE(R) ALL <1946 to June 19, 2023>	384

Search strategy history

Database name: MEDLINE

1 exp sepsis/ (141157)

2 sepsis.ti,ab. (117230)

3 blood-borne pathogens/ (3038)

4 (blood* adj2 (pathogen* or poison*)).ti,ab. (3304)

5 exp systemic inflammatory response syndrome/ (148946)

6 "systemic inflammatory response syndrome*".ti,ab. (5769)

7 sirs.ti,ab. (6445)

8 (septicaemi* or septicemi*).ti,ab. (22179)

9 ((septic or cryptic) adj2 shock).ti,ab. (26957)

10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (257)

11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (71531)

12 (hypotension adj3 induced adj3 hypoperfusion).ti,ab. (7)

13 or/1-12 (280059)

14 "Delivery of Health Care"/ (116604)

15 Critical Care/ (60373)

16 (intensive or critical or ITU or ICU or "high dependency*" or HDU).ti,ab. (1240256)

17 (intensivist* or consultant* or specialist* or senior*1 or junior*1 or sho or registrar* or spr or house officer* or houseofficer* or housestaff* or physician* or

intern*1 or internship or resident*1 or fellow*1 or foundation doctor or nurs*).ti,ab. (1289040)

18 or/14-17 (2543568)

19 Time Factors/ (1229964)

20 (time or times or timing or referral or refer or refers or referring).ti,ab. (4674226)

21 ((early or earlie* or late or later or schedul* or hour* or rapid* or fast* or slow* or delay* or immediate* or escalat* or defer* or initiate* or standby or "stand by" or manage* or managing or hospital) adj2 (care or intervention* or therap* or treatment*)).ti,ab. (396582)

22 or/19-21 (5798322)

23 13 and 18 and 22 (15022)

24 (MEDLINE or pubmed).tw. (320600)

25 systematic review.tw. (265085)

26 systematic review.pt. (231378)

27 meta-analysis.pt. (182869)

28 intervention$.ti. (198410)

29 or/24-28 (676144)

30 23 and 29 (597)

31 limit 30 to ed=20151001-20230621 (334)

32 limit 30 to dt=20151001-20230621 (376)

33 31 or 32 (399)

34 limit 33 to english language (388)

35 animals/ not humans/ (5099139)

36 34 not 35 (384)

Database name: Embase

1 exp sepsis/ (334667)

2 sepsis.ti,ab. (185958)

3 bloodborne bacterium/ (2155)

4 (blood* adj2 (pathogen* or poison*)).ti,ab. (4348)

5 exp systemic inflammatory response syndrome/ (347581)

6 "systemic inflammatory response syndrome*".ti,ab. (8645)

7 sirs.ti,ab. (11645)

8 (septicaemi* or septicemi*).ti,ab. (25961)

9 ((septic or cryptic) adj2 shock).ti,ab. (44567)

10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (133)

11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (99922)

12 (hypotension adj3 induced adj3 hypoperfusion).ti,ab. (8)

13 or/1-12 (466239)

14 *health care delivery/ (64516)

15 exp *intensive care/ (286514)

16 ((intensive or critical) adj2 care).ti,ab. (329168)

17 (intensivist* or consultant* or specialist* or senior*1 or junior*1 or sho or registrar* or spr or house officer* or houseofficer* or housestaff* or physician* or intern*1 or internship or resident*1 or fellow*1 or foundation doctor or nurs*).ti,ab. (1703821)

18 or/14-17 (2230090)

19 exp *time factor/ (1792)

20 (time or times or timing or referral or refer or refers or referring).ti,ab. (6404339)

21 ((early or earlie* or late or later or schedul* or hour* or rapid* or fast* or slow* or delay* or immediate* or escalat* or manage* or managing or hospital) adj2 care).ti,ab. (164328)

22 or/19-21 (6523605)

23 13 and 18 and 22 (22054)

24 (MEDLINE or pubmed).tw. (415310)

25 exp systematic review/ or systematic review.tw. (520633)

26 meta-analysis/ (296955)

27 intervention$.ti. (267020)

28 or/24-27 (982021)

29 23 and 28 (899)

30 limit 29 to dc=20151001-20230623 (595)

31 limit 30 to english language (580)

32 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5580097)

33 31 not 32 (399)

34 nonhuman/ not human/ (5324693)

35 33 not 34 (395)

Database name: CDSR

#1 MeSH descriptor: [Sepsis] explode all trees 6750

#2 sepsis:ti,ab,kw 13232

#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 36

#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 345

#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 7318

#6 systemic inflammatory response syndrome*:ti,ab,kw 1683

#7 sirs:ti,ab,kw 863

#8 (septicaemi* or septicemi*):ti,ab,kw 1103

#9 ((septic or cryptic) near/2 shock):ti,ab,kw 3765

#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 6522

#12 (hypotension near/3 induced near/3 hypoperfusion) 1

#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 23469

#14 MeSH descriptor: [Delivery of Health Care] this term only 1343

#15 MeSH descriptor: [Critical Care] this term only 2265

#16 (intensive or critical or ITU or ICU or high dependency* or HDU):ti,ab,kw 85216

#17 (intensivist* or consultant* or specialist* or senior*1 or junior*1 or sho or registrar* or spr or house officer* or houseofficer* or housestaff* or physician* or intern*1 or internship or resident*1 or fellow*1 or foundation doctor or nurs*):ti,ab,kw 113230

#18 #14 or #15 or #16 or #17 187989

#19 MeSH descriptor: [Time Factors] this term only 73006

#20 (time or times or timing or referral or refer or refers or referring):ti,ab,kw 570589

#21 ((early or earlie* or late or later or schedul* or hour* or rapid* or fast* or slow* or delay* or immediate* or escalat* or defer* or initiate* or standby or "stand by" or manage* or managing or hospital) near/2 (care or intervention* or therap* or treatment*)):ti,ab,kw 89260

#22 #19 or #20 or #21 624741

#23 #13 and #18 and #22 3400

#24 "conference":pt or (clinicaltrials or trialsearch):so 687567

#25 #23 not #24 with Cochrane Library publication date Between Oct 2015 and Jun 2023 1006 (96 CDSR)

Database name: Epistemonikos

(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 parasiteami* viremi* OR vireami* OR hypoperfusion* OR pathogen* OR poison*) AND (intensive OR critical OR ITU OR ICU OR "high dependency*" OR HDU OR intensivist* OR consultant* OR specialist* OR senior* OR junior* OR sho OR registrar* OR spr OR house officer* OR houseofficer* OR housestaff* OR physician* OR intern* OR internship OR resident* OR fellow* OR foundation doctor OR nurs*) AND ((time OR times OR timing OR referral OR refer OR refers OR referring OR early OR earlie* OR late OR later OR schedul* OR hour* OR rapid* OR fast* OR slow* OR delay* OR immediate* OR escalat* OR defer* OR initiate* OR standby OR "stand by" OR manage* OR managing OR hospital) AND (care OR intervention* OR therap* OR treatment*))) 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 parasiteami* viremi* OR vireami* OR hypoperfusion* OR pathogen* OR poison*) AND (intensive OR critical OR ITU OR ICU OR "high dependency*" OR HDU OR intensivist* OR consultant* OR specialist* OR senior* OR junior* OR sho OR registrar* OR spr OR house officer* OR houseofficer* OR housestaff* OR physician* OR intern* OR internship OR resident* OR fellow* OR foundation doctor OR nurs*) AND ((time OR times OR timing OR referral OR refer OR refers OR referring OR early OR earlie* OR late OR later OR schedul* OR hour* OR rapid* OR fast* OR slow* OR delay* OR immediate* OR escalat* OR defer* OR initiate* OR standby OR "stand by" OR manage* OR managing OR hospital) AND (care OR intervention* OR therap* OR treatment*)))) = 909, limited to SRs and 2015+

RCTs, observational studies, diagnosis studies – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	26th June 2023	Wiley	Issue 6 of 12, June 2023	812
Embase	26th June 2023	Ovid	Embase <1974 to 2023 June 23>	4377
MEDLINE	26th June 2023	Ovid	Ovid MEDLINE(R) ALL <1946 to June 22, 2023>	5236

Search strategy history

Database name: MEDLINE

1 exp sepsis/ (141162)

2 sepsis.ti,ab. (117313)

3 blood-borne pathogens/ (3038)

4 (blood* adj2 (pathogen* or poison*)).ti,ab. (3308)

5 exp systemic inflammatory response syndrome/ (148959)

6 "systemic inflammatory response syndrome*".ti,ab. (5769)

7 sirs.ti,ab. (6452)

8 (septicaemi* or septicemi*).ti,ab. (22185)

9 ((septic or cryptic) adj2 shock).ti,ab. (26968)

10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (257)

11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (71543)

12 (hypotension adj3 induced adj3 hypoperfusion).ti,ab. (7)

13 or/1-12 (280183)

14 "Delivery of Health Care"/ (116662)

15 Critical Care/ (60381)

16 (intensive or critical or ITU or ICU or "high dependency*" or HDU).ti,ab. (1241102)

17 (intensivist* or consultant* or specialist* or senior*1 or junior*1 or sho or registrar* or spr or house officer* or houseofficer* or housestaff* or physician* or intern*1 or internship or resident*1 or fellow*1 or foundation doctor or nurs*).ti,ab. (1289750)

18 or/14-17 (2545095)

19 Time Factors/ (1229973)

20 (time or times or timing or referral or refer or refers or referring).ti,ab. (4676784)

21 ((early or earlie* or late or later or schedul* or hour* or rapid* or fast* or slow* or delay* or immediate* or escalat* or defer* or initiate* or standby or "stand by" or manage* or managing or hospital) adj2 (care or intervention* or therap* or treatment*)).ti,ab. (396853)

22 or/19-21 (5801088)

23 13 and 18 and 22 (15027)

24 exp Randomized Controlled Trial/ (596694)

25 randomi?ed.mp. (1067211)

26 placebo.mp. (247099)

27 or/24-26 (1132828)

28 Observational Studies as Topic/ (8833)

29 Observational Study/ (143090)

30 exp Case-Control Studies/ (1424477)

31 exp Cohort Studies/ (2493612)

32 Cross-Sectional Studies/ (470000)

33 Controlled Before-After Studies/ (726)

34 Historically Controlled Study/ (227)

35 Comparative Study.pt. (1912710)

36 case control$.tw. (157862)

37 case series.tw. (102943)

38 (cohort adj (study or studies)).tw. (315203)

39 cohort analy$.tw. (11759)

40 (follow up adj (study or studies)).tw. (56197)

41 (observational adj (study or studies)).tw. (160544)

42 longitudinal.tw. (321552)

43 prospective.tw. (712384)

44 retrospective.tw. (742333)

45 cross sectional.tw. (511105)

46 or/28-45 (5492074)

47 (sensitiv: or diagnos:).mp. or di.fs. (7346131)

48 27 or 46 or 47 (11512713)

49 23 and 48 (11681)

50 (MEDLINE or pubmed).tw. (321027)

51 systematic review.tw. (265502)

52 systematic review.pt. (231544)

53 meta-analysis.pt. (182984)

54 intervention$.ti. (198544)

55 or/50-54 (676832)

56 49 not 55 (11205)

57 limit 56 to ed=20151001-20230626 (4587)

58 limit 56 to dt=20151001-20230626 (5217)

59 57 or 58 (5627)

60 limit 59 to english language (5285)

61 animals/ not humans/ (5099457)

62 60 not 61 (5236)

Database name: Embase

1 exp sepsis/ (335003)

2 sepsis.ti,ab. (186100)

3 bloodborne bacterium/ (2155)

4 (blood* adj2 (pathogen* or poison*)).ti,ab. (4348)

5 exp systemic inflammatory response syndrome/ (347951)

6 "systemic inflammatory response syndrome*".ti,ab. (8653)

7 sirs.ti,ab. (11662)

8 (septicaemi* or septicemi*).ti,ab. (25968)

9 ((septic or cryptic) adj2 shock).ti,ab. (44598)

10 (pyaemi* or pyemi* or pyohemi*).ti,ab. (133)

11 (bacter?emi* or fung?emi* or parasit?emi* or vir?emi*).ti,ab. (99952)

12 (hypotension adj3 induced adj3 hypoperfusion).ti,ab. (8)

13 or/1-12 (466663)

14 *health care delivery/ (64544)

15 exp *intensive care/ (286575)

16 ((intensive or critical) adj2 care).ti,ab. (329421)

17 (intensivist* or consultant* or specialist* or senior*1 or junior*1 or sho or registrar* or spr or house officer* or houseofficer* or housestaff* or physician* or intern*1 or internship or resident*1 or fellow*1 or foundation doctor or nurs*).ti,ab. (1705679)

18 or/14-17 (2232231)

19 exp *time factor/ (1799)

20 (time or times or timing or referral or refer or refers or referring).ti,ab. (6410393)

21 ((early or earlie* or late or later or schedul* or hour* or rapid* or fast* or slow* or delay* or immediate* or escalat* or manage* or managing or hospital) adj2 care).ti,ab. (164497)

22 or/19-21 (6529757)

23 13 and 18 and 22 (22088)

24 random:.tw. (1981275)

25 placebo:.mp. (525297)

26 double-blind:.tw. (246172)

27 or/24-26 (2258870)

28 Clinical study/ (163598)

29 Case control study/ (207430)

30 Family study/ (25780)

31 Longitudinal study/ (195601)

32 Retrospective study/ (1486600)

33 comparative study/ (1011881)

34 Prospective study/ (885023)

35 Randomized controlled trials/ (263342)

36 34 not 35 (873914)

37 Cohort analysis/ (1052490)

38 cohort analy$.tw. (19697)

39 (Cohort adj (study or studies)).tw. (473909)

40 (Case control$ adj (study or studies)).tw. (173824)

41 (follow up adj (study or studies)).tw. (74134)

42 (observational adj (study or studies)).tw. (256941)

43 (epidemiologic$ adj (study or studies)).tw. (123101)

44 (cross sectional adj (study or studies)).tw. (342523)

45 case series.tw. (149534)

46 prospective.tw. (1109507)

47 retrospective.tw. (1265556)

48 or/28-33,36-47 (5435680)

49 (sensitiv: or predictive value:).mp. or accurac:.tw. (3212687)

50 27 or 48 or 49 (9573413)

51 23 and 50 (14184)

52 (MEDLINE or pubmed).tw. (415834)

53 exp systematic review/ or systematic review.tw. (521345)

54 meta-analysis/ (297176)

55 intervention$.ti. (267384)

56 or/52-55 (983241)

57 51 not 56 (13580)

58 limit 57 to dc=20151001-20230626 (7890)

59 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5583727)

60 58 not 59 (4657)

61 limit 60 to english language (4411)

62 nonhuman/ not human/ (5327890)

63 61 not 62 (4377)

Database name: CENTRAL

FINAL

#1 MeSH descriptor: [Sepsis] explode all trees 6750

#2 sepsis:ti,ab,kw 13232

#3 MeSH descriptor: [Blood-Borne Pathogens] this term only 36

#4 (blood* near/2 (pathogen* or poison*)):ti,ab,kw 345

#5 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 7318

#6 systemic inflammatory response syndrome*:ti,ab,kw 1683

#7 sirs:ti,ab,kw 863

#8 (septicaemi* or septicemi*):ti,ab,kw 1103

#9 ((septic or cryptic) near/2 shock):ti,ab,kw 3765

#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 6522

#12 (hypotension near/3 induced near/3 hypoperfusion) 1

#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 23469

#14 MeSH descriptor: [Delivery of Health Care] this term only 1343

#15 MeSH descriptor: [Critical Care] this term only 2265

#16 (intensive or critical or ITU or ICU or high dependency* or HDU):ti,ab,kw 85219

#17 (intensivist* or consultant* or specialist* or senior*1 or junior*1 or sho or registrar* or spr or house officer* or houseofficer* or housestaff* or physician* or intern*1 or internship or resident*1 or fellow*1 or foundation doctor or nurs*):ti,ab,kw 113230

#18 #14 or #15 or #16 or #17 187992

#19 MeSH descriptor: [Time Factors] this term only 73006

#20 (time or times or timing or referral or refer or refers or referring):ti,ab,kw 570590

#21 ((early or earlie* or late or later or schedul* or hour* or rapid* or fast* or slow* or delay* or immediate* or escalat* or defer* or initiate* or standby or "stand by" or manage* or managing or hospital) near/2 (care or intervention* or therap* or treatment*)):ti,ab,kw 89260

#22 #19 or #20 or #21 624742

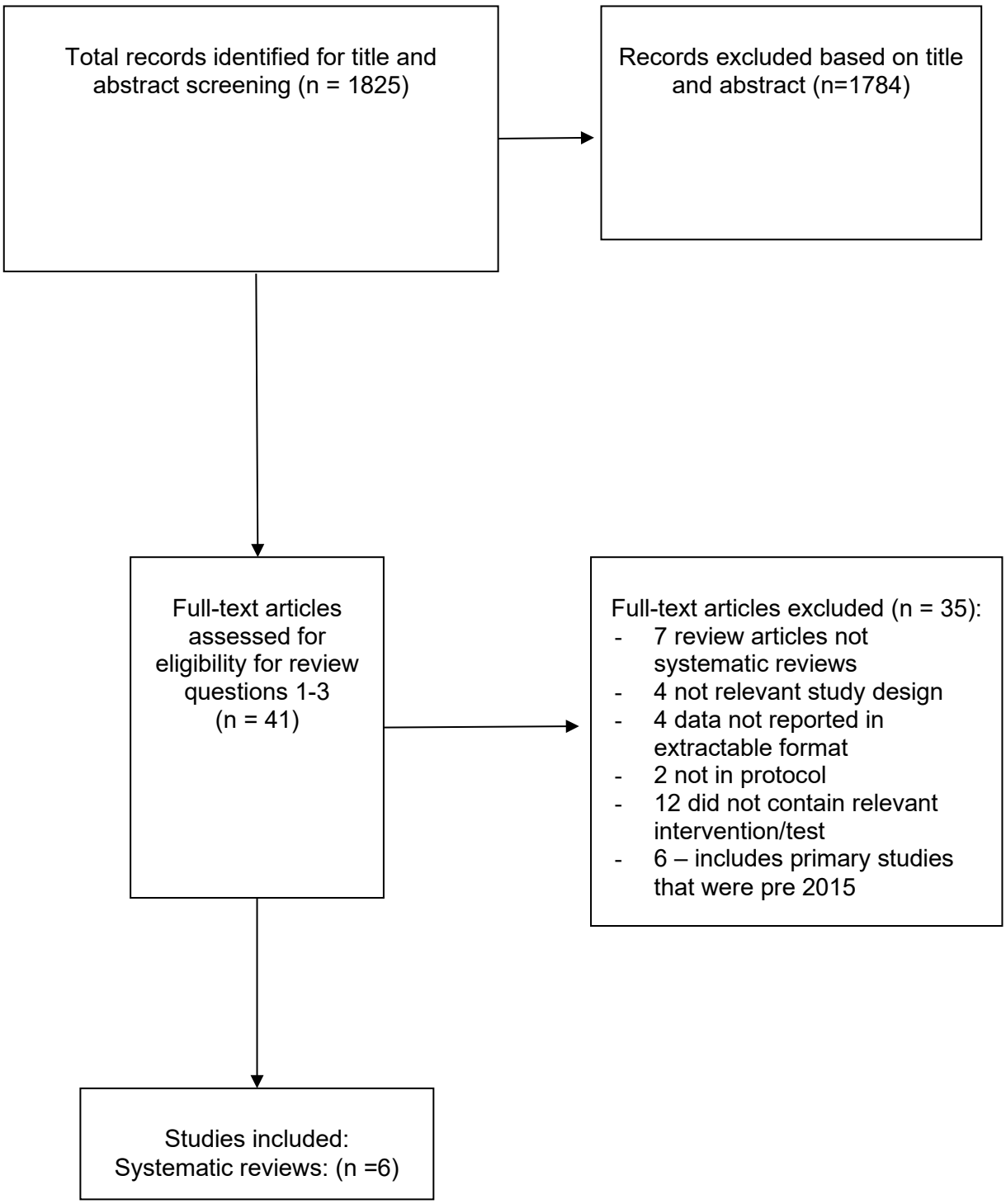
#23 #13 and #18 and #22 3400

#24 "conference":pt or (clinicaltrials or trialsearch):so 687568

#25 #23 not #24 with Publication Year from 2015 to 2023, with Cochrane Library publication date Between Oct 2015 and Jun 2023, in Trials 812

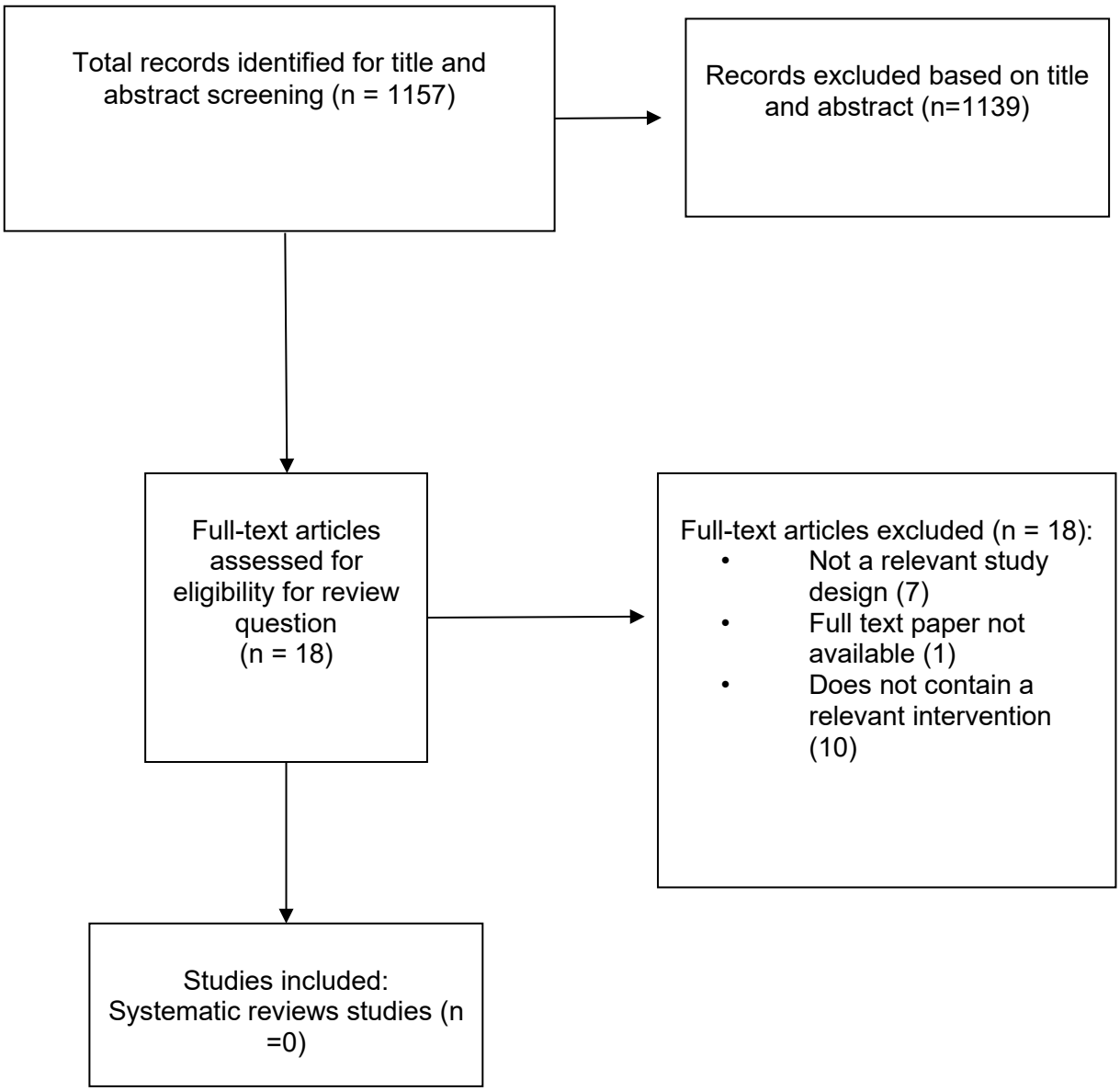
Appendix D –Scoping evidence study selection

- **RQ1-3: Blood tests, lactate and creatinine**

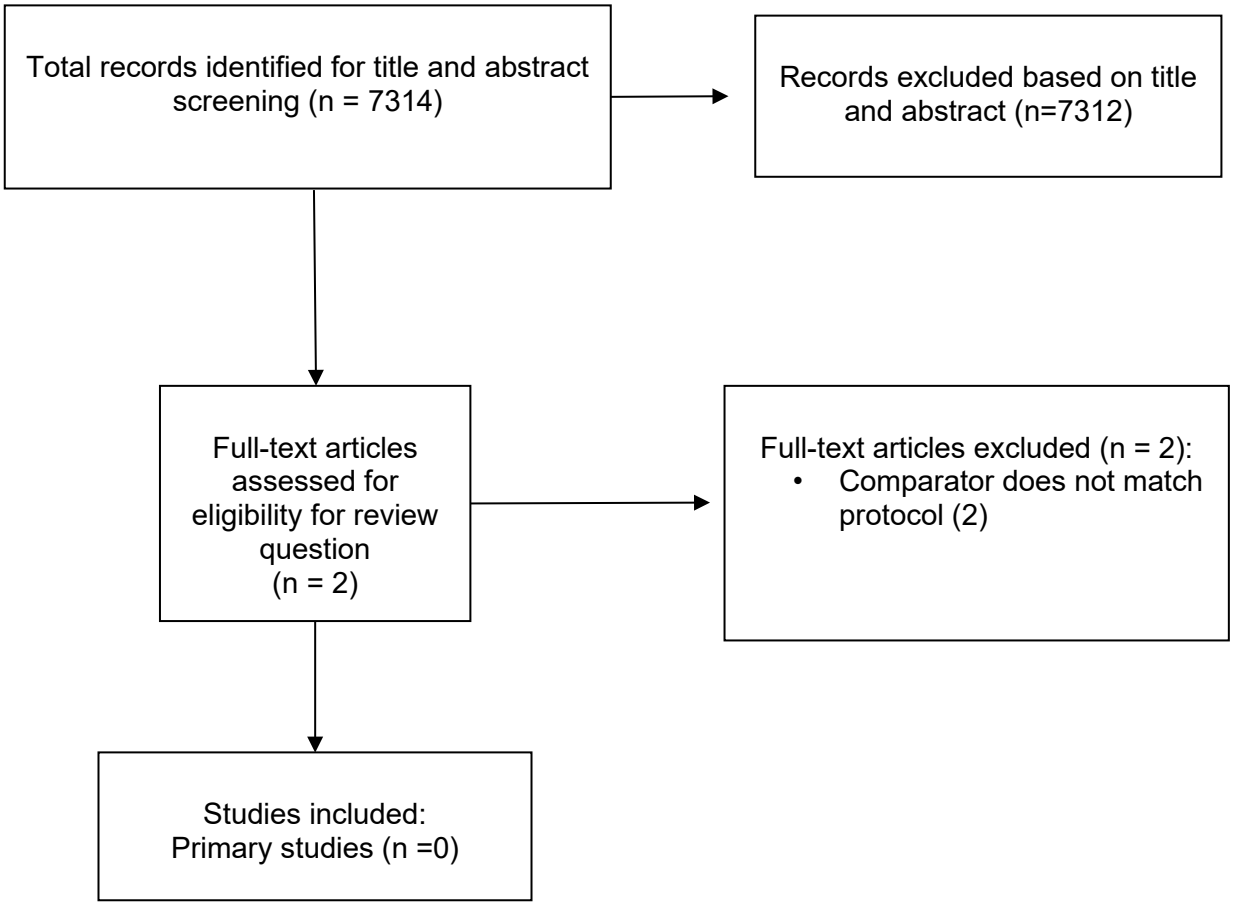


- **RQ 4: Escalation of care**

- **Systematic reviews**



- **Primary studies**



Appendix E – Scoping evidence

Huang, 2023

Bibliographic Reference	Huang, Yu-Hsuan; Chen, Ching-Jung; Shao, Shih-Chieh; Li, Chih-Huang; Hsiao, Chien-Han; Niu, Kuang-Yu; Yen, Chieh-Ching; Comparison of the Diagnostic Accuracies of Monocyte Distribution Width, Procalcitonin, and C-Reactive Protein for Sepsis: A Systematic Review and Meta-Analysis.; Critical care medicine; 2023; vol. 51 (no. 5); e106-e114

Study Characteristics

Study design	Systematic review
Study details	Dates searched Studies published before October 1, 2022 Databases searched PubMed, Embase, and the Cochrane Library Sources of funding No information
Inclusion criteria	Involved adult patients with suspected infection; 2) were conducted in the emergency department (ED), hospital wards, or the ICU; and 3) used monocyte distribution width (MDW)for the detection of sepsis with the Sepsis-2 and Sepsis-3 criteria were further selected.
Exclusion criteria	Case reports, case series, animal studies, paediatric studies, and studies with repeated human subjects
Intervention(s)	MDW, procalcitonin, CRP Comparator diagnostic criteria (Sepsis-2 or Sepsis-3)
Outcome(s)	2×2 table of true-positive, false-positive, true-negative, and false-negative counts—either extracted from the original article or calculated with the reported sensitivity and specificity.
Number of studies included in the systematic review	18 studies
Studies from the systematic review that	Ognibene 2022, Yu 2022, Poz 2022, Hausfater 2021, Woo 2021

are relevant for use in the current scoping review	

Critical appraisal - GDT Crit App - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	High *(The review aimed to identify studies that investigated the index test monocyte distribution width. The review also synthesised the results for C-reactive protein and procalcitonin from these studies, and these synthesis are missing evidence from studies that did not also evaluate monocyte distribution width. This introduces a high risk of bias in relation to study eligibility, identification and selection of studies, and synthesis and findings.)*
Overall study ratings	Applicability as a source of data	Partially applicable *(A comprehensive systematic review was not conducted for the index test of C-reactive protein.)*

Kumar, 2023

Bibliographic Reference	Kumar, Ashwani; Abbenbroek, Brett; Delaney, Anthony; Hammond, Naomi; Grattan, Sarah; Finfer, Simon; Sepsis triggers and tools to support early identification in healthcare settings: An integrative review.; Australian critical care : official journal of the Confederation of Australian Critical Care Nurses; 2023

Study Characteristics

Study design	Systematic review
Study details	Dates searched 1991 to 2020 Databases searched MEDLINE, CINAHL, EMBASE, and Scopus databases and the Cochrane Database of Systematic Reviews. To ensure a comprehensive literature search, relevant grey literature from the WHO, Global Sepsis Alliance, regional and national sepsis agencies, Australian Government

	Department of Health and Ageing, and the Agency for Healthcare Research and Quality and National Health Service (UK) was also reviewed. Sources of funding The George Institute for Global Health was commissioned by the Australian Commission on Safety and Quality in Health Care to conduct this review
Inclusion criteria	(i) study type including systematic reviews, meta-analyses, randomised controlled trials, and cohort studies; (ii) settings including prehospital, ED, acute hospital in-patients, and maternity; (iii) population including adult, paediatric, neonate, and maternal patients; (iv) interventions, i.e., the triggers and tools to identify patients with or at risk of sepsis (Supplementary Table 1); and (v) outcomes including diagnostic accuracy and process of care measures for time to diagnosis and antibiotic treatment and patient outcomes including mortality, clinical deterioration, unplanned ICU admission, and hospital or ICU length of stay
Exclusion criteria	Studies were excluded if judged not applicable to the Australian healthcare system or were not from similar healthcare settings such as the UK, Canada, US, Northern Europe, and high-come countries in Asia and were not in English language.
Intervention(s)	SIRS qSOFA LqSOFA MEWS NEWS Robson Modified Robson BAS 90-30-90 Lactate serum and point of care Biomarkers PCT, CRP, NLCR Electronic health records Sepsis alerts and algorithms
Outcomes	Diagnostic accuracy, time to antibiotics, time to treatment, ease of use, cost, Patient centred - length of stay Patient centred - ICU admission, Patient centred - mortality
Number of studies included in the systematic review	124
Studies from the systematic review that are relevant for use in the current scoping review	Ljungstrom 2017, Visveswari 2019, Karon 2017. Numerous other studies informed the meta-analysis reported by the review authors for C-reactive protein, however the authors did not publish the details of which studies were used for this.

Critical appraisal - GDT Crit App - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	High *(It appears that risk of bias was not assessed by multiple authors. However, this was not judged to be an issue as this does not deviate greatly from NICE processes. Details/study characteristics of a number of studies used to provide data in the meta-analysis for C-reactive protein were not reported however. Some of the data found also did not match what was reported in the primary study)*
Overall study ratings	Applicability as a source of data	Fully applicable

Li, 2022

Bibliographic Reference	Li, Andrew T; Moussa, Anthony; Gus, Eduardo; Paul, Eldho; Yii, Erwin; Romero, Lorena; Lin, Zhiliang Caleb; Padiglione, Alexander; Lo, Cheng Hean; Cleland, Heather; Cheng, Allen C; Biomarkers for the Early Diagnosis of Sepsis in Burns: Systematic Review and Meta-analysis.; Annals of surgery; 2022; vol. 275 (no. 4); 654-662

Study Characteristics

Study design	Systematic review
Study details	Dates searched From inception to February 14, 2020. Databases searched Ovid Medline, Ovid Embase, Ovid EBM Reviews, Cochrane Central Register of Controlled Trials, Biosis Previews, and Web of Science Sources of funding 'There was no funding source for this study.'
Inclusion criteria	Clinical studies of any design that evaluated the diagnostic accuracy of biomarkers in differentiating burns patients with sepsis from burns patients without sepsis (with or without systemic inflammation or multiple organ failure).
Exclusion criteria	Non-English and non-research articles were excluded.

Intervention(s)	The study included as biomarkers any clinical, laboratory, or radiological characteristic that could be objectively measured as an indicator of sepsis, other than vital signs observations (temperature, heart rate, respiratory rate, blood pressure)
Outcome(s)	Diagnostic outcomes were contingency tables (true and false positives and negatives), outcomes derived from these tables (sensitivity, specificity, positive or negative likelihood ratio, positive or negative predictive value, or diagnostic odds ratio), or area under the receiver-operating characteristic curve
Number of studies included in the systematic review	10
Studies from the systematic review that are relevant for use in the current scoping review	Bergquist et al, 2016 Cakir Madenci et al, 2014 Klein et al, 2020 Williams et al, 2018 Wineberg et al, 2020

Critical appraisal - GDT Crit App - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	High *(High risk of bias due to study eligibility criteria and synthesis and findings. Included studies were limited to where reference standard and index test had been measured within 24 hours of each other, and this was not pre-specified in the protocol on Prospero. The number of studies required to conduct a meta-analysis also differed between the protocol on Prospero and the publication. Funnel plots also revealed significant publication bias for white cell count.)*
Overall study ratings	Applicability as a source of data	Partially applicable *(The index tests and reference standards were directly applicable. However, the population was limited to patients with burns. Included studies also included samples from routine testing, as opposed to only those with suspected sepsis. Studies with children were also included, however the meta-analyses appeared to only contain studies with adults or all ages.)*

Tan, 2019

Bibliographic Reference	Tan, Meichun; Lu, Yunxia; Jiang, Hao; Zhang, Liandong; The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: A systematic review and meta-analysis.; Journal of cellular biochemistry; 2019; vol. 120 (no. 4); 5852-5859

Study Characteristics

Study design	Systematic review
Study details	Dates searched Up to April 2017 Databases searched The Cochrane Library, Pubmed, Embase, China National Knowledge Infrastructure, WanFang, Weipu (VIP) ScienceChina, Intute, Springer, Blackwell, Ingenta, Kluwer, OVID, ProQuest, Wiley InterScience, IEEE, EBSCO, ESI, and other databases Sources of funding No details - likely funded by Shanghai Baoshan Traditional Chinese Medicine—Integrated Hospital, Shanghai
Inclusion criteria	(1) clinical trial studies (prospective, retrospective, cross- sectional, and cohort study); (2) the research subjects were adult patients and in the experiment group, the patients were diagnosed with sepsis, severe sepsis, or septic shock; in the control group, the patients were noninfectious origin or a SIRS; (3) diagnostic criteria: the gold diagnostic criteria formulated by ACCP or SCCM; (4) only included English and Chinese articles; (5) obtained the true positive value, false positive values, true negative value, false negative values of procalcitonin and C-reactive protein in the diagnoses of sepsis
Exclusion criteria	1) a repeat of published articles (the content or the result were same); (2) data had obvious mistakes or were incomplete;(3) case report, theoretical research, conference report, systematic review, meta-analysis, expert comment, economic analysis; and (4) the outcomes were not of relevance.
Intervention(s)	procalcitonin and C-reactive protein Comparator: ACCP or SCCM criteria
Outcome(s)	True positive value, false positive values, true negative value, false negative values

Number of studies included in the systematic review	9
Studies from the systematic review that are relevant for use in the current scoping review	Hongxiang Li 2014 B Jamali 2013 Gian Paolo Castelli 2004 Karin SR Massaro 2007 Longxiang Su 2012 Kundan Kumar 2014 Fabian A Jamies 2013 Yi Yang 2016 Ozlem Cakir Madenci 2014

Critical appraisal - GDT Crit App - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	High *(The review is at high risk of bias due to study eligibility, data collection and study appraisal, and synthesis and findings, and it unclear whether identification and selection of results is a source of bias. Eligible studies had to have data for index tests procalcitonin AND C-reactive protein. This means that studies that only studied one of these index tests would have been excluded. All included studies had data for both procalcitonin and C-reactive protein. There was no evidence of a published protocol. The publication states that databases were searched using index words. However, no further details were provided about the search strategy. It also appears that the review may not have used additional methods of identifying evidence in addition to database searching, as the PRISMA flow did not show that any additional references were identified from other sources. It appears that risk of bias was not assessed for primary publications. The methods described that likelihood*

Section	Question	Answer
		ratios would be calculated, however, these were not reported for CRP.)
Overall study ratings	Applicability as a source of data	Partially applicable *(The population was patients who were diagnosed with sepsis, severe sepsis, or septic shock as opposed to those with suspected sepsis.)*

Wu, 2017

Bibliographic Reference	Wu, C.-C.; Lan, H.-M.; Han, S.-T.; Chaou, C.-H.; Yeh, C.-F.; Liu, S.-H.; Li, C.-H.; Blaney, G.N.; Liu, Z.-Y.; Chen, K.-F.; Comparison of diagnostic accuracy in sepsis between presepsin, procalcitonin, and C-reactive protein: a systematic review and meta-analysis; Annals of Intensive Care; 2017; vol. 7 (no. 1); 91

Study Characteristics

Study design	Systematic review
Study details	Dates searched until January 2017 Databases searched PubMed and EMBASE Sources of funding The study was supported by the National Science Council and Chang Gung Memorial Hospital in Taiwan (106-2314-B-182-028, CRRPG2B0125, CIR- PG2E0022, CMRPG3F1851, and CMRPG2D0012).
Inclusion criteria	(1) sepsis-related studies; (2) diagnostic instead of prognostic studies: i.e. diagnosing sepsis instead of predicting mortality; and (3) articles in English.
Exclusion criteria	(1) non-sepsis-related studies; (2) non-diagnostic studies; (3) non-original studies: e.g. literature review, editorial piece; (4) studies with no performance parameters given (i.e. sensitivity, specifcity and 2 × 2 contingency tables); and (5) non-blood specimen.
Intervention(s)	Intervention: Presepsin, PCT, and CRP

	Comparator: ACCP/SCCM / Sepsis 3 / ABA / SSIDCM / Blood Culture
Outcome(s)	Sensitivity / Specificity / 2x2 contingency table
Number of studies included in the systematic review	18
Studies from the systematic review that are relevant for use in the current scoping review	Brenner 2014 Romualdo 2014 Kweon 2014 Madenci 2014 Godnic 2015 Takahashi 2015 Romualdo 2016

Critical appraisal - GDT Crit App - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	High *(The review aimed to identify studies that investigated the index test presepsin. The review also synthesised the results for C-reactive protein and procalcitonin from these studies, and these syntheses are missing evidence from studies that did not also evaluate presepsin. This introduces a high risk of bias in relation to study eligibility, identification and selection of studies, and synthesis and findings)*
Overall study ratings	Applicability as a source of data	Partially applicable *(A comprehensive systematic review was not conducted for the index test of C-reactive protein)*

Yeh, 2019

Bibliographic Reference	Yeh, Chun-Fu; Wu, Chin-Chieh; Liu, Su-Hsun; Chen, Kuan-Fu; Comparison of the accuracy of neutrophil CD64, procalcitonin, and C-reactive protein for sepsis identification: a systematic review and meta-analysis.; Annals of intensive care; 2019; vol. 9 (no. 1); 5

Study Characteristics

Study design	Systematic review
Study details	Dates searched Up to July 2017 Databases searched PubMed and Embase Sources of funding The study was supported by the Ministry of Science and Technology and Chang Gung Memorial Hospital in Taiwan (107-2314-B-182-052-MY2, 106-2314-B-182-028, CMRPG2H0311, CMRPG2H0321, CIRPD1D0031 and CLRPG2C0024).
Inclusion criteria	(1) original, (2) dealt with the diagnostic accuracy of neutrophil CD64 for sepsis (3), included adult patients, and (4) written in English
Exclusion criteria	(1) insufficient information to construct a 2×2 contingency table; (2) a duplicated study; (3) prognosis based on the prediction of mortality from sepsis; and (4) a review article, conference paper, or case report.
Intervention(s)	Intervention CD64, CRP and PCT Comparator Sepsis 2 criteria
Outcome(s)	Diagnostic accuracy data - 2x2 contingency / sensitivity / specificity
Number of studies included in the systematic review	14
Studies from the systematic	Davis 2006

review that are relevant for use in the current scoping review	Dimoula 2014 Righi 2014 Godnic 2015 Bauer 2016 Muzlovic 2016

Critical appraisal - GDT Crit App - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	High *(The review aimed to identify studies that investigated the index test neutrophil CD64. The review also synthesised the results for C-reactive protein and procalcitonin from these studies, and these syntheses are missing evidence from studies that did not also evaluate neutrophil CD64. This introduces a high risk of bias in relation to study eligibility, identification and selection of studies, and synthesis and findings.)*
Overall study ratings	Applicability as a source of data	Partially applicable *(A comprehensive systematic review was not conducted for the index test of C-reactive protein)*

Appendix F – committee survey and results

Section 1.10 – High risk of severe illness or death from sepsis

Rec	Original recommendation wording	Proposed revised recommendation wording	Agree	Questions from survey	Summary of suggested changes / response to questions
1.10.1 (was 1.6.1)	For people aged 16 or over with suspected sepsis and 1 or more high risk criteria: arrange for the senior clinical decision maker to immediately assess the person's condition and think about alternative diagnoses to sepsis carry out a venous blood test for the following: ○ blood gas including glucose and lactate measurement ○ blood culture ○ full blood count ○ C-reactive protein ○ urea and electrolytes ○ creatinine ○ a clotting screen	For people aged 16 or over with suspected sepsis and a high risk of severe illness or death from sepsis: arrange for the senior clinical decision maker to immediately assess the person's condition and think about alternative diagnoses to sepsis carry out a venous blood test for the following: ○ blood gas including glucose and lactate measurement ○ blood culture ○ full blood count ○ C-reactive protein ○ urea and electrolytes ○ creatinine ○ a clotting screen	8/9		Committee suggested the following additions/amendments: • Do we need the line 'and think about alternative diagnosis' ? • Need to consider what needs to be done for the critically ill septic patient and not just 'is it something else' e.g., diagnostics for source identification, need to push for urgent source control. • Do we need to add eGFR? • Change immediately to 'promptly'. • Should be c-reactive protein OR procalcitonin.

	give antibiotics in line with recommendations 1.10.2 and 1.10.3 and the recommendations on choice of antibiotic therapy, in this guideline discuss with an appropriate consultant (this may be the consultant under whom the patient is admitted or a consultant covering acute medicine, anaesthetics).	give antibiotics in line with recommendations 1.10.2 and 1.10.3 and the recommendations on choice of antibiotic therapy, in this guideline discuss with an appropriate consultant (this may be the consultant under whom the patient is admitted or a consultant covering acute medicine, anaesthetics).			• Liver function tests • Urine MC&S, antigen testing, respiratory PCR • Consider need for urgent imaging • Change anaesthetics to 'critical care' (in relation to discussion with consultant) • Add in surgeon (in relation to discussion with consultant)
				Can we make the actions in this recommendation clearer to aid implementation? *Is there a clear gradation between the senior clinical decision maker and the consultant and do both need to be involved.*	Summary of responses: - There is a clear distinction between senior clinical decision maker and consultant. Senior clinical decision maker will be ST3 or ST4 and above *(state this in recommendations?)* - they will then need to discuss with a consultant.
1.10.4 (was 1.6.2)	For people aged 16 or over with suspected sepsis, any high risk criteria, and **either** lactate over 4 mmol/litre **or** systolic blood pressure less than 90 mmHg:	For people aged 16 or over with suspected sepsis, a high risk of severe illness or death from sepsis, and **either** lactate over 4 mmol/litre	8/9		Committee suggested the following additions/amendments:

	give intravenous fluid bolus without delay (within 1 hour of identifying that they are high risk of severe illness or death from sepsis) in line with recommendations on intravenous fluids for people with suspected sepsis, in this guideline **and** refer to critical care specialist or team for them to review the management of the person's condition, including their need for central venous access and initiation of inotropes or vasopressors. Referral may be a formal referral process or discussion with specialist in intensive care or intensive care outreach team.	**or** systolic blood pressure less than 90 mmHg: give intravenous fluid bolus without delay (within 1 hour of identifying that they are high risk of severe illness or death from sepsis) in line with recommendations on intravenous fluids for people with suspected sepsis, in this guideline **and** refer to critical care specialist or team for them to review the management of the person's condition, including their need for central venous access and initiation of inotropes or vasopressors. Referral may be a formal referral process or discussion with specialist in intensive care or intensive care outreach team.			• Many patients – especially young ones - have a systolic BP <90 and why wait until the lactate is >4? Isn't 3.9 mmol/l bad enough? • Change to any patient with evidence of organ hypoperfusion (features include e.g. hypotension ± tachycardia ± tachypnoea ± raised lactate ± oliguria ± altered conscious state ± peripheral shutdown) where intravascular fluid overload/severe heart failure can be excluded • The population I see most commonly with hypotension is older people with heart failure. If people are conscious and able to be encouraged/supported to drink, how strong is the evidence to give additional fluids? • 'Within 1 hour' - should be changed to 'promptly' or 'urgently'. • Would not say 'and' refer to critical care immediately. Suggest change to 'if patient not responding quickly to initial intervention, call critical care team".

				Systolic blood pressure already contributes to the NEWS2 score, so would taking it into account again here be taking it into account twice? Or is it right to give this parameter a double weight?	Summary of responses: 3 committee members felt that BP <90 should be kept in at this point due to it's importance as a sign of organ dysfunction, and that BP could be normal when NEWS 2 score has previously been assessed as high. 1 member was not as convinced it needed to be given double weight.
1.10.5 was 1.6.3	For people aged 16 or over with suspected sepsis, any high-risk criteria and lactate between 2 and 4 mmol/litre, give an intravenous fluid bolus without delay (within 1 hour of identifying that they meet any high-risk criteria in an acute hospital setting) in line with recommendations on intravenous fluids for people with suspected sepsis, in this guideline	For people aged 16 or over with suspected sepsis, a high risk of severe illness or death from sepsis and lactate between 2 and 4 mmol/litre, give an intravenous fluid bolus without delay (within 1 hour of identifying that they are at high risk of severe illness or death from sepsis in an acute hospital setting) in line with recommendations on intravenous fluids for people with suspected sepsis, in this guideline.	8/9		One member suggested this recommendation can be removed as it's covered by 1.10.1 above. The fluid guideline suggests a small-ish bolus of fluid (250-500 ml) and then to review the patient to see if they need more.
1.10.6 was 1.6.4	For people aged 16 or over with suspected sepsis, any high risk criteria and lactate below 2 mmol/litre, consider giving an	For people aged 16 or over with suspected sepsis, a high risk of severe illness or death from sepsis and lactate below 2 mmol/litre,	8/9		One member suggested this recommendation can be removed this as it's covered by 1.10.1.

	intravenous fluid bolus (in line with recommendations on intravenous fluids for people with suspected sepsis, in this guideline).	consider giving an intravenous fluid bolus (in line with recommendations on intravenous fluids for people with suspected sepsis, in this guideline).			
1.10.7 was 1.6.5	Monitor people aged 16 or over who meet any high-risk criteria continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all adult patients. [This recommendation is adapted from NICE's guideline on acutely ill patients in hospital.]	Monitor people aged 16 or over who are at high risk of severe illness or death from sepsis continuously, or a minimum of once every 30 minutes depending on setting. Physiological track and trigger systems should be used to monitor all adult patients. [This recommendation is adapted from NICE's guideline on acutely ill patients in hospital.]	7/9		2 members felt we could remove 'physiological track and trigger systems' and change to NEWS 2
1.10.8 was 1.6.6	Monitor the mental state of people aged 16 or over with suspected sepsis. Consider using a scale such as the Glasgow Coma Scale (GCS) or AVPU ('alert, voice, pain, unresponsive') scale.	N/A		*The population in this recommendation isn't defined by risk. Is the action relevant to people at high risk of illness or death from sepsis only?*	Summary of comments: 2 members felt that monitoring mental state in the population was relevant to all risk groups and specifically important for higher risk. 3 members pointed out that AVPU is already a component of NEWS 2, and therefore this recommendation can be removed.

1.10.9 was 1.6.7	Alert a consultant to attend in person if a person aged 16 years or over with suspected sepsis and any high-risk criteria does not respond within 1 hour of initial antibiotic, intravenous fluid resuscitation, or both. Not responding is indicated by any of: systolic blood pressure persistently below 90 mmHg reduced level of consciousness despite resuscitation respiratory rate over 25 breaths per minute or a new need for mechanical ventilation lactate not reduced by more than 20% of initial value within 1 hour.	Alert a consultant to attend in person if a person aged 16 years or over with suspected sepsis and a high risk of severe illness or death from sepsis does not respond within 1 hour of initial antibiotic, intravenous fluid resuscitation, or both. Not responding is indicated by any of: systolic blood pressure persistently below 90 mmHg reduced level of consciousness despite resuscitation respiratory rate over 25 breaths per minute or a new need for mechanical ventilation lactate not reduced by more than 20% of initial value within 1 hour.	8/9		One member suggested this recommendation can be removed as it is covered by 1.10.1.

Section 1.11 – Moderate risk of severe illness or death from sepsis

Rec	Original recommendation wording	Proposed revised recommendation wording	Agree	Question for committee	Summary of comments and responses to questions

1.11.1 was 1.6.8	For people aged 16 or over with suspected sepsis and **either** a 2 or more moderate- to high-risk criteria **or** systolic blood pressure 91 to 100 mmHg, carry out a venous blood test for the following: blood gas, including glucose and lactate measurement blood culture full blood count C-reactive protein urea and electrolytes creatinine Arrange for a clinician to review the person's condition and venous lactate results within 1 hour of meeting criteria. A 'clinician' should be a medically qualified practitioner or equivalent who has antibiotic prescribing responsibilities.	For people aged 16 or over with suspected sepsis and a moderate risk of severe illness or death from sepsis **or** systolic blood pressure 91 to 100 mmHg, carry out a venous blood test for the following: blood gas, including glucose and lactate measurement blood culture full blood count C-reactive protein urea and electrolytes creatinine Arrange for a clinician to review the person's condition and venous lactate results within 1 hour of meeting criteria. A 'clinician' should be a medically qualified practitioner or equivalent who has antibiotic prescribing responsibilities.	7/9		One member suggests that moderate still places people at risk of further deterioration, so same thought processes as in 1.10.1 apply but have a bit more time afforded. They would also recommend the same interactions as 1.10.1 but can be slightly slower • treatment (fluid, oxygen etc) should be ideally instituted promptly – if hypoxaemic give oxygen etc) , • an ST3 or above should then see them within 1-2 hours and a decision on a/b can be made within this time period or - if uncertain they have sepsis - within 3 hours (need to stress these are maxima and there should not be reasons for avoidable delay). • Treatment plan should be reviewed and escalated promptly if deteriorating or failing to improve.

				Is this (blood pressure) redundant? Systolic blood pressure already contributes to the NEWS2 score, so would taking it into account again here be taking it into account twice? Or is it right to give this parameter a double weight?	Summary of comments: Two members felt keeping this in was important for the reasons they previously outlined in 1.10.4, one member felt this could be removed as blood score from NEWS 2 can be used.
				Blood test list is the same as for high risk but is missing clotting screen. Should clotting screen be included here or is not something you'd do for those at moderate risk?	Summary of comments: One member would not recommend taking a clotting screen in those at moderate risk. One member would and one member suggests doing exactly the same tests as highlighted (and further suggested) in 1.10.1 - to diagnose infection (including source identification) or other causes, and do tests to look at organ function.
1.11.4 was 1.6.9	For people aged 16 or over with suspected sepsis who meet 2 or more moderate- to high-risk criteria and have **either** lactate	For people aged 16 or over with suspected sepsis who are at moderate risk of severe illness or death from sepsis and have **either**	8/9		One member suggests removing this recommendation

	over 2 mmol/litre **or** evidence of acute kidney injury, treat their condition as if they were at high risk of severe illness or death from sepsis. For definition of acute kidney injury, see NICE's guideline on acute kidney injury.	lactate over 2 mmol/litre **or** evidence of acute kidney injury, treat their condition as if they were at high risk of severe illness or death from sepsis. For definition of acute kidney injury, see NICE's guideline on acute kidney injury.			
1.11.5 was 1.6.10	For people aged 16 or over with suspected sepsis who meet 2 or more moderate- to high-risk criteria, have lactate of less than 2 mmol/litre and no evidence of acute kidney injury, and in whom a definitive condition cannot be identified: repeat structured assessment at least hourly ensure a senior clinical decision maker reviews the person's condition and need for antibiotics within 3 hours of meeting 2 or more moderate- to high-risk criteria.	For people aged 16 or over with suspected sepsis who are at moderate risk of severe illness or death from sepsis, have lactate of less than 2 mmol/litre and no evidence of acute kidney injury, and in whom a definitive condition cannot be identified: repeat structured assessment at least hourly ensure a senior clinical decision maker reviews the person's condition and need for antibiotics within 3 hours of identifying that they are at moderate risk of severe illness or death from sepsis.	8/9		One member suggests removing this recommendation
1.11.6 was 1.6.11	For people aged 16 years or over with suspected sepsis who meet 2 or more moderate- to high-risk criteria, have lactate of	For people aged 16 years or over with suspected sepsis who are at moderate risk of severe illness or death from sepsis, have lactate of	8/9		One member suggests removing this recommendation based on the rationale that if someone is at moderate risk of dying (according to the new risk strata),

	less than 2 mmol/litre and no evidence of acute kidney injury, and in whom a definitive condition or infection can be identified and treated: manage the definitive condition if appropriate, discharge with information depending on the setting (see information at discharge for people assessed for suspected sepsis but not diagnosed with sepsis).	less than 2 mmol/litre and no evidence of acute kidney injury, and in whom a definitive condition or infection can be identified and treated: manage the definitive condition if appropriate, discharge with information depending on the setting (see information at discharge for people assessed for suspected sepsis but not diagnosed with sepsis).			they are not going to be/shouldn't be discharged.

Section 1.12 – Low risk of severe illness or death from sepsis

Rec	Original recommendation wording	Proposed revised recommendation wording	Agree	Question for committee	Summary of comments and responses to questions
1.12.1 was 1.6.12	For people aged 16 or over with suspected sepsis who meet only 1 moderate- to high-risk criterion: arrange clinician review within 1 hour of meeting criterion for clinical assessment perform blood tests if indicated.	For people aged 16 or over with suspected sepsis and a low risk of severe illness or death from sepsis: arrange clinician review within 1 hour of meeting criterion for clinical assessment perform blood tests if indicated. A 'clinician' should be a medically qualified practitioner	8/9		One committee member suggests: - clinician review and blood tests within 3 hours - escalate if cause for concern (e.g. patient looks unwell, deteriorating) - Blood and other lab tests – wouldn't mandate all blood tests be done as above but should use discretion/common sense – 'tests as indicated.' - Treatment plan – 3-hour window is a maxima for antibiotics.

	A 'clinician' should be a medically qualified practitioner or equivalent who has antibiotic prescribing responsibilities.	or equivalent who has antibiotic prescribing responsibilities.			- Fluid, oxygen etc should be given sooner as indicated by markers of tissue hypoperfusion. - Imaging as indicated by clinical exam/ lab results - Failure to improve or worsening should direct prompt review by ST3 or above who should, if appropriate, contact consultant and/or critical care team
1.12.3 was 1.6.14	For people aged 16 or over with suspected sepsis who meet only 1 moderate- to high-risk criterion, have lactate of less than 2 mmol/litre and no evidence of acute kidney injury, and in whom a definitive condition cannot be identified: repeat structured assessment at least hourly ensure a senior clinical decision maker reviews the person's condition and need for antibiotics within 3 hours of meeting moderate to high criterion.	For people aged 16 or over with suspected sepsis who are at low risk of severe illness or death from sepsis, have lactate of less than 2 mmol/litre and no evidence of acute kidney injury, and in whom a definitive condition cannot be identified: repeat structured assessment at least hourly ensure a senior clinical decision maker reviews the person's condition and need for antibiotics within 6 hours of identifying that they are at low risk of severe illness or death from sepsis.	9/9	*We suggest changing this from 3 hours to 6 hours to make the action internally consistent with the phase 1 work and to align with AoMRC.*	One committee member commented that this should be similar to 1.12.1 but less rush to see patient, do blood tests, imaging etc. Two committee members questioned the wording of repeated assessments hourly, as this does not align with AoMRC recommendations for a NEWS score of 0-4. 6 hours is the maximum window for antibiotic… doesn't mean they don't need fluid, oxygen sooner.

1.12.4 was 1.6.13	For people aged 16 or over with suspected sepsis who meet only 1 moderate- to high-risk criterion and in whom a definitive condition can be identified and treated: manage the definitive condition if appropriate, discharge with information depending on setting (see recommendations on information at discharged for people assessed for suspected sepsis but not diagnosed with sepsis).	For people aged 16 or over with suspected sepsis who are at low risk of severe illness or death from sepsis and in whom a definitive condition can be identified and treated: manage the definitive condition if appropriate, discharge with information depending on setting (see recommendations on information at discharged for people assessed for suspected sepsis but not diagnosed with sepsis).	9/9		

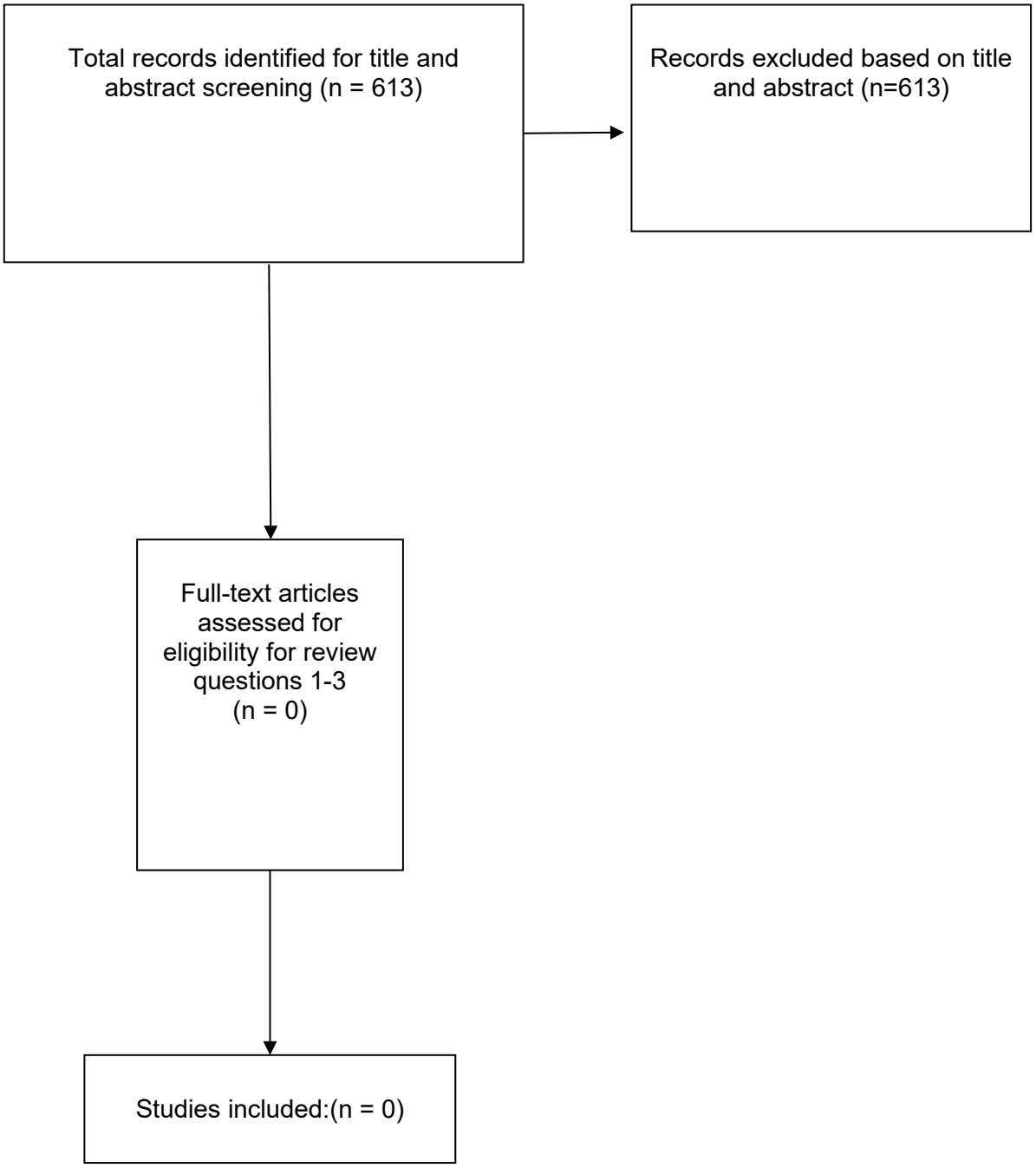
Section 1.13 - Very low risk of severe illness or death from sepsis

Rec	Original recommendation wording	Proposed revised recommendation wording	Agree	Question for committee	Summary of comments and responses to questions
1.13.1 was 1.6.15	Arrange clinical assessment of people aged 16 years or over who have suspected sepsis and do not meet any high-risk or moderate- to high-risk criteria, and use clinical judgement to manage their condition.	Arrange clinical assessment of people aged 16 years or over with suspected sepsis and a very low risk of severe illness or death from sepsis, and use clinical judgement to manage their condition. Clinical assessment should be	8/9		One committee member stated this was confusing – 'I don't think this would be able to be applied to the ambulance.'

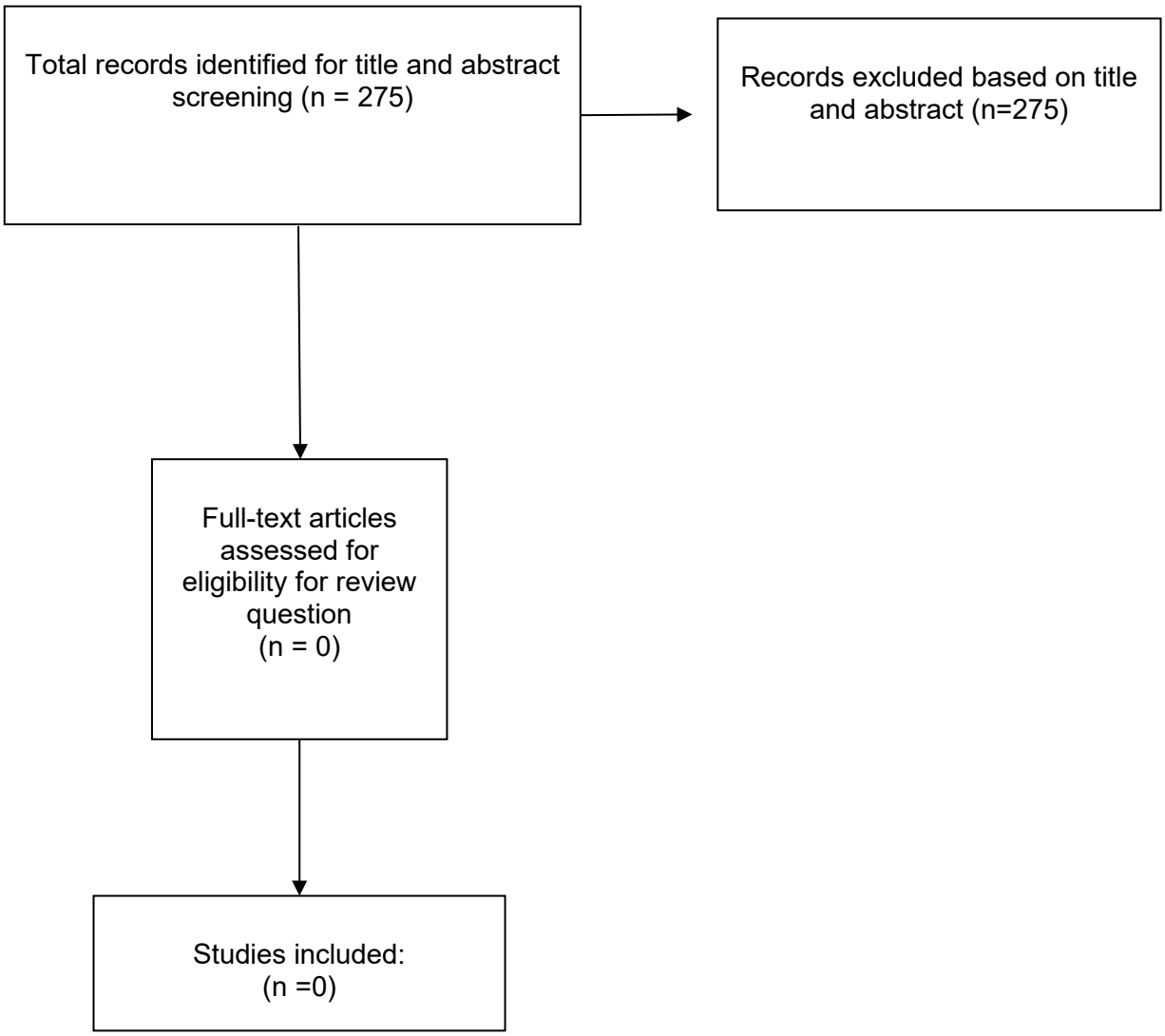
	Clinical assessment should be carried out by a medically qualified practitioner or equivalent who has antibiotic prescribing responsibilities.	carried out by a medically qualified practitioner or equivalent who has antibiotic prescribing responsibilities.			

Appendix G – Economic evidence study selection

- **RQ1-3: Blood tests, lactate and creatinine**



- **RQ 4: Escalation of care**



Appendix H – Economic evidence tables

No studies were identified for these reviews.

Appendix I – Excluded studies

Blood tests, lactate, and creatinine: excluded studies

Study	Reason for exclusion
Ahn, Chiwon, Kim, Wonhee, Lim, Tae Ho et al. (2018) The delta neutrophil index (DNI) as a prognostic marker for mortality in adults with sepsis: a systematic review and meta-analysis. Scientific reports 8(1): 6621	- Study does not contain a relevant intervention *DNI not the same as Immature to Total Neutrophil Ratio (I/T ratio)*
Al-Ashry, Haitham, Abuzaid, Ahmed, Asim, Mohammad et al. (2016) Microcirculation Alteration and Biomarker Dilemma in Early Septic Shock Diagnosis and Treatment. Current vascular pharmacology 14(4): 330-44	- Review article but not a systematic review
Beckmann, Nadine, Salyer, Christen E, Crisologo, Peter A et al. (2020) Staging and Personalized Intervention for Infection and Sepsis. Surgical infections 21(9): 732-744	- Review article but not a systematic review
Buehler, Stephanie S, Madison, Bereneice, Snyder, Susan R et al. (2016) Effectiveness of Practices To Increase Timeliness of Providing Targeted Therapy for Inpatients with Bloodstream Infections: a Laboratory Medicine Best Practices Systematic Review and Meta-analysis. Clinical microbiology reviews 29(1): 59-103	- Study does not contain a relevant intervention
Catenacci, Vanessa, Sheikh, Fatima, Patel, Kush et al. (2022) The prognostic utility of protein C as a biomarker for adult sepsis: a systematic review and meta-analysis. Critical care (London, England) 26(1): 21	- Study does not contain a relevant intervention
Chen, Kuan-Fu, Chaou, Chung-Hsien, Jiang, Jing-Yi et al. (2016) Diagnostic Accuracy of Lipopolysaccharide-Binding Protein as Biomarker for Sepsis in Adult Patients: A Systematic Review and Meta-Analysis. PloS one 11(4): e0153188	- Study does not contain a relevant intervention
D'Onofrio, Valentino, Salimans, Lene, Bedenic, Branka et al. (2020) The Clinical Impact of Rapid Molecular Microbiological Diagnostics for Pathogen and Resistance Gene Identification in Patients With Sepsis:	- Study does not contain a relevant intervention

Study	Reason for exclusion
A Systematic Review. Open forum infectious diseases 7(10): ofaa352	
de Oliveira, Vanessa Martins, Moraes, Rafael Barberena, Stein, Airton Tetelbom et al. (2017) Accuracy of C - Reactive protein as a bacterial infection marker in critically immunosuppressed patients: A systematic review and meta-analysis. Journal of critical care 42: 129-137	- Includes primary studies that are pre 2015
Dixon, P, Davies, P, Hollingworth, W et al. (2015) A systematic review of matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry compared to routine microbiological methods for the time taken to identify microbial organisms from positive blood cultures. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 34(5): 863-76	- Study does not contain a relevant intervention
Gale, Bryan M and Hall, Kendall K (2020) The Use of Patient Monitoring Systems to Improve Sepsis Recognition and Outcomes: A Systematic Review. Journal of patient safety 16(3ssuppl1): 8-s11	- Study does not contain a relevant intervention
Gatti, Milo, Bonazzetti, Cecilia, Tazza, Beatrice et al. (2023) Impact on clinical outcome of follow-up blood cultures and risk factors for persistent bacteraemia in patients with gram-negative bloodstream infections: a systematic review with meta-analysis. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases	- Not a relevant study design *Does not contain diagnostic studies/data on blood cultures*
Gill, Angus, Ackermann, Khalia, Hughes, Clifford et al. (2022) Does lactate enhance the prognostic accuracy of the quick Sequential Organ Failure Assessment for adult patients with sepsis? A systematic review. BMJ open 12(10): e060455	- Not in protocol
Gu, Wan-Jie; Zhang, Zhongheng; Bakker, Jan (2015) Early lactate clearance-guided therapy in patients with sepsis: a meta-analysis with trial sequential analysis of	- Study does not contain a relevant intervention

Study	Reason for exclusion
randomized controlled trials. Intensive care medicine 41(10): 1862-3	*Not a systematic review of diagnostic/prognostic capability of lactate - rather the effectiveness of lactate guided therapy*
Huang, Zhiwei, Fu, Zhaoyin, Huang, Wujun et al. (2020) Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: A meta-analysis. The American journal of emergency medicine 38(3): 641-647	- Data not reported in an extractable format *Does not include diagnostic accuracy measures as specified in protocol*
Khodashahi, Rozita and Sarjamee, Soroush (2020) Early lactate area scores and serial blood lactate levels as prognostic markers for patients with septic shock: a systematic review. Infectious diseases (London, England) 52(7): 451-463	- Data not reported in an extractable format *Diagnostic accuracy data not presented*
Li, Yuting, Guo, Jianxing, Yang, Hongmei et al. (2021) Comparison of culture-negative and culture-positive sepsis or septic shock: a systematic review and meta-analysis. Critical care (London, England) 25(1): 167	- Data not reported in an extractable format *diagnostic accuracy data not presented*
Liu, G., Lv, H., An, Y. et al. (2017) Early actate levelsfor prediction of mortality in patients with sepsis or septic shock: A meta-analysis. International Journal of Clinical and Experimental Medicine 10(1): 37-47	- Includes primary studies that are pre 2015
Liu, Y, Hou, JH, Li, Q et al. (2016) Biomarkers for diagnosis of sepsis in patients with systemic inflammatory response syndrome: a systematic review and meta-analysis. SpringerPlus 5(1): 2091	- Includes primary studies that are pre 2015
Morris, Elizabeth, McCartney, David, Lasserson, Daniel et al. (2017) Point-of-care lactate testing for sepsis at presentation to health care: a systematic review of patient outcomes. The British journal of general practice : the journal of the Royal College of General Practitioners 67(665): e859-e870	- Includes primary studies that are pre 2015
Pan, Jianzhen, Peng, Milin, Liao, Chao et al. (2019) Relative efficacy and safety of early lactate clearance-guided therapy	- Data not reported in an extractable format *Diagnostic accuracy data not in study*

Study	Reason for exclusion
resuscitation in patients with sepsis: A meta-analysis. Medicine 98(8): e14453	
Peksoz, Rifat, Agirman, Enes, Senturk, Fuat et al. (2022) A Focus on Intra-Abdominal Sepsis with Biomarkers: A Literature Review. The Eurasian journal of medicine 54(suppl1): 66-70	- Review article but not a systematic review
Peri, Anna Maria; Harris, Patrick N A; Paterson, David L (2022) Culture-independent detection systems for bloodstream infection. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 28(2): 195-201	- Study does not contain a relevant intervention
Prasad, Priya A, Shea, Erica R, Shiboski, Stephen et al. (2017) Relationship Between a Sepsis Intervention Bundle and In-Hospital Mortality Among Hospitalized Patients: A Retrospective Analysis of Real-World Data. Anesthesia and analgesia 125(2): 507-513	- Not a relevant study design
Póvoa, P and Coelho, L (2021) Which Biomarkers Can Be Used as Diagnostic Tools for Infection in Suspected Sepsis?. Seminars in respiratory and critical care medicine 42(5): 662-671	- Review article but not a systematic review
Russell, Clark D, Parajuli, Arun, Gale, Hugo J et al. (2019) The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: A systematic review and meta-analysis. The Journal of infection 78(5): 339-348	- Study does not contain a relevant intervention *NLR, LMR and PLR not listed in protocol*
Stevenson, Matt, Pandor, Abdullah, Martyn-St James, Marrissa et al. (2016) Sepsis: the LightCycler SeptiFast Test MGRADE R, SepsiTest TM and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi - a systematic review and economic evaluation. Health technology assessment (Winchester, England) 20(46): 1-246	- Study does not contain a relevant intervention
Sungkar, Yasmin; Considine, Julie; Hutchinson, Anastasia (2018)	- Not a relevant study design

Study	Reason for exclusion
Implementation of guidelines for sepsis management in emergency departments: A systematic review. Australasian emergency care 21(4): 111-120	*SR but not of diagnostic or prognostic accuracy*
Ticinesi, A., Lauretani, F., Nouvenne, A. et al. (2017) C-reactive protein (CRP) measurement in geriatric patients hospitalized for acute infection. European Journal of Internal Medicine 37: 7-12	- Review article but not a systematic review
Tong-Minh, Kirby, Welten, Iris, Endeman, Henrik et al. (2021) Predicting mortality in adult patients with sepsis in the emergency department by using combinations of biomarkers and clinical scoring systems: a systematic review. BMC emergency medicine 21(1): 70	- Includes primary studies that are pre 2015 *Studies including data on relevant ref standard/index test are pre 2015*
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	- Review article but not a systematic review *Not a systematic review of diagnostic accuracy studies*
Watkins, Richard R; Bonomo, Robert A; Rello, Jordi (2022) Managing sepsis in the era of precision medicine: challenges and opportunities. Expert review of anti-infective therapy 20(6): 871-880	- Review article but not a systematic review
Yoon, S H, Choi, B, Eun, S et al. (2022) Using the lactate-to-albumin ratio to predict mortality in patients with sepsis or septic shock: a systematic review and meta-analysis. European review for medical and pharmacological sciences 26(5): 1743-1752	- Study does not contain a relevant intervention
Yulan Permatasari, A.A.I., Hendra Sanjaya, I.G.P., Widiana, I.G.R. et al. (2021) Role of procalcitonin and c-reactive protein as marker of sepsis in major burn patients: A systematic review and meta-analysis. Open Access Macedonian Journal of Medical Sciences 9: 197-203	- Includes primary studies that are pre 2015 *One post Oct 2015 primary study is included in other review.*
Zacharakis, Alexandra, Ackermann, Khalia, Hughes, Clifford et al. (2023) Combining C-reactive protein and quick sequential organ failure assessment (qSOFA) to improve	- Not in protocol -of interest

Study	Reason for exclusion
prognostic accuracy for sepsis and mortality in adult inpatients: A systematic review. Health science reports 6(4): e1229	
Zhang, Zhongheng; Xu, Xiao; Chen, Kun (2014) Lactate clearance as a useful biomarker for the prediction of all-cause mortality in critically ill patients: a systematic review study protocol. BMJ open 4(5): e004752	- Not a relevant study design *Protocol for an SR*

Escalation of care: excluded studies

Systematic reviews

Study	Reason for exclusion
Arabi, Yaseen M, Al-Dorzi, Hasan M, Alamry, Ahmed et al. (2017) The impact of a multifaceted intervention including sepsis electronic alert system and sepsis response team on the outcomes of patients with sepsis and septic shock. Annals of intensive care 7(1): 57	- Not a relevant study design
Branco, Maria João Chambel, Lucas, Ana Paula Mirco, Marques, Rita Margarida Dourado et al. (2020) The role of the nurse in caring for the critical patient with sepsis. Rev. bras. enferm 73(4): e20190031-e20190031	- Study does not contain a relevant intervention
Burrell, Anthony R, McLaws, Mary-Louise, Fullick, Mary et al. (2016) SEPSIS KILLS: early intervention saves lives. The Medical journal of Australia 204(2): 73	- Not a relevant study design
Failla, Kim Reina (2016) Predictors of Septic Patient Outcomes. Predictors of Septic Patient Outcomes: 1-1	- Full text paper not available
Fathi, M; Markazi-Moghaddam, N; Ramezankhani, A (2019) A systematic review on risk factors associated with sepsis in patients admitted to intensive care	- Study does not contain a relevant intervention

Study	Reason for exclusion
units. Australian critical care : official journal of the Confederation of Australian Critical Care Nurses 32(2): 155-164	
Fleischmann-Struzek, C, Mellhammar, L, Rose, N et al. (2020) Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. Intensive care medicine 46(8): 1552-1562	- Not a relevant study design
Gale, Bryan M and Hall, Kendall K (2020) The Use of Patient Monitoring Systems to Improve Sepsis Recognition and Outcomes: A Systematic Review. Journal of patient safety 16(3ssuppl1): 8-s11	- Study does not contain a relevant intervention
Gallagher, K, Blackwell, N, Thomas, B et al. (2019) Successful prospective quality improvement programme for the identification and management of patients at risk of sepsis in hospital. BMJ open quality 8(2): e000369	- Not a relevant study design
Guarino, Matteo, Perna, Benedetta, Cesaro, Alice Eleonora et al. (2023) 2023 Update on Sepsis and Septic Shock in Adult Patients: Management in the Emergency Department. Journal of clinical medicine 12(9)	- Study does not contain a relevant intervention
Lin, Y (2020) Effectiveness of the sepsis six bundle in the management of acute adult sepsis in the UK. Emergency nurse : the journal of the RCN Accident and Emergency Nursing Association	- Study does not contain a relevant intervention
Marwick, Charis A, Guthrie, Bruce, Pringle, Jan E C et al. (2014) A multifaceted intervention to improve sepsis management in general hospital wards with evaluation using segmented regression of interrupted time series. BMJ quality & safety 23(12): e2	- Not a relevant study design
Moskowitz, Ari, Patel, Parth V, Grossestreuer, Anne V et al. (2017) Quick Sequential Organ Failure Assessment and Systemic Inflammatory Response Syndrome Criteria as Predictors of Critical	- Study does not contain a relevant intervention

Study	Reason for exclusion
Care Intervention Among Patients With Suspected Infection. Critical care medicine 45(11): 1813-1819	- Not a relevant study design
Rababa, Mohammad; Bani Hamad, Dania; Hayajneh, Audai A (2022) Sepsis assessment and management in critically Ill adults: A systematic review. PloS one 17(7): e0270711	- Study does not contain a relevant intervention
Schinkel, Michiel, Holleman, Frits, Vleghels, Richarda et al. (2022) The impact of a sepsis performance improvement program in the emergency department: a before-after intervention study. Infection	- Not a relevant study design
Sun, Lin, Joshi, Meera, Khan, Sadia N et al. (2020) Clinical impact of multi-parameter continuous non-invasive monitoring in hospital wards: a systematic review and meta-analysis. Journal of the Royal Society of Medicine 113(6): 217-224	- Study does not contain a relevant intervention
Taj, M, Brenner, M, Sulaiman, Z et al. (2022) Sepsis protocols to reduce mortality in resource-restricted settings: A systematic review. Intensive & critical care nursing: 103255	- Study does not contain a relevant intervention
Warttig, Sheryl, Alderson, Phil, Evans, David Jw et al. (2018) Automated monitoring compared to standard care for the early detection of sepsis in critically ill patients. The Cochrane database of systematic reviews 6: cd012404	- Study does not contain a relevant intervention
Zhang, Z, Chen, L, Xu, P et al. (2022) Effectiveness of automated alerting system compared to usual care for the management of sepsis. NPJ digital medicine 5(1): 101	- Study does not contain a relevant intervention

Primary studies

Study	Reason for exclusion
Ferguson, Alice, Coates, Daniel Evan, Osborn, Scott et al. (2019) Early, Nurse-Directed Sepsis Care. The American journal of nursing 119(1): 52-58	- Study does not contain relevant comparator *The study does not include late escalation as a comparator. The study aimed to assess the impact of early intervention on sepsis care.*
Ireland, Megan, Jalilvand, Anahita, Gonzalez-Gallo, Kathia et al. (2021) Transfer Status and 90-Day Mortality in Intensive Care Unit Patients With Sepsis: A Propensity Matched Analysis. The Journal of surgical research 268: 595-605	- Study does not contain relevant comparator *The study does not include early versus late escalation of care. It indirectly reviews escalation of care by assessing time to hospital transfer*

Economic evaluations: excluded studies

No studies were screened for inclusion at full text review.